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Recent Trends and Developments

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Preface

Several epidemiological studies have documented that mental health disorders are extremely prevalent in children and adolescents with rates varying from 10 to 20% depending on whether the evaluation of impairment is part of the assessment [1, 2]. In addition, data from longitudinal studies and retrospective investigations in adulthood have demonstrated that a substantial proportion of psychiatric diagnoses identified in adults have their roots in childhood and adolescence [3, 4]. Moreover, several reports in the literature have also documented the substantial amount of burden that child mental health problems impose on children, their families and society in general [5]. Thus, understanding child psychiatric disorders is a priority in the worldwide mental health agenda based on its prevalence, continuity into adulthood and impact.

Throughout the last decades, several different frameworks have influenced the field of child psychiatry. In the past, the field was strongly based on psychodynamic and social concepts [6]. In the last two decades, an enormous amount of data has emerged in areas such as neuroimaging, molecular genetics, neuropsychology, and neurophysiology, helping to better understand the biological basis of the majority of child mental disorders. Thus, we have moved from attributing the causes of severe child mental disorders like autism primarily to problematic mother-infant relationships to an era in which huge genome-wide scanning studies and longitudinal gene-environmental investigations are beginning to reveal the complex interplay of nature and nurture in normal development and in the etiology of child mental disorders [7]. Advances in biological child psychiatry may ultimately facilitate our understanding of how environmentally and psychosocially mediated risk processes operate on the developing brain and also increase our knowledge of the developmental trajectories that occur across the life course [8].

In this exciting context, the authors of this book wrote their chapters. They are among the world's leading experts, both researchers and clinicians, in the area of

biological child psychiatry. While some contributors focused exclusively on recent biological aspects of specific disorders, others preferred a more comprehensive approach describing some clinical aspects too. However, independent of the approach chosen, the reader will always find the most recent advances in neurobiological research on each of the disorders addressed in this book.

During the rapid development of child psychiatry in the last decade, investigators have also paid special attention to the impact of cross-cultural issues on the development and/or modulation of phenotype or course of child mental disorders [9]. This is another interesting aspect of this book, since the team of authors came from very diverse cultural backgrounds and, whenever possible, we tried to have authors from different cultures address specific disorders.

Finally, a very relevant issue is related to what is called 'translation research'. In other words, how very sophisticated basic laboratory findings translate into clinical practice [10]. Although the focus of this volume is on child biological psychiatry, the authors tried to present findings in an integrative context helping readers to establish the needed connections with the real clinical world.

For all the reasons mentioned above, we are confident that this book will be valuable to all practitioners and researchers both in child and adolescent mental health services and developmental and clinical neuroscience who are interested in deepening their knowledge of the recent advances in the underlying biological bases of major child and adolescent mental health disorders.

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Attention-Deficit/Hyperactivity Disorder

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Abstract

Objectives: To describe the main aspects of attention-deficit/hyperactivity disorder (ADHD), including the epidemiology, etiology, neurobiology, clinical features, comorbidities, diagnosis, outcome and treatment. **Sources of Data:** We performed a comprehensive, selective (nonsystematic) review of the literature on ADHD. **Summary of the Findings:** ADHD is highly prevalent in children and adolescents, has a clear neurobiological basis and an easily detectable set of cohesive symptoms, is associated with impairments in different areas of functioning, and treatment is very efficacious, including the use of medication in most the cases.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common mental disorders affecting children and adolescents. The core ADHD symptoms are pervasive and impairing inattention, hyperactivity, and/or impulsivity. Due to its significant prevalence during the lifespan and associated impairments, the disorder is considered a major health problem [1].

This chapter addresses recent research findings on different aspects of ADHD that might translate into relevant clinical issues. Thus, an extensive review of the abundant literature on ADHD is beyond the scope of this chapter.

Epidemiology

Epidemiological studies have contributed to the understanding of the worldwide distribution of ADHD and to an accurate planning of services for affected children. However, disparate prevalence rates can be found around the world. Thus, rates as low as 0.9% to as high as 20% can be found in epidemiological studies addressing ADHD [2].

Three recent systematic reviews on this subject have been published in a tentative to provide a 'true' prevalence rate, and to explain the reasons for the variability in results across studies [3–5]. The prevalence rate estimated by these reviews is commonly between 5 and 10%.

In a comprehensive systematic review on ADHD prevalence during childhood and adolescence conducted by Polanczyk et al. [4], an estimated pooled prevalence for the disorder was provided. In addition, meta-regression analyses were performed to evaluate the role of methodological characteristics on the variability of results. After a broad review and a rigorous analysis of papers, 102 studies comprising 171,756 subjects from all world regions were included. The aggregated prevalence of ADHD based on all studies was 5.29% (95% CI 5.01–5.56). The pooled prevalence for children and adolescents were 6.48% (95% CI 4.62–8.35) and 2.74% (95% CI 2.04–3.45), respectively. Furthermore, adjusting for methodological issues, estimates from North America and Europe were not significantly different. Differences between studies regarding the diagnostic criteria used (DSM-III, DSM-III-R, DSM-IV or ICD-10), source of information (best-estimate procedure, parents, 'and rule', 'or rule', teachers, or subjects), and requirement or not of impairment for the diagnosis were associated with significant variability of results.

Studies in children consistently suggest that the ADHD prevalence is higher in boys than in girls. The male/female ratio varies from 3:1 to 9:1, depending on the origin of the sample ascertainment [2]. In the systematic review and meta-regression mentioned above, the pooled ADHD prevalence for boys was 2.45 times higher than the one detected for girls (only non-referred samples were included). The prevalence among girls seems to be higher in community samples than in clinical samples, probably because there is a barrier to diagnosis and treatment referral for females.

The impact of ethnic and socioeconomic issues on the prevalence rates of ADHD has been much less investigated. In the study by Polanczyk et al. [4], a significantly different pooled ADHD prevalence estimate was detected for both African and Middle-East studies when compared to either North American or European estimates. However, this finding might be related to the small number of studies conducted in the first two world regions making their estimates less reliable. In a study by Angold et al. [6], the authors did not detect significantly different ADHD prevalence rates in African-American (2.1%) and white (3.2%) youths. Regarding the impact of poverty on the prevalence of ADHD, several studies also did not detect significant effects of income [7, 8].

Etiology and Neurobiology

In the following section we summarize the current knowledge on genetic and environmental risk factors and on brain structural and functional, neurochemical as well as neuropsychological and neurophysiological correlates of ADHD.

Family, adoption, and twin studies provide compelling evidence that genes play a strong role in mediating vulnerability to ADHD. Most family studies have identified a two- to eightfold increase in the risk for ADHD in parents and siblings of children with ADHD; adoption studies found that biological relatives of hyperactive children were more likely to have hyperactivity than adoptive relatives [1]. However, although twin studies demonstrate that ADHD is highly heritable with genetic factors explaining on average 76% of the phenotypic variance in the population [9], these findings must not be confused with neurobiological determinism [10].

Molecular genetic studies suggest that the genetic architecture of ADHD is complex. Family-based linkage studies have identified a number of chromosomal regions containing potential ADHD predisposing loci, some overlapping in two or more studies, including 5p, 6q, 7p, 11q, 12q, and 17p, but the genome-wide scans conducted thus far are not conclusive. Replicated association has been reported for several candidate genes, including DAT1, DRD4, SNAP-25, DRD5, 5HTT, HTR1B, and DBH [9]. A recent report by Brookes et al. [11] confirmed the association of ADHD with the DRD4 and DAT genes, and also provided suggestive evidence of association of ADHD with 16 other genes. However, the known risk alleles are widely distributed in the population and each of these risk alleles confer relatively small risk.

Emerging literature documents that various environmental risks, including pre- or perinatal complications, maternal smoking and alcohol exposure during pregnancy, low birth weight, and psychosocial adversity are additional independent risk factors for ADHD [12]. Prenatal exposition to nicotine is probably causing direct teratogenic effects [13]. Severe early deprivation, institutional rearing, idiosyncratic reactions to food, and exposure to toxic levels of lead are also considered to have etiological importance [10]. Gene-gene and gene-environment interactions seem likely, e.g., dopaminergic genotypes and prenatal smoking exposure [14, 15], as well as prenatal alcohol exposure [11] or psychosocial adversity [16].

Taken together, the findings on genetic and environmental risk factors are consistent with the hypothesis that, in most cases, ADHD is a complex disorder influenced by the interaction of multiple etiological factors. Thus, ADHD can likely be considered as the extreme expression of a trait that varies quantitatively in the population [17].

Studies using structural and functional brain imaging, electrophysiology and transcranial magnetic stimulation have shown various abnormalities in frontal, temporal, and parietal cortical regions, basal ganglia (striatum), corpus callosum, and cerebellum [18–22]. The most replicated structural alterations in ADHD include significantly smaller volumes in the prefrontal areas, caudate, corpus callosum, and

cerebellum [23, 24]. The largest structural study conducted so far using combined cross-sectional and longitudinal design revealed that the morphological abnormalities seem to be evident early in life, persist with age, show parallel developmental trajectories for all structures assessed (except for the caudate where group differences disappeared with age), and not be a result of stimulant treatment. The most robustly deviant region in brain associated with ADHD was the cerebellum [19]. Another longitudinal study suggests that reductions in thickness of the frontal and parietal brain regions may be associated with worse outcome [25].

Initial functional imaging studies in ADHD focused largely on top-down cortical control systems involving the prefrontal cortex. Less attention was given to bottom-up neural systems implicated in ADHD [26]. Across studies, a consistent pattern of frontal hypofunction is seen with altered activity patterns in the anterior cingulate, prefrontal cortices, as well as the associated parietal, striatal, and cerebellar regions [27, 28]. Patterns of hypoactivation of the ventral prefrontal and inferior parietal regions related to attentional networks appear to be present in the unaffected siblings of children with ADHD as well as ADHD cases [29]. Moreover, it was found that tasks requiring higher cognitive functioning are often associated with greater activation in regions associated with motor and visual, spatial processing in individuals with ADHD which may represent a primary abnormality or be the correlate of the use of specific compensatory strategies [30]. Similarly, individuals with ADHD tend to activate a more diffuse, wider system of brain regions to perform a task [31]. Furthermore, functional MRI findings showed that adolescents with ADHD had reduced accumbens activity in anticipation of large reward [32]. The distributed nature of these results fails to support models emphasizing dysfunction in any one sub-region. Instead, these findings suggest that the brain may be altered in a more widespread manner than has been previously hypothesized. The fronto-striatal circuits may be disrupted at numerous loci with similar functional consequences; thus, functions of fronto-striatal circuits could be affected by dysfunctions of the posterior cortical regions, the cerebellum or ascending arousal systems, which closely interact with the prefrontal cortex and have also been implicated in ADHD.

Concerning the involvement of specific neurotransmitter systems in the pathophysiology of ADHD, converging evidence from molecular genetic findings, animal models [33], and functional imaging studies [34] as well as the effectiveness of stimulants [35], suggests that catecholaminergic dysregulations are centrally involved in ADHD. Furthermore, there is some evidence for a role of central nicotinic cholinergic systems in cognitive deficits in ADHD [36].

Neuropsychological research indicates that children with ADHD have impairments in various executive function domains [37]. An association between ADHD and motor inhibitory control deficits is seen as one of the most consistent findings [38]. However, mean effect sizes for executive function measures were found consistently in the medium range (0.46–0.69), suggesting that there is considerable overlap between children with and without ADHD and controls, and that at most a small majority of

ADHD children have a significant executive function deficit. In other words, executive function weaknesses are neither necessary nor sufficient to cause all cases of ADHD [38]. Thus despite considerable evidence indicating differences at the group level, executive function measures do not appear to have the sensitivity or specificity to adequately classify most individuals with ADHD relative to normal controls [38, 39]. Furthermore, there is little evidence to suggest larger effect sizes for executive function deficits in ADHD than impairments in other cognitive domains in ADHD.

Although available research suggests that executive functions are deficient in ADHD, the primacy of executive function deficits in ADHD has been questioned as these impairments might be preceded and or caused by other more fundamental, simpler problems, 'non-executive' dysfunctions. Thus, neuropsychological and event-related potential studies have found that measures of domains with less of an executive component, such as processing speed, rapid naming, fine and gross motor skill, timing functions, and early and automatic information processing stages, are impaired as well [40]. Neuropsychopharmacological studies have also demonstrated a wide range of non-executive neuropsychological deficits in ADHD [41], suggesting the involvement of temporal and/or amygdalo/hippocampal brain regions in ADHD.

EEG studies consistently indicate that the spontaneous or resting EEG of children with ADHD is characterized by increased slow and decreased fast activity [18]; alpha power recorded during cognitive activation may be a putative endophenotype for ADHD [42]. Studies using event-related potentials found that early automatic information processing stages related to the initial orienting and stimulus evaluation are altered [43]. Children with ADHD exhibit increased early attentional orienting before failing to allocate sufficient attentional resources in further processing stages [43]. Importantly, these attentional deficits occur without concomitant responses or performance deficits, temporally precede inhibitory or executive control, and predict subsequent performance. While inhibitory control deficits are also found in children with ADHD, they are preceded by state regulation deficits or accompanied by executive control deficits, particularly at slow event rates [43]. Taken together, EEG/ERP research on ADHD have shown the occurrence of a sequence of multiple activation deficits of posterior and anterior attention networks within a sub-second range, causally preceding inhibitory or executive control [43].

Moreover, altered motivational processes and altered learning mechanisms may be relevant [33, 44]. Thus, children with ADHD tend rather to reduce the total delay than to maximize the reward [44]. This characteristic, which is most pronounced in situations where choosing immediacy reduces overall delay, can be dissociated from deficits in executive functions and especially in inhibitory control [45]. The importance of the involvement of altered learning mechanisms is supported by animal studies of dopamine reinforcement learning; a retrograde reinforcement effect that is shorter and decreased (steep 'delay-of-reinforcement gradient') may explain an impaired behavior control by external stimuli [33]. Altered error processing [46], associated with a dysfunction of the anterior cingulate, may similarly lead to impaired

learning processes. Deficits in learning to detect regularities or irregularities in the environment could lead to impaired signaling to cognitive control systems that alter or adjust behavior accordingly; likewise, intact signaling but inefficient top-down control could result in poor regulation of behavior in a more general way [47, 48].

Taken together, the common perception of ADHD as a cortico-striato-thalamo-cortical disorder may be too limited [40] and should be revisited [49]. A more general state or response regulation problem may underlie ADHD [50, 51]. Alternatively, the findings could support the idea of multiple interacting causal pathways to ADHD [39, 40, 44, 52, 53]. Many components of these etiological pathways may well be shared with other conditions, others may be unique to ADHD [40, 53].

Clinical Presentation and Diagnostic Process

The classic triad of symptoms characterizing this syndrome includes inattention, hyperactivity and impulsivity. It is important to note that inattention, hyperactivity and impulsivity as isolated symptoms may be the final path for many problems related to conflicts with parents and/or colleagues and friends, inappropriate educational systems, or may even be associated with other disorders that are commonly observed in childhood and adolescence. Therefore, for the diagnosis of ADHD it is always necessary to contextualize the symptoms in the child's history. Some clues that indicate the presence of ADHD are the following.

(a) Length of symptoms of inattention and/or hyperactivity/impulsivity. Quite often, children with ADHD have a history of symptoms that start in the preschool age, or at least a period of several months with intense symptoms.

(b) Frequency and intensity of symptoms. For the diagnosis of ADHD, it is crucial that at least six symptoms of inattention and/or six symptoms of hyperactivity/impulsivity described in table 1 be frequently present (each of the symptoms).

(c) Persistence of symptoms in several places and over time. Symptoms of inattention and/or hyperactivity/impulsivity have to occur in different environments (e.g., at school and at home) and be constant during a stable period. Symptoms that occur only at home or only at school should warn clinicians of the possibility that inattention, hyperactivity or impulsivity may simply reflect a chaotic family situation or an inappropriate educational system. Likewise, oscillating symptoms with asymptomatic periods are not characteristic of ADHD.

(d) Clinically significant consequences on the child's daily activities. Symptoms of hyperactivity or impulsivity with no effect on the child's daily activities may reflect different functioning or temperament style other than a psychiatric disorder.

(e) Understanding the meaning of the symptom. For the diagnosis of ADHD, it is necessary that a careful assessment of each symptom, and not only a list of symptoms, be made. For instance, a child may show difficulty following instructions due to an oppositional defiant behavior towards parents or teachers, which characterizes a

Table 1. DSM-IV diagnostic criteria for ADHD

A Either 1 or 2

1 Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level

Inattention

- a Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- b Often has difficulty sustaining attention in tasks or play activities
- c Often does not seem to listen when spoken to directly
- d Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- e Often has difficulty organizing tasks and activities
- f Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- g Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
- h Is often easily distracted by extraneous stimuli
- i Is often forgetful in daily activities

2 Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level

Hyperactivity

- a Often fidgets with hands or feet or squirms in seat
- b Often leaves seat in classroom or in other situations in which remaining seated is expected
- c Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
- d Often has difficulty playing or engaging in leisure activities quietly
- e Is often 'on the go' or often acts as if 'driven by a motor'
- f Often talks excessively

Impulsivity

- g Often blurts out answers before questions have been completed
- h Often has difficulty awaiting turn
- i Often interrupts or intrudes on others (e.g., butts into conversations or games)

B Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before 7 years of age

C Some impairment from the symptoms is present in 2 or more settings (e.g., at school [or work] or at home)

D There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning

E The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or other psychotic disorder and are not better accounted for by another mental disorder (e.g., mood disorder, anxiety disorder, dissociative disorder, or personality disorder)

symptom of an oppositional defiant disorder instead of ADHD. It is essential to check whether the child does not follow instructions because he/she cannot concentrate while they are being given. In other words, it is necessary to check whether the supposedly present symptom is correlated with the basic characteristics of the disorder, that is, attention deficit and/or difficulty in inhibitory control.

Clinical presentation may vary according to the stage of development. Symptoms related to hyperactivity/impulsivity are more frequent in preschool children with ADHD than symptoms of inattention. As more intense activity is characteristic of preschool children, the diagnosis of ADHD should be made with caution before the age of 6 years. This, among other reasons, is why information on a child's normal development is essential for the psychopathological assessment in this age group. The literature indicates that symptoms of hyperactivity subside in adolescence, but symptoms of inattention and cognitive impulsivity are more intense in this period [54]. An extensive discussion on assessment for ADHD in children and adolescents can be found in the recent Practice Parameters from the AACAP [55].

The DSM-IV subdivides ADHD into three types: (a) predominantly inattentive type; (b) predominantly hyperactive-impulsive type, and (c) combined type. The predominantly inattentive type is more common in females and, together with the combined type, seems to have a higher impact on academic performance. Children with the predominantly hyperactive-impulsive type are more aggressive and impulsive than those with the other two types of ADHD, and tend to be unpopular and highly rejected by their peers. The combined type causes more impairment to global functioning, comparatively to the other two types [54].

Studies show a high prevalence of comorbidity between ADHD and disruptive behavioral disorders (conduct disorder and oppositional defiant disorder), which ranges from 30 to 50%. The comorbidity rate also is significant with the following disorders: (a) depression (15–20%); (b) anxiety disorders (around 25%), and (c) learning disabilities (10–25%). Several studies have shown a high prevalence of comorbidity between ADHD and drug abuse or dependency in adolescence, especially in adulthood (9–40%) [54]. There is a debate in the literature whether ADHD alone is a risk factor for drug abuse and dependency in either adolescence or adulthood (comorbidity rate = 9–40%) [54]. In figure 1, the ADHD comorbid profiles in three different clinical samples from Brazil [57], the US [58], and Europe [59] are described suggesting a consistent profile of high comorbidity.

The diagnosis of ADHD is clinical, based upon clear and well-defined operational clinical criteria established by classification systems such as the DSM-IV (table 1) [60] or ICD-10 [61]. Thus, there is no need to perform neuroimaging and/or neuropsychological tests to confirm or refute the diagnosis. These additional investigations are extremely important to advance our knowledge on the pathophysiology of the disorder in the research field, but until now their findings do not translate into the clinical world [55]. Although the lists of 18 symptoms from the DSM-IV and the ICD-10 for ADHD are similar, ICD-10 is more restrictive as some symptoms must be

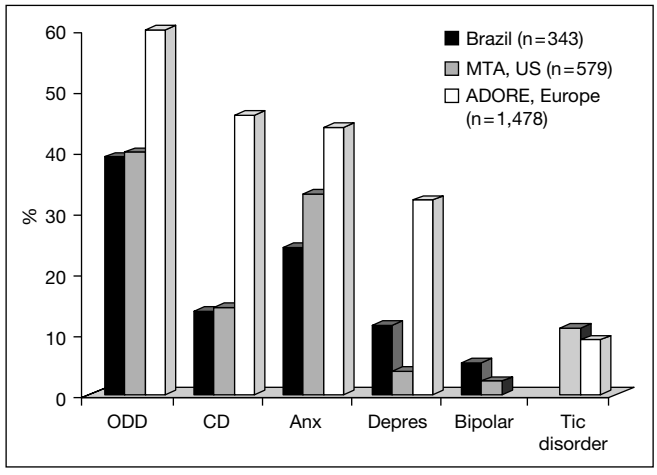

Fig. 1. ADHD comorbid profile in three studies: The MTA [58], the ADORE [59], and Souza et al. [57] (Brazil). Data are presented as percentages. In the Brazilian study, the comorbid profile is described only for one site (Porto Alegre) and no information is reported for tic disorders. In the MTA, only ADHD-combined type is included and several restrictions were applied to enroll patients with severe mood disorders. No information is available for bipolar disorder in the ADORE study. ODD = Oppositional defiant disorder; CD = conduct disorder; Anx = anxiety; Depres = depression.

present in the three dimensions (inattention, hyperactivity and impulsivity), and hyperkinetic disorder (the nomenclature used in the ICD-10 that correspond to ADHD in the DSM-IV) is excluded if depression and/or anxiety disorders are also identified. Improvements in the diagnostic criteria for ADHD in future classifications systems are expected [for an extensive review see, 62]. The two main areas that deserve special consideration are: (a) reformulation of diagnostic criteria for adults, and (b) the age-at-onset of symptoms in the ICD-10 and age-at-onset of impairment in the DSM-IV (7 years). This criterion is solely based on a committee decision and recent investigations do not support its validity.

Outcome

The ADHD was first conceptualized as a disorder restricted to childhood and adolescence. Longitudinal studies showed that although there is a clear decline of symptoms with age, they tend to persist in a variable proportion of people who are more frequently impaired than controls in several major life activities [2]. Faraone et al. [63] conducted a systematic review and a meta-analysis of longitudinal studies of ADHD. They found a 15% persistence rate when full diagnosis was defined and 40–60% when cases of ADHD in partial remission were included. These findings fuelled the debate whether the symptom threshold should be lower in adults.

Recently, Grevet et al. [64] compared the ADHD severity dimensions in two age-defined groups from an ADHD outpatient clinic (351 children and adolescents and 319 adults). The SNAP-IV inattentive and hyperactive/impulsive scores where significantly higher in boys than in adult males, but no significant difference was detected between girls and women in both dimensions. There was significant age × gender interaction in both measures. These results suggest that the age-dependent decline in symptoms observed in referred ADHD samples is true only for males.

The risk factors determining the persistence of ADHD diagnosis in adults remain unclear. However, some studies suggested that the severity of ADHD symptoms and the presence of comorbidities in children, adversities during childhood, and family history of ADHD might be associated with a higher rate of persistence. In the National Co-Morbidity Survey Replication, Kessler et al. [65] documented that only the severity of symptoms and treatment in childhood were predictors of ADHD persistence in adults in multivariate analyses. However, this study did not address a family history of ADHD.

Although the issue of ADHD in adults is beyond the scope of this chapter, it is important to note that a recent study by Fayyad et al. [66] documented a prevalence of DSM-IV ADHD of around 3.4% (range 1.2–7.3%) in a huge sample from ten different countries in the Americas, Europe and Middle East. Lower prevalence rates were found in low income countries compared with high income countries. This estimative was based on complex multiple imputation methods involving calibration of the estimative based on findings from just one country (USA). Other studies in adults found similar prevalence rates [67, 68].

Finally, it is important to note that a massive amount of data documents a worse outcome in subjects affected by ADHD compared to non-ADHD controls during the life span. Thus, a diagnosis of ADHD is associated with a higher rate of: (a) several psychiatric comorbidities such as disruptive behavior disorders, anxiety, mood disorders and substance use disorders; (b) school problems such as grade repetitions, suspensions, lower performance and school dropout; (c) accidents and driving impairments; (d) unemployment and sub-employment; (e) family dysfunction such as divorce and poor quality of family relations; (f) social problems; (g) risk-taking behaviors, and (h) medical care costs [69, 70].

Treatment

Psychoeducational, behavioral and medication treatments all have a place in the treatment of those with ADHD. Treatments should be planned on an individual basis taking into account the severity and pervasiveness of the core ADHD symptoms and impairment, the presence of comorbidity and the individuals' circumstances. Most cases seen by clinicians will have problems in several functional domains and will therefore require some form of multimodal intervention.

Psychoeducation

Psychoeducation will form the cornerstone of any treatment package and should be offered to every individual diagnosed with ADHD, their families, teachers and others in regular contact with the child. Psychoeducation should include an assessment of the child and parents' beliefs and understanding about ADHD, its causes and its consequences, followed by an informed discussion of the current scientific and clinical knowledge about ADHD, its comorbidities and its treatment including acknowledgement of both what is and is not known. Even if formal parent management training is not being offered, it is almost always appropriate to help parents and teachers to identify specific problem situations and find behavior management techniques for them. If medication is being considered, a full and frank discussion about the various drug treatments, addressing potential benefits and risks should be implemented. Discussing patient and parental beliefs and fears about medication to treat ADHD may improve adherence with treatment.

Psychosocial Treatments

Psychosocial treatments, in particular family-based behavioral interventions, reduce ADHD symptom and are well supported by randomized trials [71]. Whilst there is a wide range of such treatments, they share several common components and themes such as: the identification of problem situations and behaviors; their antecedents and any triggers; analysis of parental responses to positive and negative behaviors; enhancement of appropriate positive behaviors with positive reinforcement; reduction in negative, coercive and critical responses to negative behaviors; enhancement of parental communication styles and effective rule setting; the use of effective token reward systems to increase desirable behaviors and use of response cost systems, and 'time out' to reduce difficult behaviors. Overall the goal is to improve both behavior and the parent-child relationship resulting in reduced symptoms and increased quality of life. Similarly behavioral strategies have also been demonstrated to be effective in reducing ADHD symptoms and improving social adjustment within the school setting [72]. School-based approaches include discussion with the teacher about classroom structure and task demands (e.g. , having the child seated close to the teacher, brief academic assignments, interspersing classroom lectures with brief periods of physical exercise) and the identification of potentially difficult situations and problem behaviors. Again interventions focus on identifying and rewarding positive behaviors and reducing negative, coercive responses to problem behaviors.

The efficacy of direct psychological treatment with the child has been less easy to evidence. Whilst there is some support for group-based treatment programs which include social skills training and contingency management, isolated self-instructional approaches have not been shown to be effective. They may however be helpful in individual cases when used in combination with other behavioral approaches but treatment generalization is however often limited [73, 74].

Pharmacological Treatments

Pharmacological treatments for ADHD are supported by a strong evidence base. The most widely used medications are the psycho-stimulants including both methylphenidate and amphetamine preparations. These drugs block monoamine transporters, thus inhibiting the reuptake of dopamine and noradrenaline from the synapse. The literature supporting their use includes numerous placebo-controlled randomized control trials that confirm substantial short-term benefits with a pooled effect size of around 0.9 [75]. The psycho-stimulants markedly and rapidly reduce the core ADHD symptoms, decrease aggression, improve the quality of social interactions, and increase compliance. Methylphenidate has been reported to improve task performance on some but not all of the neuropsychological deficits which have been associated with ADHD [76]. Methylphenidate and amphetamines are each effective in around 70% of children with ADHD, and between 90 and 95% of those treated respond to one or both [77]. Although relatively few subjects drop out of clinical trials due to problems with tolerability [78], a significant minority (around 20–25%) do not wish to remain on stimulants due to adverse effects in the clinical world. The adverse effects of ADHD medications have been extensively reviewed elsewhere [79]. Common adverse events include interference with sleep and loss of appetite. The 36-month results of the Multi-Modal Treatment of ADHD (MTA) study suggest that stimulant medications can result in the initial slowing in growth rates [80]. Whilst the rate of growth was normalized by 36 months, there was no rebound growth during this time. It is therefore recommended that both height and weight should be routinely monitored. A recent FDA review of 25 deaths (19 of which in subjects under 18 years) and 54 serious cardiac complications in patients taking stimulant medications, reported to Medwatch in the USA between 1999 and 2003, prompted a call for the addition of 'black box' warning labels to stimulant medications advising the prescriber in relation to potential cardiovascular risk [81]. However a pediatric advisory committee later modified this to a requirement for clarified labeling [82]. Concern particularly surrounds the potential for stimulants as a group to raise heart rate and systolic and diastolic blood pressure. The adverse reports equated to less than 2 non-fatal cardiovascular events per million prescriptions, and less than 1 death per million. It is unlikely that this is greater than the rate in the untreated population, but it is also almost certainly the case that the true figures of adverse reactions are probably greater than reported. The main practical implications are to include physical examination before prescribing stimulants to seek cardiovascular abnormalities such as raised blood pressure or heart murmurs (ECG is optional) and enquire about symptoms such as syncope on exercise, with cardiological evaluation if a warning sign is found. Also pulse and blood pressure should be routinely monitored during treatment. Motor tics may emerge or worsen during treatment in a proportion of cases, however recent evidence suggests this is less of an issue than previously thought [83]. Whilst stimulants probably lower the convulsive threshold, experience suggests that they can be used safely and effectively in children with coexisting seizure disorders as

long as seizures are well controlled [84]. Although concerns have been raised that exposure to stimulant medications early in life may lead to the development of substance misuse later in life, a meta-analysis of the available literature reported that stimulant treatment reduced rather than increased the risk of substance misuse problems by a factor of almost two [85]. In the follow-up period of the MTA study, whilst those subjects that had received the MTA behavioral package for the 14 months of the original study were less likely to have substance misuse problems, the use of stimulant treatment at 24 or 36 months did not predict substance misuse [86].

Recently several long-acting stimulant preparations, which are a mixture of immediate- and extended-release medications, have been developed and licensed. These preparations differ with respect their duration of action (Equasym XL®/Metadate CD®, Ritalin LA®, Medikinet Retard® = 8 h duration; Adderall XR® = 8–10 h; Concerta® = 12 h) and the proportion of immediate-release to extended-release (Concerta® 22:78; Equasym XL®/Metadate CD® 30:70; Ritalin LA®, Medikinet Retard®, Focalin XR®, Adderall XR® 50:50). As a consequence, each preparation has a different profile over time, a factor that can be useful when matching a particular patient to a particular drug. The effects of these preparations have been extensively reviewed by Banaschewski et al. [87]. Although still to be fully demonstrated empirically, these preparations have several potential advantages over their immediate-release predecessors including: a reduction in stigma at school; improved compliance, and possibly a reduced risk of misuse. In view of these potential benefits, most commentators have agreed that, whilst they should not replace short-acting drugs, extended-release preparations should be available and should be used [55, 87, 88]. Other recently licensed stimulant preparations include a methylphenidate transdermal patch system and lisdexamfetamine, an amphetamine prodrug.

Atomoxetine, a selective noradrenaline transporter blocker, is the first non-stimulant drug licensed for the treatment of ADHD. Its efficacy in reducing ADHD symptoms and increasing quality of life is supported by several randomized clinical trials [89, 90]. Although it may have some immediate effects [91], full clinical effects take around 6–8 weeks to appear [92]. Whilst the half life is relatively short (around 5 h), the clinical effects appear to last longer and, once established, daily dosage is sufficient for most patients and may last across the whole 24-hour period. A systematic review of published and unpublished data estimated the effect size of atomoxetine to be 0.7 [87]. Common adverse effects include nausea, sedation and appetite loss. Most adverse effects appear to diminish over the first months of treatment. As with stimulants, pulse and blood pressure may increase and should be monitored. Although atomoxetine is metabolized by the cytochrome P450 2D6 enzyme, there does not appear to be a significant increase in adverse events in poor metabolizers.

The most common serious events reported with atomoxetine have been seizures, although in many cases those affected were already prone to seizures or were taking other drugs that can cause them. Thus, it is not clear whether atomoxetine can cause seizures. The warnings given for serious idiosyncratic hepatic events are similar to

those for stimulants and medication should be discontinued in patients who present with signs or symptoms of liver injury. Routine monitoring of hepatic function is, however, not recommended [87]. Preliminary data on atomoxetine do not show any potential for abuse or long-term effects on growth.

Since the licensing of atomoxetine and the extended-release stimulants, other unlicensed non-stimulant drugs known to have some efficacy in treating ADHD are used much less frequently. These include the tricyclic antidepressants, clonidine, guanfacine and bupropion.

When medication is considered, which drug and preparation should be used in which situations? Clearly this will depend on a range of patient and practical considerations and individual choices need to be made for each patient. However general recommendations can be made. Following a systematic review of the available evidence, Banaschewski et al. [87] concluded that whilst long-acting preparations should be available and used, they should not replace short-acting drugs (which will continue to be the initial treatment for many children for reasons of cost and flexibility of dosing). They suggest that although a stimulant will be the first choice in many patients, atomoxetine may be preferred in some cases particularly where substance abuse or comorbid tics are a problem, if there is a strong family preference for a non-stimulant, if a 24-hour action is particularly strongly required, or if there is comorbid anxiety. If starting an extended-release stimulant preparation, the choice of preparation will depend upon the profile of action required over time, and upon the availability of drug. Where a child has responded well to an immediate-release stimulant, there may still be reasons to shift to extended-release, for example, to avoid the stigma or inconvenience of repeated dosing. Where a child has suffered adverse effects on immediate-release methylphenidate, then the next step will often be to proceed to atomoxetine. If a child has failed to respond to one immediate-release stimulant, because of lack of efficacy rather than adverse effect, then the next option is to try an alternative stimulant or atomoxetine depending on the relative balance of advantages [87].

With several effective treatments approaches available, an important decision concerns the order in which these treatments are considered. Many of these decisions are currently based on the various results of the influential MTA study [58]. These results have been discussed in detail in the literature and it is only possible to discuss a few major points here. The primary findings of the 14-month randomized trial were that: the children in all four treatment arms (community 'as usual' treatment, intensive behavioral treatment, intensively monitored medication treatment, and a combination of the behavioral and medication arms) improved considerably; that the medication and combined arms were significantly better on most measures than the other two arms, and that the addition of the behavioral package to the medication arm produced few benefits. As a consequence it has been suggested by some authorities that medication treatments should be considered as 'first line' for cases of combined subtype ADHD [55]. This position is challenged by a reanalysis of the MTA dataset [93] which suggests that whilst the superiority of medication was clear for children meeting

criteria for ICD-10 defined hyperkinetic disorder, the situation was less clear for those children with the broader DSM-IV combined type ADHD, with the behavioral and medication treatment arms having equal effectiveness. The European Guidelines Group have therefore suggested that medication should be the first treatment for those with hyperkinetic disorder, whilst those with combined subtype ADHD but not hyperkinetic disorder should be first offered a trial of behavioral treatment with medication reserved for those whose symptoms persist [10].

The superiority of the medication arm of the MTA over the community treatment arm, in which a substantial proportion also received medication, may point to several other important treatment factors. The children in the medication arm started treatment with an intensive 28-day double-blind titration trial, were treated with doses 10 mg/day greater, had 3 times daily dosing versus twice daily dosing, received supportive counseling and reading materials, and had their dose adjustments formed by monthly teacher consultation with the pharmacotherapist [94]. These results suggest that effective pharmacotherapy for ADHD involves more than selecting the right drug. This is consistent with the 36-month findings from the MTA study where the earlier advantage of having had 14 months of the medication algorithm over the behavioral and community treatment arms was no longer apparent at 36 months [95]. The overall message is that to achieve maximal effectiveness requires careful titration at the beginning of treatment and well-designed and executed continuing care protocols constructed to ensure that treatment continues to be effective. Whilst such practices are possible in routine clinical care, they require thoughtful planning and careful execution [96]. Finally it must be remembered that the majority of children with ADHD seen in clinics suffer from at least one comorbid disorder which will also require treatment. Thus multimodal multidisciplinary treatments will be the norm rather than the exception.

Potential Conflict of Interests

The ADHD Outpatient Program receives research support from the following pharmaceutical companies: Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag, and Novartis. Prof. Rohde is on the speakers' bureau or is a consultant for the same companies and is on the advisory board for Eli Lilly & Company. Dr. David Coghill is an advisory board member for Cephalon, Eli Lilly, Janssen Cilag, Shire, Pfizer and UCB, and has received research funding from Eli Lilly and Janssen Cilag. Prof. Banaschewski served in an advisory or consultancy role for Lilly, Medice, Novartis, Pfizer, Shire, and UCB. He received conference attendance support or was paid for public speaking by Lilly, Janssen McNeil, Medice, Novartis, UCB.

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Autism

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Abstract

We summarize findings from postmortem, neuroimaging, neurochemical, developmental, and genetic studies, as well as diagnostic issues, and animal models that have proven useful in autism research. Consistent findings suggest abnormalities in brain volume and size, neurotransmitters, and a number of candidate genes have emerged. In addition, specific brain regions appear to be affected in autism, and include the cerebellum, medial temporal lobe, hippocampus, amygdala, and cortical regions. Advances in our understanding of the neurobiology of autism will hopefully lead to more successful interventions.

Autism is a complex neurodevelopmental disorder diagnosed on the basis of three dysfunctional domains: social interactions; language and communication skills, and stereotyped or repetitive behaviors (DSM-IV). Despite several decades of studies, the etiology of autism remains an enigma, and its neuropathophysiology is poorly understood [1]. The degree of impairment varies among individuals with autism, and displays a high degree of clinical heterogeneity. Commonly associated symptoms include: mental retardation [2]; seizures [3]; anxiety [4]; sleep disturbances [5]; self-injury; aggression, and stereotypies [6].

Although classical autism is phenotypically well defined, it is often classified within a broad spectrum of disorders termed 'autism spectrum disorder' (ASD) that include autism, Asperger and Rett syndromes, childhood disintegrative disorder, and pervasive development disorder not otherwise specified [7]. The prevalence of autism was estimated to be around 5 per 10,000 in the 1960s and 1970s, while current estimates have increase to between 10 and 20 per 10,000 [8, 9]. The prevalence of ASD remains relatively constant at approximately 60 per 10,000 [10–12]. The increase in prevalence

of autism is likely due to several factors, including study design, diagnostic instruments used, samples size, and/or characteristics of the population studied [9, 13].

Since the first description of autism, a variety of research approaches has been used, including epidemiology, neuroimaging, neurotransmission, genetics, animal models and, more recently, evolutionary psychiatry, in an effort to understand the underlying etiologies of autism and related disorders. In this chapter, we summarize current knowledge of the neuropathology of autism as well as a speculative evolutionary approach to these findings.

Behavioral and Cognitive Characteristics

Autistic symptoms include language impairments such as speech delay followed by a gradual regression in communication and failure to learn new words, lack of meaningful language, monotonous patterns of speech, and repetition of other's words or sentences [14, 15]. Other dysfunctional behaviors include repetitive behaviors such as flapping, spinning or twisting, a restricted interest (e.g. in dinosaurs or numbers), resistance to changes in their environment or to their routines, and self-abusive behaviors [16]. As a consequence of these impairments, the development of social skills is severely compromised. People with autism have reduced joint attention and imitation as well as an inability to perceive feelings, to read the intentions of others, to develop normal social relationship, and tend to develop poor conversations skills [17].

Among the three core dysfunctional symptoms in autism, the social difficulties have been explored using three cognitive theories. *Executive function* refers to the ability of planning, abstract thinking and cognitive flexibility that permit behavioral adaptations in order to reach a goal. Autistic individuals present inappropriate responses to environmental stimuli, and exhibit disorganized actions and strategies in daily affairs [18]. Nevertheless, autism is not exclusively a disorder of executive dysfunction [19], and there is no strong relationship between the level of social impairment and executive functioning [20–22].

A second cognitive theory has focused on *central coherence*, the ability to understand the context of a situation and to give it meaning and coherence [23]. A number of studies have proposed a relationship between weak central coherence and autism [24–26]. Perceptual or verbal-semantic tasks suggested that autistic individuals have a tendency for fragmented perception [27, 28], but some groups failed to replicate these findings [24, 25]. One of the reasons may be the autistic preference to process information in a detailed fashion, rather than globally; although, autistic individuals can process information globally if they are instructed to do so [26, 29].

The last and most studied theory, *theory of mind*, refers to the ability to learn about others' mental states and appreciate that others have beliefs, intents and desires that are different from one's own [30]. Autistic individuals perform poorly in theory of mind tasks; however, these characteristics can also be associated with other disorders,

such as non-verbal learning disabilities and semantic pragmatic disorders [31, 32]. Among the criticism of this theory as a core deficit in autism is that some of the main symptoms appear before theory of mind skills are fully established [33].

Diagnosis

At the present time, the diagnosis of autism remains clinical, as there are no biological markers that are of use. The current emphasis is on making the diagnosis as early as possible. Autism is commonly diagnosed between the ages of 2 and 4 years. Some studies analyzing homemade videos and parental perception of symptom onset have suggested that some children may be exhibiting abnormal behaviors and developmental delays within the first postnatal months, while in other children symptoms develop sometime in the 2nd or 3rd year of life [12, 34–36]. These onset discrepancies suggest the possible involvement of different pathophysiologies.

A large number of measurement tools have become available over the last 20 years. Besides the clinical interview, the family history and the current diagnostic criteria proposed by the American Psychiatric Association [37], several screening questionnaires, structured interviews and structured observations are now used. Screening tools include the Modified Checklist for Autism in Toddlers [38] and the Autism Screening Questionnaire [39]; interviews with parents can be done using Parent Interview for Autism [40] and Autism Diagnostic Interview-Revised [41], and systematized observations include the Childhood Autism Rating Scale [42] and the Autism Diagnostic Observation Schedule [43]. These systematic interview schedules are standardizing the diagnosis of autism. The more internationally accepted instruments include the Autism Diagnostic Interview and the Autism Diagnostic Observation Schedule, which require training for reliability in administration and scoring. Unfortunately, this requirement is expensive for mental health workers in non-developed countries, limiting the worldwide use of these instruments.

Neuroanatomical Abnormalities

Despite the wide acceptance that autism is caused by developmental abnormalities affecting the nervous system, there is controversy regarding which brain regions are mainly affected. In general, several studies have showed brain enlargement, based on the increased brain weight [44] or increased head circumference [45–47]. However, it seems that the more prominent brain enlargement might be restricted to the early childhood period (2–4 years old) [48], although differences in brain volume between 5 and 16 years old can be observed when autistic individuals are compared to controls [49].

To identify which brain structures are abnormal in autistic individuals, different methodologies have been applied, including postmortem studies, structural and

functional magnetic resonance imaging. In general, three main brain regions have been described as relevant to autism: the brainstem and cerebellum, the limbic system (hippocampus and amygdala), and the cortex.

Brainstem and Cerebellum

The brainstem consists of the midbrain, medulla oblongata and pons which are involved in alertness, arousal, and autonomic functions such as breathing and blood pressure control, as well as motor nuclei related to facial movements. Postmortem studies suggest substantial loss of several brainstem nuclei, such as superior olive nuclei and facial motor nuclei in autistic individuals [50, 51]. Magnetic resonance imaging studies have also shown abnormalities in brainstem regions [52, 53] and the cerebellum [53–58].

More than 90% of postmortem studies have shown some degree of abnormality in cerebellar structures [55]. Regions of abnormality include the granular cell layer, the deep nuclei of the cerebellum, and Purkinje cell layers [50, 59–64]. Purkinje cells are the cerebellar neurons that project out of the cerebellum [65]. Some reports have suggested an association between cerebellar abnormalities and motor, cognitive and social deficits [66–69]. Only a few imaging studies have looked specifically at cerebellar function in autism [70, 71]. Cerebellar activation during attention [70] or motor tasks [71] showed atypical patterns of activation in comparison to normal control populations. More recent anatomical studies have shown that besides the well-established connections between the cerebellum and primary motor, there are connections between the cerebellum and other cortex regions, including higher order processing cortical areas such as premotor, oculomotor, prefrontal and inferotemporal [72]. These studies shed light on a possible cerebellar contribution to the development of specific features of autism such as dysfunction in communication and social interaction, restricted interests, and stereotyped behaviors.

Lobe Temporal, Hippocampus and Amygdala

A postmortem study using two autistic individuals, 9 and 7 years old, compared with two normal age-matched controls found a decreased level of dendritic branching in the CA1 and CA4 regions of the hippocampus [73]. Another study reported high neuronal packing density in areas related to memory formation, maintenance, and retrieval, such as the hippocampus, subiculum, entorhinal cortex, medial septal nuclei, and several amygdala nuclei [49, 61], but the increase in packing density in CA1 and CA4 could not be reproduced by Bailey et al. [51], perhaps due to the limited number of samples and differences in the ages of the subjects.

The amygdala has frequently been associated in the pathophysiology of autism [74]. Reduced cell bodies and increased cell packing in central, medial, and cortical nuclei in autistic individuals have been reported [59, 75]. Magnetic resonance imaging studies suggest an abnormal growth pattern during early infancy that results in an enlargement of the amygdala [76, 77]. Stereological analyses suggest that autistic brains have fewer neurons in comparison to controls especially in the lateral amygdala

nucleus, but neither the total volume nor the subregion volumes were different [78]. As mentioned by the authors, the differences described might be due to the inclusion of affected individuals with epilepsy in some studies, but not in others [78]. A summary of the existing data suggests that the amygdala contributes to the expression of normal socio-emotional behaviors and, together with other temporal regions, comprises part of the social brain. In addition, recent structural and functional neuroimaging studies have shown that certain skills, such as prosody, may reside in the superior temporal sulcus [79]. The autistic brain presents with anatomic and functional discrepancies in this region when listening to the human voice or observing body movements [79].

Cortical Regions: Columnar Architecture

A careful study was conducted to check which brain regions were responsible for the enlargement of the brain observed in autistic individuals. The results suggested that the frontal lobes are more prominent in these patients [80, 81]. A disproportional increase of frontal lobe gray and white matter in comparison with other cortical areas was found in a sample of autistic subjects [80]. Some studies suggest that the overall brain volume enlargement is due to the increase in cerebral white matter [82], but others pointed that the brain enlargement is caused not only by white matter but also by gray matter [80, 81]. An abnormal cortical neuron growth rate could lead to an increase in dendritic branching followed by an increase in the rate of synaptogenesis and axon myelination and/or reduced elimination of aberrant connections [83].

Postmortem studies have found alterations in cortical minicolumn organization. Ectopic neurons in the white matter and layer 1 as well as disoriented pyramidal neurons in layer 5 were found in the superior temporal gyrus [51]. Cassanova et al. [84] showed an increase in the number of minicolumns in the prefrontal cortex and temporal lobe of autistic individuals as compared with control subjects. This increased minicolumn number was concomitant with decreased minicolumn width and smaller neuronal size.

During the evolution of mammals, the cortical brain surface expanded by increasing the number of gyri rather than their thickness. There is a model postulating that the increased number of minicolumns was a result of natural selection [85]. During the evolutionary process, the cortical brain area increased while the minicolumn and macrocolumn size remained constant [86]. Selection pressures probably ensured that the new columns benefit the organisms. However, autistic individuals probably cannot take advantage of the higher number of minicolumns because this increase was not the result of selection pressure, but rather an individual process [84].

Mirror Neuron System and Autism

Mirror neurons are a class of cortical neurons that are discharged when one executes a movement, as well as when one observes other individual's actions. A number of

different studies suggest that mirror neuron engagement may reflect an understanding of another's intentions. Based on that, abnormalities in the development of the mirror neuron system have been proposed for developmental disorders such as autism [87, 88]. Mirror neurons are localized within the inferior parietal lobule and inferior frontal gyrus, brain regions implicated in ASD individuals [89–91]. This system appears to be involved in speech [92], theory of mind [93] and imitation in monkeys [94] and in humans [95]. When asked to imitate lip movements, persons with Asperger's syndrome showed a weak activation of the inferior frontal lobe and the primary motor cortex with a significant delay as compared to healthy controls [88]. Activation delays reflect an abnormal connectivity between the sensorial input, e.g. visual, and brain regions that form the mirror neuron system [90].

Within an evolutionary perspective, imitation behavior in humans possibly developed from an already existing mirror neuron system that had been previously used for broad kinds of social skills. Among the skills supported by a mirror neuron system, empathy may be one of the most important abilities developed in human beings. The ability to develop empathic relationships would likely strengthened interpersonal connections, allowing more complex social organization. Williams et al. [87] have hypothesized that if the mirror neuron system is involved in human imitation, this system possibly first arose in monkeys to advance the first imitation behaviors, and eventually theory of mind. Furthermore, if imitation and theory of mind are connected and supported by the mirror neuron system, this system probably has a key contribution during ontogenesis.

Neurotransmission in Autism

Glutamate and γ-aminobutyric acid (GABA) are the principal excitatory and inhibitory transmitters in the brain, respectively. There are suggestions that glutamate is essential during the formation of brain cytoarchitecture by the regulation of processes such as neuronal sprouting and synaptogenesis [96]. In addition, GABA plays a key role in the ontogeny of the nervous system. During early development, GABA is important for establishing neural networks [97], modulating the rate of cell migration during cortical development [98], as well as modulating cell proliferation [99] and differentiation [100].

Different neurochemical systems are potentially involved in the pathophysiology of autism. Some studies suggest that affected individuals have a disequilibrium in the balance between excitation and inhibition in the cortex, with an impairment in the GABAergic system [101], which can affect the neural network in relation to perception and attention. Some studies have also suggested that autism is a hypoglutamatergic disorder [102–104], while others have found reduced GABAergic inhibition [105–107].

Serotonin, dopamine and norepinephrine systems have been suggested to be dysregulated in autism. The increased synthesis of 5-hydroxytryptamine during early

development and infancy may cause loss of serotonin terminals and neural development damages [108]. Gradually, the level of 5-hydroxytryptamine returns to normal during adulthood [109, 110]. Dopamine and norepinephrine have been investigated in autistic patients, but there is little evidence supporting their involvement in the etiology of autism [111].

Many studies use blood, urine or cerebral spinal fluid samples as well as postmortem tissue to investigate brain neurochemistry dysfunction in autism in an effort to identify possible neurotransmitters involved in the neuropathology. However, the levels of neurotransmitters in the peripheral system often do not reflect levels within the nervous system, and this might explain the inconsistent findings across studies.

Studies using proton magnetic resonance spectroscopy permit analysis of a number of metabolites in vivo within different brain regions, and thus can begin to address neurochemical abnormalities in autism [112–118]. Magnetic resonance spectroscopy allows the detection and quantification of metabolites such as N-acetylaspartate, creatine and phosphocreatine, choline-containing compounds, and glutamate and glutamine in different brain regions of interest.

Briefly, these studies suggest a decrease in N-acetylaspartate in the temporal gray matter, cingulated gyrus, frontal and parietal [113, 116, 118, 119], or an increase in prefrontal N-acetylaspartate [120]. Creatine and phosphocreatine levels reflect the cell's energy disposal to oxidative metabolism, and lower levels were found in structures such as the thalamus, insula, caudate body, occipital gray matter, and frontal and parietal matter [113], while increased levels were found in the head of the caudate [117]. The presence of choline-containing compounds is correlated with cell membrane synthesis, and reduced levels were found in the temporal lobe, anterior cingulate, and thalamus [117, 120], and elevations in choline-containing compounds were reported in the frontal lobe and head of the caudate [117, 120]. Only two reports have examined glutamate and glutamine levels, one of them did not find any difference between groups [114], while the other found lower levels in the whole gray matter and cerebellum [121]. Taken together, these data suggest abnormal neuronal function in autistic individuals, although additional studies will be needed to help confirm or expand on these findings.

Genetics of Autism

A large number of studies have used twins, as well as more distant relatives to establish the importance of genetic factors in the etiology of autism and ASD [45, 122]. Monozygotic twins have a concordance rate of between 40 and 60%, while dyzigotic twins have rates of less than 25% [45, 123–125]. Although there is a strong consensus that autism is a genetic disorder and one with a high heritability component of around 90%, the genes that are mutated in this disorder remain unknown. Researchers have been using different genetic techniques to discover genes that contribute to the etiology of autism.

The broader phenotype found autism is probably a consequence of interactions between multiple genes. Estimates are that over 10 genes contribute to ASD susceptibility [126, 127]. Linkage studies have suggested the involvement of genes that lie on several different chromosomes, with the most frequent being 2q, 3q, 7q, 11p and 17q [128]. The area on chromosome 7q is the most frequently reported, but the risk loci are different across studies [129, 130]. Association and candidate gene studies have implicated many different genes, including genes essential for neurotransmission such as the serotonin system [131–134], *PIK3CG* (7q22), *MET* (7q31) [135], *RELN* (previously reelin, 7q22) [136, 137], *NRCAM* (7q22.3) [138, 139], *LAMB1* (7q31.1) [138, 139], *WNT2* (7q31.2) [140], and *FOXP2* (7q31) [141].

Gupta and State [142] discussed two theories in which autism would result from either a common gene variation or from a rare gene variation. Polymorphisms are variations in the DNA sequence that are normally found in the general population. The common gene hypothesis evolves from the fact that autism has a high prevalence and may result from dysfunction of more commonly found alleles. On the other hand, the inheritance pattern across families suggests that multiple genes may contribute to autism, each one with a small contribution to the disorder. Mutations in rare genes could also be the cause of autism. To address this question, direct sequencing of candidate polymorphisms should be done; however, this approach is more expensive than the conventional genotyping and there is always the risk of not finding enough affected individuals for statistical validations [142].

Animal Models in Autism

Animal models are being used with increased frequency to study the genetic, neuroanatomy, and molecular basis for a number of disorders [143]. Rodents are the most common species used as an animal model for autism, and individual core symptoms are being investigated to test theories regarding neurochemistry and genetics. At the present time, there is no animal model that captures all three core symptoms of autism, and animal models have been generated to test theories related to each of the symptoms [144–146].

Core Symptoms

Inappropriate social behaviors, impairments in social reciprocity, and apparent lack of interest in social contacts are characteristics of autism. Investigators are using animal models of sociability to examine social behaviors in animals bearing mutated genes and comparing them to normal littermate controls. In addition, studies have employed brain lesions restricted to specific brain regions as well as infusion of agonists or antagonists of specific signaling pathways. Prairie and montane voles have a pattern of social interaction that has proven useful to researchers studying social behaviors [143]. Monogamous or polygamous behaviors in these animals have

enabled investigators to study and gain a better understanding of the neuroanatomy and neurophysiology involved in the sociability domain [147].

Mice have been used due to their higher social behavior as well as the fact that the genes of interest can be manipulated in these animals. Early aberrant social behaviors can be detected by investigating a mouse's ability to build a nest or socialize in the home cage [148, 149]. Several structured tasks are commonly used in these studies, and include the intruder-resident paradigm, social investigation and discrimination tasks to access social skills. In the intruder-resident paradigm, a resident meets an intruder and, after some period of time together, they are separated. Either the same or a different intruder is then placed in the resident cage. Social behaviors can then be measured, such as anogenital, body or head investigation, dominance and aggressive behaviors [150]. A decrease in social behaviors toward the familiar intruder is interpreted as an inability to develop appropriate social memories, and disruption of specific pathways will provide clues as to the signaling events that are required to develop normal social memories [150, 151].

Social proximity is often tested using a three-chambered apparatus [152, 153]. A mouse is placed in the central chamber and can chose between a chamber with a mouse in a wire cage or a chamber with only a wire cage. The time spent in each chamber, how many times the mouse changes chambers as well as the time sniffing the wire cage is scored. Normally a mouse spends more time with another mouse than in the empty wire cage, and comparisons are made between a wild-type mouse and a mouse carrying a mutation [152, 153]. Social discrimination can also be tested using the same apparatus. A familiar and a strange mouse are placed in each of the arms of the chamber, and the time spent in each chamber, the frequency of chamber changes, and social interactions are counted. Normal social discrimination skills are assessed by measuring the amount of time a mouse will spend in the chamber with the stranger mouse inside compared to the time spent with a familiar mouse [153, 154]. It is recommended that each domain of interested should be tested by using at least two behavioral tasks [154].

Mutations of genes, such as PTEN, have been proposed as contributing to the ASD phenotype, and animal models with this mutation have been developed. PTEN inhibits phosphatidylinositol 3-kinase, a pathway that has been implied in neural migration and neurite extension. Additional studies have suggested that mutations of *PTEN* occur in autistic individuals with macrocephaly [155–157]. A mouse with a restricted expression pattern of PTEN was generated to study the role of PTEN in post-mitotic neurons derived from layers III–V of the cerebral cortex and granular and polymorphic neurons of the dentate gyrus. These mice showed reduced maternal care, social interaction, altered home cage behavior, cognitive deficits as well as increased anxiety [158]. Detailed anatomical analyses of these mice suggest soma hypertrophy, and these mice also develop macrocephaly and die prematurely [158]. The investigators suggest that dysfunctions of synaptic protein translation and abnormal synaptic connectivity may be both associated with dysfunctional social interaction and anxiety in this animal model.

Social Communication

Autistic individuals showed impairment in social communication [41]. Mice have strong social communication and use both ultrasonic vocalizations as well as olfactory signals to communicate [159–161]. In the laboratory, maternal separation has been used as one way to test social communication [162, 163]. The *FOXP2* gene localized at the chromosome 7q31 has been associated with language and communication impairments in human [164, 165]. Mice with a disrupted *FOXP2* expression pattern showed abnormal ultrasonic vocalization after maternal separation, but learning and memory skills were intact [165]. These early abnormal vocalizations have been related to the communicative impairment described in infants with autism in first year of life, suggesting precocious abnormalities in the child–mother social interactions.

Repetitive Behaviors

Rigid habits, restricted interests and a predilection for sameness are included in the autistic phenotype. To approach this issue, behavioral tasks are used that require habit formation and study changes to learned routines [154]. Two spatial learning tests that involve learning a habit to receive a reward (safety or food) have been studied. In the Morris water maze, mice are placed in water and must learn where a hidden platform is by using spatial cues, while in the T maze they have to find food in a maze arm. After animals have learned the task, the platform or the food is relocated to test their ability to reverse the learning. Mice need to change from the old strategy in order to succeed. Impairment during reversal learning has been suggested to be a measure of the inflexibility found in autistic individuals [154]. Our group is studying rodents exposed during embryogenesis to valproate as a model for autism, applying the T maze test to explore the reversal learning in these animals. The preliminary results suggest impairment in this task.

Evolutionary Perspectives

Some investigators are trying to explore psychiatric disorders from an evolutionary perspective. This field has significant limitations due to the difficulty in applying research methodologies; however, the insights obtained from these studies can help us to understand how the human brain works. Homo sapiens, different from other species including other primates, pride themselves on their ability to read the minds of others [166]. This ability requires the understanding of the other's desires, beliefs, and intentions [166]. Comprehending the intentions of others provides essential information about what the others are doing or intend to do, increasing the ability to better explore the social interaction. It has been speculated that this ability to read the minds of others, named Theory of Mind [167], together with the evolution of the frontal lobes, and the increased sophistication of executive functioning observed in

Homo sapiens [168], supported the group's enlargement, preserving close relationships among its members, resulting in an increase in group power [169].

It is reasonable to posit that the evolution of the social brain supported the better survival of Homo sapiens. Thousands of years of selection and evolution in simple tasks such as deception [170] had an enormous impact on what we are today. To better understand how social behaviors change across evolution, it is necessary to study the phenotypes and genotypes of our predecessors. Knowledge acquired from how primates interact socially or share intentions can help us to understand social cognition. Evidence suggests that the evolution of human social cognition may be a result of brain enlargement, mainly of the frontal lobe, the extended juvenile period, and socially complex environment [171]. Similar to human beings, some primates have high social-cognitive skills in competitive situations. However, unlike humans, primates are not skillful in cooperative situations [166]. Probably, during the emergence of modern man, around 150,000 years ago, individuals who could read intentions were able to engage in social relationships and collaborate in social activities leading to selective advantages [166]. Indeed, those individuals who developed skills to use tools as well as making them by imitating others were able to plan and have goals [166]. As a consequence of improved communicative skills, human beings became able to share plans and goals. This biological adaptation supported by the cognitive abilities provides a scenario where the ability to create artifacts and social complex routines have resulted in the development of culture.

As a consequence of the super specialization of the social brain, some individuals who have significant deficits in this skill have been classified as outsiders [172]. Autistic individuals might be classified as outsiders as they present impairments in recognition, understanding and sharing of emotions with others [173]. During the first year, babies have motivation to share their emotions with others. Ontogenetic studies have shown that infants detect human-like action from 6 months of age. Children at the age of 3 months can understand animate action and engage in a dyadic relation, i.e. they can interact and mutually respond to someone using emotional expressions. After 6 months, they are able to pursue goals and engage in a triadic relation, i.e. the child can interact with someone toward shared goals. By 14 months of age, a child can choose a plan and engage in collaborative activities using joint intentions and attention skills [166].

Wing [174] presented reports where parents of autistic individuals noticed their children were unresponsive from the first year of life suggesting a lack of motivation or abilities for emotional exchanges. Some of the children with autism present at 1 year of age with impairments in orientation to social stimuli (e.g. social orientation, joint attention, social interaction and anticipation), babbling, gesture, word pronunciation and imitation [175–177]. Moreover, around 50% of autistic individuals display atypical development, mild delays between 15 and 24 months of age, and impairments in language, communication and/or social skills [41, 178, 179].

Today, it is reasonably to hypothesize that the ASD develops as a consequence of a disruption in the normal ontogenic process in a specialized evolutionary social brain

(phylogeny). It is equally possible that polymorphisms in conservative genes related to the development of the social brain underlie some of these disruptions to normal adaptive skills.

Conclusions

Autism is often described as part of a spectrum of disorders defined by impairment in social living skills. One model proposes that the mechanisms underlying these disorders are related to an abnormal development of the social brain. It is hoped that research in the future will make headway into identifying genes involved in the social neural circuitries. For this, better phenotypic and endophenotypic definitions will have to be developed to enable a more accurate study of genes and their possible relationship to well-defined autistic traits. Moreover, well-designed functional and structural neuroimaging studies need to be conducted. Only then will we gain a better understanding of ASD, the strengths and limitations related to these profiles, and will hopefully be able to generate more effective interventions programs to assist affected individuals and their families.

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Brain Model for Pediatric Bipolar Disorder

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Abstract

Introduction: Pediatric bipolar disorder (PBD) is increasingly being diagnosed with active attempts to provide biological validation of the phenotype. PBD, by virtue of rapid cycling, mixed with depressive symptoms and greater irritability, presents with distinct phenomenology compared to that of adult bipolar disorder. Early recognition of the biological thumb print of this developmental disorder will help us understand the neurobiological basis of the illness, and pave the way for effective treatment strategies. **Methods:** Structural, functional, and neurochemical imaging studies in PBD were selected for review using the key words brain, structural imaging, functional imaging, magnetic resonance spectroscopy, diffusion tensor imaging, child, adolescent, bipolar, affective, biological, neural mechanisms, and further following up on the references at the end of each original article, where warranted, with no limit to time window. **Results:** Several cortical and subcortical abnormalities collectively offer a cogent brain model of PBD. Specific cortical regions that are implicated in this disorder include prefrontal and medial temporal structures, and subcortical regions include amygdala, striatum and hippocampus. **Conclusion:** The cortical and subcortical structure and function lead us to believe that there is hierarchical control or top-down regulation of affect. Additionally, studies collectively illustrate the link between affective and cognitive circuits that serve the corresponding neural functions operating in an integrated manner.

Pediatric bipolar disorder (PBD) is the most severe and devastating form of bipolar disorder (BD), presenting with rapid mood cycling, irritability, high energy, depression and mixed mania, posing a treatment challenge for clinicians and a burden to the families. In spite of the forthcoming advances in characterizing the phenomenology of PBD, there is still a relative dearth of studies on the underlying pathophysiology. The brain model of the bipolar diathesis is a compilation of structural, functional and neurochemical issues playing a potentially integrated role in the disease manifestation. There is an emerging role of fronto-limbic, fronto-striatal and fronto-temporal circuitries that are thought to be involved in PBD. Conventional structural neuroimaging laid the ground for further studies of brain function. The

combined use of structural, functional, and biochemical imaging hold great promise in uncovering the aberrations in the connectivity and neurochemical makeup of the illness that will ultimately allow us to think in terms of dysfunctional brain model. Once we understand the type and location of impairment, our attempts to reverse this dysfunction through more refined and tailored treatment techniques becomes feasible.

Structural Neuroimaging

A range of morphometric abnormalities in the cortical, subcortical and limbic regions of the brain have been suggested in PBD, with overwhelming evidence to implicate the prefrontal cortex (PFC). The discrete brain regions alluded in the pathophysiology of the disorder include the amygdala, basal ganglia, cerebellum, orbitofrontal cortex, and subgenual PFC. The *ventral-dorsal hypothesis* suggests that mood episodes are attributed to hypoactivity of the dorsal PFC and hyperactivity of the ventral PFC, coupled with a reduction in inhibitory input from the subcortical regions including the amygdala or, vice versa, with reduced top-down regulation. Tallying the similarities and differences between adult and pediatric findings pertaining to these neural systems allows us to further understand the evolution and continuity of the disease process of the BD across the lifespan.

Cortical Structures

Total Cerebrum

Mounting research findings in bipolar youths suggest smaller total cerebral volume compared to controls [1–3] as opposed to most adult studies. Sulcal enlargement, both frontal and temporal, as well as decreased intracranial volume were observed to an equal degree in subjects with adolescent BD and schizophrenia when compared to healthy controls [1]. Similar abnormalities such as frontal lobe asymmetry [4] and reduced left superior temporal gyrus [5] have been reported. At the same time, some studies yielded negative results with regard to cerebral volume changes [6], while a statistical trend for decreased total cerebral gray matter was noted in another few [7].

An analysis evaluating cortical gray matter differences revealed that bilateral parietal and temporal lobes displayed a substantial reduction in gray matter, chiefly in the bilateral postcentral gyrus, left superior temporal and fusiform gyri, along with bilaterally increased parahippocampal gyri [8]. Regional abnormalities in the superior temporal gyrus, a putative biomarker of social dysfunctioning and assumed to be involved in language and communication, were most obvious, with changes such as increased gray matter [9] as well as a general reduction in size [1, 5].

Prefrontal Cortex

The PFC, a functionally heterogeneous region, is believed to be involved crucially in the regulation of mood and attention. MRI studies of adults with BD have found decreased PFC volume, both of the PFC en masse and of the subgenual PFC in particular, and decreased PFC density. Comparable abnormalities are described in adolescent bipolar subjects. Gray matter deficits in specific prefrontal regions, principally in the dorsolateral PFC (DLPFC)/Brodmann area 9, ventral PFC, orbitofrontal cortex, anterior cingulate and medial temporal lobe were demonstrated in a voxel-based morphometric study of adolescent bipolars, contrary to adult studies portraying no cortical gray matter deficits [9]. A similar voxel-based morphometric study hints at reduced gray matter volume in the left DLPFC [10] though findings on such a decrease in orbito-frontal cortex (OFC) were divided with no difference [10] to decreased OFC volume [9]. However, with regard to subgenual PFC, no reduction in volume was noted in medicated bipolar adolescents with a familial history of mood disorders when compared to healthy adolescents, unlike the adult studies. Similarly, some studies failed to demonstrate prefrontal gray matter abnormalities in the affected youths [7].

Corpus Callosum

The corpus callosum, serving as the major inter-hemispheric commissure in the brain, helps to integrate the activities of the left and right cerebral hemispheres. Prefrontal and temporoparietal cortical areas, essentially entailed in affect and cognition modulation, are predominantly connected via the genu and splenium of the corpus callosum.

Variations in corpus callosal shape, such as significantly decreased circularity of splenium, have been described in bipolar adolescents, contrary to adult studies stating differences in callosal length and area.

Ventricles

It is believed that atrophy of specific structures may possibly account for increased ventricular volumes; amygdalar and hippocampal volume reduction, increased lateral ventricle, thalamic and hypothalamic reduction, and third ventricle increases being potentially interrelated. Only one of all the studies inspecting ventricular volumes gave positive results of ventriculomegaly [11] in PBD and schizophrenia when compared to healthy subjects, similar to adult findings.

Pituitary Gland

No substantial size abnormalities in the pituitary gland could be discerned in the pediatric and adolescent bipolar patients, contrary to reports involving adult patients.

Subcortical Structures

Amygdala

Several recent findings in PBD studies have shown structural aberrations in the amygdala. Significantly reduced amygdalar volumes were observed in adolescent bipolars, with decreases occurring bilaterally [2, 6] or predominantly on the left side [5, 10]. Amygdalar volumes were negatively correlated with the duration of illness and prior antidepressant exposure [2], whereas they were positively correlated with lithium or divalproex exposure [7]. Chen et al. [12] also found that amygdala size was positively associated with age in bipolar adolescents contrary to an age-related decrease in size in healthy adolescents. A smaller amygdala size was thereby reflected as one of the more consistent neuroanatomical findings in children and adolescents with BD by these studies and could be deemed as one of the biological markers of the illness. The presence of comorbid attention deficit/hyperactivity disorder (ADHD) appeared to be unrelated to volumetric changes in the amygdala. On the contrary, adult studies on the amygdala have revealed mixed results – enlargement, reduction as well as no change – in part signaling the lack of pruning in adult BD, hypertrophy with over activation of amygdala with length of illness, or early degenerative changes in PBD.

Hippocampus

Reduced hippocampal volume is purported to be a finding unique to PBD. Most of the adult studies, in general, reported a normal hippocampal size. In contrast [13], a bilateral decrease in hippocampal volume – an effect driven predominantly by female bipolar subjects – is seen in PBD [3]. Likewise, a trend to decreased hippocampal volume was also noticed in a study by Blumberg et al. [6].

Thalamus

An imaging study using a group of schizophrenia and BD patients combined revealed a significant reduction in bilateral thalamic size relative to controls [13], extending evidence to the role of the thalamus in bipolar psychopathology. However, the study was limited by its selection of patients as well as the region of interest. On the contrary, some studies have consistently reported no thalamic alterations [2, 3, 7] in bipolar youths, while a trend towards a nonsignificant but meaningful decrement in thalamic volumes was noticed in a few [3].

Basal Ganglia

Emotion modulation is directly linked to the striatal circuitry function. Anatomical alterations in the basal ganglia, most commonly greater volumes of striatum and globus pallidum, have been illustrated in many adult imaging studies. Likewise, bilaterally larger basal ganglia [9], specifically a larger putamen [2] and nucleus accumbens [10], have been reported in adolescent BD. Putamen enlargement was more

predominant in bipolar girls than in boys, which is explained by the co-occurrence of ADHD among boys [2], as previous MRI studies in boys with ADHD have reported reductions in striatal volumes unseen in girls with ADHD. An enlarged putamen was noticed primarily in bipolar adults presenting with a first manic episode, postulating it as a putative trait abnormality that may also manifest in children and adolescents early in the disease course. A significant inverse relationship between age and the volumes of the bilateral caudate and left putamen was also seen in young bipolar patients, but not noted in healthy youths.

Cerebellum

Along with motor function, the cerebellum plays an important role in affect modulation. There is much recent evidence supporting the role of the cerebellum, particularly the midline cerebellum, in mood regulation. The association is particularly evident by its projections to areas known to be involved in cognition and affect, namely the hypothalamus, parahippocampus, PFC, anterior cingulate gyrus (ACC), and temporal and parietal cortices (cerebro-cerebellar circuit). Decreased cerebellar and vermal volumes are reported in adult and adolescent bipolar patients [14]. Considering the involvement of subregions of the vermis (V1, V2 and V3), specifically vermal area V3 was found to be considerably smaller in multiple-episode patients than in first-episode patients or healthy controls.

White Matter Hyperintensities

The first neuroimaging study in bipolar youths was published by Botteron et al. [4], who observed cerebral asymmetry and deep white matter hyperintensities (WMH) in 4 of 10 BD subjects compared to 1 control subject. Likewise, a statistically increased prevalence of WMH (10 of the 15 BD adolescents vs. 5 of the 16 healthy controls) in bipolars was reported by Pillai et al. [15]. A contemporary study of bipolar youths with a bipolar parent found no increases, mild or moderate, in the WMH, although there was a statistical trend for elevated rates of severe WMH in affected youths [7]. Most of WMH in bipolar subjects were sited in the PFC. WMH are the most consistently replicated findings in qualitative studies of adult BD. However WMH, being nonspecific to PBD, are also associated with other disease processes such as ischemia, inflammation, and demyelination.

Diffusion Tensor Imaging

The connectivity of white matter tracts, especially linking fronto-limbic and fronto-striatal areas are hypothesized to be abnormal in bipolars. Diffusion tensor imaging (DTI) is a magnetic resonance technique that serves on measurement of water diffusion to analyze white matter tracts in vivo and has the added advantage of identifying abnormalities more subtle than qualitative assessment for WMH. Water

diffusion in white matter is highly anisotropic (i.e., not equal in all directions), as diffusion tends to be much higher parallel to the fiber axis than perpendicular to it. The commonly employed measures of anisotropy in DTI include fractional anisotropy and relative anisotropy. Trace apparent diffusion coefficient (TADC) is the DTI measure exemplifying the distance through which water molecules freely diffuse. Increments in TADC have been associated with axonal demyelination and localized edema.

Adult studies demonstrate decreased fractional anisotropy in white matter tracts especially that adjoining PFC to subcortical structures. Adler et al. [16] expounded significant decreases in fractional anisotropy in superior-frontal white matter tracts in unmedicated first-episode bipolar adolescents in comparison to controls. Bipolar youths were noted to have smaller left and right superior temporal gyri white matter volumes thought to be due to underlying white matter connections basing the neurocognitive deficits [17]. Likewise, decreased functional anisotropy in anterior corona radiata and inferior longitudinal fasciculus as well as higher TADC values for the anterior corona radiata, inferior longitudinal fasciculus and superior longitudinal fasciculus were demonstrated in bipolar adolescents [18], signifying the underlying disintegrity of white matter joining fronto-temporal and fronto-parietal areas. Also the superior lateral fasciculus cingulum bundle and inferior lateral fasciculus will have decreased fractional anisotropy in very early BPD relative to controls.

Studies of Brain Function

Neurocognitive Function

The abnormal brain structures are putative substrates of the dysfunctional neurocognitive domains found in children with BD. The key neurocognitive domains signifying impairment in PBD include attention, working memory, verbal memory, and executive function. Impairments in affected cognitive domains were found to be present in the acutely ill as well as remitted bipolar youths, suggesting the persistence of the deficits regardless of illness state or medication status. Cognitive flexibility, the ability to adapt to changing environmental stimuli, has been shown to be greatly impaired in a study evaluating subgroups of narrow-phenotype BD, and severe mood dysregulation in comparison to healthy controls [19]. Social cognitive deficits include facial-emotional recognition [20] and emotional processing [21]. Bipolar youths were shown to be particularly likely to misinterpret the happy, sad, and fearful expressions of their peers, but not of adults, as angry. Similarly, regardless of clinical and treatment status, marked impairments in the ability to correctly identify emotionally intense happy and sad facial expressions, tending to misjudge extreme facial expressions as being moderate to mild in intensity is noted.

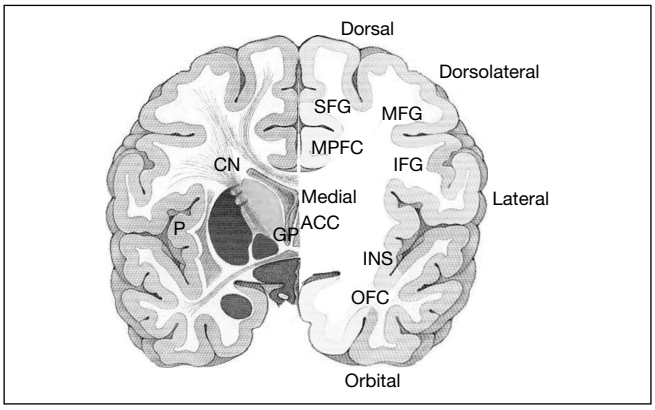

Fig. 1. Drawing of a coronal section of the brain demonstrating the important areas implicated in affect and cognitive regulation of pediatric bipolar disorder (PBD), one half shows the basal ganglia structures while the other half shows the prefrontal cortex. Illustrated on the right side are the allied gyri, including the superior frontal gyrus (SFG), middle frontal gyrus (MFG), inferior frontal gyrus (IFG), medial prefrontal gyrus (MPFC), anterior cingulate gyrus (ACC), insula (INS) and orbital prefrontal cortex (OFC), broadly sub-regioned as dorsal, dorsolateral, medial, lateral, and orbital regions of the prefrontal cortex. Hidden below and unseen is the ventral prefrontal cortex. On the left side are amygdala and basal ganglia structures, including caudate nucleus (CN), globus pallidus (GP), and putamen (P) related to the allied areas.

Functional Neuroimaging

Functional neuroimaging studies help to scrutinize the association between neurocognitive test performance and the particular brain circuits in BD patients by exploring patterns of brain activation as subjects execute cognitive tasks in an MRI scanner. The paradigms are tailored to probe the hypothesized areas of dysfunction in BD. These studies may be broadly categorized into those examining the functions of affect, cognition and affect-cognition interaction.

Brain circuitry in PBD encompasses the interplay of two pathways presumed to regulate mood and cognitive processes, namely, the ventral/fronto-limbic pathway, consisting of ventrolateral, prefrontal and orbitofrontal cortex and amygdala engaged in regulating mood, and the dorsal-subcortical pathway, which includes the DLPFC, thalamus, and basal ganglia for modulating cognitive-attentional systems, with these pathways further interconnected directly or indirectly through other brain structures, such as the ACC (figs 1, 2).

fMRI Studies Probing Cognitive Functions

Tested for visuospatial working memory, adolescents with familial BD displayed abnormalities in several areas of prefrontal and paralimbic structures portrayed by greater activation in left DLPFC, bilateral ACC, left thalamus and right inferior

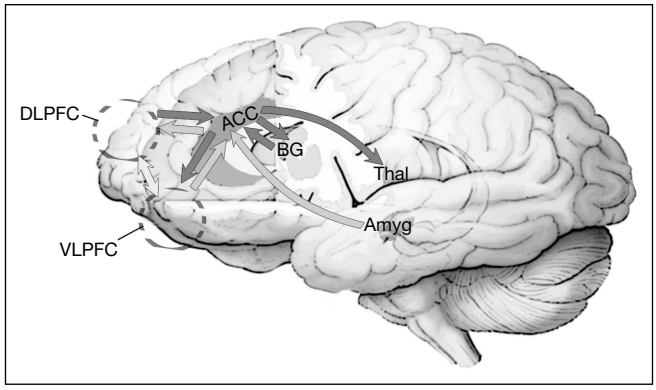

Fig. 2. Illustration of a sagittal section of the brain at the level of the corpus callosum depicting the indicted fronto-striatal and fronto-limbic circuitry in pediatric bipolar disorder (PBD). The deranged fronto-striatal pathway (dark grey arrows) of PBD is constituted by the 'hypoactive' dorsolateral prefrontal cortex (DLPFC), hyperactive ventrolateral prefrontal cortex (VLPFC) along with the thalamo-basal ganglia. Also shown in the picture is the fronto-limbic pathway (light grey arrows), comprising the prefrontal cortices (DLPFC and VLPFC) and the hippocampal-amygdalar complex. The double arrow signifies the reciprocal influences between the ventrolateral and dorsolateral regions of the prefrontal cortex, a balanced interplay of which promotes the apt regulation of affect and cognition.

frontal gyrus while controls showed an increased activation in cerebellar vermis [22]. Additionally, while viewing the emotional pictures in the attention tasks, negatively valenced stimuli activated the bilateral DLPFC, inferior frontal gyrus and right insula compared to the posterior cingulated gyrus in controls while positive stimuli elicited greater activation in the bilateral caudate, putamen and thalamus, left frontal gyrus, and left ACC in PBD. Using a color-naming Stroop task, Blumberg et al. [23] demonstrated a lack of normal age-related activation increases in the prefrontal region (rostroventral PFC) though no upfront prefrontal activation abnormalities were seen in PBD subjects in comparison to controls, and also there was a positive correlation between depressive symptoms and signal increases in the ventral PFC. Increased activation in the left thalamus and putamen was seen in the study. A study on bipolar youngsters with comorbid ADHD using a simple attention task showed decreased activation in the ventrolateral prefrontal regions and ACC, but heightened activation of the posterior parietal and temporal cortex, compared with bipolars without ADHD, possibly hypothesizing activation of alternative pathways with comorbid ADHD [24]. Moreover, bilateral striatal and right ventral PFC activation was noted to be greater in controls than in PBD in a study using motor inhibition tasks [25]. Deficits in motor inhibition may contribute to impulsivity and irritability in bipolar children.

Thus, the studies convergently suggest the role of dorsal cortical-subcortical circuit abnormalities in contributing to the dysfunctional cognition in bipolar youths as shown by a string of neural functioning abnormalities in DLPFC and limbic, striatal and thalamic

regions. The absence of normal age-related increases in prefrontal function in the affected children hints at a progressive and atypical development in these youths.

fMRI Studies Probing Affect Modulation

Beyond these cognitive tasks, assessments of social cognition are also crucial in BD. Children with BD were noted to misinterpret sad, happy and fearful child faces, but not adult faces, as angry, compared to anxious and healthy groups, suggesting that bipolar youths possibly perceive anger among peers. Two studies that directly probed fronto-limbic circuitry in PBD [26, 27] showed ventrolateral PFC (VLPFC) dysfunction with increased activation in the amygdala in response to emotional faces in PBD. In response to both angry and happy faces relative to neutral faces, a reduced activation of the right rostral VLPFC together with increased activity in the right pregenual anterior cingulate, amygdala, and paralimbic cortex was noticed in bipolar patients [26]. Also, bipolar patients showed reduced activation of visual areas in the occipital cortex together with greater activation in higher-order visual perceptual areas, including the superior temporal sulcus and fusiform gyrus with angry faces and the posterior parietal cortex with happy faces. PBD subjects perceived greater hostility in neutral faces reporting more fear while viewing them compared to controls. Similarly, greater activation in the left amygdala, accumbens, putamen, and ventral PFC when rating face hostility, and a greater activation in left amygdala and bilateral accumbens when rating their fear of the face was reported in bipolar patients when compared with controls [27]. Therefore, aberrant affective-cognitive circuitry interactions explain the pathophysiological mechanisms in PBD that directly impinge on the synchrony of the dorsal and ventral streams corresponding to the cognitive and affective circuitries.

fMRI Studies Probing the Interaction of Affective and Cognitive Functions

Pavuluri et al. [28] examined 10 euthymic unmedicated bipolar children and healthy controls using fMRI while employing a task to probe the affect and attention integrity. In the negative affect condition, relative to the neutral condition, patients with BD demonstrated greater activation of the bilateral pregenual ACC and left amygdala, and less activation in the right rostral VLPFC and DLPFC at the junction of the middle frontal and inferior frontal gyri, whereas in the positive affect condition there was no reduced activation of PFC or increased amygdala activation. This pattern of reduced activation of VLPFC and greater amygdala activation in bipolar children in response to negative stimuli substantiates both the disinhibition of emotional reactivity in the limbic system and the reduced function in PFC systems that regulate the responses.

In another study of the kind using 'directed' and 'incidental' emotion processing conditions, a greater activation in the incidental condition relative to the directed condition in the right amygdala, parahippocampal gyrus, inferior frontal gyrus, bilateral occipital cortex, fusiform gyrus, and posterior cingulate cortex was seen in the PBD group, while the directed condition showed greater activation in the left subgenual and bilateral pregenual ACC, bilateral insula, and temporal cortex [29]. On the

contrary within the controls, the incidental condition relative to the directed condition as well as the directed condition relative to the incidental condition failed to yield the respective activations of the limbic and pregenual ACC. This augmented amygdala activation in PBD seen only in the incidental emotion processing could be related to an exaggerated emotional reactivity, rather than a failure of top-down regulation of emotional reactions.

Emotional expressions, especially the negative facial emotions at school or at home, are likely to impact affective and cognitive circuitry functions. Results from these studies highlight the overactivity of the pregenual ACC and amygdala as well as reduced activation at the dorsal convexity of the PFC at the junction of the VLPFC and DLPFC areas during negative emotional affect plus an increased activation of the amygdala in response to incidental emotion processing relative to direct emotion processing in PBD patients.

Biochemical Neuroimaging

Magnetic resonance spectroscopy (MRS) is a noninvasive, non-ionizing procedure that offers details on neuronal substrates of relevance such as N-acetyl-aspartate (NAA), choline, myoinositol, and creatine (Cr)/phosphocreatine and the neurochemical predictors of response to bipolar medications. The most commonly employed modality is the ^{1}H-MRS. NAA is found in high concentrations in neurons as opposed to glial cells and may serve as a marker for neuronal integrity. Cr is present in both white and grey matter and is used as a reference point for the amount of brain tissue in the voxels placed in the region of interest. Choline, being a product of myelin breakdown, is advocated to represent axonal turnover. Myoinositol is crucial for the resynthesis of phosphoinositides and plays a role in neuronal homeostasis. Glutamate, the primary excitatory, and GABA, the primary inhibitory amino acid neurotransmitters, are also being targeted in recent study.

Castillo et al. [30] examined 6- to 12-year-old BD subjects and showed an elevated glutamate/glutamine ratio in fronto-striatal areas. The levels of NAA and choline were not increased in fronto-temporal areas. In contrast, bipolar offspring carrying a bipolar diagnosis, who are euthymic on multiple medications, showed decreased NAA/Cr ratios in the right DLPFC [31]. There was a tendency of NAA/Cr ratios to decrease with the duration of illness. It may be that a decreased DLPFC NAA/Cr ratio is specific to familial BD. In two separate studies, Cecil et al. [32, 33] noticed a trend towards lower NAA and choline in the gray matter of the medial orbitofrontal cortex along with elevated levels of composite amino neurotransmitters (aspartate, GABA, glutamate and glutamine) [32], and a lower NAA/Cr ratio was noted in the cerebellar vermis in 8- to 12-year-old bipolar subjects [33], suggesting that these biochemical differences may represent early markers for the underlying neurochemical changes. Cecil et al. [33] also found that the myoinositol concentration was elevated in the

frontal areas in BD subjects compared to healthy controls. Similarly in another study, the myoinositol/Cr-phosphocreatine ratio and myoinositol levels (mmol/l) were found to be higher in the anterior cingulate cortex in acutely manic BD compared to subjects with intermittent explosive disorder and healthy controls [34]. Findings such as these could potentially aid in the early detection and differential diagnosis.

Further, MRS studies can also be applied to examine the mechanisms of treatment efficacy. In PBD, lithium treatment was shown to reduce the high baseline myoinositol/Cr ratio in acute mania [35] which was evident from the 7th day of drug treatment. In contrast, Patel et al. [36] failed to demonstrate any significant changes in ml (myo-inositol) concentrations in the medial as well the right and left lateral prefrontal cortices following acute and chronic lithium treatment, arguing against the inositol-depletion hypothesis. In another study employing lithium-7 MRS to measure in vivo brain lithium levels in bipolar children, adolescents and adults, lower brain-to-serum concentration ratios were measured in juvenile subjects compared to adults [37], suggesting a need for higher serum lithium concentrations in children and adolescents with BD than in adults for maintenance of therapeutic brain lithium concentrations. Considering changes in neurochemical makeup with newer antipsychotics, bipolar manic adolescents successfully treated with olanzapine had greater prefrontal NAA and choline levels, primarily noticed between days 7 and 28, than non-remitters [38]. There was an association between the increases in NAA levels with decreases in manic symptoms.

Collectively, these MRS studies advocate biochemical dysregulations in the frontal lobe and basal ganglia, which are nominal in the cerebellum of youngsters with BD. However, much more work is needed in the application of MRS to BD in children. The MRS studies conducted to date are often based on different a priori hypotheses of specific regions of interest, have small sample sizes, and are not always controlled for medications that by design affect brain chemistry. These factors, together with differing results from various studies, require that studies on larger samples controlling for potential confounders are needed to solidify our understanding of brain chemistry in BD.

Conclusion

Interfacing affective and cognitive circuitry dysregulations explain the emotional instability and interlinked cognitive deficits that persist in PBD. The proposed brain model constituted by several distinct circuits (fronto-limbic, fronto-striatal, and face responsive circuitry regions connected by white matter tracts) explains the baseline dysfunction which may or may not be reversed with treatment (fig. 3). The evolution of neuroimaging techniques, from merely inspecting anatomy to the current state of analyzing the neurochemical makeup, has helped to confirm the functional and connective abnormalities in PBD. While these abnormalities are apparent, their liaison with the disease phase and treatment strategies still remains unclear and warrants exploration.

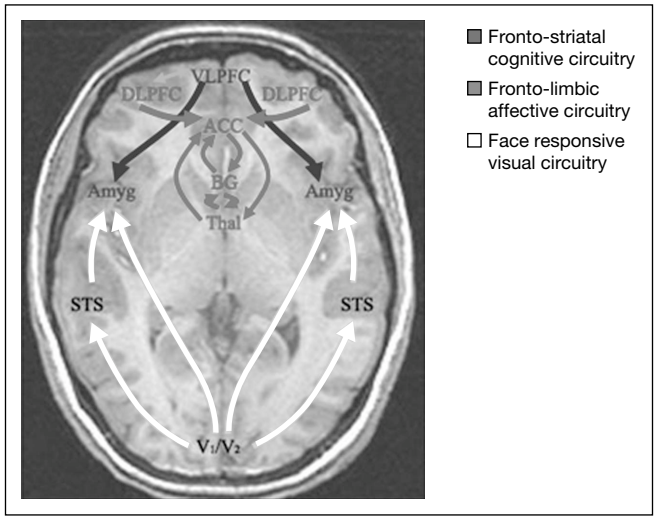

Fig. 3. Illustration of the axial section of the brain detailing the interface of the major pathways of bipolar disorder. Shown are the fronto-striatal cognitive circuitry (black), fronto-limbic affective circuitry (grey) and face responsive visual circuitry (white), streamlined into 'anterior' and 'posterior' conduits. The anterior conduit, comprising of the fronto-striatal and fronto-limbic pathways, essentially modulate affect and cognition while the posterior conduit, including the face responsive circuitry, regulates the emotional facet. Fronto-striatal circuitry proceeds from the dorsolateral prefrontal cortex (DLPFC) majorly onto the anterior cingulate (ACC) with further relays onto the basal ganglia and vice versa. In contrast, the fronto-limbic circuitry is composed of projections from the ventrolateral prefrontal cortex (VLPFC) onto the limbic areas of amygdala, hippocampus, cingulate gyrus and insular cortex. A particular amount of information is relayed from both these pathways onto thalamus, the 'relay station'. The diagram also portrays the interplay between the two anterior conduits, testifying that deployment of affective circuitry shuts down cognitive circuitry function. The posterior face responsive circuitry has its chief origins from the primary visual (V1) and secondary visual (V2) cortices. At the outset different emotional and expressive submodalities are relayed by feed-forward projections through different lobes en route to the prefrontal cortex with particular dispatches at the amygdala and superior temporal sulcus (STS). Deranged development and/or deviant inputs and outputs from these circuits present in some bipolars could be considered as the potential attributes to the dysfunctional affective, cognitive and emotional intonation.

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Neurobiology of Depression in Childhood and Adolescence

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Abstract

In the past decade a great deal of success has been achieved in our understanding of the neurobiological basis of depressive syndromes. Genetic factors, structural changes and neuronal networks, which are important in generating pathological cognitive processes, emotional and behavioral patterns have been identified and characterized. These findings have lead to an improvement in therapeutic interventions and drug therapy. Risk factors have been described thus allowing the early detection of affective disorders. At present the main focus of research is to gain greater understanding of the functional polymorphism in the serotonin transporter promoter region. Furthermore, the genetic basis of neurotoxic and neuroprotective processes (neurotrophic factors) and their relation to anatomical changes are being examined. The functional polymorphism in the serotonin transporter promoter region increases stress-related vulnerability which has been found to be associated with a higher risk for affective disorders. Structural and functional neuroimaging of the amygdala, hippocampus and the prefrontal cortex allow detailed descriptions of morphological changes. Imbalances in different neurotransmitter systems and factors modulating monoamine receptor sensitivity have been characterized and their correlations with genetic, structural and psychosocial factors influencing depressive syndromes are being studied. Research in the field of etiology and pathogenesis of the disease has lead to considerable advances in our understanding of developmental neurobiology, the vulnerability and resiliency of the young patient, and has improved the possibility of intervention at an early stage of the disease. These pathogenetic mechanisms including genetic causes, morphological correlates and the resulting functional consequences are outlined.

'In der Schwermut hingegen liegt etwas anderes, Eigenes, was das Wehtuende, man möchte sagen, an den Nerv herantreibt. Ihr Leiden hat einen besonderen Innerlichkeitscharakter; eine besondere Tiefe, etwas Ungeschütztes, Blossliegendes. Hier fehlt eine bestimmte Widerstandskraft; das macht, dass das Wehtuende sich mit etwas im Innern selbst verbindet.'

('There is in the melancholy something else, something different, which drives the pain, as one would like to say, close to the nerve. The suffering of the melancholic individual has a specific inwardness, a unique depth, something unprotected, something unveiled. A clear power to resist is missing, so the pain is linked directly to the heart.')

(Vom Sinn der Schwermut, Romano Guardini, 1949)

Depressive disorders include major depressive disorder (unipolar depression), dysthymic disorder (chronic mild depression) and bipolar disorder (manic depression). The following chapter focuses on major depression.

Major depression is of greatest significance in children and adolescents, affecting 3–5%. Up to 15% suffer from some of the defining symptoms. Five percent of 9- to 17-year-olds fulfill the criteria for major depression [1] and 3% fit the criteria of dysthymia [2]. Depression beginning in childhood tends to continue into adulthood [1]. The incidence for both sexes increases considerably after puberty. This is due to the challenges associated with physical, intellectual and psychosocial development and the strengthening of identity. Furthermore the detachment from parents and the identification with the gender conflict are of importance. At the age of 14 depressive disorders are more than twice as common in girls as in boys [3]. There are several reasons to explain this finding: girls deal differently with emotional disturbances than boys of the same age. Both genders differ greatly in their ability to and the way in which they express their emotions. Furthermore, the beginning of puberty is accompanied by strong physiological differences caused mainly by hormonal changes and changes in physical development. The increased incidence of depressive disorders in girls in puberty is strongly related to changes in androgen and estrogen levels [3].

Definition

The diagnosis of major depression is based on the criteria of ICD-10 which is the international standard diagnostic classification. The diagnostic criteria are the same as for adults. There are only minor differences between ICD-10 and DSM-IV-TR. According to ICD-10 the symptoms have to be present for at least 2 weeks. Major symptoms include emotional impairments and disturbances of the autonomous nervous system. For diagnosis it is important for the first three symptoms mentioned in table 1 to be present. Five or more of these symptoms have to have been present during the same 2-week period and must represent a change from previous functioning; at least one of the symptoms has to be either depressed mood or loss of interest or pleasure.

Symptomatology

From birth until the age of 4 years the child develops the ability to express basic emotions such as sadness and happiness. On the contrary the ability to express self-reflexive emotions such as depressive experiences changes from childhood to adulthood. The expression of emotions, hence the symptomatology of depression, depends on the age, developmental stage and personal differentiation of the young patient. These factors enable the patient to approach his internal state of mind and its articulation. From infant to preschool age the cognitive and linguistic development is still imma-

Table 1. Criteria for a major depressive episode

1	Persistent sad or empty mood most of the day, nearly every day, as indicated either by subjective report or observation made by others Irritable mood
2	Loss of interest or pleasure in all or almost all activities most of the day, nearly every day
3	Children fail to make expected weight gain Significant appetite change, weight loss
4	Insomnia Hypersomnia
5	Psychomotor agitation or retardation, concomitant with mood change
6	Fatigue or loss of energy Disengagement from peer play, school refusal or frequent school absences
7	Self-depreciation Feelings of worthlessness Excessive or inappropriate guilt
8	Difficulty with attention or concentration Indecisiveness
9	Recurrent thoughts of death Recurrent suicidal ideation

ture and variable. In this age group the patients are rarely able to verbally express their feelings. Children express their emotions through diffuse somatic symptoms and physical complaints, they have poor eye contact, sadness in facial expression as well as loss of interest in different contexts. The patients disengage themselves from family affairs as well as from friends and retract from school activities. This can lead to school refusal mainly due to concentration problems and limited attentiveness.

At the somatic level depressive emotions are mainly expressed through diverse symptoms of the autonomous nervous system, for instance deficiency in physical development, weight loss and insomnia. Children suffering from atypical depression are affected by hypersomnia and weight gain due to overeating.

In particular adolescents suffer from a deficiency to express negative emotions. Consequently negative emotions find their expression through somatic symptoms. Patients present with irritable mood, lack of self-respect and self-depreciation. Depending on age depressive disorders can be accompanied by inattentiveness, hyperactive behavior, substance abuse, personality disorders, compulsive acts and thoughts, and anxiety disorders. These disorders occur as secondary symptoms of depression. In some of the cases they may conceal major depression. Eighty percent of the patients suffering from prepubertal major depression are affected by another psychiatric illness. The main complication during depression is suicidal behavior and suicide [4].

Classification of Depressive Symptoms

The categorization of depressive symptoms depends on age and the developmental stage of the patient. Table 2 presents the diverse emotions of depressive disorders

Table 2. Classification of depressive symptoms depending on age and developmental stage

Very young children	1	Children show little emotions
	2	Sad facial expression
	3	Irritability
	4	Difficulties in eating and sleeping
	5	Jactatio capitis
	6	Loss of creativity and imaginative play
	7	Lack of perseverance in activities
	8	Lack of energy
Elementary school children	1	Children feel tired and irritable
	2	Sad facial expression
	3	Feelings of guilt
	4	Feelings of hopelessness
	5	Somatization (headache, stomach pain)
	6	Loss of interest in friends, activities
	7	Weight loss
	8	Insomnia
Teenagers	1	Criteria for a major depressive episode
	2	Patients move and speak more slowly
	3	Problems in school achievement
	4	Hallucinations
	5	Delusions
	6	Psychosomatic syndromes
	7	Loss of self-confidence
	8	Suicidal ideation
	9	Hypersomnia

from childhood to adolescence depending on the developmental process of the patient.

In addition, there are also differences between males and females in the ability to express emotions. Girls in childhood and youth express their emotional disturbances in dysphoria, depressed mood, guilt, self-blame, self-disappointment, feelings of failure, concentration problems, working difficulties, eating and sleeping disorders, fatigue and psychomotor retardation, anxiety disorders, body image dissatisfaction, and somatization. The disorder begins earlier among females than males. Boys show disturbances in emotional flexibility, anhedonia, depressed morning mood and morning fatigue, impulsivity, and disturbances in social behavior with introverted or agitating behavior [5]. In summary it can be hypothesized that depressed girls express more mood symptoms and cognitive symptoms whereas depressed boys express more irritability. Because of the lack of specificity of symptoms, the diagnosis is often not accurately defined; treatment depends on precise description and diagnosis. The symptomatology influences the physical and psychological development of the child, growth and integration of the child in school and peer groups [4].

Table 3. Risk factors for the pathogenesis of depression in childhood and youth

Biomedical factors	Chronic illness Female gender Pubertal changes in hormone level Family history in affective disorders Genetic risk (serotonin transporter gene polymorphism)
Psychosocial factors	Neglect and deprivation Abuse in childhood (physical, emotional, sexual) Loss of a loved person
Not otherwise classified factors	Anxiety disorders ADHS

Etiology and Pathogenesis

Risk factors can be classified into different groups, they include biomedical, psychosocial factors and a group of not yet classified causes of the disorder [4] (table 3). These risk factors are influenced by the following pathogenetic phenomena.

Neurotransmission

Earlier theories explained neuroaminergic depletion as a major cause of affective disorders. These theories have been substituted by dysregulation models of different neurotransmitter systems, in particular the serotonergic and noradrenergic systems.

Regarding neurotransmitter imbalance the following dysregulation models can be differentiated: changes in monoamine receptor sensitivity which can lead to depletion in neurotransmission, changes in concentration of neurotransmitters as well as precursor deficits [6].

Imbalance of Neurotransmitters

It is assumed that the imbalance of different neurotransmitter systems causes affective disorders as in the case of schizophrenic psychosis. This hypothesis is strengthened by the depletion of metabolites of the monoaminergic system, mostly serotonin (5-HT) and dopamine in the cerebrospinal fluid, and the urine and blood plasma of patients with depression. However, there is no explanation for the cause of neurotransmitter imbalance. Dysregulation of monoamine receptor sensitivity is important in the genesis of depression. The major therapeutic function of antidepressant drugs influences the sensitivity of receptors.

Various attempts have been made to discover the genetic and psychosocial causes of neurotransmitter imbalance. Several psychosocial risk factors are mainly discussed such as sexual abuse, physical and psychological negligence, and loss of a loved person. However there is still a lack of knowledge on the neural mechanisms connecting social factors and transmitter systems. The neurobiological systems evolve significantly during childhood and may play different roles in the genesis of depression during childhood and adulthood.

Implication of the Serotonergic System in the Genesis of Affective Disorders and Its Influence on Suicidal Behavior

Serotonergic neurons are localized in the raphe nuclei, they form connections to different areas of the brain, the cortex, hippocampus and basal ganglia. The level of serotonergic neurotransmission is influenced by the 5-HT transporter (5-HTT). The positive effect of fluoxetine in childhood depression in contrast to the inefficiency of tricyclics indicates the involvement of the serotonergic system in the genesis of depression in childhood [7]. Children and adolescents suffering from affective disorders have lower levels of 5-HT in blood compared to patients with other psychiatric disorders [8]. Children with hyperactive behavior have higher levels of 5-HT in blood than children suffering from affective disorders. With regard to the blood level of 5-HT, no differences have been found when comparing depressive children with a healthy control group. There is a significant negative correlation between the plasma 5-HT levels and suicidal behavior in adolescents [9]. However there is a negative correlation between the level of 5-hydroxyindolacetoacetate in cerebrospinal fluid, a metabolite of 5-HT, and aggressive behavior [10].

Stimulation of the serotonergic system using L-5-hydroxytryptophan, the precursor of 5-HT, increases the turnover of 5-HT in the central nervous system. The stimulation of the serotonergic systems triggers the release of cortisol and prolactin. In female depressive patients the release of cortisol is lower compared to a healthy control group, whereas the release of prolactin is considerably higher. This also applies to children of families with a higher risk of major depression. The increase in prolactin release affects mainly sexually abused children suffering from depression. A significant relationship has been determined between the aggressive behavior and high prolactin release. The above-mentioned results indicate intense neurobiological changes resulting from specific environmental influences and psychosocial stress. Aggressiveness and suicidal behavior are associated with a different pattern of greater receptor responsiveness of 5-HT1A and 5-HT2A, 5-HT receptors affecting prolactin release [11].

Neuroendocrinology

Dysregulation of the Hypothalamus-Pituitary-Adrenal Axis

The anatomical structures and hormonal factors involved in the neural circuitry of depression are the following: neurons in the paraventricular nucleus of the hypothalamus

secrete corticotropin-releasing factor which stimulates the synthesis and release of adrenocorticotropic hormone (ACTH) in the anterior pituitary. Furthermore ACTH stimulates the synthesis and release of glucocorticoids from the adrenal cortex of the suprarenal gland. Glucocorticoids affect the metabolism and influence the behavior controlled by different regions of the brain. The activity of the hypothalamus-pituitary-adrenal (HPA) axis is top-down modulated by different brain pathways, particularly connections to the hippocampus and the amygdala. Bottom-up regulation is based on feedback mechanisms, thus glucocorticoids influence the hippocampus and the paraventricular nucleus [12]. The assumption that disorders in the hormonal circuitry cause psychiatric diseases originates from the notion that the dysregulation of the hormonal circuitry causes somatic diseases with severe psychological impairments.

Dexamethasone Suppression Test

The dexamethasone suppression test (DST) in depressed patients indicates non-suppression of cortisol or early escape from dexamethasone suppression. The pathomechanism is associated with a reduction in expression of corticosteroid receptors in the hippocampus, hypothalamus and pituitary and contributes to HPA axis hyperactivity in depressed adult patients. A pathologic DST is related to the severity of depression; the test normalizes after recovery from depression. In children the DST is more sensitive for depression, however with little specificity. In the adolescence the specificity of the DST is greater. The non-suppression was described for suicidal depressed children. In general the meaningfulness of the DST for mood disorders is limited; the DST indicates a dysregulation of the HPA axis as a major cause of depressive disorders [11].

Stress-Induced Activation of the HPA Axis

Permanent stress induces a long-term increase in glucocorticoid levels. This leads to the damage of pyramidal cells in the CA3 region of the hippocampus, in particular of the dendritic arborization and the formation of dendritic spines [13]. Stress-induced hypercortisolism reduces the mentioned structures as well as the birth of new granule cell neurons in the adult hippocampus. Neurogenesis in the hippocampus is affected by morphological impairments. These phenomena implicate disorders of subtle memory functions and cognitive processes. The toxic effect of hypercortisolism on hippocampal neurons, implying a reduction in the dendritic arborization as well as a deficiency in neurogenesis, could be related to the small reductions in hippocampal volumes in patients with depression [14]. In animal models several classes of antidepressants revert the stress-induced morphological changes [15]. There are ongoing studies regarding the medication and enhancement of hippocampal neurogenesis and dendritic arborization. Early psychosocial stress factors, separation and sexual abuse in childhood influence the level of ACTH. Depressive and abused children have a higher peak after corticotropin-releasing hormone infusion in the secretion of ACTH in comparison to depressive children without a history of abuse. Hyperreactivity of the HPA axis is influenced by corticotropin-releasing factor.

Increase of the cortisol secretion after stimulation by ACTH results in the hypertrophy of the adrenal axis [11].

Neurotrophic Factors

Impairment of Neurotrophic Mechanisms

Neurotrophic factors regulate the neuronal growth and the differentiation of the neurons during development. In addition they are of importance to the neuronal plasticity and to the survival of adult neurons and glia cells. Certain genes which code for the brain-derived neurotrophic factor (BDNF) modulate and balance the function of neurotoxic and neuroprotective processes and are responsible for a particularly strong activation of the HPA axis. Neurotoxic effects lead to damage of hippocampal neurons if there is a deficit in the function of neuroprotective peptides. Acute and chronic stress leads to a reduced level of BDNF expression in the dentate gyrus and the pyramidal cell layer of the hippocampus as well as in the neocortex and the amygdala, at the same time there is an increased BDNF level in the hypothalamus. The reduction is mediated via stress-induced excessive corticotropin activity and the inflammatory effects of cytokines and via other mechanisms such as the induced increase in serotonergic neurotransmission. There is evidence that antidepressants increase the hippocampal level of BDNF regulated through the transcription factors, cyclic adenosine monophosphate (cAMP) and cAMP response element-binding protein. Antidepressants have been shown to enhance neuroprotective effects, they counteract damage to the hippocampal neurons induced by stress and protect vulnerable neurons from damage [12].

Genetic Factors

Increased Risk of Being Affected by Major Depressive Disorders Exists for Children and Adolescents with a Parent Suffering from Major Depression

A genetic predisposition could be identified in connection with affective disorders during childhood and adolescence. The heritability of major depression for homozygote twins is 40–50% and is hence higher than for schizophrenia; for dizygotic twins it is in the order of 20% [16]. An early age at onset of major depressive disorders is characteristic for a greater family risk. The illness of the parents leads to an early outbreak of affective disorders in their children and a significantly more serious symptomatology.

Functional Polymorphism in the 5-HTT Promoter Region

In the past decade priority has been given to the exploration of functional polymorphisms in the investigation of genetic reasons for psychiatric diseases. A functional polymorphism was identified in the 5-HTT promoter region of the 5-HTT gene on chromosome 17q11.2, which is of special relevance in the genesis of affective disorders.

The mutation consists in either an insertion of 44 basepairs (L allele) or a deletion of basepairs (S allele). A connection exists between the functional polymorphism in the promoter region of the 5-HT promoter gene and the outbreak of major depression as well as reduced hippocampal volume [17]. The short allele (SS, SL) leads to a reduced production of transporter molecules with a limited activity of 5-HT reuptake in comparison to individuals who have the L allele. These individuals show higher expression of the 5-HTT. With regard to adolescents these differences described above are not clearly linked to an increased outbreak of depression or a higher suicide rate; however, they do show a connection with an increase in aggressiveness. In addition a connection could be found between polymorphism of the 5-HT receptor gene 2A and affective disorders. The reduced serotonergic neurotransmission can be attributed to a change in the number of receptors as well as changes in the responsiveness of the receptor [11].

The polymorphism described above shows an increased risk of illness only in connection with a traumatic life experience and personality characteristics, including psychosocial environmental factors [18].

Structural Differences

Several brain regions participate in the complex symptomatology of depressive syndromes in childhood and adolescence. Neuroimaging techniques show differences in blood flow in several brain regions as well as in the relative proportions of individual brain regions. In depressive patients the proportion occupied by the frontal cortex is reduced whereas the proportion of the lateral ventricle is enlarged. Possibly the morphological changes tend to represent a chronicity characteristic of the disorder [19].

The neocortex and hippocampus influence cognitive aspects. Impairment of memory function, self-depreciation, hopelessness, feeling of guilt and suicidal thoughts – all characteristics of major depressive disorders – indicate the involvement of the structures mentioned above. A 10–20% reduction in the volume of the hippocampus has been determined in several studies [20]. The volume differences correlate with the severity, duration and frequency of depressive episodes. An association between a change in volume and a strong expression of glucocorticoid receptors can be observed in the prefrontal cortex and the hippocampus. Animal models indicate that postnatal stress increases the concentration of glucocorticoids and glucocorticoid receptors in the prefrontal cortex and hippocampus and increases the vulnerability of the neurons. The cells become vulnerable mainly for neurotoxic effects and glucocorticoids.

Disturbances in emotional memory, anhedonia, anxiety and a reduction in motivation indicate structural changes in the amygdala and striatum. The hypothalamus and subcortical structures such as the nucleus accumbens and the amygdala influence the function of the autonomous nervous system, sleeping disorders, loss of appetite and energy, and disturbances in circadian rhythm. These symptoms occur regularly in affective disorders.

Depressive patients with an inherited family history have a reduction in the left subgenual cortex [21]. Twin studies indicate that these structural differences are caused genetically [22]. During depressive episodes the activity of this region is reduced, this may be due to a volume reduction in the gray matter. Studies indicate that the subgenual cortex is responsible for emotional situations. The subgenual cortex has connections to the amygdala, to the lateral hypothalamus, the nucleus accumbens and to noradrenergic, serotonergic and dopaminergic systems of brain stem.

Chronobiology and Sleep

The phenomenon of rhythm disturbances of sleep has been described especially for patients with bipolar disorders and seasonal depression. Seasonal depressions are characterized by an increase in appetite and an increased need to sleep. They can positively be influenced through light therapy.

Children and adolescents with major depression describe significant subjective sleep disorders [23].

The results of research in adults with regard to circadian rhythm disorders could not be clearly repeated for children and adolescents. A shortened REM latency between falling asleep and the appearance of the first REM phase could be proven for children with major depression [24]; the results become clearer with the increasing severity of the illness. A larger study showed no EEG evidence of objective sleep disturbances in children with major depressive disorders compared with controls. Depressive patients need a longer time to fall asleep, they suffer from an increased number of moments of sudden awakenings and from a reduced relaxation while asleep. More frequently they have phases with REM sleep occurring after a shorter latency from the onset of sleep. The frequency of phases with rapid eye movements is higher during REM sleep [25].

After improvement in the depressive symptomatology the short latency mostly continues until the beginning of REM sleep in which the increased number of phases of REM sleep mostly returns to normal. It has been suggested that the observations above are caused by an increased central cholinergic activity and a reduced neurotransmission passed on through 5-HT. Reduced levels of L-tryptophan, the molecule preceding 5-HT, lead to an increase in REM sleep and a decrease in REM latency [23].

Life Events and Personality Factors

The described neurobiological factors generally lead to a manifestation of major depression in childhood and adolescence in connection with a specific traumatic experience and together with personality factors. The following events in life are connected to an increased vulnerability for the development of depressive disorders: of major significance are problems in the continuity of the relationship amongst a family

through the loss of a parent or a longer term of separation of the major role models during the first years of life. Of high relevance are chronic psychiatric or physical diseases of a parent, such as depressive disorders, substantial abuse of drugs and alcohol, anxiety disorders, psychosis and disorders of the personality influencing the inner and outer stability of the role model for the child. In addition the intra-familial interaction and communication is of importance for the development of affective disturbances. Emotional and physical deprivation as well as physical and sexual abuse of the child play an essential role in the pathogenesis of the disease [26]. Divorce of the parents, the status of single parents, disharmonic ways of communication in the family, and a dense sequence of brothers and sisters may result in significant problems in the relationship which can increase the risk of illness of a child.

Psychosocial changes such as unemployment, migration and poverty can also contribute to the development of depressive disorders. The slowly crystallizing personality of a young person during childhood and adolescence stands as an underlying factor on the border between genetic factors, with the importance of the personality structure on one side and the neurobiological gifts, the psychosocial environment and the influence of forming events during life on the other. Factors of personality such as emotional instability, increased interpersonal dependence as well as aggressiveness constitute a high risk for depressive illness.

Personality characteristics can appear as a subclinical manifestation of depression, which can be of importance in the predisposition for a major depression or can be integrated in a complex model of injury. In addition personality characteristics can influence the clinical symptoms and their development and can influence the reaction to treatment. Retrospectively depression may result in a modification of the structure of the personality and has an influence on the development of the personality during childhood and adolescence [27].

Interaction between the Genetic Constitution of a Patient and His Environment

Epigenetic Reasons for the Development of Major Depression in Childhood and Adolescence

Genetically determined dispositions as well as changes in the genetic constitution of an individual during the course of his development through forming events during lifetime and the environmental influences play decisive roles in the genesis of major depression. A traumatic experience in early childhood results in an increased risk of depressive syndromes and an increased risk of suicide at a later stage of development; this is to a high degree true for children who in early childhood have been victims of abusive experiences, specifically sexual abuse.

A number of different animal experiments exploring the various pathomechanisms of human depression start out from this basic assumption [6]. The results of the animal experiments can mostly be applicable to human beings. The animals are exposed to dif-

ferent psychosocial stressors during their development which may at a specific developmental stage cause depressive syndromes. After exposure the animals' development is analyzed in more detail. The following stressors have been examined: learned helplessness; chronic stress; social neglect, and separation from the mother. Following the model of learned helplessness according to Seligman, chronic biographical burdens may lead to a feeling of discouragement and helplessness. These feelings increase the probability of depressive reactions later on. The model of early separation of the animal from its mother refers to the following hypothesis for the development of depressive disorders. Early traumatic experiences may later on result in depressive syndromes, in particular when they occur at a sensitive stage of development where the affected animal or child is in a phase in which the plasticity of the brain still reacts sensitively to external stimuli with morphological changes. The stress sensitization hypothesis proposes that individuals become sensitized to the life events that precipitate depression [26]. Experiences of separation from the mother not only have an influence on the behavior of an animal but also on the neuroendocrine response of the HPA axis.

The functional polymorphism in the 5-HTT promoter region has different effects on the function of the brain depending on the prevailing stress situation of the individual. As a reaction to adverse stimuli in the environment of the individual, genes may be diminished through methylization of vulnerable parts in the promoter region. Likewise environmental influences may switch on pathogenic genes or the interaction of environment and genes favors a behavior which may induce individuals to enter dangerous situations [11]. A functional polymorphism in the 5-HTT promoter region moderates the influence of stressful life events on the development of major depressive disorders [28]. Individuals carrying the S allele show more frequently depressive reactions on traumatic experiences in their life than individuals with the l/l genotype. Individuals with the s/s genotype more frequently show depressive symptoms and an increased risk of suicide in reaction to burdensome situations in their life. With regard to children, the psychosocial support they are embedded in also has decisive influence on the way they react and on their psychophysical development [18]. The highest rate of depression can be found among abused children without reliable social support who are bearers of the s/s polymorphism. In comparing abused to not abused children, the risk of being affected by depressive syndromes is nearly twice as high within the same genotype. The risk is passed on through genetic and environmental factors on the basis of the quality and reliability of the psychosocial environment, which guarantees the stable support of a child. This psychosocial stability is an important factor for the resilience of abused children, even when these children bear an increased risk of falling ill through the burden of the s/s polymorphism, which passes on a certain genetic disposition for vulnerability. Persons who are bearers of the short allele present with a higher probability of psychological characteristics dominated by anxiety and a higher risk of being affected by depressive symptoms in comparison to persons who are bearers of the l/l polymorphism. There is an association between the short allele and the hyperactivity of the amygdala as well as the hippocampus in the reaction to stimuli of

anxiety. Also the resting activity of the amygdala is increased in such persons who are generally exposed to a stronger stress.

The mental burden of children who are mistreated or abused is combined with an increased activity of the amygdala as an answer to adverse stimuli and a higher production of ACTH in reaction to the suffered separation.

Children have an especially high risk of being affected by a major depressive disorder if there is poor and little reliable psychosocial support in addition to a high number of mistreatments. In addition the risk is higher if the activity of the amygdala is high in response to adverse stimuli and if there is a high release of ACTH in reaction to suffered experiences of separation [29, 30].

Genetic examinations indicate a polygene modus of heredity, psychosocial factors seem to have an influence on the time when the illness breaks out.

The occurrence of a depression not only depends on the genotype. Traumatic experiences during childhood and adolescence modulate consequences of the genetic disposition and the risk of illness.

It can be summarized that the genotype influences in particular the stress vulnerability of the individual and less the immediate manifestation of a major depression. Adverse life events further increase the susceptibility of dynamic and adaptive neuronal mechanisms. This vulnerability leads to a permanent hyperactivity of the HPA axis. In an animal experiment it could be demonstrated that deprived rats show an increased density of the glucocorticoid receptors in the prefrontal cortex and hippocampus. As described above, the increased level of glucocorticoids is connected to a significant neurotoxicity and thereby the ability of the hippocampus to inhibit the activity of the HPA axis in the mode of a negative feedback loop is reduced.

The differential interplay between genetic, neurobiological, structural and functional causes for depressive syndromes appears to be complex and to a great extend still unsolved. Possibly the variety of pathogenetic pathways indicates different forms and effects of interaction. These might lead to the designation of different subtypes of depressive disorders and to the necessity to design different therapeutic interventions.

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The Neurobiological Basis of Anxiety in Children and Adolescents

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Abstract

The components of anxiety development in children and adolescents are reviewed. Abnormal orienting responses to perceived threats are among the earliest and most universal features of an anxiety diathesis. The effect of temperament on the control of children's attention can generate biases that influence the stages of social information processing such as encoding and interpretation of social and emotional cues. Behaviorally inhibited children interact with peers in socially non-effective ways further cementing distorted notions related to social learning, meanwhile internalizing notions of causality of this experience in relation to self. Neuroanatomical correlates of anxiety implicate the amygdala and related circuitry (hippocampus, parahippocampal regions, insula, medial prefrontal cortex, orbitofrontal cortex and anterior cingulate cortex) while molecular data support key pathways in γ-aminobutyric acid, serotonin, glutamate, dopamine as well as brain-derived neurotrophic factor and corticotrophin-releasing factor bioactive molecules. Neurophysiologic studies are consistent in isolating attentional orienting responses, threat appraisal and aspects of memory and learning as specific to mechanisms that underlie anxiety. A developmental framework for pediatric anxiety disorders is in an expectant stage, with breakthroughs expected in neuroimaging and molecular work.

Anxiety is a mental and physical state that encompasses a range of behavioral, physiological responses including avoidance, vigilance and arousal that are meant to protect an individual from danger. The manual of psychiatric disorders, DSM-IV, recognizes up to 10 anxiety disorders characterized by distress in reaction to feared situations [1], underscoring the notion that there are possibly shared etiological substrates underlying most anxiety disorders, with the possible exception of post-traumatic stress disorder. This review will focus on shared biological factors among pediatric anxiety disorders, while highlighting select disorder-specific factors. The approach will use recent findings in developmental psychopathology in pediatric

anxiety disorders and discuss biological factors identified in anxiety disorder research in order to provide an integrative view of the neurobiology of pediatric anxiety disorders.

Developmental Psychopathology of Anxiety Disorders

It is generally accepted that clinical continuity exists between individual childhood anxiety and later adult manifestations of anxiety, a continuity that is shared between the individual and family members. One way of conceptualizing early manifestations of anxiety is through the presence of a temperamental trait termed 'behavioral inhibition' (BI). BI refers to the reaction inherent in some young children and toddlers to manifest withdrawal and autonomic arousal in the face of novel situations or unfamiliar people [2]. Although BI is a well-known precursor of later anxiety, it may have specificity for social phobia (SocP) over other forms of anxiety. When toddlers with BI are followed over time, they have a significant increase in social anxiety but not in specific fears, separation anxiety or performance anxiety in adolescence [3], suggesting that temperamental factors may lead to some forms of anxiety later in life. A familial component to BI is also recognized. Parents and siblings of BI children manifest a significantly increased risk for the development of anxiety disorders, compared to parents and siblings of non-inhibited children [4], suggesting a shared genetic basis for anxiety proneness. Conversely, children 'at risk' of anxiety due to parental anxiety also clearly exhibit an excess of BI and anxiety disorders [5].

Longitudinal studies additionally bear out a relationship between early life anxiety disorders and adult anxiety, with increased specificity for specific phobia (SP) and SocP, and less specificity for generalized anxiety disorder (GAD). GAD, from a longitudinal perspective, appears to be more closely associated with later life major depression [6]. Other studies support the longitudinal specificity for SocP and separation anxiety disorder (SAD) but less specificity for GAD [7]. In high-risk studies, parental panic/agoraphobia was associated with the same disorder in children, but major depression in parents increased the risk of SocP in children. At the same time, parental panic and depression were also associated with the child's increased risk of SAD and multiple anxiety disorders [8]. These and other studies show a shared genetic risk between some anxiety disorders and depression while demonstrating specificity for panic disorder. It is also important to recognize that a substantial number of high-risk children do not go on to develop anxiety disorders in adulthood while another group will develop mood disorders and not anxiety disorders later in life. The mechanisms that result in later life anxiety, mood disorder or no disorder are of great interest to elucidate, bringing into play biological risk factors as well as environmental protective factors.

Physiologic studies in pediatric anxiety, to be discussed in more detail below, have been key in clarifying the possible mechanisms in SAD and SocP. Threats of smothering or smothering sensations are associated with panic disorder in adults and anxiety in

children [9]. This defensive physiologic reflex is prominent in children with SAD relative to children with SocP: children with SAD report increased fear and manifest more physiologic symptoms in CO_2 breathing under minimally suffocating circumstances than children with SocP. In situations of social threat, conversely, children with SocP but not SAD report abnormal subjective appraisal responses. Thus, there is a double dissociation between SocP and SAD for specific fear-enhancing stimuli but it appears that other threatening stimuli are not disorder-specific. The anticipation of an anxiety-provoking situation, for example, induces an excessive response in both children with SAD or SocP, regardless of the nature of the anxious stimuli. Additionally, in a recent study of high-risk children from 151 families, it was observed that early SAD led to later SP, agoraphobia, panic disorder and major depression; while the early manifestation of agoraphobia led to later life GAD [10]. In summary, it is difficult to posit specificity in longitudinal trajectory path or in triggering mechanisms for the biological substrates of any anxiety disorders with the possible exception of SAD and SocP.

Biological Factors in Pediatric Anxiety

Biological risk factors for pediatric anxiety disorders have at their core the inborn reactivity to threatening stimuli captured under the concept of fear conditioning. Extensive animal and human data support the notion that fear conditioning is a basic underlying mechanism in pathological anxiety. Below, we review the construct of fear conditioning and place it in the context of other anxiety-generating mechanisms.

Concept of Fear Conditioning

The threat response, a function classically attributed to the amygdala in the brain, is central in understanding the higher organism's experience of anxiety. A response denominated 'conditioned fear', the pairing of a neutral conditioned stimulus (CS) such as light or tone, with a fear-inducing unconditioned stimulus, such as a mild foot shock, can generate in the organism a conditioned fear response (CR) to the CS [11]. Both the basolateral complex and the central nucleus of the amygdala play a role in the generation and perpetuation of CR [12]. Subjects with SocP, SP and healthy subjects undergoing fear conditioning consistently show greater amygdala and insula activity associated with negative emotional responses than matched comparison subjects, strongly reinforcing the concept that these are the key brain areas in CR phenomena [13]. The CR is thus understood to constitute the prototype of fear-associated responses in animal studies that include freezing, startle reflexes, autonomic changes, analgesia and behavioral response suppression. An important concept ensues, that is, when the CR is associated with non-reinforced CS presentations a startling phenomenon is observed. There is a decrease in the amplitude and frequency of the CR in response to non-reinforced CS. This phenomenon is the basis for the behavioral

technique known as behavioral extinction. The extinction process is currently understood to be an active learning process distinct from acquisition of fear and requires additional training to develop [14], and as such, implies additional learning through neural plasticity mechanisms [15]. This property of extinction allows it to be an independent entity of study and manipulation, linking to neural and molecular mechanism yet to be uncovered. In an experiment with rabbits, for example, the extinction of a CR was blocked by synaptic receptor antagonists to inhibitory input that affected climbing fibers in the cerebellum [16]. However, the complexity of the extinction process itself is realized by the observation of spontaneous 'recovery' (decrease in the CR over time) and 'renewal' (increase in the CR through new experience) that can also play a role in modulating the CR. In summary, it can be said that extinction is not the same as forgetting [17]. From a brain-based perspective, excitatory and inhibitory responses to a CS may be orchestrated by different brain structures (e.g., amygdala vs. prefrontal cortex), different populations of cells within a structure (e.g., glutamatergic cells vs. GABAergic cells) or different types of molecules within individual cells (e.g., kinases vs. phosphatases; activators vs. repressors of transcription). The multiple levels of biological action inherent in anxiety responses reflect the need for a multiple levels of analysis approach in cognitive neuroscience [18].

Animal Experiments in Fear Conditioning

Animal experiments have shown that a network of brain structures modulate the extinction of conditioned fear or the loss of CR. These structures include the hippocampus [19], lateral septum [20], sensory cortex [21] and prefrontal cortex [22]. The sensory cortex, in particular, with its connections to the amygdala, has been the object of extinction mechanism studies. Lesions of the sensory cortex were observed to retard extinction [23]; in this vein, auditory cortex lesions can produce differential bradycardia-conditioned responses in rabbits [24]. The cingulate, subiculum and/or prefrontal cortex potentially receive sensory cortex input that is related to extinction. The role of increasingly evolved brain strata in anxiety phenomena determines that while plasticity in the amygdala may be susceptible to rapid conditioning of the fear response to potentially dangerous stimuli, other cortical areas are operative in higher-order memory and attentional processing of fear experiences [25]. Notwithstanding, studies on the role of prefrontal areas in relation to the extinction of fear-related CR in rats have yielded variable results. Some studies found that medial prefrontal cortical lesions had no effect on initial acquisition of fear conditioning but influenced retarded subsequent extinction to a sound tone [26]. Other studies did not replicate the extinction-related difference in medial prefrontal lesioned and non-lesioned animals [27]. More recently, additional studies support the role of the medial prefrontal cortex in the extinction of CR. Milad et al. [28] found that infralimbic tone activity correlated with the extinction response in rats. Stimulation resembling extinction-induced tone activity is able to stimulate extinction memory, a mechanism that may inhibit fear during subsequent encounters with fear stimuli [28]. Other factors may also play an important

role in mediating the extinction response. For example, even when dopamine 6-OH-dopamine depletion in rat brains resulted in a residual 13% dopamine prefrontal cortex function relative to controls, similar CR acquisition or fear conditioning was still observed in lesioned animals and controls. With fear conditioning intact in the lesioned animals, significant delayed extinction was observed suggesting a role for prefrontal dopamine neurons in adaptability to stress-related changes in the external environment [29]. Given the poor representation of prefrontal regions in rodents, and the complexity of CR extinction implied by the above animal studies, it is important that these studies be replicated in non-human primates and in humans.

While the fear reaction continues to be explored in its inherent complexity, other studies have shown that threat processing may following distinct pathways in the brain depending on the type of threat. In this manner, rats that are presented threats respond differentially to benzodiazepine and 5-HT1A active drugs, depending on the type of threat [30]. In mice, global disruption of 5-HT2A receptor signaling in the brain reduces inhibition in conflict anxiety paradigms without affecting fear-conditioned and depression-related behaviors, suggesting a specific role for cortical 5-HT2A functioning in the modulation of conflict anxiety [31]. In nonhuman primate studies, young rhesus monkeys who have their amygdalae ablated early in life have a striking lack of fear of normally fear-inducing stimuli such as snakes but demonstrate more fear when placed in novel social situations, suggesting that the amygdala specifically evaluates the environment for potential dangers and thus modulates social behaviors. This line of work suggests that amygdala hyperactivity is associated with SocP or maladaptive social behaviors [32]. In another experiment, neonatally amygdala-lesioned nonhuman primates showed more fear-related behaviors during social encounters than did control or hippocampal-lesioned animals, again suggesting specificity for the amygdala in social fears [33]. Thus, ongoing work is elucidating specific pathways for distinct threat experiences in the organism.

Human Fear Circuitry

In humans, fear circuitry studies consistently involve several key brain structures. The amygdala, in particular, has been the focus of the exploration of fear-related circuits, given its central role in pairings of neutral CS with aversive unconditioned stimuli in fear conditioning [34]. This single finding has supported the study of emotion-based brain research as opposed to brain-based cognitive studies in anxiety, which is based on the assumption that conscious processing of information is necessary in the formulation of paradigms of anxiety. On the contrary, unconscious processing mechanisms have been repeatedly shown to exist in emotional brain-based responses [35]. The amygdala, a central component in this paradigm, facilitates learning by regulating the allocation of attention to the neutral CS in reactions to both positive- and negative-valence stimuli, interacting with autonomic, hormonal and attentional systems to drive the fear response [36]. In addition, it has been recognized in this model that

emotion and cognition are intertwined from early perception to reasoning, with interactions of the amygdala, hippocampus and prefrontal cortex supporting these connections [37]. In particular, contextual information processed by the hippocampal and prefrontal cortex appear to be important in the fear reaction to stimuli in humans, including interpretation of body movements related to fear [38].

While in children the amygdala may mature well before adolescence, cortical-amygdala connections continue to develop over a longer period of time, including amygdala-temporal and amygdala-prefrontal circuits, making developmental considerations a key component in pediatric anxiety research [39]. Few relevant structural studies exist in children in relation to anxiety that could shed light on developmental models of anxiety. Both increased [40] and decreased [41] amygdala volumes have been reported in pediatric anxiety. Vasa et al. [42] report an association of less anxiety in children who have sustained severe traumatic brain injury, if there is a lesion in the orbitofrontal cortex. These data suggest that the orbitofrontal cortex is part of a neural circuit that underlies the expression of anxiety in children and adolescents, and that children with such lesions do not mount normative anxiety or fear responses [42]. Threat appraisal theories (see below) suggest that specific regions of the developing child's brain are involved in the genesis of anxiety. The brain-based correlates of developmentally evolving appraisal threats are still unknown but probably encompass the amygdala (attention to threats), posterior temporal cortex (representation of complex stimuli) and ventral prefrontal cortex (stimulus salience) [43]. Hippocampal structures, in turn, appear to play a central role in the contextual modulation of the acquisition of conditioned fear and of its renewal or reinstatement following extinction [44]. The data support a specific mnemonic role for the dorsal hippocampus, in particular, in the acquisition and consolidation of contextual representations [45]. In this respect, the developmental features of hippocampal function will be important in understanding how children and adolescents show different reactions to threatening stimuli (e.g., children to threatening animals and adolescents to social situations). The insular cortex lies within the lateral sulcus and sports adjacent opercula which are parts of temporal, parietal and frontal lobes. The insula plays an important role in the processing of body orientation and subjective emotional experience, and may play a role in processing visceral states important to feeling and emotion, although the complexity of its function cannot be overstated [46]. The relation of the insula to anxiety proneness is under investigation and one recent study found increased bilateral activation of the insulae during an emotion face assessment task [47]. In summary, anxiety disorders in children and adolescents are hypothesized to result from biases in attention and orienting, threat appraisal and learning (see below) associated with deficient prefrontal, medial temporal lobe and striatal function. While structural studies lend scarce information to support definitive fear circuitry in pediatric anxiety, functional imaging studies are incipient due to the relatively immature understanding of threat circuit hyperactivation in relation to task demands and developmental considerations [48].

Physiologic Studies of Anxiety

The physiologic mechanisms that underlie pathological anxiety are complex. At least three processes have been described that need to be taken into account to encompass the range of reactions found in anxious children: attentional systems, threat appraisal and learning [43]. While these processes underlie the response to threat in normal individuals, they display excessive or deviant characteristics in pathologically anxious children.

Mechanisms that modulate attention play a key role in the early development of the anxiety response. Threat-related stimuli garner the most attentional resources independent of organism-specific features and independent of goal demands, but organism-dependent factors also play a role. In this complex interaction, the orienting response, arousal states and the regulation of attention under competing goal demands come together to conform the elements of the anxiety response. Most research to date has focused on studying attention orienting, based on reaction time dot-probe paradigms which capture the degree of attentional resources harnessed by stimuli perceived as threatening. In this paradigm, the orienting response of anxious individuals are driven by the nature of the threat-related information relative to non-anxious peers, with an effect size across studies in the order of 0.45 [49]. The utility of the orienting response in anxiety research is underscored by its ability to differentiate between anxious and depressive children and adolescents, with only anxious children responding excessively to the threatening stimuli [50]. The pathological anxiety response sequence is thus established where first an initial vigilant-monitoring tendency (automatic reactivity) occurs determining a lower threshold for appraising threat. This initial reaction is later overcome by an avoidant response (regulation) as the magnitude of the perceived threat increases. The automatic reactivity and regulation phases are different in anxious and non-anxious individuals. In the latter, the threshold for engaging vigilance is higher and regulation is not geared towards an avoidance response. What becomes clear from this research, is that while the initial response is driven by automatic or innate mechanisms, the threat appraisal rather than the attention allocation is the key aspect in the total anxiety response that later develops [51]. Thus, developmental aspects of threat perception influencing orienting have recently been examined. In a study of GAD adolescents there was greater attention bias away from angry faces. At the same time, ventrolateral activation was inversely associated with reports of anxiety [48]. Since this is not the pattern found in anxious adults, the authors postulate that maturation may produce an increase in thresholds for threat. From a nosological perspective, attentional biases do not appear to differentiate between different anxiety disorders, even when disorder-specific stimuli are employed in paradigms [49]. From a treatment perspective, there is preliminary evidence that the manipulation of attentional bias can modify emotional response supporting the notion that attentional bias causally mediates emotional vulnerability [52].

More recent threat appraisal studies further support a key role for this physiologic response in the genesis of anxiety. As stated above, attentional bias towards threatening stimuli occurs automatically, with little regard for the organism's conscious goals. However, over time, these stimuli undergo classification within the organism, orienting increasingly complex responses in concordance with more explicit goals. As such, an 'appraisal bias' reflects individual differences in output given the classification of the stimuli by the organism. Such a response has recently been modeled [13] and operationalized by individual self-report or physiologic measures [53]. The level of threat intensity is related to early attention and later appraisal occurring with the maturation of response systems determine the growing influence of increasingly abstract and complex situations on threat appraisal. For example, cultural parameters have been observed to influence threat appraisal, with increased fears expressed by children exposed to inhibition, compliance and obedience expectations [54]. Additionally, developmental considerations may influence young children to classify dangerous animals as threatening while adolescents may increasingly focus on social and relational situations as threatening, highlighting the complexity of determining which anxiety-related situation should be studied in which children. Most studies that associate measures of threat appraisal to clinical anxiety in both adults and children find that anxious individuals have a lower threshold for classifying stimuli as dangerous. The abnormal experience of heightened threat appraisal over time thus builds a scaffold for a heightened anxiety response leading to pathological anxiety, a process that is in turn reinforced by learning mechanisms.

The learning process influences manifestations of anxiety by adapting the organism to repeated exposures related to threat content so that threat is now anticipated and neutral stimuli can be treated as dangerous. Conflict monitoring, a role usually ascribed to the anterior cingulate cortex, may play an role in adapting to future threatening stimuli so that increasing conflict augments performance monitoring. In this respect, error-related negativity amplitude measures are increased in the anterior cingulate cortex in children with an anxiety disorder [55]. Children with BI also show greater activation of striatal circuits when confronted with reward situations, possibly reflecting an enhanced or learned sensitivity to stimuli in children classified early in life as BI [56]. These findings support the notion that a stable and general hypersensitivity to environmental stimuli in BI children exists in the form of an enhanced reactivity of the fear circuitry of the brain to novel stimuli [57]. It furthers extends this concept to encompass an enhanced neural sensitivity to stimuli that facilitate motivated behavior in response to nonsocial rewards, such as over-concern with making errors. The learning process in anxiety is thus not only crucial in establishing the scaffold on which pathological anxiety over the lifetime will rest. Learning research also allows the models presented above to interface with molecular research. Thus, molecular models of learning are increasingly relevant to understanding the modulation of the anxiety response in children and adults.

Molecular Basis of Anxiety

From a molecular perspective, extinction learning is a key neurophysiological process that illustrates the interaction of molecules, cognitive processes and behavior in relation to pathological anxiety. It is known that glutamate is involved in learning and memory through the vehicle of synaptic plasticity. To highlight the importance of the molecular approach to the learning process in anxiety, Miserendino et al. [58] effected intra-amygdala infusions of N-methyl-D-aspartate (NMDA) receptor antagonists in rats thereby blocking excitatory fear conditioning to a visual CS using fear-potentiated startle measurements. This technique blocked the acquisition but not the expression of fear conditioning using fear-potentiation of the acoustic startle reflex. A similar result was later observed with auditory and olfactory cues [59] and by diverse methods such as conditioned freezing [60]. Interestingly, a specific disruption of the 2B subunit of the NMDA receptor is capable of blocking fear conditioning [61]. The 2B subunit of the NMDA receptor is operative early in brain development and is the current target of pharmacotherapeutic investigation [62]. Pre-extinction training of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, a subtype of glutamate receptors that appear later in development, does not occur in this paradigm, making the effect specific to NMDA receptors [17]. Given the occurrence of NMDA-mediated neural plasticity in extinction learning, it is plausible that NMDA receptor gain of function is associated with enhanced extinction. In the clinical realm, D-cycloserine, a partial agonist at the glycine-binding site on the NMDA receptor complex, has been used to attempt facilitated extinction by facilitating new associative learning [63]. No current trials are published in children; however, in a study with 10 children and adults with autism D-cycloserine showed a positive effect on social withdrawal [64]. It is plausible that the developing brain would be the most susceptible to the effects of a drug that enhances NMDA receptor function given the higher levels of neural plasticity naturally present at early stages of development.

A host of putative anxiety susceptibility genes have been studied in animals (e.g., knockout mice) and humans; most of these studies are based on animal research into 'anxiolytic' or 'anxiogenic' molecules. Among these genes are those influencing the function of the neurotransmitters acetylcholine, serotonin, γ-aminobutyric acid (GABA), histamine, glycine, glutamate and neuropeptides such as corticotrophin-releasing factor (CRF) receptor, thyroid hormone receptor, brain-derive neurotrophic factor (BDNF), and others [65]. GABA has long been recognized as a central molecule in anxiety and memory function given the amnestic/anxiolytic effects of GABA modulators. Several GABAergic genes have been associated with an anxiety diathesis in animals and humans. For example, in humans a variant of the GABA-A-α6 subunit gene is associated with neuroticism scores [66] and an attenuated stress response and lower extraversion scores are associated with the T1521C polymorphism of the GABAR6 gene [67]. Given its central role in learning and memory, genetic variants that affect glutamate metabolism and function are prime candidates in regulating the anxiety response. Eight subtypes of metabotropic glutamate (mGlu) receptors have

been identified of which two, mGlu5 and mGlu7, are highly expressed at synapses made between CA3 and CA1 pyramidal neurons in the hippocampus. In one study, short-term synaptic potentiation was greatly attenuated in mGlu7−/− mice, suggesting a role for this receptor in synaptic plasticity in the hippocampus and potentially in anxiety-related learning [68]. Other glutamate receptors also play a role in learning potentially related to anxiety. In a study of inbred mice, the densities of AMPA and kainate glutamate receptors correlated positively with learning capacity in the spatial 8-arm radial maze, suggesting that spatial learning is dependent on these genetic variants [69]. Dopamine has also been associated with fear conditioning in humans [70] and a quantitative trait locus for intersession habituation, a trait that is associated with memory and anxiety in mice, has been mapped to a region containing D1 and D2 receptors [71]. Serotonin is another strong candidate molecule with an impact on anxiety expression. Serotonin receptor families and the serotonin re-uptake transporter (*SERT*) have been targets of drug manipulations in the treatment of anxiety. Mouse models of serotonin have been associated with anxiety-like behaviors, reduced aggression and exaggerated stress responses [72]. Another mouse model produced by a loss-of-function mutation in the C-terminus of *SERT* correlated with depression- and anxiety-related behavior in mice highlighting the role of this gene across a broader range of emotion expression [73]. A combination of serotonergic and dopaminergic genetic contributions to pathological anxiety is a plausible hypothesis that requires further biologic exploration [70]. Gene-environment interactions are also likely to play a strong role in complex behavioral responses such as anxiety. A recent study examining *SERT* variants and maternal reports of social support found that the child's *SERT* SS allele and low social support predicted an increased risk of BI in middle childhood [74]. BDNF may also play a role in mediating aversive experiences. Mice exposed to repeated aggression showed long-lasting aversion to social contact, which was reversed by a viral knockdown of mesolimbic-specific BDNF; interestingly, this same effect was produced by the chronic use of fluoxetine or imipramine but not a benzodiazepine (chlordiazepoxide) in the mice [75]. This study implies that BDNF is necessary for the consolidation of the anxiety response and behaviors associated with depression and anxiety, and that reduced BDNF function is 'protective' in this instance. However, other studies support an anxiolytic role for BDNF, abundant in the hippocampus and amygdala, in association with enhanced learning [76]. Additional studies also support a role for BDNF in spatial task learning but not in specific behaviors, some of which are related to anxiety [77]. Human data are supportive of a role for BDNF in memory, learning [78] and anxiety proneness [79]. Studies examining the brain 'anxiogenic' neuropeptide CRF in mice show that mutants lacking the CRF1 receptor have reduced spatial recognition memory but also lower anxiety, emphasizing a role for CRF in mounting an effective anxiety response [80]. The complexity of the action of CRF in anxiety proneness is highlighted by its action at the amygdala and bed nucleus of the stria terminalis for sustaining and the medial prefrontal cortex for modulating fear-related behaviors [81]. CRF also has a dynamic association with the timing

of the anxiety response. CRF increases quickly in response to a threatening stimulus in sheep amygdala exposed to predator stress. This first sudden rapid increase occurs independent of cortisol after stimulus presentation and a smaller and more prolonged increase paralleling a rise in cortisol, which may serve to sustain fear-related behaviors, ensues later [82]. Candidate molecules such as BDNF and CRF play a plausible role in mediating anxiety responses and active ongoing research should further open avenues to explore their specific contributions.

Integrative Approach to Pediatric Anxiety Disorders

The integration of current anxiety research into a framework for pediatric anxiety disorders requires the cogent understanding of multiple levels of inquiry. While it is understood that early innate anxiety-proneness together with life experiences crystallize into later overt expressions of clinical anxiety, the etiologic pathways are only preliminarily examined. Important advances at the physiological, neuroimaging and molecular levels have been made but an overarching framework for pediatric anxiety is yet to be formulated.

Even as the component parts of an emergent model are generally understood, how they fit into a developmentally informed framework is not clear. Abnormal orienting responses to perceived threats appear to be the earliest and most universal feature of an anxiety diathesis [43]. The effect of temperament on the control of children's attention can generate biases that influence the stages of social information processing such as the encoding and interpretation of social and emotional cues [57]. BI children interact with peers in non-effective ways further cementing distorted notions related to social learning, internalizing notions of causality of this experience in relation to self. Ambiguous situations are increasingly interpreted as negative or threatening [83]. As development advances, the threshold for perceived threat diminishes as life experience and contextual factors play an ever larger role. Throughout development, biological correlates present moving targets in relation to anxiety symptom expression. Neuroanatomical correlates of anxiety implicate the amygdala and related circuitry (hippocampus, parahippocampal regions, insula, medial prefrontal cortex, orbitofrontal cortex and anterior cingulate cortex) while molecular data support key pathways that implicate GABA, serotonin, glutamate, dopamine as well as BDNF and CRF bioactive molecules. Neurophysiologic studies are consistent in isolating aspects of memory and learning that are specific to anxiety such as orienting responses and threat appraisal.

Less recognized in anxiety research to date is the contribution that comorbid conditions may make to understanding anxiety mechanisms, especially in childhood. As an example, the concurrence of anxiety and impulsive/inattentive tendencies in children may reflect a common etiologic mechanism. Anxiety may impair the efficient functioning of goal-directed attentional systems thereby decreasing attentional control [84] and

it has been suggested that high-trait anxiety is inherently associated with a general inability to maintain attentional focus, rather than exhibiting automatic attentional bias towards threatening information [85]. The intrusion of threat-related material into cognitive domains may explain the relative cognitive inefficiency of anxious subjects [86]. This inefficiency may result from a specific deficit in cognitive inhibition or the inability to suppress irrelevant information from working memory [87]. It is of interest to note that in family studies of attention-deficit hyperactivity disorder, a behavioral disinhibition disorder, relatives have a clear excess of anxiety disorders in association with their own diagnosis of attention-deficit hyperactivity disorder (co-segregation) [88]. Thus, future research in pediatric anxiety disorders needs to consider the interplay of different streams of biological vulnerability factors to better understand which mechanisms may be shared and which may be unique.

In summary, current research in pediatric anxiety disorders is in an expectant position with potential breakthroughs expected in neuroimaging and molecular areas. Genetic research continues to pose great potential for uncovering more specific mechanisms. The understanding of the phenotype of anxiety, in relation to commonly occurring comorbid disorders, is the main challenge confronting a comprehensive understanding of the neurobiological basis of anxiety and related psychopathology.

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Obsessive-Compulsive Disorder in Childhood

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Abstract

Obsessive-compulsive disorder (OCD) is a common disorder affecting all age ranges. Studies have indicated that OCD is a heterogeneous disorder with many possible subgroups. It has a bimodal age at onset, which emphasizes the hypothesis that early-onset OCD patients represent a distinct subgroup. Some of the most relevant studies on the early-onset OCD subtype are presented. These studies have reported a male predominance, high comorbidity rates, and higher familial risk for OCD and tic disorders among first-degree family members. Similar to the treatment recommendations for adults, there are empirical data showing the efficacy of both serotonin reuptake inhibitors and cognitive behavior therapy in the treatment of children and adolescents with OCD. Future research is warranted and should integrate categorical and dimensional approaches in the search for a better understanding of the complex interaction between OCD phenotypes and genotypes.

Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder affecting all age groups, independent of country of origin, socioeconomic status or religion. It is characterized by the presence of obsessions and/or compulsions that are time-consuming and cause distress and/or interference. The World Health Organization (WHO) estimates OCD to be among the 10 leading causes of years lived with illness-related disability by the year 2020 [1].

It is important to emphasize that if untreated, the obsessive-compulsive symptoms (OCS) often persist until adulthood, and can have a major adverse impact on a person's level of academic achievement, social abilities and self-esteem.

Even though both the Diagnostic and Statistical Manual, IV ed (DSM-IV) and the International Classification of Diseases, 10th ed (ICD-10) regard OCD as a unitary disorder, results from a variety of studies have indicated that OCD is a heterogeneous

disorder, with many possible subgroups [2]. Moreover, consistent results, from epidemiology, clinical, genetic, neuroimaging and treatment response studies have indicated that both children and adolescents, as well as adults with an early onset of their OCS probably represent a specific subgroup within the OCD diversity. The main objective of this chapter is to present some of the most relevant studies about the early-onset OCD subtype.

Epidemiology

A number of epidemiological studies conducted in the 1980s and 1990s indicated that OCD is not a rare disorder.

Until the 1980s, descriptions of OCD in children and adolescents were rare and limited by the small sample sizes. It was only in 1989 that the National Institute of Mental Health published the first longitudinal study of OCD children and adolescents using specific diagnostic criteria. Some studies have reported prevalence rates ranging from 1.9 to 4.1% [3]. More recent studies have presented lower rates, around 1% for adults [4] and 0.25% in children aged 5–15 years [5].

Independent of the prevalence rates, epidemiological studies revealed that OCD has two peaks of incidence, with different sex distributions: one peak in childhood with a male predominance, and a second peak in the early adult years affecting a higher proportion of females [3]. Approximately one third to one half of OCD adults had their first symptoms before adolescence [4].

Clinical Phenotypes

Initial Descriptions of OCD

Descriptions of the obsessive-compulsive phenomena are not new. In fact, OCS have been identified since the 17th century. At that time, obsessions and compulsions were often described as symptoms of religious melancholy and sufferers were considered to be 'possessed' by outside forces. By the first half of the 19th century, OCD shifted from the religious to the scientific field of enquiry. In 1838, Esquirol first described a medical disorder quite similar to contemporary OCD and classified it as a 'monomania' (a kind of partial delusion) [6].

Janet (1903) proposed that obsessional patients possessed an abnormal personality (called 'psychastenia'), with features such as anxiety, excessive worrying, and doubting, and described the successful treatment of compulsions and rituals with techniques that are similar to the ones used currently in behavioral therapy [6]. Janet reported the case of a 5-year-old boy presenting with 'psychastenia' characterized by repetitive thoughts and 'mental tics'. This is considered to be the first description of OCD in childhood [6].

Currently, the most widely used diagnostic manuals are the DSM-IV and the ICD-10. For both of them, OCD diagnostic criteria for children and adolescents are the same as for adults, except for the fact that in children the term 'insight' does not apply.

According to the DSM-IV, an OCD diagnosis requires the presence of obsessions and/or compulsions that take at least 1 h/day, originate subjective distress (to the patient and/or his family) and cause functional impairment in one or more domains.

Obsessions can be defined as intrusive, non-wanted ideas, images, fears, thoughts or worries that are experienced as uncomfortable, unpleasant, distressing and/or anxiety provoking. Compulsions are repetitive behaviors or mental acts usually performed with the intention of ignoring, suppressing or neutralizing the anxiety or discomfort caused by the obsessions. Compulsions are typically performed a certain number of times or according to certain private rules that the individual is driven to complete, even though he/she might perceive them as excessive.

Early studies reported that the most common obsessions in pediatric samples were fear of contamination, fear to harm one's self and others, and urges related to a sense of exactness, symmetry and perfectionism. Common compulsions were excessive washing/cleaning, checking, counting, repeating and touching.

In 2001, Geller et al. [7] compared OCS across different age groups. Even though there were no differences in clinical severity between the three groups, some differences in the frequencies of OCS were found. For instance, children and adolescents presented higher rates of aggressive/harm obsessions, when compared to adults. On the other hand, children had a lower frequency of sexual obsessions. Religious obsessions were more common in adolescents than in the other two groups. Interestingly, hoarding compulsions were the only symptoms that were significantly more common in both children and adolescents. Also, another common symptom in childhood was the fear of losing one's parents and the need to perform corresponding rituals, like reassurance seeking. This type of ritual often requires the involvement of another person, who is frequently asked to answer the same question(s) over and over again. The frequent involvement of family members in the performance of the compulsions is characteristic of early-onset OCD and reflects the need for the clinician to include the family in the treatment interventions.

Although most of the OCD children have multiple obsessions and compulsions (like adult patients), the younger the patient, the higher the chance of having compulsions without obsessions. Depending on their cognitive developmental level, children might better describe obsessions or elaborate why they need to perform specific rituals.

It is common for the compulsions to precede the onset of obsessions. For instance, a study stratifying adult OCD patients according to the age at onset of their symptoms found that in the early-onset group compulsions started on average 2 years before the obsessions, whereas in the late-onset group obsessions and compulsions started at the same time. The early-onset group also presented higher frequencies of

repetition, hoarding, and 'tic-like' compulsions, as well as higher frequencies of sensory phenomena (SP) preceding their compulsions [8].

SP are defined as uncomfortable and/or disturbing sensations, perceptions, feelings or urges, either preceding or accompanying repetitive behaviors (such as compulsions or tics). OCD patients might feel driven to repeat the compulsions until they experience a sense of relief from these uncomfortable sensations. They can be divided into physical and mental SP. Some examples include sensations in the skin, 'just-right' perceptions, and feelings of incompleteness. The evaluation of the presence and severity of these SP is relevant because some studies have reported that early-onset and tic-related OCD subjects present higher frequencies of SP and some patients report that these SP might cause more distress than the compulsions.

Age at Onset

Despite all the relevant data supporting the idea that early-onset OCD is a distinct subgroup, there are still relevant questions that remain unanswered. For instance, there is no consensus about the best way to define age at onset. Some studies have considered age at onset as the earliest age when the patient or a family member first noticed the presence of an OCS. Others define it as the age when subjects displayed clinically significant distress or impairment associated with the OCS. Others yet consider age at onset as the age when the patient started to fulfill DSM-IV OCD criteria [8].

Another controversy in the literature relates to the ideal threshold for determining an 'early onset' of the OCS. Some authors have proposed cutoff points at the ages of 7, 10, 15, and 17 years [8].

A recent study assessing 330 OCD subjects reported that even though comorbidity differences started to emerge at the age of 10 and were more pronounced at the age of 17, more prominent differences were obtained when age at onset was analyzed as a continuous value [de Mathis et al., submitted].

The course of the OCS is also heterogeneous. Patients frequently report an insidious onset, with a chronic waxing and waning course. Specific OCS may change with time, even though symptoms often maintain a certain thematic consistency.

There is usually a time gap between the onset of the OCS and the time when the patient and/or the family seek medical or psychological assistance. Geller [3] documented a gap of 2.5 years between the age that the OCS first began to cause impairment and the age at diagnosis. A possible explanation for this time lag is the secretiveness of many patients concerning their OCS. Most patients conceal their symptoms until they become nearly incapacitating. Mild or moderate cases may only be diagnosed through indirect signs like an increase in time for completing any task, isolation, or severely chapped skin as the result of frequent washing compulsions.

Children and adolescents engage in a significant amount of ritualistic, repetitive, and compulsive-like activities, as part of their normal behavioral repertoire. For example, young children need to repeat certain behaviors until they feel 'just right',

and feel very uncomfortable when these routine behaviors are not performed the same way every time. During school age years, it is common for children to collect objects such as coins, pens or stamps. In adolescence, grooming rituals commonly take a long time. In adulthood, intrusive thoughts, ideas or images with aggressive content relating to close family members are not uncommon during the perinatal period. It is not clear, however, how these normal obsessive-compulsive behaviors relate to OCD.

There are no limits to the possible variety in OCS. Clinical phenotypes are heterogeneous and symptoms are normally different from patient to patient and also within the same patient over time.

Dimensional Approach

As described above, OCD is a heterogeneous disorder, and its complex phenotypes have variable clinical expressions across and within subjects. Even though the strategy of subtyping patients according to the age at onset has proven to be valuable, a dimensional approach may prove to be of even greater value.

Recent factor-analytic studies have reduced the OCS to a few fairly consistent and clinically meaningful symptom dimensions. In adult samples, many factor and cluster analytical studies, involving more than 2,000 patients, have consistently identified at least four OCS dimensions, often named: contamination/cleaning; obsessions/checking; symmetry/ordering, and hoarding. These studies have demonstrated that these dimensions are temporally stable, and correlate meaningfully with various genetic, neuroimaging and treatment response variables [for review, see 9].

So far, there have been few published factor-analytic studies in pediatric samples, and it is important to emphasize that despite a few differences in one of the studies, the results were extremely similar to those seen in the adult samples.

In a recent exploratory factor-analysis of OCS in children and adolescents, Delorme et al. [10] reported four symptom dimensions, similar to those described in adults, and most importantly, after a mean follow-up of 4 years, these symptom dimensions remained stable. These results emphasize the hypothesis of a phenotypic continuum of OCS from childhood to adulthood.

The first longitudinal twin study of OCS stability in children and adolescents was performed by van Grootheest et al. [11] in children from ages 7 to 12 years. They found that the obsessive-compulsive behavior in childhood was moderately stable. When categorical approaches were used, the symptom stability was lower than when quantitative and dimensional approaches were used. They also found that stability was influenced by genetic factors, by environmental factors shared by children growing up in the same family, and by non-shared environmental factors.

Comorbidity

Like adults, OCD children and adolescents also present high rates of comorbidity, frequently ranging from 60 to 80%.

Geller et al. [7] compared frequencies of psychiatric comorbidities in OCD children, adolescents and adults and found differences regarding comorbid psychopathology. The pediatric OCD showed higher rates of attention deficit/hyperactivity disorder (ADHD, 51%), oppositional defiant disorder (47%), and pervasive developmental disorders (5%). The comorbidity with ADHD was more common in boys (53%) than in girls (24%). These authors reported that non-OCD anxiety disorders were highly prevalent in all age groups but that separation anxiety disorder was more frequent in children (56%) and adolescents (35%) than in adults (17%). On the other hand, major depression rates were higher in adults (78%) and adolescents (62%) when compared to children (39%).

Other studies have also reported high rates of comorbid conditions, especially simple phobias, separation anxiety disorder, disruptive behavior disorders (ADHD and oppositional defiant disorder), mood disorders and tics.

Even though other disorders are also very frequent, the association with tics is the most striking. OCD children have reported rates of tics ranging from 20 to 59%, compared to 9 and 6% in adolescents and adults, respectively. Similarly, 48% of early-onset adult OCD patients presented tics and/or Tourette syndrome (TS), compared to just 10% of the ones with a late-onset [8]. The impact of this association has led authors to describe 'the tic-related OCD' subgroup. This subgroup has been characterized by a higher risk of transmission of both OCD, subclinical OCD and tics among first-degree relatives of OCD probands; higher male frequency; an earlier age at onset; and a differential treatment response.

Etiology of OCD

Genetics

Genetic family studies have shown that phenotype definition as well as age at onset appear to influence the familial recurrence risk of OCD. It is now believed that the earlier the onset of the OCS in the probands, the higher the morbid risk for first-degree family members to develop OCS, OCD, tics and/or TS [12].

Rosario-Campos et al. [12] evaluated the effects of early onset of OCS in 106 childhood probands and the risks of OCD and tics in their 325 first-degree relatives, compared to 44 controls and their 140 first-degree family members. Familial aggregation of OCD was largely concentrated among families of early-onset probands, with a very high morbid risk. In a recent study, the same group investigated the age at onset concordance for OCD in sib-pairs (40 siblings, 18 families), finding more siblings with early-onset OCS when compared to late onset, and the ages at symptom onset were positively correlated between the siblings. In 2005, Hanna et al. [13] performed the first segregation analyses on data from 35 early-onset OCD families, compared to 17 control families, including specific parameters for gender, age and diagnoses. They reported evidence for a major susceptibility locus when age at onset was included in the analyses.

Association and linkage studies have investigated many candidate genes and linkage regions with inconclusive results. Promising leads for early-onset OCD are the SLC1A1 gene and chromosome region 9p24 [2].

Neuroimaging

In the past decade neuroimaging studies have played an important role in advancing our understanding of the pathophysiology of OCD and in developing neurocircuitry models of this psychiatric illness. Structural and functional neuroimaging studies in both pediatric and adult OCD samples propose a dysregulation of fronto-cortical-striatal-thalamic circuits [14, 15].

Most morphological neuroimaging studies assessing OCD children and adolescents reported reduced striatum volumes, compared to controls [16]. Volumetric abnormalities in the frontal cortex and anterior cingulate gyrus described in pediatric OCD appear to be specific to the gray matter, while adult OCD appears to affect both the gray and the white matter [16]. These anatomic findings are consistent with functional neuroimaging studies that revealed anterior cingulate hypermetabolism [14, 15].

Functional neuroimaging studies suggest that the metabolic activity of the orbitalfrontal cortex, of the anterior portion of the cingulate gyrus, and of the caudate nucleus is abnormal in both adult and pediatric OCD patients [14, 15].

Neurochemistry

The evidence for the involvement of the serotonergic system in OCD pathogenesis was initially originated by the observed efficacy of selective serotonin reuptake inhibitors (SSRI) in alleviating OCS. Moreover, studies in humans showed that SSRI may 'normalize' the morphology and metabolism in cortical and striatal substrates [17]. However, it remains controversial if SSRI efficacy is due to its direct action in the serotoninergic system or indirect action in other neurochemical systems [18].

There is growing evidence that the dopamine system may also be involved in the pathogenesis of OCD [18]. Regarding the neuroanatomical perspective, OCD frequently occurs in comorbidity with TS, Parkinson disease, and Huntington chorea, in which dysfunctions in dopaminergic neurons play an important role. The effectiveness of dopamine receptor blockers in tic-related OCD patients also corroborates the dopaminergic hypothesis of OCD. Recent neuroimaging and genetic data support the involvement of the dopaminergic system in the OCD pathogenesis. Future research studies are warranted to explain how dopaminergic and serotonergic pathways interact and play a role in the genesis and maintenance of OCS [17, 18].

Investigation beyond the monoamine systems suggests that oxytocin might play an important role in OCS in the later age at onset group [19]. Evidence from preclinical studies suggests that neuropeptides may have important influences on: memory acquisition, maintenance and retrieval; grooming, maternal, afilliative, sexual and aggressive behavior; fixed action patterns, and stereotyped behavior. These phenomena may relate to some obsessive-compulsive features. In addition, extensive interactions have

been identified in the brain between neuropeptidergic and monoaminergic systems, including co-localization among specific populations of neurons [19]. Other neurochemical abnormalities regarding the cholinergic, noradrenergic and glutamatergic systems have been correlated to OCD with limited and inconsistent evidence.

Immunology

A recent field of interest in psychiatry has investigated the immune system and its influence on the central nervous system. Clinical observations and systematic investigations have shown that a subgroup of OCD and/or tic disorder patients are reported to have a post-infectious autoimmune-mediated etiology. This possible subgroup was designated by the acronym 'pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)' [20]. Five clinical characteristics define the PANDAS subgroup: (1) the presence of OCD and/or tic disorder; (2) a prepubertal symptom onset; (3) sudden onset or abrupt exacerbations; (4) an association with neurological abnormalities during exacerbations (adventitious movements or motoric hyperactivity), and (5) a temporal association between symptom exacerbations and antecedent streptococcal infections [20]. These psychiatric symptoms may arise when antibodies directed at attacking bacteria cross-react with basal ganglia structures activating some circuits that could trigger repetitive behaviors [20].

Treatment

Three of the biggest challenges in the treatment of OCD are: the correct identification of the most troublesome OCS; the delay for patients and families to seek help, and the difficulties in working with the families.

OCD is also known as the 'hidden epidemic' or the 'secret illness'. Therefore, it is particularly common for children and adolescents to be secretive of their symptoms and to go unrecognized. Other difficulties in the diagnostic process include: differences in the OCD course (insidious vs. acute onset), and the frequent waxing and waning course.

Therefore, before establishing a therapeutic program, thorough questions and examples should be part of a careful initial assessment, involving both the patient, family members and school. Standardized and valid assessment instruments should be used. Some options are: (1) the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), a reliable and valid clinician-rated instrument composed of a checklist of OCS and a severity scale [21], and (2) the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS), which assesses the presence and severity of six distinct OCS dimensions that combine thematically related obsessions and compulsions [22].

Another important issue is an accurate assessment of comorbid conditions that usually accompany OCD. Comorbid conditions, if not evaluated or detected, can complicate treatment goals.

Similar to the treatment recommendations for adults, the treatment of OCD children and adolescents relies on cognitive behavioral therapy (CBT), pharmacotherapeutic interventions, and psychoeducation for the patient and his/her family. Both SSRI and CBT have been systematically studied and empirically shown to be useful in the treatment of children and adolescents with OCD.

Cognitive Behavioral Therapy

CBT is the only psychological therapy recognized to be effective in the treatment of childhood OCD, even though there are less studies than in adults. Exposure and response prevention (ERP), a behavior technique largely used in CBT, has also been demonstrated to be effective in the treatment for childhood OCD. ERP efficacy in pediatric OCD has been shown in numerous open studies, and controlled trials.

It has been demonstrated that CBT plus ERP significantly decrease symptom severity as well as symptom-related distress and impairment, and also that the treatment gains are maintained over time.

A recent meta-analysis of the existing literature on childhood CBT revealed the effectiveness of CBT [23]. They also reported that for young children an early intervention model might be preferable to a treatment model, and that future research could address the treatment of sub-syndromal children. The application of CBT techniques for non-clinical OCD symptoms could be used as a model of prevention of the development of the full syndrome.

The success in CBT depends on a good understanding of the illness, as well as the basis of the therapy process. It is also part of the process to recognize and understand the cognitive processes implicated in the maintenance of the disorder. CBT involves gradually exposing the patient to anxiety-provoking stimuli while having the patient refrain from engaging in compulsive or avoidance behaviors. The goal is to make the patient habituate to anxiety. At the same time, the patient learns objective information that is incompatible with previous distortions perceived as dangerous.

During treatment, it is important to monitor all the process and outcomes using global measures of impairment and improvement. This may help the evaluation of the course and the need for additional sessions. The CY-BOCS [21] should be applied before and after treatment. Despite its potential benefits, the DY-BOCS [22] sensitivity to treatment has not been established in children and adolescents yet. In CBT for pediatric patients, the clinician acts as a 'coach' to teach the patient a set of more adaptive strategies for reducing OCS. CBT also works with specific targets throughout the treatment and the clinician should establish and identify with the patient which goals they want to accomplish. Rewards are especially important for children, more so than adolescents.

An important issue regarding treatment is the evaluation of all family members who live with the patient, and often the referral of the family to family-based interventions in order to enhance the patient's response to treatment.

Table 1. Pharmacological agents for pediatric obsessive-compulsive disorder (OCD)

Name of medication	FDA approval in childhood/ adolescence	FDA approval for OCD	Maximum recommended doses, mg/day
Clomipramine (Anafranil)	5 years	+	300
Fluoxetine (Prozac)	8 years	+	80
Sertraline (Zoloft)	6 years	+	200
Fluvoxamine (Luvox)	8 years	+	200
Paroxetine (Paxil)	18 years	−	60
Citalopram (Cipramil)	−	−	60
Escitalopram (Lexapro)	−	−	30

Pharmacological Treatment

The serotonin reuptake inhibitors are considered the first-line pharmacological options for the treatment of OCD [24].

Clomipramine, a serotoninergic tricyclic agent, was initially tested in children and adolescents in 1989 [25]. Since then, a number of double-blind placebo-controlled clinical trials have reported great efficacy. Despite its anti-obsessional properties, side effects, including gastrointestinal, autonomic, hepatic, and cardiac conduction problems, limit its clinical use, especially in children and adolescents.

Rigorously designed clinical trials have demonstrated the efficacy and safety of fluoxetine, sertraline and fluvoxamine (alone or combined with CBT) in children and adolescents with OCD [24]. Paroxetine and citalopram have also demonstrated efficacy in children and adolescents with OCD, even though the FDA has not yet approved its pediatric administration [24]. Table 1 presents the drugs commonly used for OCD in children and adolescents and the maximum recommended doses of psychiatric medications mentioned in this chapter. Figure 1 presents an algorithm for the treatment of childhood OCD.

Since as many as 50% of OCD patients treated with an adequate trial of SSRI fail to fully respond to treatment and continue to exhibit significant symptoms, many studies have assessed the effectiveness of antipsychotic augmentation in SSRI-refractory OCD [17]. Haloperidol was the first antipsychotic agent studied in OCD and found to have documented efficacy in the treatment of tic-related OCD patients, tic disorders and other obsessive-compulsive spectrum disorders, such as trichotillomania [17]. However, the potential cognitive, metabolic and cardiologic and extrapyramidal side effects have limited its use in comparison with the second-generation antipsychotics.

Risperidone, a second-generation agent, has the strongest evidence base to support its use as an augmenting agent. Less compelling data also support the use of

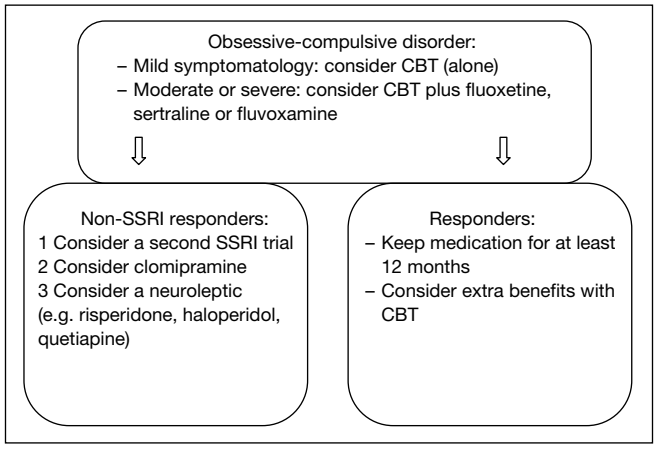

Fig. 1. Algorithm for obsessive-compulsive disorder treatment in children and adolescents. CBT = Cognitive behavior therapy; SSRI = selective serotonin reuptake inhibitors.

quetiapine and aripiprazole [17] when combined with SSRI to manage partial responders. Ziprasidone, as other atypical agents, has been associated with electrocardiogram abnormalities in children and adolescents. Olanzapine should be avoided in children due to weight gain and other metabolic side effects [17].

Another strategy to treat SSRI-refractory OCD is the combination with clomipramine. Due to P450 cytochrome metabolism interaction it is recommended that the serum levels of clomipramine should be closely monitored.

Studies with adult patients have suggested that an early age at onset may be a predictor of poor response to treatment with clomipramine or fluoxetine [26]. A study assessing age at onset of obsessive-compulsive symptoms in adult patients showed that only 31% of the early-onset patients responded to psychopharmacological treatment, compared to 81% of the late-onset ones [8]. However, the effect of age at onset on treatment response to SSRI in still a controversial issue. These inconsistencies may be partially explained by the different thresholds for considering age at onset and follow-up duration. Early age at onset seems not to influence the treatment response in studies with a longer follow-up, and may act only as a predictor of worse response to short-term treatment.

Finally, a recent meta-analysis demonstrated that antidepressant use in pediatric patients is associated with a modestly increased risk of suicidability [27]. Although this statement is more applicable to depressive disorders, every management of children and adolescents with SSRI and other psychoactive agents requires close supervision. Another recent meta-analysis concluded that relative to placebo, antidepressants were efficacious for OCD, other anxiety disorders, and depression. They also concluded that the benefits of the antidepressants were much greater than the risks from suicidal ideation and/or suicide attempts [28].

Conclusions

The last decades have provided consistent evidence that OCD is a heterogeneous disorder and that early-onset patients may represent a distinct subgroup with specific clinical and etiological characteristics.

Factor analytic studies have shown that a dimensional approach may bring interesting advances to OCD research and have demonstrated that obsessive-compulsive symptom dimensions in childhood are similar to the those presented in adults. This temporal stability emphasizes the hypothesis that these obsessive-compulsive symptom dimensions are fairly consistent, and might be more useful in clinical, genetic and treatment response studies more than traditional approaches.

Future research should focus on the search for the distinct clinical, genetic and neural substrates of the early-onset OCD subgroup. The integration of categorical and dimensional approaches is likely to offer a better understanding of the complex interaction between OCD phenotypes and genotypes. This understanding will lead to the development of more efficient treatment strategies to help patients and their families.

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Neurobiological Background of Tic Disorders

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Abstract

Although over the last decades research on chronic tic disorders including Tourette's syndrome has progressed the understanding of their etiology and pathophysiology, no clear picture can be drawn. The present review provides a comprehensive overview based on the evidence from family, genetic, neurochemical, neuroimmunological, neurophysiological and imaging findings indicating the pathogenic complexity of this disorder in which neuronal disturbances in the striatum may play the essential role. Beyond that, the review highlights existing points of indistinctness and suggests further pathways of research in this field.

Tic disorders including Tourette's syndrome (TS) are neurodevelopmental disorders characterized by childhood onset and the presence of tics – sudden, rapid, repetitive, non-rhythmic movements or vocalizations. While simple tics (e.g. eye blinking) involve only a single muscle or a group of muscles causing a brief, jerking movement, complex tics (e.g. jumping) are usually longer, more goal-directed in character and more muscle groups are involved. Complex motor tics commonly occur together with simple motor tics and are rarely seen in isolation. Tics are often misplaced in context, can be easily mimicked and at times confused with goal-directed behavior. They can be classified by their duration, anatomic location, severity (number, frequency, intensity, impairment) and complexity.

Whereas transient tics are present over a period of 4 weeks to 1 year, a diagnosis of chronic tic disorder (CTD) is made when either motor or phonic tics, but not both, have persisted continuously or intermittently for more than a year. The combination of chronic motor and vocal tics is called TS. Tics arise in bouts over the course of a day and wax and wane in phenomenology, localization and severity. Knowledge of the temporal patterning of tics is important because the spontaneous changes in tic severity confound, e.g. medication effects. Stated simply, if a clinician begins or

changes a treatment at the end of a waxing period, the patient's condition will improve regardless of the efficacy of the intervention. But not only in the dimension of months but also over years there are changes in tic severity. Motor tics usually begin between the ages of 3 and 8 years, with transient periods of intense eye blinking or some other facial tic. Phonic tics, such as repetitive bouts of sniffing or throat clearing, typically follow the onset of motor tics by 2–3 years. In most cases the severity of motor and phonic tics peaks early in the second decade of life, with many patients showing a striking reduction in tic severity thereafter. Only 20% or fewer of children with TS continue to experience a moderate level of impairment of global functioning by the age of 20 years [1].

Although tics are usually multifocal and can migrate from one anatomic region to another, they most commonly start in the face and broaden towards more distal regions. The most common presentation is facial twitching (50–70% of patients).

The intensity of the tics is also quite different, i.e. some tics are not recognized by others and some tics call attention to themselves simply by virtue of the exaggerated fashion in which they are performed or uttered. Additionally, the most severe cases of tics involve forceful bouts of self-injurious motor tics, such as hitting or biting, and socially unacceptable obscene vocalizations and gestures.

With increasing age more and more patients wit CTD report associated sensorimotor phenomena, including premonitory urges that incessantly prompt tics and feelings of momentary relief that follow performance of a tic [2]. These urges, and the internal struggle to control them, can be as debilitating as the tics themselves. A large range of auditory or visual cues can also prompt tics, but the nature of these cues is usually highly selective for individual patients – a cough, a particular word, an alignment of angles or specific shapes.

In most patients several factors such as stress, emotional excitement, anxiety and fatigue aggravate their tics, whereas activities requiring focused attention (e.g. playing a musical instrument, sports) are commonly associated with a reduction of tics. Polysomnographic studies revealed much lower frequency and severity of tics during sleep as well as a decreased quality of sleep and increased arousal phenomena [3]. The latter may increase daily stress leading again to more pronounced tics and so on, which might result in a vicious circle [4].

Whereas in TS, and especially in clinical samples of TS, up to 85% of the patients suffer from co-occurring psychiatric conditions [5], this rate is lower in patients with simple and transient tics [6]. In clinical samples of CTD about half of the cases also meet criteria for attention deficit/hyperactive disorder (ADHD), and vice versa CTD are seen in about 20% of children with ADHD [7]. In most cases this co-occurrence of CTD and ADHD is associated with more psychopathological, social and academic impairment in an additive manner of CTD plus ADHD [8–10]. Besides ADHD patients with CTD frequently also suffer from obsessive-compulsive symptoms or disorders (about 50%). Especially the need to achieve a 'just right' feeling in CTD has to be seen as an indicator for a continuum between CTD and OCD [11].

Still more clarity is needed if the co-occurrence of depression and anxiety symptoms with TS is the consequence of the psychosocial burden of having tics and/or represents a shared biological diathesis [12].

Epidemiology

Up to the 1990s tics and particularly CTD and TS have been seen as rare phenomena. However, based on the analysis of different community surveys within the last 15 years tics can be observed in about 10% of elementary school children and about 4–18% of adolescents. The variability depends on the sample and the procedure chosen. Accordingly recent studies report prevalence rates of up to 3–4% for CTD and 1% (range 0.05–3%) for TS. This might be caused by combining community-based surveys with more comprehensive ascertainment techniques as well as a more widespread definition of CTD by including also individuals with non-disabling tics [13–19].

In children and adolescents the reported frequency is clearly higher compared to adults because early adolescence is the time of remission of tics as well as CTD-associated impairment [20]. The rate for spontaneous remission (seen over years) is about 50–70% for CTD and between 3 and 40% for TS. Follow-up studies of TS suggest that approximately one third of children with TS will be essentially symptom free as adults and another one third will have only mild symptom severity that does not require clinical attention. Adults who still have symptoms severe enough to be referred (remember, there is an underreporting and low awareness even for severe tics in adults!) for clinical treatment are therefore unusual representative of all subjects who have a lifetime diagnosis of TS. But it has to be considered that there is a disparity between subjectively reported and objectively rated tics. In a follow-up video analysis 90% of patients still had tics in adulthood [21]. However the male preponderance of 3–4:1 remained stable over lifespan.

Genetics

To date there is a consensus that CTD has a strong heritable component as indicated by a high percentage of patients with affected first-degree relatives [22–26]. The morbid risk of TS among relatives ranges between 10 and 15% and of CTD between 15 and 20% [27–30]; these rates are significantly elevated compared to that of CTD and TS in controls. In sum, these data suggest that family members share either genetic or environmental risk factors contributing to CTD. The existence of a strong genetic component is particularly supported by twin studies. Monozygotic twins display about 50–70% concordance for TS and approximately 77% for CTD, whereas dizygotic twins show solely 9% concordance for TS and 23% concordance for CTD [31, 32].

However one should bear in mind that the twin data also point to an important role of environmental factors in contributing to CTD and TD risk as even the monozygotic twins are far from 100% concordance.

Segregation studies of TS led to widely varying results, suggesting different inheritance modes. Once indicated to be inherited as a single major autosomal dominant condition with incomplete penetrance, both those excluding relatives with CTD and obsessive-compulsive disorder and those including them [30, 33–36], more recent studies point to a complex model, with TS being transmitted via additive inheritance with a significant multifactorial background [37–40].

Because genetics in CTD are complex with the available evidence favoring polygenic inheritance and linkage data pointing to several loci, it is not surprising that chromosomal rearrangement studies have not been successful. Several studies have examined possible relationships between TS and chromosomal rearrangements on 7q, 8q, 18q, and 13q [41].

Recently 39 GTS patients have been screened for the disruption of the inner mitochondrial membrane peptidase 2-like (IMMP2L) gene by a chromosomal breakpoint [42], but no deleterious mutations in IMMPL2 (other than the inverted duplication identified previously) could be identified [42].

Also during routine prenatal studies of one child who later developed TS, an apparently balanced chromosome 13 inversion SLITRK1 was found [43]. Sequencing of SLITRK1 in 174 unrelated subjects with TS identified two sequence variations (var321 in two patients and varCDfs in one patient) but no mutations were found at this locus in 3,600 control chromosomes [43]. Both mutations are thought to cause haploinsufficiency. The SLITRK1 protein is expressed widely in developing and postnatal brain, and is associated with axonal-dendritic development in embryonic mouse cells. However, in another study of Caucasian patients with TS none of 82 patients showed the non-coding sequence variant (var321) [44].

Previous candidate gene studies revealed negative or equivocal results for an association between CTD and, e.g. DRD1, DRD2, DRD3, DRD4, DRD5, dopamine transporter, serotonin transporter, glycine receptor, 5q33-q35 neuroreceptors, adrenergic receptors, methyl-CpG binding protein 2, and human leukocyte antigen [23]. This trend continues as indicated by the findings that polymorphisms detected for both serotonin receptor subunit genes, HTR3A and HTR3B, are probably non-TS-related [45]. But recent examination of the genotype proportions of Taq I DRD2 and DRD2 (H313H) polymorphisms demonstrated an association between the dopamine receptor D2 gene and TS. Hence the authors concluded that their data suggest that the dopamine receptor D2 gene or a closely linked gene might be still one of the susceptibility factors for TS [46].

Several genome-wide linkage studies for TS have been reported [28, 35, 47–50] but none have found strong evidence for linkage except the largest genetic linkage study undertaken to date for TS. A whole-genome screen of 238 nuclear families yielding 304 'independent' sibling pairs and 18 separate multigenerational families, for a total

of 2,040 individuals with the use of 390 microsatellite markers gave nonparametric logarithm of odds scores nearing 4 of linkage to marker D2S144 on chromosome 2p32.2, which is considered significant on a genome-wide level. Other chromosomal regions, including 3p, 3q, and 14q, had a nonparametric logarithm of odds scores of >2.5 in the sib-pair sample but not in the multigenerational pedigrees. These results are consistent with a complex inheritance model that includes locus heterogeneity and a gene of major effect on 2p32.2 [51]. In a large Dutch TS pedigree linkage analysis resulted in three linkage peaks on different chromosomes, 3q, 9q, and 13q. Multipoint analysis resulted in a single linkage peak with a logarithm of odds score of 2.55 with marker D3S1311 on chromosome 3q [52].

In conclusion, several types of genetic studies have demonstrated that TS is a genetically complex disorder of likely multiple genes interacting with each other as well as with environmental components. To further progress this field differentiating TS phenotyping could be a promising approach. Using a large, multiple affected pedigree containing 35 subjects diagnosed with TS and a further 14 with CMT, Robertson and Cavanna [53] identified three significant factors accounting for approximately 42% of the symptomatic variance suggesting that there are more than one TS phenotypes and it is not a unitary condition: factor 1 (predominantly pure tics), factor 2 (predominantly attention deficit hyperactivity disorder and aggressive behaviors) and factor 3 (predominantly depression-anxiety-obsessional symptoms and self-injurious behaviors). They suggest that association-based studies should be carried out on these three factors to produce further evidence for localization and to carry out fine mapping.

In sum, this vast amount of data does not really clarify the issue of genetics in CTD/TS and it indicates the need for further studies using many different techniques to explore other genetic and epigenetic mechanisms at work that could mimic the expression patterns seen in CTD/TS.

Neurochemistry

Findings from clinical medication studies, mainly using dopaminergic antagonists, selective serotonin reuptake inhibitors (SSRIs) and the noradrenergic clonidine, from PET/SPECT imaging studies as well as from blood, urine, cerebrospinal fluid and postmortem brain tissue analyses of relatively small samples led to the common hypotheses on neurochemical deviances in TS. Although there is the strongest evidence for deviances in the dopaminergic system, there are also hints for imbalances in serotoninergic, noradrenergic, glutamatergic, GABAergic, cholinergic, and opioid metabolism in TS [54, 55].

Studies have shown an increased number of striatal [56] and cortical [57, 58] dopamine receptors, but equivocal data on binding to dopamine transporters in the basal ganglia [59–63] and release of dopamine following stimulant application [64, 65].

Nevertheless, Singer et al. [65] proposed a neurochemical background of CTD involving deviances of the tonic-phasic release of dopamine. So far the details of the model are problematic as similar mechanisms are proposed for ADHD as well [66]. It might be helpful to include D2 receptors in order to model different/common neurochemical pathways of TS vs. ADHD, e.g. in TS, D2 receptor availability measured by PET was significantly lower in the orbitofrontal cortex, primary motor cortex, anterior cingulate gyrus, mediodorsal nucleus of thalamus, and hippocampus, areas important for motivation and reward, sensory gating, movement, and attention. Altered dopaminergic function in mesolimbocortical systems and thalamus may contribute to increased motivational salience of tics [67].

Recent studies support some sort of a phasic dopamine hypothesis in CTD/TS. (1) The mechanisms of action of the new antipsychotic drug, aripiprazol, are explained by its partial agonism at D2 receptors in general behavior [68, 69] as well as in TS [70]. Furthermore, improvement of tics with very low doses of dopamine agonists, such as pergolide [71], likely leading to a presynaptic reduction in phasic dopamine release, takes the same line. (2) Factors associated with increased phasic bursts of dopamine, e.g. stress and anxiety, may lead to an increase of tics [72]. (3) Dopamine release from the axon terminal by stimulant medications may lead to the exacerbation of tics in a small minority of patients [73, 74]. However, there are also results not supporting a dopaminergic deviance in TS, e.g. postmortem brain studies have not found differences in a range of presynaptic dopaminergic markers [75, 76], and a large study did not find altered levels of the principal dopamine metabolite, homovanillic acid, in the cerebrospinal fluid of subjects with TS [77]. However, also previous studies such as that of Yeh et al. [62] found no significant differences in dopamine transporter activity between patients with TS and control subjects in the striatum and its sub-regions.

Besides dopamine the role of the serotonergic system in TS should not be underestimated: SSRIs commonly also have a beneficial impact on tics especially in the case of co-occurring obsessive-compulsive symptoms [11]. However, they might occasionally precipitate or exacerbate tics at higher dosages [78]. Decreased levels of serotonin and tryptophan have been found in serum [79], and decreased levels of the serotonin metabolite 5-hydroxyindoleacetic acid have been found in cerebrospinal fluid [80] and basal ganglia [81]. On the other hand, normal 5-hydroxyindoleacetic acid levels have been reported in the cortex [82] as well as normal platelet 5HTPR capacity [83] The negative correlation between vocal tics and [^{123}I]β-CIT binding to the serotonin transporter in the midbrain thalamus [84] was congruent with a SPECT study showing reduced serotonin transporter-binding capacity in patients with TS, but the findings appeared to be associated with the presence of obsessive-compulsive disorder [85]. Increased 5-HT2A receptor binding was found not only in regions closely related to subcortical regions in patients with TS (independent of the subclinical obsessive-compulsive or anxiety symptoms present in a minority of them), but also in most other brain regions [86].

In addition to the dopaminergic and serotoninergic neurotransmitter systems, limited additional neurochemical data are also available which suggest alterations in other neurotransmitter systems, including the noradrenergic [77], the glutamatergic [76], the GABAergic [87] system, the central cannabinoid receptor system [88] and endogenous opioid peptides [89].

Despite of the increasing consensus that dopaminergic dysfunction is mainly associated with TS compared to other neurotransmitter systems, one should bear in mind that focusing on one neurotransmitter deviation takes a too narrow view because there are many relationships, e.g. between the dopaminergic and serotonergic system [90]. Hence, a more comprehensive look at the different systems should be undertaken.

Neuroimmunology

The old speculations concerning a post-infectious etiology for TS and/or OCD have recently become an intense and controversial area of research [91, 92].

It is known that in genetically predisposed individuals rheumatic fever could occur after an upper respiratory tract infection with group A β-hemolytic streptococci (GABHS). These immune-mediated inflammatory reactions could affect not only the joints and heart but also the central nervous system. Hence, it has been argued that a subset of children with TS and/or OCD have an abrupt exacerbation of symptoms in close timely relationship to a GABHS infection [93, 94]. Swedo et al. [93] even suggested that these cases of pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) represent a distinct clinical entity. In PANDAS it is postulated that antibodies against GABHS cross-react with neuronal tissue in specific brain regions and result in tics and/or obsessive-compulsive symptoms [95]. Besides GABHS also other infectious processes in TS etiology including Lyme disease [96] and *Mycoplasma pneumoniae* infection [97, 98] have been reported to be associated with immunological reactions underlying TS.

The PANDAS hypothesis in TS is supported by the description of additional cohorts [99], familial studies showing that first-degree relatives of children with PANDAS have higher rates of TS and OCD than do those of the general population [100], and expanded expression of a trait marker for susceptibility in rheumatic fever (the monoclonal antibody D8/17) in individuals with PANDAS [101]. Recently Mell et al. [102] strongly supported the PANDAS hypothesis in TS by reporting that patients with OCD and/or tics were more likely than matched controls to have had streptococcal infection in the 3 months before the date of onset. Having multiple infections with GABHS during 1 year was associated with an increased risk of TS with an odds ratio of 13.6 (95% confidence interval 1.93–51.0). Whereas preliminary reports about immunomodulatory therapies alleviating tics in PANDAS support this hypothesis [103], the data concerning antibiotic prophylaxis have not been particularly compelling [104, 105].

To date the debate about the existence of PANDAS in TS continues [94, 106], e.g. two prospective longitudinal studies showed no clear relation between GABHS infections and the development or exacerbation of tic or OCD symptoms [107, 108].

Accordingly, the hypotheses and data about the exact immunological mechanisms involved in TS remain unclear. Several groups have reported increased titers of antistreptococcal antibodies [109–112], whereas others have not [107, 113]. Accordingly, several groups found antineural antibodies in the serum of TS and OCD patients [112–115] whereas others did not [116]. Recently, it was shown that status of antineuronal antibodies does not differentiate a specific phenotype of TS [117].

In research on immunological mechanisms in TS, recently elevated proinflammatory cytokines (tumor necrosis factor-α and interleukin-12) in TS patients compared with controls at baseline and during symptom exacerbation have been found [118] and preliminary data indicate decreased numbers of regulatory T cells [119].

In sum, additional prospective longitudinal studies are needed to examine the relationships between an array of immune modulators and T cell mechanisms as well as to strictly control for potentially confounders of the phenotypic variability commonly associated with TS, such as a normal fluctuation in the frequency and severity of symptoms, exacerbation of tics by stress, fatigue, and illness, occurrence of 'sudden, abrupt' onset and recurrence of tics in patients without PANDAS [120].

Neurophysiology

Although a variety of earlier electrophysiological studies using electroencephalographic methods revealed normal findings in TS [121–123], more recent studies on event-related brain potentials (ERPs) measured in TS subjects during different paradigms have found altered inhibitory neuronal processes and difficulties in sustaining attention [124–128]. Using two response-locked ERPs, Bereitschaftspotential and motor potential, investigators have suggested an abnormal modulation of circuits involving motor excitation or inhibition [129].

The absence of Bereitschaftspotentials (negative electrical potentials that normally precede the performance of routine volitional motor activities) before spontaneous simple tics and the presence of tics during all sleep stages suggested that these movements were involuntary and not generated from typical motor pathways [130–133]. However, the finding that even some tics but not all voluntary movements are preceded by these potentials, make the interpretation of Bereitschaftspotential results in TS more difficult [131, 134]. Recently identified sensorimotor-frontal connections shown by increased EEG coherence in the α-frequency band (8–12 Hz) range during suppression of voluntary movements in individuals with TS compared with healthy subjects during a Go-Nogo task [135] as well as earlier Bereitschaftspotential studies [132] suggest that patients with TS may develop frontal premotor compensatory mechanisms to control for their tics. This is in congruence with brain imaging

findings [136] and the fact that the frontally increased Bereitschaftspotentials normalize after successful treatment of the tics with neuroleptics [137].

Case-control studies using transcranial magnetic stimulation to investigate cortical excitability in patients with TS by assessing short interval intracortical inhibition (SICI) and the cortical silent period (CSP) have yielded the following results [138]. In adults with TS reduced SICI and shortened CSP were found [139], whereas in children with TS a shortened CSP but no difference in SICI has been revealed [140]. Studies in children with tics or ADHD found that the CSP was shorter in children with tic disorders and SICI was reduced in children with ADHD [138, 141]. However, it remains unclear whether these abnormalities [142] reflect specific developmental processes and/or compensatory mechanisms in TS [143–145]. In addition to these deficits in the motor system, deficits in inhibitory sensorimotor gating as indicated by prepulse inhibition abnormalities in TS [146, 147] are consistent with the idea that there is some diminished ability to appropriately gate sensory inputs [2] to motor programs, which might be released as tics [148]. This is supported by the fact that voluntary motor drive in CTD/TS seems to be normal but its guided inhibition is reduced [149]. Furthermore, impairment of various attention-related behaviors in TS has been reported, e.g. impairment of visual modalities [124], of visual attention on tactile performance [150] and of performance on a vibrotactile choice reaction time task [151].

Polysomnographical studies in patients with TS have shown markedly altered sleep quality and difficulties with initiating and maintaining sleep [3, 152, 153]. Based on a positive correlation between variables of sleep disturbance and the severity of TS, some investigators have suggested an impact of hyperarousal on TS [4].

More indirect neurophysiological information about TS comes from deep brain stimulation (DBS) as an alternative to neurosurgical procedures, e.g. the most promising being bilateral anterior capsulotomy [154] in extremely severe and not otherwise treatable TS. Bilateral thalamic stimulation with promising results on tics and associated behavioral disorders [155–157] as the main target and posteroventral globus pallidus internus [155, 156] and anterior limb of the internal capsule [158] as alternative targets of successful DBS have been reported. The success of DBS fits well with the hypothesis that TS is the result of aberrant neural oscillations [159].

Future studies combining imaging techniques with real-time neurophysiological techniques (e.g. with EEG and magnetoencephalography) would help to disentangle the impact of CTD/TS and compensatory mechanisms on the group differences found [160].

Functional Neuroimaging

In general in TS there are fewer functional imaging studies compared to other neuropsychiatric disorders, also even to those with an increased risk of motion artifacts during image acquisition such as ADHD [161]. Interestingly, despite of this concise

amount of data, no review to date has reported on all existing functional MRI (fMRI) studies in TS (actually n = 8).

Before the first fMRI studies were published, several studies used FDG-PET to study adults with TS during rest. However, it must be noted that although patients were not explicitly instructed to suppress their tics, they were asked to rest still during imaging and thus tics were rarely observed. Hence the identified small-amplitude metabolic reductions in the midbrain, ventral striatum, and orbitofrontal and insular cortical regions [162] might be attributable more to tic suppression than behavioral rest. A subsequent second analysis of the data revealed a correlation of orbitofrontal cortical metabolism changes with non-motoric behavioral features, such as impaired impulse control, attentional dysfunction, and obsessive-compulsive behavior [163]. This suggests that these TS-associated symptoms might be related to deviances in orbitofrontal regions whereas tics as the core symptom of TS might be associated with deviances in the midbrain, ventral striatal and insular regions. Using FDG-PET with a more sophisticated statistical analysis revealed reduced activity in the midbrain, striatum, thalamus, and both lateral and mesial temporal cortices indicating a TS-specific network [164] likewise found in a similar study using correlation analyses of metabolic interrelationships [165].

As mentioned above, tic occurrence and suppression during the imaging procedure might have confounded the results. Hence, Stern et al. [166] used $[^{15}O]H_2O$ PET measures of cerebral blood flow corrected for spontaneous tic frequency by a weighted score for each scan, reflecting the contribution of radiotracer deposition during tics to the image. Increases in activity correlated with tic performance in several cortical and subcortical structures associated with the planning and execution of movement, including the prefrontal and premotor frontal cortices, primary motor cortex, and striatum. Activations were also observed in the temporal neocortex, cingulate cortex, and insula. Accordingly, Lerner et al. [167] also used $[^{15}O]H_2O$ PET but sleep stage 2 as baseline instead of rest to identify brain regions generating tics in patients with TS. Congruent with their a priori hypothesis based on evidence in the literature that regional brain metabolism does not differ much between wake and sleep stage 2, a random effect analysis of the contrast (rest minus sleep) showed no significant activity in the controls. However, in patients with TS random effect analysis of the tic state (contrast: tics minus sleep) showed activation of the bilateral cerebellar hemispheres, posterior parts, crus I and II, and lobule VII B, as well as both putamen and thalami, right anterior cingulate, and left insula, claustrum, and globus pallidus.

In a fMRI study Peterson et al. [145] used the same design of contrasting conditions of free spontaneous expression of tics with periods of voluntary tic suppression. Differences in the blood oxygenation level-dependent (BOLD) signal were observed in the basal ganglia, thalamus, and cingulate, prefrontal, temporal, and parietal cerebral cortices, but speculation remains regarding whether single regions are involved in tic generation and expression or they reflect attentional and other mechanisms required for tic suppression. Interestingly, the severity of motor tics was inversely correlated with

the intensity of the BOLD signal change in the basal ganglia and thalamus, suggesting that these components might be most closely related to the generation of tics, as also suggested by the oscillation model of Leckman et al. [159] and Sukhodolsky et al. [168].

Although imaging acquisition requires rest for good quality, in the few other studies using fMRI in TS there is either no statement whatsoever or only insufficient control for possible confounding effects of possible tic suppression. The same could be stated for problems with the confounding effects of medication, comorbidity and automated long-term compensatory neuronal mechanisms probably present in adults still suffering from TS.

Biswal et al. [169] reported a preliminary fMRI investigation (5 adult patients with TS versus 5 healthy control subject) of finger tapping in TS. They reported higher and less focused activation in the TS group in the expected regions, i.e. the primary and supplementary motor cortices. This suggests an underlying alteration in the control or regulation of cerebral cortical function in TS, at least with regard to its role in volitional movement.

While moving a hand-held object with rhythmical single-handed or bimanual (iso-directional/anti-directional) movements, patients with TS showed deviant grip-load force control and no (or greatly reduced) activation of secondary motor areas [170]. The latter may be explained by continuous neuronal activation (even in the baseline condition) due to the involuntary sensorimotor urges to move combined with reduced neuronal inhibition seen in patients with TS.

Fattapposta et al. [171] non-statistically compared a 24-year-old man with childhood onset of tics and stuttering with an age-matched control subject. Whereas in the healthy control subject the expected differences in activation between usual and unusual self-paced voluntary movements were found, in the patient with TS there were no differences. The increased supplementary motor area (SMA) activity during both kinds of movement in the patient with TS may be related to constrained preprogramming activity modulated by the SMA. Furthermore, the authors suggested that the increased SMA activation in TS patients may reflect the use of more cerebral cortex to perform a voluntary motor task as a result of the additional mental effort required to suppress tic activity.

Similarily, Gates et al. [172] investigated a 15-year-old boy diagnosed with TS and oppositional defiant disorder suffering from a prominent phonic tic consisting of coprolalic utterance. An age-matched healthy boy mimicked the phonic tic during fMRI. Whereas both showed activity in the right precentral gyrus and the posterior region of the left middle frontal gyrus, in the control subject (in contrast to the patient) no activity was observed in the caudate nucleus, cingulate gyrus, cuneus, left angular gyrus, left inferior parietal gyrus, and occipital gyri. These differences support the existence of a broader network for tic generation even in vocal tics [145, 166].

To determine the neural correlates of tics and that of premonitory urges, event-related fMRI was used in 10 adult patients with TS. A brain network of paralimbic areas such as the anterior cingulate and insular cortex, SMA and parietal operculum

was found to be predominantly activated 2 s before tic onset. At the beginning of tic action significant fMRI activities were found in cortical sensorimotor areas as well as the superior parietal lobule bilaterally and the cerebellum. The authors concluded that their results indicate that paralimbic and sensory association areas are critically implicated in urges before tic performance, similar to movements (e.g. sneezing) triggered internally by unpleasant sensations, as has been shown for pain or itching [173].

In view of the dopaminergic abnormalities in TS Hershey et al. [174] performed a working memory task in 6 adult subjects with TS and 2 with chronic motor tic disorder (4 suffered additionally from ADHD and 2 from OCD) compared to 10 healthy controls before and after infusion of the dopamine prodrug levodopa (while blocking dopamine production outside the brain). There were no performance differences between both groups before and after levodopa infusion. But in the patients the excessive brain activity induced by the working memory task in the medial frontal, left parietal cortex and left thalamus normalized after the infusion of levodopa.

In another work including the same groups but using a Go-Nogo task neither performance nor activation differences were found [175].

Just recently, a large sample of patients with TS (n = 66) and healthy controls (n = 70) with a broad age range (7–58 years) were investigated with fMRI during Stroop performance. In patients with TS less deactivation with advancing age indicated disturbed activity in the frontostriatal circuits that subserve self-regulatory control. These disturbances might contribute to the development, persistence and severity of tic symptoms only if compensatory neural responses are not given [176].

In summary, functional studies in TS suggested a tic-generating network, regions active during tic suppression and a less focused activation during voluntary movements. Moreover, functional studies in TS identified deviances in the midbrain, striatum and associated limbic and frontal cerebral cortical regions. Although, the distinctions to healthy controls are subtle in terms of 'pure' CTD/TS, their consistent identification with a multiplicity of experimental approaches strongly suggests that dysfunction in these regions or in the regulation of activity within this interconnected neural network is characteristic of CTD/TS. However, the pieces of the puzzle found still stand quite alone and further studies are required to see the complete picture (for details see Future Directions, below). Additionally, the unresolved confounding of tic execution as well as the more or less voluntary tic suppression during image acquisition needs further elaboration. In this context, longitudinal studies would be of great value to disentangle the short- and long-term influences of the compensatory mechanisms of tic suppression.

Morphometric Imaging

Initial studies on basal ganglia volumes in TS revealed a volume reduction in the left lenticular nuclei (significant only with one-tailed statistical testing) in adults but not in

children. Contrarily, a reduction or even reversion of the normal (left > right) asymmetry of lenticular and total basal ganglia volumes in TS was found in both age groups [177, 178]. Subsequent studies failed to replicate the observation of reduced lenticular volume [179, 180] or asymmetry probably due to gender differences in normal control lenticular and striatal asymmetry [180]. The asymmetry of globus pallidus volume, particularly smaller on the left side, seems to be associated with ADHD and not TS per se [178, 181, 182]. In a study restricted to MRI of monozygotic twins with TS, the reduction in right caudate and left frontal horn ventricular volume found in the more symptomatic twin suggests an epigenetic effect of the individual TS course or of medications [183]. The largest volumetric study including 155 adults and children with TS and 131 control subjects revealed a volume reduction in the putamen and a more pronounced reduction in the caudate of children with TS; the globus pallidus was slightly larger [184]. In adults with TS the lenticular nuclei as well as all basal ganglia subregions including the caudate, putamen, and globus pallidus showed reduced volumes. In a subsequent extension of this analysis, smaller childhood caudate volumes predicted the severity of tics and OCBs in early adulthood [185]. In contrast to findings of other studies no abnormalities on lateralization of the basal ganglia were observed. Finally, individuals taking typical neuroleptic medications had significantly larger basal ganglia volumes when compared with other TS patients and controls, consistent with similar findings in schizophrenic patients [186]. This finding of smaller basal ganglia volumes in neuroleptic-naive patients but larger volumes in neuroleptic-exposed patients raises the possibility that medication may reduce the severity of tic symptoms by over-correcting the volume abnormalities in the basal ganglia in TS. It is also possible, however, that these volume differences due to medication status are characteristic of a particular subset of patients more likely receiving neuroleptic medication.

In a group of treatment-naive boys with TS, volumetric MRI revealed a significantly larger left thalamus in TS whereas no group difference was observed for the right thalamus. The boys with TS also showed a significant reduction in rightward asymmetry in thalamic volume compared with the healthy subjects [187]. A recent voxel-based morphometry study of high-resolution MRIs in 31 TS patients compared with 31 controls found an increase in left midbrain gray matter volume in the TS patients compared with controls but no group difference in gray matter volume in either striatum [188]. The same analysis method comparing 14 boys with TS and 15 age-matched controls revealed locally increased gray-matter volumes bilaterally in the ventral putamen in TS and regional decreases in gray matter in the left hippocampal gyrus [189] confirming striatal abnormalities and suggesting the involvement of temporolimbic pathways which needs replication. In a large sample of children and adults with TS, ferritin and serum iron were significantly lower in patients with TS although still within the normal range. While ferritin did not correlate with caudate volume, it did correlate positively with putamen volume. In the comparison subjects, ferritin correlated inversely with caudate volume but did not correlate significantly with putamen volume. Regardless of the presence or absence of TS, ferritin correlated positively with

volumes of the sensorimotor, midtemporal, and subgenual cortices [190]. The authors concluded that lower iron stores may contribute to hypoplasia of the caudate and putamen, increasing the vulnerability to developing tics or to having more severe tics. Lower iron stores may also contribute to smaller cortical volumes and, as a consequence, to reduced control of tics. However, one should also bear in mind that in ADHD lower ferritin levels have either been found [191] or not [192], questioning the specificity of ferritin levels in the pathophysiology of TS.

Based on these and other lines of evidence suggesting aberrant asymmetry and disturbances in cerebral lateralization, anatomical imaging studies focused also on the corpus callosum. Adult patients with TS showed reduced cross-sectional areas in the corpus callosum [193], whereas children with TS had larger areas in the rostrum and splenium of the corpus callosum [194]. A study including different ages questioned these findings, i.e. in the large sample (158 subjects with TS) children with TS had smaller and adults with TS had larger corpus callosum volumes, yielding a prominent interaction of diagnosis with age [195].

Using a semi-automated segmentation approach to study frontal cortical volumes in TS revealed decreased volumes of the prefrontal cortex in ADHD but not in TS [196] which calls for frontal lobe preservation to compensate for tics. Another study of cortical and cerebellar volumes in boys with TS used automated voxel classification and an atlas-based lobar parcellation [197]. The results suggest increases in the normal frontal lobar asymmetry (left $>$ right) in TS. Additionally, frontal lobe white matter volume is increased in boys with TS [197, 198]. Peterson et al. [199] reported an increased volume of the dorsal prefrontal, parieto-occipital and inferior occipital cortex volume as well as decreased premotor, orbitofrontal and subgenual volumes in children with TS. Whereas in childhood there was no gender effect, in adulthood volume differences between the TS and the control group were gender specific. Parieto-occipital volumes were smaller in women with TS and greater in men with TS than in their controls. Prefrontal volumes were smaller in women with TS and premotor volumes were larger in men with TS.

Amat et al. [200] suggested that more hyperdensities in children with TS might support the notion that subcortical injury may play a role in the pathophysiology of TS.

In summary, morphometric studies have suggested changes in TS, but most of them have not been replicated. Many investigations have relied on manual segmentation of anatomy for the delineation of large cerebral structures and assessed relatively small numbers of subjects. Given recent evidence that brain structure continues to change into the patients' 20s, a full-scale prospective study of CTD/TS subjects and healthy controls from early childhood through their mid-20s would be necessary to completely characterize the structural changes in CTD/TS. Nevertheless, the frequent implication of striatal volume changes in TS is in concordance with the results of several of the previously discussed functional brain imaging studies and with the implication of changes in striatal dopaminergic neurochemistry suggested by radioligand imaging studies.

Future Perspectives

Recent studies in CTD/TS using different technical approaches frequently implicated abnormalities of the striatum and its dopaminergic neurochemistry and function. Additionally, frontocortico-striatal, thalamic, limbic, and midbrain deviances have been identified in CTD/TS. However, inconsistencies still remain between the findings which require replication in larger samples as well as with better control of possible confounders. (1) Although comorbid conditions (especially ADHD and OCD) are frequent in CTD/TS (up to 80%) [5, 201], they are often insufficiently controlled probably due to the increased effort to recruit a 'pure' CTD/TS group. (2) The short- and long-term effects of medication (e.g. medication effects on morphometric deviances in TS) [184] have to be considered sufficiently, but the withdrawal of neuroleptics only due to participation in a study is a difficult matter of ethical debate. Hence, inclusion of medication-naïve patients would be the best solution, although it is much more laborious. (3) The same has to be stated for the studies including only adult subjects with TS. This is problematic because more long-term compensatory mechanisms might be found instead of original deviances specific for CTD/TS. Additionally, this focus on adults adds the important confounder that findings might merely represent interaction of basic CTD/TS neurobiology with environmental effects and not the pathophysiology of CTD/TS itself. Lastly, the selection effect by including only adults still suffering from tics possibly limits generalization. Hence, in this way longitudinal studies will extend the evidence gathered by cross-sectional studies of different age groups. (4) Only some of the studies in CTD/TS looked for gender differences, although it could be an important confounder (e.g. in morphometric studies) [199]. (5) More coherence of the kind of tics under investigation (e.g. simple versus complex, distal versus proximal) [149] would perhaps reveal more prominent and circumscribed deviations in patients with CTD/TS compared to healthy controls.

Moreover, studies overcoming the boundaries of using only one single method should be performed to gain a broader insight into the obviously complex etiology and pathophysiology of CTD/TS. These suggestions in combination with the rapid advancement of methods promise further progress in neurobiological CTD/TS research.

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Schizophrenia in Children and Adolescents

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Abstract

Schizophrenia occurs in 1% of the world's population, regardless of country and culture. The prevalence of very early-onset schizophrenia (below age 13) is about 2 in a million children in the general population. In adolescence, the prevalence increases and the symptomatology becomes similar to disorders in adults. The clinical presentation comprises cognitive symptoms (distortions of thinking, delusions, hallucinations), emotional symptoms (e.g. blunted affect, mood disturbances, irritability), disturbances of speech and language as well as motor disturbances (motor disharmony, stupor or catatonia). The concept of positive and negative symptoms can also be applied to schizophrenic disorders of this age group. Diagnosis is made according to ICD-10 and DSM-IV criteria, but is more difficult than in adults. At an early age, false-positive diagnoses are frequent. Etiological factors comprise a genetic background, structural abnormalities of the brain, neurodevelopmental anomalies, electrophysiological dysfunctions, biochemical irregularities, and neurocognitive dysfunctions. An interaction of these factors with environmental influences such as distorted communication in the family and trauma is assumed. The etiological concept of the stress-vulnerability hypothesis has been complemented by the neurodevelopmental and the neurodegeneration hypothesis. Treatment is based on four components: antipsychotic medication, psychotherapeutic measures, family-oriented measures, and specific measures of rehabilitation for those patients whose disorder is likely to become chronic. Course and outcome of childhood and adolescent-onset schizophrenia are poor and much worse than in adult patients.

Schizophrenic disorders in childhood are severe but rare disorders within the spectrum of psychoses. They become increasingly more common during adolescence and the symptomatology with age becomes similar to disorders in adults. With regard to age at onset, schizophrenic disorders in children and adolescents are subdivided into very early-onset schizophrenia (VEOS, onset before age of 13 years) and early-onset schizophrenia (EOS, onset before age 16 or 17 years) [1]. The term childhood-onset schizophrenia (COS) is used for children below age 12 years of age.

Classification and Epidemiology

Classification

Currently schizophrenic disorders in children and adolescents are classified according to ICD-10 and DSM-IV which has led to a greater convergence of diagnoses. Many categories correspond with one another in both systems. There are, however, some differences. These concern the subtypes of schizophrenia and the inclusion of psychotic disorders due to general medical conditions and in substance-induced psychotic disorders. These disorders are classified in ICD-10 under other categories. The schizophreniform disorder in DSM-IV is somewhat different when compared to the schizotypical disorder in ICD-10. The diagnosis requires the identical criteria of schizophrenia, except for two differences: the total duration of the illness is at least 1 month but less than 6 months, and impaired social or occupational functioning during some part of the illness is not required. There are also some other differences but they are less important for childhood and adolescent schizophrenia. A major query is, however, that the diagnosis schizophrenia according to DSM-IV requires a duration of 6 months, whereas in ICD-10 a duration of only 1 month is sufficient. With regard to these differences, some disorders may be diagnosed as schizophrenia according to ICD-10 criteria, but not to those of DSM-IV. In spite of the assumption that childhood and adolescent schizophrenias lie on a continuum with adult schizophrenia, there are special difficulties in applying the 'adult criteria' to younger children with suspected schizophrenia. Symptoms at an early age are less specific and show remarkable overlap with a number of developmental disorders. This leads to a greater uncertainty regarding the diagnosis, especially in younger children, and not seldom to false positives [2].

Epidemiology

Very Early-Onset Schizophrenia (13 Years or Under)

The prevalence of VEOS is very rare and seems to be below 2 in 1 million children in the general population. The male/female ratio in these young cases is about 2:1 or even higher [3]. The youngest ages at onset reported in the literature are 3 years in one case and 5 years in some other cases [4]. As far as symptomatology is concerned, there is considerable age-dependent variation, with well-formulated delusions being extremely rare. However, hallucinations and disorganized thinking do occur. There is some evidence that VEOS is probably associated with a lower IQ than that of the general population [1]: about 10–20% score about 70 or below in standardized intelligence testing, and mental retardation as well as language delay, language abnormalities and delays in motor development are considered as premorbid features. The same applies to attention deficit and hyperactivity [5].

Early-Onset Schizophrenia (13–17 Years of Age)

According to a review by Gillberg [1], there is some evidence that the incidence of schizophrenia occurs about 50 times less often before the age of 15 years than after. In inpatient child and adolescent psychiatric settings, up to 5% of 13- to 19-year-olds are typically diagnosed as schizophrenic. The male/female ratio varies to some extent and is characterized in the younger patients by a preponderance of males. Several studies found a significant increase in the frequency of the diagnosis of schizophrenia between the ages of 13 and 18 years [6], and onset during adolescence seems to be more acute than in VEOS. The diagnosis of EOS has a high stability over time, and follow-up studies show that the outcome and prognosis are poor [7, 8].

Diagnosis and Differential Diagnosis

Clinical Presentation

The clinical presentation of VEOS and EOS comprises cognitive symptoms, emotional symptoms, and changes in social functioning, disturbances of speech and language and motor disturbances.

Cognitive symptoms include distortions of thinking, delusions, and hallucinations. Thought distortions comprise thought insertion, breaks and interpolations in the train of thoughts, thought echo, or incoherent and vague thinking that sometimes cannot verbally be expressed in a comprehensible way.

Delusions may include ideas of reference, beliefs of being persecuted, bodily changes, delusions of control, and a variety of other types of delusions. As far as delusions are concerned, systematized delusions are very rare in childhood (below the age of 12) and become more frequent during adolescence.

Hallucinations manifest themselves mainly as threatening voices giving comments or commands to the patient or as auditory hallucinations without a verbal structure, such as laughing, humming, or whistling. Auditory hallucinations are the most frequent, while visual hallucinations or those involving smell or taste or other bodily sensations are rare. Visual hallucinations are, if occurring at all, more frequently found in younger children (below the age of 13 years) and raise differential diagnostic questions as they also can occur in intoxications.

Emotional symptoms and *changes in social functioning* include blunted affect, mood disturbances such as irritability, fearfulness, and suspicion, negative symptoms such as marked apathy, paucity of speech, or incongruity of emotional responses resulting in social withdrawal and lowering of social performance.

Disturbances of speech and language are characterized by a paucity of speech or logorrhea, perseverations, or speech stereotypies, sometimes also by echolalia and phonographism. Neologisms can also occur. With regard to these symptoms, the differential diagnosis regarding autism is important, especially in children below the age of 8 years.

Motor disturbances are manifold and can extend from clumsiness and motor disharmony to strange postures, stupor, and symptoms of catatonia. Bizarre movements and motor stereotypies such as finger stereotypies are frequent. Initially, and also during the course of the disorder, compulsive acts or rituals resulting in strange and unexpected movements can also be observed.

The well-known concept of positive and negative symptoms in adult psychiatry can also be applied to childhood and adolescent schizophrenia. It could be demonstrated that negative as well as positive symptoms appear in both VEOS and EOS, even quite a long time before the clinical manifestation of the disorder which led to admission. While many patients showed both negative and positive symptoms before the index admission, both categories of symptoms become more frequent and converge at the time of admission [9].

Diagnostic Procedures

Schizophrenia in children and adolescents is normally diagnosed according to the criteria of ICD-10 and DSM-IV. Usually, the diagnosis is based upon a careful history of the patient and his family, taken from the parents and the patient himself, and a thorough clinical investigation of the patient including psychological and neuropsychological testing. The test-psychological investigation should include cognitive measures on intelligence, concentration, memory, language, and motor functions. In addition, it is very important to also include measures covering the emotional states of the patients. Depressive symptoms are frequently either precursors or a common trait in the beginning of adolescent schizophrenia. Approximately 20% of adolescents with schizophrenia start the disorder with a depressive episode. In addition to the already mentioned clinical investigations, many instruments exist for use in children and adolescents with suspected psychotic disorders, including schizophrenia (table 1). These instruments can be divided into two categories: diagnostic interviews, and symptom rating scales. Whereas the diagnostic interviews have been constructed with the aim of arriving at categorical diagnosis according to the DSM or ICD systems, the symptom rating scales have a broader focus and are constructed with the aim of assessing psychopathological symptoms on a continuous scale (e.g. positive symptoms, negative symptoms, thought disorders, functional impairment). In contrast to the diagnostic interviews, they produce scores on certain dimensions, thus following the dimensional approach to schizophrenia. For the diagnosis of childhood and adolescent schizophrenia, it is important to collect all information available, not only from and about the child, but also from other sources. Usually, a battery is used that includes rating scale data from parents, children, and teachers, whenever possible. Moreover, we feel that the most valid diagnoses integrate data from all available sources by using either 'best estimate' or PLASTIC (prospective, longitudinal, all source, treatment, impairment, and clinical presentation) procedures. This information is included in the schedules described in table 1.

This approach is different from the use of schedules in adult psychiatry which usually rely on the information gathered only or primarily from the patient.

Table 1. Instruments for the diagnosis of schizophrenic disorders in childhood and adolescence

Clinical interviews		
K-SADS-E (schedule for affective disorder and schizophrenia for school-age children)	Parents/child	6–17 years
ICDS (interview for childhood disorders and schizophrenia)	Parents/child	6–18 years
CAPA (child and adolescent psychiatric assessment)	Parents/child	8–18 years
DICA (diagnostic interview for children and adolescents)	Parents/child	6–17 years
NIMH DISC	Parents/child	9–17 years
Scales		
KIDDIE-PANSS	Interviewer parents/child	6–16 years
CPRS (children's psychiatric rating scale)	Interviewer/ child	Up to 15 years
TDS (thought-disorder scales)	Child	5–13 years

Differential Diagnosis

There are several disorders that have to be distinguished from schizophrenia during the age of childhood and adolescence.

Autism

Autism is now looked upon as a pervasive developmental disorder with manifestation in the first 30 months of life with a characteristic symptomatology that differs from schizophrenia, but may have several symptoms in common. Hallucinations and delusions, however, are not found in autism and such an early onset of the disorder is not found in schizophrenia. In most cases, the differential diagnosis can be based upon the history taken from the parents, clinical observation, and the course of the disorder.

Desintegrative Disorder (Heller's Syndrome)

This syndrome is characterized by a normal development until the age of 3 or 4, followed by a progressive deterioration and the loss of already acquired abilities. The syndrome is very rare as compared to autism and also less frequent than EOS. Characteristic is the loss of already acquired functions, including language, together with characteristic abnormalities of social, communicative and behavioral functioning. The children frequently become irritable, anxious, and overactive before the full clinical picture becomes apparent. There are again at least two distinct criteria by which

this disorder can be distinguished from schizophrenia: (1) the early loss of acquired skills, and (2) the early onset of the disorder.

Multiplex Complex Developmental Disorders and Multiple Developmental Impairment

These disorders are not yet included in the ICD-10 or DSM-IV classification systems.

Multiplex complex developmental disorder (MCDD) was first described by Towbin et al. [10] as a syndrome characterized by 'disturbances in affect modulation, social relatedness and thinking', whereas multiple developmental impairment (MDI) [11] is a label for children who are characterized by brief transient psychotic symptoms, age-inappropriate fantasies, and magical thinking which cannot be clearly looked upon as a delusional phenomenon, social withdrawal, emotional lability, and deficits in information processing. The criteria for childhood schizophrenia are not fulfilled, and the major difference between schizophrenic children and MDI children is twofold: they reveal less negative symptoms and are less socially impaired.

The two syndromes MCDD and MDI overlap to a certain extent. Whereas the MCDD construct seems to be closer to the concept of pervasive developmental disorders, the MDI concept seems to have a greater affinity to schizophrenia. The relationship of both syndromes to schizophrenia is not completely clear, however, a follow-up study on MCDD children demonstrated that approximately 20% developed schizophrenia later on in their lives [12].

A follow-up study of 19 MDI patients, however, did not confirm this development. So the question arises if this syndrome is a precursor syndrome of schizophrenia [13].

Affective Psychoses (Psychotic Depression, Bipolar Disorder)

As already stated above, adolescent schizophrenia often starts with a depressive episode. On the other hand, there are studies that demonstrate that bipolar disorders are very often initially diagnosed as schizophrenia [14].

In most cases, however, a differentiation is possible during the first half year of observation. This can be done by observing the typical symptom clusters that are different between schizophrenia and bipolar disorder.

Asperger's Syndrome

The leading features that enable the differentiation of Asperger's disorder from schizophrenia are the individual history of the patient (symptoms of autistic spectrum disorder, very early language acquisition), the clinical observation and the course. As far as the clinical picture is concerned, patients with Asperger's syndrome usually do not reveal positive symptoms and a deterioration of their scholastic and social functioning is missing. It is, however, known that some cases of Asperger's syndrome may develop schizophrenia later on in life [15].

Drug-Induced Psychosis

This may be to date the most frequent differential diagnosis. Many adolescents who are seen clinically with a psychotic state have consumed drugs, and it is difficult to decide if the clinical picture represents schizophrenia or a psychotic state caused by organic brain conditions. And even if the clinical symptomatology fulfils the criteria of schizophrenia, the question arises if the disorder was caused by the consumed substances or only triggered. There are many drugs that are known to induce psychotic states (marihuana, LSD, cocaine, amphetamines, alcohol hypnotics, anxiolytics). The differentiation from schizophrenia can be made by a thorough history taking including an inquiry about all substances taken during the last year and by laboratory investigations. The diagnosis of schizophrenia can be confirmed if the symptoms persist for several months after drug withdrawal.

Organic Brain Disorders

There are several organic brain disorders that are known to be associated with psychotic states, among them temporal epilepsy and some neurodegenerative disorders such as morbus Wilson, Huntington's chorea and juvenile metachromatic leukodystrophy. These disorders can be detected and delineated from schizophrenia by thorough neurological examinations including laboratory tests. The clinical picture is very often characterized by movement disorders and a progressive deterioration of cognitive functions.

Etiology

Genetic Factors

As far as genetics is concerned, family studies, twin and adoption studies demonstrate very clearly the importance of genetic influences. Most studies, however, were carried out in adult patients. Genome-wide genetic linkage screen studies have identified loci on chromosomes 1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 18, 22 and the X-chromosome with positive lod scores. This underlines that schizophrenia is not caused by a single major locus. Association studies have so far generated disappointing results with regard to the identification of susceptible DNA sequence variants [16]. However, polymorphisms in the 13q33.2 gene G72/G30 were found to be associated with COS and psychosis not otherwise specified [17]. Further, neuregulin1(8p12) seems to be important for the manifestation of COS. A risk allele has been identified that was associated with poorer premorbid social functioning as well as with different trajectories of change in lobar volumes. It was stated that this is the first demonstration of a disease-specific pattern of a gene action in schizophrenia [18]. Considerable research has been carried out on the possible association of the 22q11 deletion syndrome (velocardiofacial syndrome) and early-onset psychosis or schizophrenia. Recent studies have cast some doubt regarding the specificity of this association as the syndrome

is also correlated with several other psychopathological conditions such as attention deficit/hyperacitivty disorder, depression, and anxiety disorders. However, nearly 50% of 25 velocardiofacial syndrome patients reported transient psychotic experiences [19]. In spite of these and other interesting results, we are still far from a convincing genetic explanation of the disorder. Current results underline the notion that schizophrenia is a complex disorder caused by quite a number of genes and also influenced to a considerable extent by environmental factors.

Structural Abnormalities of the Brain

Facilitated by neuroimaging techniques, quite a number of structural and functional brain abnormalities have been identified in recent years. Mehler and Warnke [20] reviewed the results until the end of 2001, summarizing that the most consistent findings are ventricular enlargement and reduced total brain volume as well as volumetric changes in the temporal and frontal cortex, thalamus, basal ganglia, and the limbic system, as well as hemispheric asymmetries and, conversely, a reduction in normal hemisphere differences. The findings regarding the corpus callosum and the cerebellum were inconsistent. Interestingly enough, the differences were more pronounced in COS than in adolescent or adult-onset schizophrenia. Finally, there are several reports in the literature that found a reduction in total brain volume as a progressive process throughout the course of the disorder. In the meantime, a number of new results have been published that can be summarized as follows.

(1) Total brain volume is significantly smaller in EOS relative to a matched control group, especially for the left hemisphere in males. Decreased left hemisphere volumes in males and decreased rightward hemispheric asymmetry in females correlates with reduced IQ [21].

(2) Also siblings of patients with COS have a smaller total cerebral volume and total, frontal and parietal grey matter volumes than matched volunteers [22].

(3) There is a significant relationship between minor physical anomalies and lateral ventricular enlargement in child and adolescent-onset schizophrenia. It was found that the Waltrop score (a measure of physical anomalies) was significantly higher in the EOS vs. late-onset schizophrenia group. It can be assumed that minor physical anomalies are an index of early prenatal CNS maldevelopment which leads to the conclusion that EOS may be a subset within the schizophrenia spectrum [23].

(4) There is also a progressive loss of cerebellar volume in COS during adolescence. Cerebral as well as cerebellar volume decreases are significantly correlated in COS. The loss appears secondary to a generalized process [24]. Of course, the question arises if this loss of cerebral and cerebellar volume is specific for schizophrenia. This issue was reviewed by Lahuis et al. [25] on the basis of 28 studies on autism and 12 studies on childhood schizophrenia. Larger lateral ventricles were found to be a common abnormality in both disorders. Disorder-specific abnormalities in COS were smaller brains, smaller amygdala and thalamus and a larger nucleus caudatus. Further, in subjects with

Table 2. Developmental events and precursors of very early and early-onset schizophrenia

Soft neurological signs [59] and pandysmaturation [60]
Deviant patterns of brain maturation [for review see, 61]
Neurosensory and neuromotor deficits in 'high-risk children' [47, 62]
Marked autonomic reactions [63]
Slow habituation and high baseline autonomic activity [35]
Premorbid anxiety status and social withdrawal [64]
Overactivity in preschizophrenic boys [65]
Withdrawal in preschizophrenic girls [66]
Significant developmental delays (language development, motor development and coordination) [46, 48, 67]
Poor premorbid adjustment in scholastic performance, school adaptation and social functioning [48, 56]
High rate of developmental disorders of speech and/or language [13, 68] and transient symptoms of pervasive developmental disorders [13]
Global negative and positive thought disorders and negative symptoms years before the onset of schizophrenia [9, 69]
Overall cognitive impairment reflected by lower IQ as compared with normal children [43, 56, 70]
Specific cognitive deficit in three areas: distractability, verbal comprehension and perceptual organization [71]

COS, abnormalities appeared to progress over a limited period of time. In contrast, disorder-specific abnormalities in patients with autism were larger brains, larger thalamus area, and a smaller right cingulate gyrus. The authors conclude that, before abnormalities are acknowledged as being disorder-specific, it will be essential to perform large longitudinal and cross-sectional follow-up studies [25].

(5) In the meantime, several times replicated progressive brain volume loss during adolescence in COS was found also to be related to premorbid impairment and baseline symptom severity [26].

(6) Finally, gyrification abnormalities were discovered in COS in comparison with matched controls. These changes may be an indicator of aberrations in cerebral and subcortical connectivity [27].

Developmental Abnormalities

Remschmidt [28] and Remschmidt and Theisen [29] reviewed developmental events and precursors in relation with COS. The main results from the literature are condensed in table 2. As table 2 demonstrates, there is ample evidence for the neurodevelopmental hypothesis of VEOS and EOS. By combining these results with longitudinal data from MRI and neuropsychological studies VEOS and probably also EOS can be looked upon as progressive deteriorating developmental disorders [28, 30].

Central Nervous Infections

The role of infections of the CNS in the etiology and development of schizophrenic disorders is still unclear. The results of a Finnish cohort study suggesting that childhood viral CNS infections were associated with a fivefold increased odds ratio of developing schizophrenia in adulthood [31] could not be replicated in another Finnish sample [32]. However, by comparing register data of adults who had suffered in childhood from CNS infections with regard to the rate of schizophrenia and non-schizophrenic psychoses in adult age, Koponen et al. [33] found that viral CNS infections during childhood may play a role as a risk factor for schizophrenia.

Another group found that childhood meningitis significantly increases the risk of schizophrenia, in particular in adulthood, and of psychosis in general. The study was carried out by following up 190 individuals affected by meningitis in the first 4 years of life during an epidemic in Sao Paulo and comparing them with a control group [34]. A replication of this result seems to be necessary. In conclusion, it cannot be decided which role, if any, CNS infections play in the pathogenesis of schizophrenia.

Electrophysiological Findings

Electrophysiological studies in EOS have mainly concentrated on two areas: skin conductance and event-related potentials (ERPs). As far as skin conductance is concerned, marked autonomic reactions and slow habituation as well as a high baseline autonomic activity have been observed [35].

Currently, it is still unclear if those schizophrenic children who show high baseline autonomic activity are more therapy-resistant to neuroleptic treatment than those who do not show this type of reaction as found in adults.

The ERP studies in schizophrenic children concentrated on four components: contingent negative variation, processing negativity, event-related positive component (P300) and hemispheric asymmetry in the amplitude P1/N1 component complex. According to a review by Asarnow and Karatekin [36], contingent negative variation differences between normal and schizophrenic children were not consistently found across several studies. Processing negativity was found to be smaller in schizophrenic than in normal children. A diminished processing negativity amplitude was the earliest consistent ERP of a schizophrenic information-processing deficit and reduced P300 amplitudes were consistently observed in schizophrenic children on the span of apprehension and the continuance performance test. As far as the latency of the P300 component is concerned, the results are contradictory. Finally, the absence of right-lateralized P1/N1 amplitudes in visual ERPs was consistently found in 4 studies in schizophrenic children on the continuance performance test and in span of apprehension tasks.

An interesting result was recently published regarding ERPs in adult patients with first-episode and chronic schizophrenia: A novelty P300 amplitude reduction was only present in patients with chronic schizophrenia and not in first-episode schizophrenia patients, this variable may be an indicator of a progressive process [37].

Biochemical Studies

The few biochemical studies carried out so far in children and adolescents with schizophrenia have mainly concentrated on the neurotransmitter systems during pharmacological treatment. Not much is known about the development of these transmitter systems in humans. There are, however, interesting results from animal research. From animal studies, two systems seem to be important within a developmental perspective of schizophrenia: the glutamatergic system and the dopaminergic system.

Glutamate is the most important transmitter for the pyramid cells and is much involved in brain development. The glutamatergic system undergoes remarkable developmental changes in rats during adolescence. Adolescent rats become sensitive to glutamate antagonists and remain so until adulthood [38]. In a clinical context, the causation of psychotic states by the glutamate antagonist phencyclidine is well known during adolescence and young adulthood. From these observations, it was concluded that a dysfunction of the N-methyl-D-aspartate receptor might be a key mechanism explaining adolescent onset of schizophrenia [39].

In spite of the many changes the dopamine hypothesis of schizophrenia has undergone, there seem to be some new aspects focusing on the relationship between reduced dopamine activity in the prefrontal cortex and stress-sensitive changes in subcortical dopamine activity [39]. A dysregulation in the dopaminergic system may cause working memory deficits which have been observed in non-human primates after chemical lesioning of the dopamine innervations to the prefrontal cortex [40]. A reduction of dopamine in the prefrontal cortex was also observed in schizophrenic patients in PET studies [41].

From clinical studies, it is evident that also the serotoninergic system and the noradrenergic system play important roles in schizophrenia. This was demonstrated by Schulz et al. [42] in a study of biogenic amines during clozapine treatment in a group of 40 patients (aged 14–22 years) with schizophrenia, half of them treated with clozapine, the other half treated with standard neuroleptic medication. Blood levels of serotonin 3-methoxy-4-hydroxyphenylglycol (MHPG), norepinephrine and epinephrine were significantly higher in the clozapine-treated patients than in the conventionally treated patients. During long-term treatment, higher serotonin levels were associated with significantly less negative symptoms of schizophrenia, whereas higher MHPG levels were associated with less depression. In addition, the response to clozapine could be predicted by epinephrine levels prior to initiation of treatment with clozapine. Subjects who responded to clozapine showed increased mean plasma concentrations of MHPG and epinephrine during treatment with this drug in comparison to the levels measured during pretreatment with typical neuroleptic medication. Non-responders to clozapine failed to show this increase.

Neuropsychological and Neurocognitive Dysfunctions

Several studies have found cognitive impairments in patients with EOS. These comprise overall cognitive impairment reflected by lower IQ as compared to normal

children, but also specific cognitive deficits in different areas (distractability, verbal comprehension and perceptual organization). Specifically, the following results reflect the importance of cognitive functioning for the manifestation of EOS.

(1) Poor intellectual performance at age 18 is associated with EOS [43].

(2) Childhood IQ is strongly predictive of social outcome and service utilization, but not clinical symptoms [44].

(3) Cognitive deterioration is also present in EOS with mental retardation [45].

In addition, significant developmental delays concerning language development, motor development and coordination have been described [46] and also transient symptoms of pervasive developmental disorders [13].

In a review of 16 high-risk studies Niemi et al. [47] concluded that factors which appear to predict schizophrenia include problems in motor and neurological development, deficits in attention and verbal short-term memory, poor social competence, positive formal thought disorder-like symptoms, higher scores on psychosis-related scales in the MMPI and severe instability of early rearing environment. These results have been confirmed to a large extent by other groups [48].

Three other issues have been discussed widely with regard to EOS: neurointegrative deficits, attentional dysfunctioning and communication deficits [for review see, 28]. Meanwhile, there is ample evidence that these three issues are decisive either as precursors, early symptoms, or deficits during the course of childhood and adolescent-onset schizophrenia.

Environmental Factors

In spite of the great importance of genetic factors in the etiology of COS and EOS, environmental factors cannot be neglected. While in the past, family-focused paradigms (e.g. double-bind concept, deviant patterns of family relations, expressed emotions) were widely discussed, individual (premorbid) characteristics of the patients and the role of traumatic experiences are now prevailing. A small number of population-based studies provide evidence of an association between childhood trauma and the later onset of schizophrenia. Several mechanisms, e.g. the effect of exposure to trauma on the dopaminergic system leading to elevated dopamine metabolisms, have been postulated based on research in animals and in humans [for review see, 49]. Nevertheless, the issue is still a matter of controversy. It can, however, be assumed that, as in many other psychiatric disorders, gene–environment interactions are not only important for the manifestation of schizophrenia, but also for its course.

Treatment and Rehabilitation

There are at least four components that are important for treatment and rehabilitation in child and adolescent schizophrenia: treatment with neuroleptics; psychotherapeutic measures; family-oriented measures, and specific measures of rehabilitation.

Treatment with Neuroleptics (Antipsychotics)

As in adult psychiatry, currently atypical neuroleptics are mainly used that are characterized by the following properties:

(1) A different receptor-binding profile as compared to conventional neuroleptics (lower binding to dopamine receptors, higher affinity to 5-HT_{2A} and α1 receptors) which is responsible for a different action;

(2) A low rate of extrapyramidal side effects as a consequence of this receptor-binding profile;

(3) Efficacy also with regard to negative symptoms in contrast to most conventional neuroleptics, and

(4) Absence of hyperprolactinemia and a low rate of other adverse effects.

Table 3 gives an overview of the most frequently used antipsychotic (neuroleptic) medications and figure 1 demonstrates a decision tree for the selection of antipsychotics in childhood and adolescent schizophrenia.

The psychopharmacological treatment has at least three foci: management of acute psychotic states; prevention of relapses, and controlling of side effects.

(1) Acute psychotic states normally require inpatient treatment during which antipsychotic drugs play a predominant role. Currently, treatment will be started with an atypical antipsychotic drug in case of severe agitation and aggressive outbursts, a benzodiazepine or a typical moderate or low potency neuroleptic (e.g. levomepromazine) can be used additionally. The further strategy of pharmacological treatment can be applied according to the algorithm displayed in figure 1. Depending on the individual reaction (efficacy and side effects), the decisions for switching or maintaining the present medication are made. In most countries, clozapine can only be initiated after two different compounds have not proven effective or were not tolerated by the patients. The usual oral dosages, and for depot neuroleptics the intramuscular dosages, are given in table 3.

(2) Prevention of relapses requires the application of a long-term antipsychotic medication. Relapses are frequently triggered by emotional stress, adverse life events, but also by positive emotional experiences. With regard to these factors, it is very important to anticipate a relapse prevention either by maintaining low-dose oral medication or by switching to a depot neuroleptic. Especially when the compliance is a problem, a depot medication is recommended. Currently, to our knowledge, only Risperdal-Consta is available as an atypical depot neuroleptic, at least in Germany.

(3) The third major focus is controlling side effects. The incidence rates of extrapyramidal symptoms caused by typical neuroleptics are higher in children and adolescents than in adults. Therefore, atypical neuroleptics are usually preferred. The advantage of the atypical neuroleptics is the fact that they do not induce or have only a low risk of inducing extrapyramidal side effects. Several atypical neuroleptics, however, cause other side effects that are also a considerable strain for the patients, among them extreme weight gain, most pronounced after the application

Table 3. Most frequently used antipsychotic medications in child and adolescent schizophrenia

	Sedation	Positive symptoms	Negative symptoms	Neuroleptic potency	Usual oral dose (usual depot dose i.m.)
Typical high potency neuroleptics					
Benperidol	+	++	++	100	1–6 mg/day
Flupenthixol (–decanoate)	+	++	++	50	2–10 mg/day (20–100 mg/2–4 weeks)
Fluphenazine (–decanoate)	+(+)	+++	++	30	5–20 mg/day (12.5–100 mg/2–4 weeks)
Fluspirilene	+	+++	++	300	(2–10 mg/week)[1]
Haloperidol (–decanoate)	+	+++	++	60	2–20 mg/day (50–300 mg/2–4 weeks)
Perphenazine (–enanthate)	++	+++	++	8	12–64 mg/day (50–200 mg/2 weeks)
Pimozide	+	+++	++	50	4–20 mg/day
Typical moderate and low potency neuroleptics					
Chlorpromazine	+++	+++	++	1	150–600 mg/day
Chlorprothixene	+++	++	++	0.8	150–600 mg/day
Levomepromazine	+++	++	++	0.8	75–600 mg/day
Perazine	++	++	++	0.5	75–600 mg/day
Pipamperone	++			0.2	120–360 mg/day
Promethazine	+++				50–400 mg/day
Sulpiride	+	++	+++	0.5	100–800 mg/day
Thioridazine	+++	++	++	0.7	200–700 mg/day
Tiapride	+				300–600 mg/day
Zuclopenthixol	+++	++	++		20–150 mg/day
Atypical neuroleptics					
Amisulpiride	+	+++	+++		50–300 (400) mg/day[2] 200–800 (1,200) mg/day[3]
Aripiprazol	+	+++	+++		10–30 mg/day
Clozapine	+++	+++	+++	(0.5–2)	25–6,001 mg/day
Olanzapine	++	+++	+++	(8–20)	10–20 mg/day
Quetiapine	+	+++	+++		150–750 mg/day
Risperidone *(Risperdal Consta® 25/37.5/50 mg)*[4]	+	+++	+++	(50)	1–12 mg/day *(25–50 mg/2 weeks)*
Sertindole	+	+++	+++		16–24 mg/day
Ziprasidone	++	+++	+++		80–160 mg/day
Zotepine	++	+++	+++	(2)	75–300 mg/day

The neuroleptic potency of typical neuroleptics was calculated in relation to chlorpromazine (= 1). The neuroleptic potency of atypical neuroleptics was geared to the average clinical effective dosis. + = None or low; ++ = moderate, +++ = high.

[1]Available only as depot neuroleptic.

[2]If negative symptoms predominate.

[3]If positive symptoms predominate.

[4]Currently the only atypical depot neuroleptic (in Germany available since July 2002).

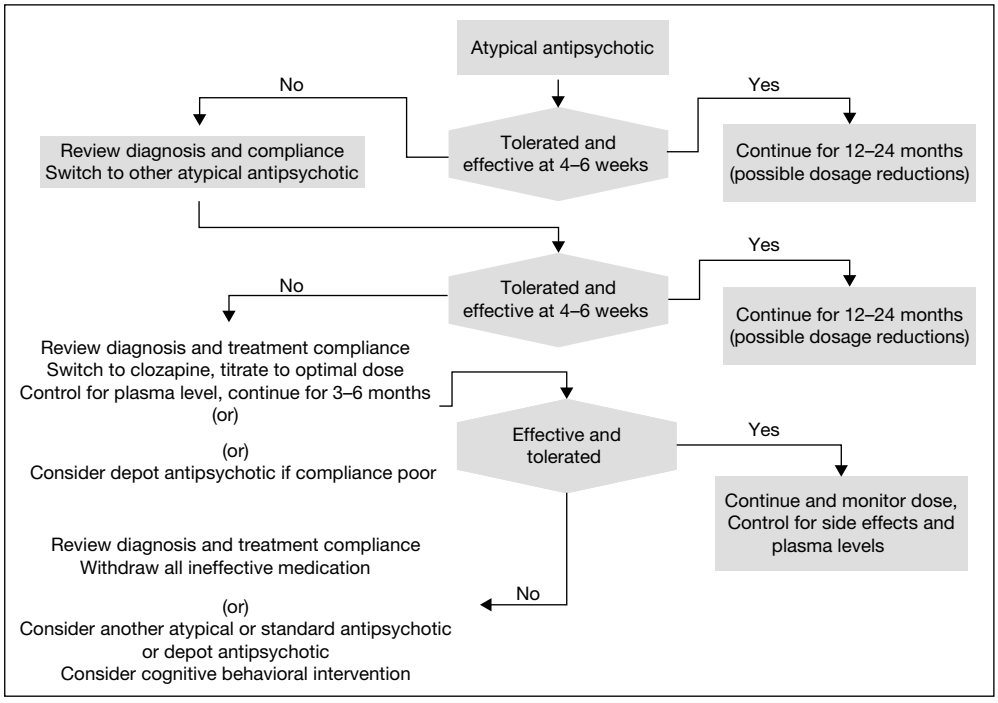

Fig. 1. A decision tree for the antipsychotic treatment selection in childhood and adolescent schizophrenia. Adapted and modified from Clark and Lewis [72].

of clozapine and olanzapine. Therefore, recently new compounds have been developed with a lower risk of weight gain such as aripiprazole. To date, however, there are only a few experiences with this kind of treatment in childhood and adolescent-onset schizophrenia. Especially, during adolescence, weight gain is one of the most frequent causes of noncompliance and causes further complications such as diabetes and metabolic syndrome. There are several other adverse effects related to different types of antipsychotics which cannot be described in detail here [for review see, 50].

Psychotherapeutic Measures

Psychotherapeutic treatment includes at least four components: (1) careful and comprehensive information about the disorder within the psychoeducational approach; (2) cognitive psychotherapy and other behavioral measures; (3) emotional management therapy, and(4) group programs.

The *information about the disorder* is essential and should also include the family. All explanations have to be adapted to the phase of the disorder and the cognitive and emotional level of the patient.

Psychotherapeutic measures based on *cognitive interventions* include different strategies such as distraction treatment, rationale responding, belief modification, and the enhancement of coping strategies. The aim of all these treatment approaches is to give the patient an active role and to enhance his specific abilities to cope with symptoms of the disorder, distress and anxiety. There exist integrated approaches based on several combined components, e.g. the Integrative Psychological Therapy Program for Schizophrenic Patients (IPT) developed in Switzerland [51, 52].

Emotional management therapy so far has not yet been demonstrated to be effective in young patients with schizophrenia; however, there is no doubt that the emotional sphere is of great importance in the course of the disorder. But studies are needed to evaluate the effect of this approach. *Group programs* have been thought to be helpful in the treatment of young patients with schizophrenia and have been applied with the main focus on the improvement of skills (e.g. social skills training, problem-solving, communication) and education (e.g. information about illness and treatment, management of medication and relapses). The already mentioned IPT program has frequently and successfully been applied as a group program.

Family-Oriented Measures

It is evident that the families of children and adolescents with schizophrenia have to be included in the planning and concept of treatment. However, empirical research has shown that ambitious family therapy concepts which have been propagated in the last decades have not brought the benefits hoped for. It is now quite clear that neither does the 'typical psychotic family' exist nor the 'schizophrenogenic mother'. On the other hand, the concept of expressed emotions is important and demonstrates the weighty role of the family with regard to relapses of the disorder. Therefore, in every case of child and adolescent schizophrenia, one has to decide how far the family should be integrated into the therapeutic process. This depends largely on the patient, the disorder, the structure and stability of the family, as well as the therapist's experience.

The following components that can be included in family-oriented approaches in the treatment of schizophrenia [50].

(1) Family counseling and psychoeducational approaches, applied in every case.

(2) Supportive and structural family therapy aiming at neutralization and control of symptoms.

(3) Extended development-oriented family therapy, focusing on patterns of relationship of family members and family conflicts. This type of intervention requires very experienced therapists, cooperative families, and can be used only in rare cases.

Specific Measures of Rehabilitation

Approximately 40% of children and adolescents with schizophrenia are not able to continue on their pre-psychotic level with regard to school, professional work,

communication, and social integration. For these patients, residential rehabilitation may be indicated because of either the nature or the course of their illness. Especially in patients with marked negative symptoms after treatment of their acute episode, a re-integration into the family might not be possible. For these patients, programs have been developed including the following components [50, 53]:

(1) A well-structured educational facility with expertise in dealing with particular special needs of these adolescents.

(2) As an integral component of the rehabilitation process helping the adolescents realize their educational capacity, with the acquisition of relevant qualifications.

(3) Individual supportive psychotherapy and additional group work involving social skills training.

(4) Occupational therapy as an important rehabilitation measure and, for older adolescents, integration into appropriate work activities.

(5) Finally, individually tailored medication in order to minimize the risk of relapse.

These general principles have been realized in an integrated rehabilitation program and have been found to be successful. For a more detailed description of the program see, Remschmidt et al. [50].

Course and Outcome

With regard to the course and outcome, the results of the few existing studies [for review see, 8, 54] can be summarized as follows:

(1) Schizophrenic disorders manifesting before the age of 14 years have a very poor prognosis. The disorder continues in most cases into adolescence and adulthood and can be diagnosed by the same criteria as for adults [55].

(2) Patients with acute manifestations of the disorder and with productive schizophrenic symptoms such as hallucinations and delusions (positive symptoms) have on average a better prognosis than those with a slow manifestation, insidious course and with continuous impairment of cognitive functions and/or depressive states [56].

(3) Premorbid personality is of great importance. Patients who had been described in the premorbid phase as socially active, intelligent and well-integrated children and adolescents have a better prognosis than those who had been cognitively impaired, shy, introverted and withdrawn before manifestation of their disorder [14, 53, 57].

(4) Finally, the prognosis seems to be better in patients without any family prevalence of schizophrenia, whose families cooperate well, and who have a rapid improvement during inpatient treatment [53, 56].

(5) The few course and outcome studies confirm the result that prognosis and outcome in childhood and early adolescent schizophrenia is much worse than in adult schizophrenia [8, 58].

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Eating Disorders

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Abstract

Eating disorders are serious psychiatric disorders with significant medical and psychological morbidity and mortality. Most research has focused on the psychological and psychosocial risk factors for these disorders; however, recent genetic, neurocognitive, and neurotransmitter studies illustrate the biological underpinnings of these disorders. Treatments have generally focused on psychological interventions as well; however, a range of medications have been studied. Unfortunately, for anorexia nervosa, medications do not appear to be acceptable to most patients and therefore studies have not yet demonstrated their efficacy. For bulimia nervosa, antidepressants are useful in adults, though they have not been systematically examined in adolescents. The biological understanding of eating disorders is in its infancy and investment in future research in genetics, neurotransmitters, and neurocognitive studies is needed.

Eating disorders are relatively common and serious and at times life-threatening psychiatric disorders that often have their onset during adolescence and young adulthood [1]. Although anorexia nervosa (AN) and bulimia nervosa (BN) are specific diagnostic categories in the various psychiatric schemes, an eating disorder not otherwise specified (EDNOS) is actually the most common clinical presentation of eating disturbances in children and adolescents [2]. Regardless of the specific diagnosis, individuals with eating disorders have severe difficulty maintaining a normal pattern of eating, as well as a normal weight range. Excessive exercise and use of laxatives, diuretics as well as other types of behaviors or medications to try to control or lose weight, and distortion of own body image are also often present.

The roles of multiple risk factors have been studied, namely genetic, biological, psychological, familial and sociocultural variables. The latter include Western culture, urban lifestyle and dieting history. On the other hand, socioeconomic status and ethnicity have no clear causal relationship to eating disorders. In fact, they occur

globally, in both developed and developing countries [3–5]. The psychological risk factors consist of a group of personality traits. Individuals with AN tend to be obsessional and perfectionist, have low self-esteem and difficulty in recognizing their feelings. Individuals with BN tend to be impulsive and self-critical. The predisposing role of specific childhood experiences, including sexual abuse, is uncertain. The weight gain and change in body shape due to puberty itself may also contribute to the onset of these disorders.

The psychological and psychosocial risk factors for eating disorders have been the focus of much investigation [6]; however, the biological basis of these disorders has received comparatively little attention until recently. The current chapter reviews the major findings related to the biological underpinnings, maintaining factors, and treatments for eating disorders.

Epidemiology

AN prevalence rates range from 0.5 to 0.9% among females. For partial syndromes the prevalence rates range from 2.8 to 6.6% among females and from 0.5 to 0.8% among males (eating disorders, EDNOS) [7, 8]. For adolescent BN, studies suggest rates of 1–2% for full BN, but another 2–3% for partial BN [9]. Eating disorders are more commonly seen among girls and women, with estimates of the male-female prevalence ratio ranging from 1:6 to 1:10 [7]. Longitudinal studies reveal an upward trend in the incidence of AN and BN. The increase is most substantial among 15- to 24-year-old females [7]. In clinical samples, the younger the patient, the more likely he/she is to receive a diagnosis of EDNOS and less likely to present purging behaviors (vomiting, use of laxatives and diuretics) [10].

Classification of Child and Adolescent Eating Disturbances

Data suggest that the current classification system for eating disorders is inadequate, especially for children and adolescents, as the majority of cases are relegated to the EDNOS category [11]. However, as there are no field tests available for the current diagnostic schemes and no biological test available to assist with categorization, the current system will remain in use. Perhaps future studies will provide data to support more specific categorization.

Anorexia Nervosa

There are four main symptoms which characterize AN: (1) being underweight, e.g., less then 85% of the expected weight for height due to weight loss or to lack of expected weight gain; (2) intense fear of gaining weight or becoming fat, even though underweight; (3) disturbance in the way in which one's body weight or shape is

experienced, and (4) amenorrhea in post-menarche females [2]. However, most often, these diagnostic criteria are inadequate for classifying children with eating disturbances as illustrated below [11].

Early-onset cases of AN with a short history of illness often present with loss of weight enough to be of concern but not enough to fulfill the weight criteria. Still in relation to the weight, a more accurate parameter to measure weight loss in children and adolescents is a decline in weight percentile, which is not included in the weight criteria. On the other hand, a decrease in body mass index (BMI), which is the parameter suggested, is not suitable for pre-menarche individuals in most cases [12]. Another problem with the current classification is the criteria related to the disturbance in the way in which one's body weight or shape is experienced. This is a symptom that may be either absent or not comprehensible to young individuals with an immature cognitive development. Moreover, the amenorrhea criterium is not applicable to prepubertal children, males, or women on birth control pills. If the 4 criteria are not fulfilled, an EDNOS will be the case. This is the most frequent diagnosis among children and young adolescents [10]. For these reasons, the existing diagnostic criteria are not sufficiently age-adjusted for application to younger patients [13–15].

Bulimia Nervosa

There are two main criteria for BN: (1) recurrent episodes of binge eating which are characterized by eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat and a sense of lack of control over eating during the episode (i.e. a binge episode), and (2) recurrent inappropriate compensatory behavior to prevent weight gain such as self-induced vomiting, misuse of laxatives/diuretics, fasting or excessive exercise [2]. The common clinical presentation in young adolescents includes an increased focus on weight and shape concerns followed by increased dieting and exercise. Ultimately, the concern about weight and shape increases to the point that unhealthy strategies for weight loss such as severe restriction, overexercise, and purging may begin. However, in most cases, it is impossible to maintain this regimen and binge eating ensues. With binge eating, anxiety about weight gain is heightened and purging begins again. In this way a vicious cycle of dieting, binge eating, purging and anxiety about weight and shape is maintained [16].

Psychiatric Comorbidity

Studies investigating clinical and community adult samples show high rates of comorbidity in eating disorders, including depression, anxiety disorders, and personality disorders [17–22]. Affective disorders generally co-occur or start after the eating disorder in 52–98% of the patients. The anxiety disorders often onset prior to or co-occur with the eating disorder. These disorders are also frequent with approximately

65% of individuals with AN having some form of anxiety disorder. Anxiety disorders are present in between 36 and 58% in individuals with BN. Among the anxiety disorders, obsessive-compulsive disorder is most commonly associated with AN and social phobia with BN [22, 23]. Comorbid psychiatric diagnoses also persist after recovery from eating disorders and are an appropriate target of treatment [24–28].

Potential Biological Contributions to the Etiology of Eating Disorders

Despite the focus of most research on psychological and psychosocial risk factors for eating disorders, investigators have begun preliminary examinations of biological factors related to the development and maintenance of these disorders. Genetic, neurotransmitter, and neurocognitive examinations are underway that may ultimately increase both the understanding of the etiology of eating disorders as well as identify potential targets for novel treatments.

Genetic Studies of Eating Disorders

Familial and genetic factors are often difficult to disentangle even with the use of adoption studies, which are methodologically difficult to conduct in the case of uncommon disorders such as AN. A family history of AN appears to be a risk factor for AN [29, 30]. However, this could be due to genes, environment or both. Family aggregate studies suggest AN is familial and that genetics might account for more than 50% of the heritable risk for becoming afflicted with AN [31, 32]. An exact mechanism for the genetic basis of AN is unclear, but this elevated heritability risk is probably linked to inherited vulnerabilities to temperament and anxiety [33]. Heredity estimates are similar for BN and unknown for EDNOS [34].

Twin studies elucidate whether disorders run in families, however it leaves uncertain if this is due to shared genes or shared environment. Studies have shown an up to tenfold increased risk for first-degree relatives of individuals with AN than relatives of unaffected individuals [35]. Evidence of familial aggregation emerged for both AN and BN, with a higher relative risk for AN [31]. Furthermore, additional studies have demonstrated co-aggregation of the two disorders, thus relatives of individuals with an eating disorders have higher risk for a range of eating disorders rather than for a specific disorder [32].

Linkage studies can identify the genomic regions that might allocate predisposing or protective genes and does not require a priori assumptions about the nature and locations of genes. Linkage studies require large samples. Genetic markers are genotyped and used to identify chromosomal regions. Genes known to be in these chromosomal regions become positional candidate genes. A recent broad review of genetic studies in AN found an association with a susceptibility locus on chromosome 1 for classic restrictive AN. Another linkage study showed an association on chromosome 1 (serotonin 1D receptor HTR1D; delta opioid-receptor), 2 and 13 for drive for thinness

and obsessionality [31]. There is one published linkage study of BN reporting significant linkage in chromosome 10 [31]. These early findings are exciting, but preliminary, and require replication.

Association studies require a substantial prior knowledge of the pathophysiology of a disease. These studies are designed to compare genotype frequencies in cases and controls. Existing studies of eating disorders have generally targeted genes involved in feeding, appetite and mood. Serotonergic, dopaminergic and genes involved in neuropeptide and feeding regulation, namely ghrelin, hypocretin receptor-1 and opioid receptor-δ1, have been tested in association studies. Currently, the accumulated data do not support the involvement of ghrelin or hypocretin receptor-1 in the etiology of AN. The involvement of the opioid receptor δ1 was shown in yet another study. Each of these studies was small and replication of the findings is needed to understand the significance of the results.

Neurotransmitter Studies

Examination of the role of neurotransmitters in the etiology of eating disorders has been initiated. Disturbances in serotonin (5-hydroxytryptamine or 5-HT) pathways may contribute to the development of AN [36]. Impairment of serotonin pathways is associated with many behavioral characteristics that are known to correlate with AN [37], including changes in impulsivity, obsessive-compulsivity, anxiety, depression, fear, rumination, and disturbed appetite regulation. Data suggest that for both AN and BN, 5-HT is impaired [38, 39]. In addition, low concentrations of 5-HT metabolites in the cerebrospinal fluid are commonly found in eating disorder populations [40]. Unfortunately, no specific conclusions about the link between abnormalities in the serotoninergic neurotransmitter system and eating disorders can be made. Further, the usefulness of antidepressant medications targeting this system, at least for AN, also remains uncertain. On the other hand, patients with BN show abnormalities in the orbital-frontal serotonergic circuits, which are known to contribute to behavioral dyscontrol [41]. Hence, the use of serotonergic agents for BN, which have been shown to be useful, have data supporting a biological rationale for their use [42]. The dopaminergic system has more recently received increased attention in eating disorders [43]. AN patients appear to be hypersensitive to novel stimuli leading to a theory that AN patients may exhibit hypersensitive dopaminergic systems which dictate obsessive-compulsive thinking, enjoyment, and the reward system. Additional study of dopaminergic systems is needed to elucidate the role this neurotransmitter system may play in contributing to the increased vulnerability for AN.

There is evidence that there may be a biological and neurochemical basis for disinhibition in BN based on a number of studies of serotonin that suggest that lower levels of this neurotransmitter increase disinhibition in a variety of disorders including alcoholism, obsessive-compulsive disorder, attention deficit/hyperactivity disorder, depression, and sexual abuse [44, 45]. In relation to eating disorders, low serotonin increases carbohydrate cravings and appetite, leading to appetitive disinhibition or

counterregulation. Jimerson et al. [46] found lower levels of the metabolites of serotonin in the CSF of BN patients compared to healthy controls. Other psychobiological investigations comparing patients with BN with healthy control subjects have demonstrated diminished CNS serotonergic activity as manifested by blunted neuroendocrine responses to a serotonergic agonist [46–48]. Further, a higher frequency of binge eating episodes is associated with decreased serotonergic responsiveness [49]. More recently Kaye et al. [39] described continued alteration in serotonin after recovery from BN. Other reports have suggested that serotonin dysregulation is state-dependent wherein those who are actively binge eating and purging have lower levels than those who are remitted or healthy controls [50]. Indeed, the efficacy of antidepressant medications in decreasing binge frequency is believed to reflect the enhanced efficiency of signal transduction at serotonin synapses [51]. Functional MRI (fMRI) studies of receptor-binding sites found reduced orbito-frontal 5-HT2a receptor binding in recovered BN subjects that are similar to that found in borderline personality disorder and related to impulsiveness [52]. In addition, women with BN failed to show common correlations of age and 5HT2a binding, raising the possibility that women with BN may have alterations in developmental mechanisms of the 5HT system. Another study found reduced 5HT transporter binding in the thalamus and hypothalamus in ill BN subjects [53]. Reduced 5HT activity could reflect a trait disturbance involved in mood, anxiety, and impulse control.

Neuroimaging Studies

Other recent studies offer indirect evidence for the presence of a neural basis of eating disorder pathogenesis. fMRI investigations of AN patients have shown differences in their activation responses to stimuli such as food [54]. Also, studies that included PET and SPECT scans demonstrated that AN patients show neurotransmitter and, more commonly, neurotransmitter receptor abnormalities. Neuroimaging studies have disclosed the presence of enlarged sulci and decreased brain mass in AN patients who have reached the acute malnourished phase. Malnutrition and elevated cortisol are currently blamed for these phenomena; however, studies show that recovered patients never completely regain their grey matter mass after recovery [55, 56].

A few fMRI studies have investigated disinhibition in BN. In general, food craving-related signal changes in fMRI were identified in the hippocampus, insula, and caudate, three areas also reported to be involved in drug craving [57]. When images of food are presented to patients with eating disorders while being scanned, areas related to affective processing and the control and planning of behavior are activated, i.e. the limbic system, the anterior cingulate cortex (ACC), and prefrontal cortex (PFC), as opposed to the inferior parietal lobule and left cerebellum which were activated in the healthy comparison group [58, 59]. However, in BN, there is less activation in the dorsolateral region of the PFC which is an area that has been linked to inhibition [60, 61]. As the lateral PFC is involved in suppressing undesirable behaviors,

diminished activity in this region may account for the loss of control in the eating behavior of bulimic patients [61].

In addition, assessment of reward circuitry using fMRI has yielded some interesting preliminary findings related to impulsivity. Studies found activation in the lateral fusiform gyrus and inferior parietal cortex to body image cues was less marked in people with eating disorders and aversion ratings were positively correlated with activity in the right medial apical PFC [62]. Further, BN patients show increased sensitivity to appetitive motivational system in response to food that parallels findings in substance abuse. These results suggest that binge eating and substance dependence might share alternations in brain reward circuits [63, 64]. In addition, an fMRI study by Frank et al. [54] identified reduced ACC activity compared to controls in response to a glucose challenge in recovered bulimic subjects. The ACC is a cuneus area that is involved in error monitoring and also anticipation of reward. In the paradigm used by Frank et al. [54], the subjects knew which taste stimulus to expect, therefore higher activity in controls would suggest higher reward expectation by controls than anticipated by BN subjects.

Future fMRI studies might focus on better understanding of reward circuitry, the relationship between impulsivity and the subtypes of eating disorders, as well as continued examination of structural aspects of the brain during the recovery process.

Neurocognitive Impairments in Anorexia Nervosa

Neuropsychological research has established that AN is associated with cognitive inflexibility and an excessively detailed information processing style (weak central coherence), with a neglect of the overall picture (gestalt) [65–71]. These deficits are manifest both in the core psychopathology of AN and in other areas of patients' lives [72].

Interest in cognitive contributions to the evolution and/or maintenance of AN goes back at least to the clinical observations of Bruch [73]. Initially, cognitive impairment in AN was viewed as directly or indirectly related to malnutrition [55] and therefore expected to return to normal after weight restoration. This perspective has been increasingly challenged by findings from neuropsychological research which has documented similar types of impairments in both malnourished and weight restored patients with AN [18, 74–76]. These impairments generally consist of deficits in executive functioning associated with the PFC. Executive functioning includes processes that organize other cognitive processes such as inhibition, selective attention, goal setting, planning, set maintaining, decision making, and set shifting [68, 72]. Studies by Tchanturia et al. [65, 66] and Roberts et al. [68], among others, have focused specifically on impairments in set-shifting (perseverative style) and excessive focus on details (weak central coherence) in AN. Studies suggest that individuals with AN take significantly longer to set-shift than subjects with similar IQs who did not have AN [66]. Further, in longitudinal studies these difficulties persist in

women who recovered from AN [65, 66]. There is also good evidence that patients with AN demonstrate deficits related to an overly perseverative thinking style associated with excessive preoccupation with details to the neglect of the overall picture [74], sometimes referred to as a deficit in central coherence [77–79].

To date, only a handful of studies has examined potential mechanisms underlying weak central coherence in AN. These have focused exclusively on possible links between coherence problems and obsessive-compulsive personality traits in AN. Specifically, Tokley and Kemps [70] showed that obsessive-compulsive personality traits contributed to poor performance on the Object Assembly subtest in women with AN. Similarly, Lopez et al. [80] reported an association between obsessive-compulsive traits and poor coherence on the Rey-Osterrieth Complex Figure Test.

The application of these neuropsychological findings to clinical practice is just being developed. The use of cognitive remediation therapy (CRT) as a strategy to address deficits in preservative thinking, and weak central coherence has been proposed by Baldock and Tchanturia [81] and Tchanturia et al. [82]. CRT has been used effectively for related disorders such as obsessive-compulsive disorder [83]. In CRT, specific cognitive exercises are used to 're-train' the brain with the hope that these activities will lead to decreased cognitive rigidity enabling for participation in more specific therapies addressing the symptoms of AN. Preliminary data suggest that CRT may indeed be both acceptable and useful in these regards; however, definitive trials are needed to explore this question further [82, 84].

Temperament and Personality Characteristics in Anorexia Nervosa

Studies show that patients with AN are frequently perfectionists and have obsessive-compulsive personality traits as children before the onset of their eating disorder [19, 85, 86]. In addition, a substantial body of literature suggests that early onset anxiety disorders are a risk factor for the development of AN [76, 87–90]. A recent study found that 42% of those with eating disorders reported one or more anxiety disorders in childhood [91]. This is substantially higher than the frequency (4.7–17.7%) of overall anxiety disorders in childhood [92]. Similarly, as noted above, those with eating disorders have a higher frequency of childhood onset obsessive-compulsive disorder (23%) than community samples (2–3%) [93], and of childhood onset social phobia (13%) versus controls (0.6–5.1%) [92].

Moreover, a substantial number of studies [17–19, 39, 75] have found that recovered women with AN have anxiety, perfectionism, inflexible thinking, restraint in emotional expression, social introversion, and obsessions related to symmetry, exactness, and order. The persistence of these traits after recovery, and hence not associated with malnutrition, raises the question of whether a disturbance of such behaviors occurs premorbidly and likely contributes to the pathogenesis of AN. Family studies suggest that many of these traits are familial, with relatives of AN probands showing higher frequencies of anxiety [32], obsessive-compulsive personality, perfectionism [94], and negative emotionality [33].

There are many types of treatments used to address eating disorders in children and adolescents as well as a range of treatment intervention settings. Family therapy, individual therapy, group therapy and medications are used both separately and in combination with one another. Treatment settings include traditional outpatient settings as well as more restrictive settings, such as hospital, day hospital, and residential treatments, in order to control eating-related behaviors. In addition, treatment often includes other professionals working in a collaborative team, consisting of a psychotherapist, a child psychiatrist, a dietician, and a pediatrician. At the same time, few of these treatments have been systematically evaluated either in adults or children [95].

Specific systematic studies of treatments for eating disorders in children and adolescents are small in number but growing [95]. For BN in adults, evidence suggests that cognitive-behavioral therapy (CBT) and medications are helpful. For adults with AN, there is little evidence that anything is helpful [21, 96]. For AN among adolescents, family treatment of various types appear to be useful, though large randomized studies comparing treatments are not yet available [97–99]. For adolescent BN, there are two studies suggesting that adolescents respond to specific treatments (CBT and family therapy), but these studies are small and need replication [100, 101]. Family therapy has also been examined for adolescent BN and appears to be helpful [102, 103], though its superiority to CBT remains uncertain.

Medication Treatments for Eating Disorders in Children and Adolescents

There is almost no systematic research on medication treatments for eating disorders in children and adolescents. With regard to antidepressant treatment of AN, even the available adult studies are not encouraging. Older studies found no benefit of tricyclic antidepressants in terms of weight gain in hospitalized patients [104, 105]. More recently, studies of serotonin reuptake inhibitors (SSRIs) have demonstrated mixed results. Fluoxetine showed no benefit compared to placebo in hospitalized patients [106], even with the addition of tryptophan which was used in an effort to increase serotonin substrate [107]. Some studies have shown an increased time to relapse with fluoxetine treatment in patients who have been weight restored [108], but this result was not replicated in a recent large randomized controlled trial [109]. There have been no studies of fluoxetine in adolescents with AN.

The use of antipsychotics, particularly because of the potential for these medications to induce weight gain, has also been tentatively explored without much evidence of efficacy. Early studies of typical antipsychotics led to weight gain for patients with AN, but unfortunately patients had increased rates of seizures and purging [110]. In addition, risks of a prolonged QT interval and cardiac arrhythmias were seen with the typical agents. Case reports are available suggesting that the use of atypical antipsychotics may be useful both in adults and children with AN at low body weights [111, 112]. Improvements in treatment adherence, decreases in agitation and anxiety were

reported with olanzapine at a dose of 2.5 mg in four patients aged 10–12 years. In adult patients with AN, there have been several open trials of olanzapine [107, 113, 114] and one randomized trial in which olanzapine (10 mg average dose) was compared with chlorpromazine (50 mg average dose) [115]. This randomized controlled trial demonstrated that that the group treated with olanzapine had decreases in rumination; however, no differences in weight were seen.

For adults with BN, antidepressants of various types have been shown to be efficacious. Fluoxetine is the most commonly used medication for adults with BN and has received approval from the FDA for treatment of adults with BN. It has been shown to be effective in reducing bulimic symptoms in two 8-week double-blind trials [116], and in one 16-week double-blind trial [117] at a dose of 60 mg/day. In addition, data from a long-term follow-up study over a 1-year period suggest that for those who had responded to fluoxetine, there was increased time to relapse. The mechanism of action of SSRIs in BN appears to be reducing binge eating and purging frequency [118]. At the same time, the effectiveness of fluoxetine does not appear to be related to the presence of a comorbid depression [117]. There has been only on one small pilot study evaluating the use of fluoxetine in adolescents with BN. The results of this small case series suggested that fluoxetine was well tolerated and reduces symptoms in adolescent BN [119].

Thus, for AN, no medication treatments are indicated as a first-line intervention. Current studies demonstrate problems with the acceptability of medications by AN patients, with dropout rates of over 50% in most studies [120]. Thus, it is indeed possible that for some AN patients medications are helpful, though identifying this subset remains a challenge. However, comorbid conditions may well respond to appropriated medications. For BN, antidepressants, particularly SSRIs, are effective [42] in adults and appear to be safe for use in adolescents. In comparing the effectiveness of CBT to antidepressants, CBT is superior to medication alone, though antidepressants are more cost-effective according to one study [121, 122].

Summary and Conclusions

Eating disorders in children and adolescents are an increasingly prevalent and serious mental health problem. The biological underpinnings of these disorders are poorly understood; however, recent studies suggest strong familial and genetic components in eating disorders. Further studies of neurotransmitters, neurocognitive deficits, and pharmacological interventions demonstrate several important avenues for future research. Investigating these biological substrata may well lead to an enhancement of the current effective treatments or the development of novel treatment approaches, including new medications targeting specific neurotransmitter deficits or cognitive remediation therapies aimed at neurocognitive deficits. Basic brain research aimed at obsessionality, rigidity, symmetry, and perfectionism may help to identify

commonalities between anxiety and eating disorders. Such phenotypic studies may also lead to a deeper and more complex understanding of the interaction between brain and behavior in eating disorders.

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Conduct Disorder

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Abstract

Biological research on conduct disorder has been making vast progress over the last two decades. We discuss findings from recent studies in the fields of genetics, psychophysiology/neuroendocrinology and neuroimaging. Possible implications for current psychiatric assessment methods and directions for future research are brought forward.

Conduct disorder (CD) is defined by a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated. Criteria fall into the following categories: aggression to people and animals; destruction of property; deceitfulness or theft, and serious violation of rules (DSM-IV). CD is a disruptive behavior disorder (DBD), together with the oppositional defiant disorder (ODD), which is characterized by a pattern of negativistic, hostile, and defiant behavior toward authority figures. From a developmental perspective, ODD has been postulated as a precursor of CD [1], with CD itself being a precursor for antisocial personality disorder (APD) [2]. Both CD and ODD are amongst the predominant juvenile disorders seen in mental health and community clinics [3, 4]. Prevalence rates observed in studies have varied largely, depending for example on age, socioeconomic status and gender, with rates varying from 1.8 to 16% in boys and 0.8 to 9.2% in girls [1]. As such, contrary to popular notion, CD is not only common in boys but also in girls, especially in clinical settings [5].

Children diagnosed with CD are not only of concern because of their risk for developing APD, but also because of their likelihood of showing other negative outcomes in adulthood, for example criminal behavior, social isolation, unemployment, and psychiatric disorders such as depression, anxiety disorders and substance abuse [6]. Moreover, they constitute a major public health problem, as these children cost society at least ten times as much as well-developing children [7] and may cause physical or

psychological problems to victims of their behavior. Currently, although the short-term effectiveness of intervention strategies (e.g. parent managing training, cognitive behavioral therapy) has been demonstrated [8], the long-term effectiveness of treatment is considered to be limited, although this has hardly been investigated [9].

Therefore, research aimed at increasing our understanding of the factors influencing the development and persistence of CD is warranted. Although a large body of literature has shown that antisocial behavior can be partly explained by psychosocial factors [10], research over the past decades has increasingly shown the importance of taking into account neurobiological mechanisms as well [11]. Therefore, contemporary models of antisocial behavior comprise both social and biological factors, reflecting the assumption that both types interplay in a complex fashion to influence the development and persistence of antisocial behavior [12]. In this chapter, we summarize recent findings on the biology of CD, focusing on the fields of genetics, psychophysiology/neuroendocrinology and neuroimaging. Because biological research on CD children has been scarce, we include relevant studies in juveniles with otherwise defined antisocial behavior patterns (e.g. DBD, criminal behavior, aggression) and antisocial adults (e.g. psychopaths, criminals).

Genetics

Twin studies, adoptive studies, studies in twins reared apart, and molecular genetic studies clearly support the notion that there are genetic influences on antisocial and aggressive behavior [1, 13, 14]. Still, heritability estimates (i.e. the magnitude of genetic influences) vary largely from one study to another [15]. Significant progress in our understanding of these two issues, and the mechanisms through which genes exert their effect on antisocial behavior, is likely to be made in the near future for three main reasons.

First, researchers have started to disentangle which distinct subtypes and aspects of antisocial behavior are particularly under genetic influence. For example, genetic influences were suggested to be greater for life course-persistent antisocial behavior than for adolescent-limited antisocial behavior [16], and greater for aggressive antisocial behavior than for non-aggressive antisocial behavior [17].

Second, investigators have started to study associations between specific genes and antisocial behavior. As a result of technological advances, a large number of genetic markers are now available for studying DNA polymorphisms, while new laboratory techniques allow for rapid genotyping; the process of identifying which alleles are present for any given marker for a particular person. As such, in general medical research, an increasing number of genetic variations are being associated with syndromes. With respect to antisocial behavior, Brunner et al. [18] reported a single-gene mutation in the gene encoding the neurotransmitter-metabolizing enzyme monoamine oxidase A (MAOA) in an extended Dutch family in which multiple members exhibited violent

criminal behavior. However, particularly in psychiatry, such isolated mutations are rare [19] and it is clearly not plausible to consider them as major determinants of multifactorial conditions like antisocial behavior. Indeed, today's precision of genetic research techniques makes it increasingly apparent that multiple genes are simultaneously involved in creating susceptibility for antisocial behavior.

Third, investigators have started to acknowledge the interplay between genetics and the environment, i.e. whether or not genetic susceptibility leads to antisocial behavior may depend on the influence of environmental factors. Just like a genetic susceptibility for lung cancer may only result in disease after smoking cigarettes, a genetic susceptibility for antisocial behavior may remain latent in the absence of 'bad' environmental factors like harsh parenting or living in a criminal neighborhood. Importantly, for a person with both a genetic risk factor and an environmental risk factor for antisocial behavior, the actual risk for developing antisocial behavior may be far more than just the sum of the two [20, 21].

An illustrating example, incorporating both the influence of a specific gene and its interaction with the environment in relation to antisocial behavior, is a recent highly influential study by Caspi et al. [22]. A large sample of male children in New Zealand was studied from birth to adulthood on a functional polymorphism in the gene encoding MAOA. Maltreated children with a genotype conferring high levels of MAOA expression were found to be less likely to develop antisocial problems than maltreated children with a genotype conferring low levels of MAOA expression. As such, these findings provide evidence that specific genotypes can moderate children's sensitivity to environmental insults, which may partly explain why not all victims of maltreatment grow up to victimize others. The recently increased interest in this kind of biosocial interactions is reflected in the fact that the findings of this study have already been replicated in humans [23] and in rhesus monkeys [24], although one human study did not find the same effect [25].

An interesting interaction effect of a different kind is imbedded in the 'social push' theory. Under this perspective, when an antisocial child lacks social factors that 'push' or predispose him/her to antisocial behavior, then biological factors may be more likely to explain antisocial behavior [26, 27]. In contrast, in those exposed to adverse early home conditions, social causes of criminal behavior may be more important explanations of antisocial behavior. This is not to say that antisocial children from adverse home backgrounds will never show evidence of biological risk factors for antisocial and violent behavior, they clearly will. Instead, the argument is that in such situations the link between antisocial behavior and biological risk factors will be weaker (relative to antisocial children from benign social backgrounds), because the social causes of crime camouflage the biological contribution. Evidence supporting this theory comes from studies in various sub-fields of research. Within the field of genetic research, Christiansen [28] found heritability for crime in a Danish sample of twins to be larger in (a) those from high socioeconomic backgrounds and (b) those who were born in a rural setting.

At present, vast progress is being made in our knowledge of genetic contributions to antisocial behavior and the interplay of genetic factors with the environment. The exact mechanisms through which genetic factors lead to antisocial behavior, though, are not well understood yet, and prove to be very complex.

Psychophysiology and Neuroendocrinology

A number of psychophysiological and neuroendocrinological correlates of aggressive, antisocial, and violent behavior have been reported, although findings have not always been consistent [11, 29–32]. Several studies however have related antisocial behavior to low serotonin [33], high testosterone [34], and low epinephrine [35]. As discussing the whole range of findings in the different areas involved would be too lengthy and because current insights do not provide clear conclusions to be drawn, a specific subgroup of psychophysiological and neuroendocrinological factors will be focused on in this chapter: those related to arousal.

The arousal theory postulates that low arousal is related to antisocial behavior. Two explanations have been put forward for this assumption. First, the sensation-seeking theory argues that low arousal represents an unpleasant physiological state. As such, antisocial behavior is viewed as a mode of sensation seeking, which is displayed in order to increase arousal levels to an optimal or normal level [36–38]. Second, the fearlessness theory argues that low levels of arousal, as measured for example during mildly stressful psychophysiological test sessions, are markers of low levels of fear [11, 38]. For example, fearless individuals such as bomb disposal experts were found to have particularly low heart rate levels and reactivity [39]. Antisocial and violent behavior (e.g. fights and assaults) is considered to require a degree of fearlessness to execute, and lack of fear of socializing punishments in early childhood may contribute to disturbed fear conditioning and lack of conscience development [11]. For a more extensive overview of the underlying theoretical framework see, Raine [11, 27].

The most studied biological parameter of arousal is heart rate, a measure of autonomic nervous system (ANS) activity. Moreover, low heart rate is the most frequently replicated biological correlate of antisocial behavior in children and adolescents [40]. Importantly, a low heart rate has repeatedly been shown to predict antisocial behavior, opposing the notion that living a delinquent way of life may have caused low heart rate [41]. For example, one study showed that the resting heart rate as early as at age 3 years relates to aggressive behavior at age 11 years [42]. Moreover, an important feature of the relationship is its diagnostic specificity, as CD appears to be the only psychiatric disorder to have been linked consistently to a low heart rate.

Although a low heart rate has been found to be a predictor of violence independent of other social risk factors, there is accumulating evidence that a low heart

rate, similar to genetic susceptibility as described above, interacts with social factors in relation to antisocial behavior. For example, boys with low resting heart rates are more likely to become violent adult offenders if they also have a poor relationship with their parent, and if they come from a large family [43]. Furthermore, boys with a low heart rate are especially likely to be rated as aggressive by their teachers if their mother was a teenage parent, if they come from a low socioeconomic status family, or if they were separated from a parent by age 10 years [43]. Moreover, studies of arousal also support the social push perspective. Although the resting heart rate level is generally lower in antisocial individuals, it is a particularly strong characteristic of antisocial individuals from higher social classes [38, 44].

In line with findings from studies on heart rate, other direct and indirect parameters of arousal, including resting EEG [45] and skin conductance activity [11], have been related to antisocial behavior as well. An interesting and recently increasingly investigated neuroendocrinological parameter related to arousal is cortisol; the final product of the hypothalamus-pituitary-adrenal (HPA) axis. Together, the ANS and the HPA axis constitute the two most important arousal-regulating biological systems in humans. In line with the arousal theory, several studies have found low basal cortisol levels, particularly in the morning, to be associated with antisocial behavior in clinical-referred, delinquent, and general population samples of children and adolescents [46–48]. Also, a blunted cortisol responsiveness to stress has been found in clinical-referred CD children [49] and arrested delinquent DBD adolescents [50]. To date one study has investigated the effect of cortisol levels on future antisocial behavior and found low cortisol levels at age 10–12 years to predict aggression at age 15–17 years [51].

As with genetic and ANS factors, hormonal factors are likely to interact with additional factors in relation to antisocial behavior. These additional factors may be social but also biological. For example, cortisol was found to influence the relationship between testosterone and aggression, such that a significant relationship between testosterone and aggression was only present at low levels of cortisol but not at high levels of cortisol [52]. So far, only one study investigated how cortisol levels interact with social factors in relation to antisocial behavior. Scarpa and Ollendick [53] found that high cortisol after a stressor was associated with aggression in victims of community violence, but not in non-victims. Moreover, relationships between testosterone and risk-taking behavior and CD symptoms have been shown to vary depending on the quality of the parent–child relationship [54] and the presence of deviant peers [55].

Summarizing, psychophysiological and neuroendocrine factors have been shown to relate to aggressive and antisocial behavior. As with genetic correlates, interaction effects with social and biological factors have been found. As such, this research underscores the complexity of the field, and the necessity to pursue the growing research initiatives.

Neuroimaging

Neuroimaging is a growing and increasingly influential sub-area within biological research on antisocial behavior. With respect to CD, imaging studies have predominantly focused on two theoretical constructs: lack of empathy, and deficient emotional regulation. Findings from recent studies derive from two types of neuroimaging techniques: structural (studying the size and shape of brain structures) for example by using MRI, and functional (studying the performance of brain structures) for example by using functional MRI (fMRI).

Lack of Empathy (Amygdala, Anterior Insular Cortex)
The propensity toward antisocial and aggressive behavior was shown to be associated with a lack of empathic response to the suffering of another [56], which is likely to result from a structural or functional deficit in the neural circuits involved in recognizing emotional expressions of distress in other people such as the amygdala and the anterior insular cortex (AIC) [57–59]. While fMRI studies in aggressive and antisocial adults have found evidence for this notion [60–62], similar research in children and adolescents is scarce. So far, only one functional study in adolescents with CD was performed, and was in line with findings in adults [63]. In addition, a structural study in adolescents showed a significant reduction in grey matter in bilateral AIC and the left amygdala in CD patients compared to healthy subjects [64]. Interestingly, bilateral insular grey matter volume in adolescents with CD correlated significantly with empathy scores.

Deficient Emotional Regulation (Orbitofrontal Cortex, Anterior Cingulate Cortex)
In addition to a lack of empathy, functional deficits in brain regions involved in the regulation of emotional behavior, such as the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) may underlie aggressive and antisocial behavior [59]. Findings from lesion studies suggest the OFC to be involved in constraining affective impulses through its connections with other prefrontal regions and the amygdala [65]. In line with this theory, studies in antisocial and psychopathic adults showed structural [66] and functional [61, 67] deficits in OFC.

There is a body of evidence showing the ACC to be important in regulating cognitive and emotional processes [68]. Abnormal functioning of this region has been observed in APD patients [62] and adult criminal psychopaths [61]. The same result was found in a study of CD adolescents [63].

Summarizing, results from the few neuroimaging studies in CD adolescents that have been performed to date suggest structural and/or functional deficits in regions involved in empathy (amygdala and AIC) and emotion regulation (OFC and ACC). As for genetics and psychophysiology/neuroendocrinology, the biological correlates of antisocial behavior found in brain imaging research are likely to be even more informative when interactions with environmental factors are taken into account [12].

For example, one functional study in adults showed that a biological risk factor (right hemisphere dysfunction), when combined with a psychosocial risk factor (severe early physical abuse) predisposed to serious violence [69]. At present however, studies using neuroimaging techniques to investigate aggressive and antisocial behavior in children and adolescents have been scarce. In order to investigate interaction effects, a prerequisite will be to increase the sample size of studies as well.

Implications of Biological Research for Clinical Practice

Although our understanding of the biological underpinnings of CD and related behavior problems is rapidly increasing, the implications for clinical practice are still unclear and often debated. Obviously, it is to early to draw firm conclusions on how findings from biological studies may be translated to patient care, although the contours of potential clinical usefulness may be outlined [70]. In the next paragraphs, this will be done in relation to four crucial tasks of (forensic) psychiatric assessment: (1) diagnostic identification; (2) providing treatment options; (3) risk taxation, and (4) treatment evaluation.

Diagnostic Identification

For several reasons, biological factors may be of use in the process of diagnostic identification. First, they may bring an innovative diagnostic perspective for conditions that are extremely difficult to evaluate. For example, callous and unemotional traits are intricate and difficult to assess by means of an interview or paper and pencil questionnaires. Especially in forensic settings, a tendency towards socially desirable answering may hamper the evaluation of these crucial characteristics. As callous and unemotional traits have been related to parameters such as blunted heart rate reactivity, biological measurement may enable the development of objective measurement methods [32]. Furthermore, neuroimaging research is beginning to identify the structural and functional correlates of pathological lying and malingering that, at least in theory, could have long-term future implications for subtyping characteristics that underlie antisocial behaviors [71, 72]. As such, using parameters of neurobiological functioning may help to identify psychobiological deficits for which no sound psychometric instrument is available at present.

Second, diagnostic assessment may reach a more clear and valid differentiation when biological factors are taken into account. It is widely accepted that psychiatric disorders in general, and hence also externalizing disorders, are developmentally heterogeneous. At present, this heterogeneity hinders research, assessment and treatment, because specific characteristics or outcomes of subgroups may not appear because distinct subgroups are lumped together. Using biology to define subgroups of patients may make it possible to detect relatively homogenous subgroups, resulting in the possibility of detecting specific markers and outcomes for this subgroup. For

example, with respect to aggression, a wealth of research has focused on the differentiation of subtypes of aggression, e.g. proactive versus reactive, without satisfying and clinical useful result. Therefore, recent research has focused on specific neurobiological profiles for these groups.

Evidently, developing tools for diagnostic differentiation is not just an academic exercise, but of particular relevance for each of the three following tasks crucial to psychiatric assessment.

Providing Treatment Options

Improvements in diagnostic identification resulting from neurobiological assessment may simultaneously benefit the selection of optimal effective treatment alternatives for a specific individual. Moreover, it may stimulate the development of new intervention approaches.

First, improving our knowledge on biological factors of antisocial behavior may help to target appropriate interventions to specific subgroups of patients. In many sub-fields of somatic clinical practice biological markers are already standard determinants of intervention. For example, in cancer treatment, somatic markers are used to choose the most effective chemotherapeutic agent. In psychiatry, researchers have now also started to investigate biological markers as predictors of treatment outcome. For example, in depressed patients, pretreatment baseline prolactin levels have been shown to predict the response to antidepressant treatment [73], suggesting that subtyping specific patient groups based on this biological profile can improve the effectiveness of treatment.

Notably, this idea may not only be relevant for pharmacological treatment programs, but also for psychotherapeutic interventions. Preliminary evidence for this assumption comes from a study by Van de Wiel et al. [74], who studied cortisol responsiveness during stress in 22 clinically referred behavior disordered children before psychotherapeutic treatment. They found that low cortisol responsiveness during stress predicted poor treatment outcome. As such, the subgroup of children with this biological profile might need other forms of treatment than those with a strong cortisol response to stress.

Second, new treatment possibilities may arise, as biological factors that are related to antisocial behavior may be taken as direct foci of intervention. For example, as discussed above, low arousal has been related to antisocial behavior. There is evidence that stimulants, e.g. methylphenidate, both increase arousal and reduce aggressive behavior [75]. As such, progress in pharmacological treatment possibilities may be established by improving our knowledge on the actual underlying biological deficits, in combination with the possibility of detecting individuals who can benefit from such interventions.

In addition, understanding the biological vulnerabilities in juvenile antisocial behavior can also lead to new non-pharmacological intervention approaches. For example, some evidence supports the efficacy of biofeedback for increasing physiological arousal in hyperactive children [76]. With respect to HPA activity, preliminary

evidence for the potential of non-pharmacological programs to alter biological vulnerability for antisocial behavior has been provided by Fisher et al. [77] in a study evaluating a foster care intervention program. A group of aggressive maltreated juveniles were found to have a flattened diurnal pattern of cortisol levels before entering the program. After the intervention, diurnal cortisol patterns were found to be more normal, with high cortisol levels in the morning and a decrease during the day, while aggression levels had diminished. As such, a non-pharmacological intervention effectively influenced a biological profile. Additional indirect evidence for this assumption comes from prevention studies. For example, there is initial evidence that positive environmental manipulations are capable of both producing long-term shifts in arousal and psychophysiological information processing as well as adult criminal behavior. In one study, children were randomly assigned to experimental and control conditions and matched on early psychophysiological functioning, a nutritional, physical exercise, and an educational enrichment program from ages 3–5 years; this enrichment resulted in increased psychophysiological arousal and orienting at age 11 years, and reduced crime at age 23 years [78].

Summarizing, gaining insight into the biological basis of antisocial behavior may extend the range of treatment alternatives and improve effectiveness by giving the right intervention to the right person.

Risk Taxation

A specific task of forensic assessment is not only to detect psychiatric problems and provide optimal treatment, but also to predict recidivism. In situations were forensic assessment is ordered by judicial authorities, it is obligatory to assess the likelihood that an individual will commit new crimes in the future. At present, a range of instruments is used for this purpose. Although current research has shown these instruments to predict future delinquency, results are at most moderate. Reasons for this are the difficulty to assess conditions related to recidivism (e.g. empathy or callous unemotional traits), as well as the heterogeneity of the population. Research in related fields has proven that neurobiological parameters may be of help in this respect. For example, a heightened cortisol response to dexamethasone post-treatment levels was found to predict earlier relapse of depression [79]. In another study, Prichep et al. [80] distinguished two separate subgroups of cocaine-dependent males on the basis of a qualitative electroencephalogram. By using this biological typology, they were able to predict the relapse rate after treatment. Longitudinal investigation of neurobiological parameters related to aggression and antisocial behavior, as described before, may similarly offer possibilities in the field of forensic psychiatry. Of course, ethical issues may arise, as each prediction will always be imperfect. Even the most optimal cutoff point will classify future non-recidivists as at risk, while future recidivists will not be recognized as such. Although this issue arises for prediction in other fields as well, the issue is crucial in forensic psychiatry, as the risk of predicting fault may bear grave consequences for both the subject under investigation as well as the future victim.

Treatment Evaluation

When a specific biological profile is correlated with the condition before treatment, reassessing this profile post-treatment may aid the evaluation of treatment outcome and effect. As discussed above, Fisher et al. [77], suggested that successfully diminishing aggressive behavior by means of a foster care intervention program coincided with normalization of diurnal cortisol patterns. As such, cortisol levels may be a parameter that could inform practitioners on treatment efficacy. Again, no studies to date investigated the potential of biological parameters to evaluate treatment outcome with respect to CD.

In summary, though largely hypothetical at this moment, evidence from studies in general medicine and several subfields of psychiatry support the notion that biological parameters may bear clinical relevance in (forensic) psychiatry. When considering future research in this area, practical issues need to be taken into account. For example, some of the biological factors discussed above are difficult to assess, e.g. brain imaging, particularly in forensic conditions with individuals who are unwilling to collaborate and/or who pose an immediate threat to society. However, other methods are fairly simple, quick, and cost-efficient; most genetic tests only require a swab with some cells from the oral cavity, heart rate can be measured by taking the pulse by hand or with a simple chronometer, while cortisol and several other hormones can non-invasively and reliably be analyzed from saliva.

Conclusions

Evidence is accumulating to show that biological parameters, in interaction with psychosocial factors, play an important role in the development and persistence of CD. As insights are still largely incomplete and often inconsistent, additional studies with larger sample sizes, both in adolescents and in children, are warranted. Moreover, research should focus on the possible clinical relevance of such research, with respect to the diagnostic identification, improving treatment options, risk taxation, and evaluation of treatment effects.

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Substance Use Disorders in Adolescence

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Abstract

Substance use disorders (SUDs) are most prevalent among adolescents worldwide. Adolescent SUDs can be chronic disorders, resulting in diverse negative outcomes. Adolescents with SUDs generally present one or more psychiatric comorbidities, the most prevalent of which are disruptive behavior disorders. SUDs in adolescents have a multivariate etiology, in which neurobiology plays a relevant role. In this selective review of the literature, we discuss several studies documenting the effects of dopaminergic system dysfunctions, genetics, intrauterine exposure to drugs, psychiatric comorbidity, age at the first consumption, and other issues on further SUDs. An understanding of how neurobiology and/or environmental factors influence SUD onset and progression can contribute to guide governmental policies toward drugs and preventive SUD approaches. There is support in the literature for different specific SUD interventions and some medications have been systematically used in adolescents with SUDs, despite the clear need for more pharmacological trials in this population.

According to the World Health Organization (WHO) [1], psychoactive substances (PSs) are substances that 'when taken in or administered into one's system, affect mental processes, e.g. cognition or affect'. They include both licit and illicit substances, although in most countries the use of any PS by adolescents is not allowed despite being a 'licit' (such as alcohol) or 'illicit' (such as cannabis) substance.

The first drug contact generally occurs during the adolescence, since this developmental period offers a special context for that [2]. Adolescent substance use disorders (SUDs) are a major mental health concern [3, 4] and one of the most prevalent disorders in adolescents [5]. Usually, adolescents start experimenting with adult licit (legal) drugs (alcohol and/nicotine) and, afterwards, some will experiment

with illicit drugs. A subgroup will move on to repeated drug use and SUDs. According to the WHO, the main PSs consumed are nicotine, alcohol and cannabis [6]. In the United States about 3,000 adolescents begin to smoke per day, of which 30% turn into regular users [7]. Over 80% of American adolescents have already used alcohol by the end of high school [8]. In Australia, 60% of adolescents have already tried cannabis [9]. The presence of SUDs has been associated with several negative outcomes: higher criminality rates [10], motorcar accidents [11], school dropout [12], exposure to traumatic situations [13], exposure to sexually transmittable diseases and pregnancy [14], and suicide [15]. The frequent use of cannabis has resulted in higher chances of developing depression and anxiety in Australian students [9].

According to the DSM-IV, SUDs reflects a diagnosis of abuse or dependence of drugs [16]. For a dependence diagnosis, the adolescent must present three of seven symptoms (such as tolerance, withdrawal, or persistent use despite adverse consequences). For a diagnosis of abuse, the adolescent must have a repeated pattern of drug use resulting in one or more (of four) symptoms (such as legal problems). The diagnosis of dependence is sovereign over the diagnosis of abuse. Although lately the majority of studies rely on SUDs diagnoses from DSM-IV-TR criteria, some empirical data have suggested the need of a diagnostic system to deal with specific issues relating to adolescents, such as the developmental context of use and a variable distribution of SUD symptoms, since DSM-IV was developed based on adult substance use behavior and its sequelae [17]. Thus, when evaluating a SUD diagnosis, especially in a clinical practice setting, clinical judgment is recommended. Finally, some studies present alcohol as a separated category (alcohol use disorders), in order to distinguish it from illicit drug use. Although generally, SUDs have common pathways, research has suggested different patterns of preceding comorbidity and genetic influence according to drug category (for example, alcohol or cannabis), and for experimentation, abuse or dependence. Thus, when etiological studies combine drug categories and clinical presentation, some specificity is lost.

The Role of Psychiatric Comorbidities

Usually an adolescent with SUDs will have a psychiatric comorbidity. The comorbidities can just coexist with SUD, have an etiological influence or might be a consequence of drug use. The comorbidities often have a negative impact on SUD, with higher rates of treatment, impaired role functioning, suicide attempts, and academic problems [18].

There are several studies suggesting that certain psychopathologies precede early experimentation (before 13 years of age) or the regular use of drugs. Considering only experimentation with a PS, a strong association with an oppositional defiant disorder (ODD; OR 4.2, 95% CI 1.0–17.8) is found [19]. It is known that the

presence of a mental disorder in childhood is associated with the regular use of marijuana during adolescence (17.3 vs. 21.5%; RC 1.87, 95% CI 1.17–2.98, $p < 0.008$) [20]. The dependence of PS is higher in children/adolescents with conduct disorder (CD; OR 6.0, 95% CI 1.7–20.9), ODD (OR 4.1, 95% CI 1.1–14.7), attention deficit/hyperactivity disorder (ADHD; OR 3.6, 95% CI 1.0–13.5), affective disorders (OR 3.2, 95% CI 1.1–9.3), and anxiety disorder (OR 5.5, 95% CI 1.8–16.3) [19]. Among psychopathologies, CD is the best established as conferring a risk of developing SUDs [21, 22]. Recently, it was reported that a diagnosis of CD between 11 and 14 years of age was a powerful predictor of substance disorders by 18 years of age (OR $>$ 4.27), even adjusting for potential confounders [23]. Bipolar disorder is also related to the development of dependence of SP [19]. It is important to note that there might be an interaction between gender, age and comorbidity. For instance, anxiety increases the risk of SUD in girls at age 16 years, but not before that [24].

It is interesting to note that there are contradictory data in the literature regarding ADHD as an independent risk factor for SUDs, when adjusting results for the presence of CD. CD is highly prevalent among adolescents with ADHD [24–26] and some evidence suggests that only those ADHD youths with comorbid CD would be at a higher risk. Interestingly, studies trying to disentangle the role of ADHD in the development of SUD have contradictory results. In a longitudinal community-based study in New Zealand [27], it was found that ADHD had no effect over SUD liability. In Brazilian adolescents, however, ADHD was associated with a significantly higher OR for illicit SUD, even when results were adjusted for the presence of CD (OR 9.12, 95% CI 2.84–29.31, $p < 0.01$) [28]. A recent study in the USA replicated these findings, demonstrating that a categorical diagnosis of ADHD was associated with a higher OR for nicotine (OR 2.1) and illicit PS (OR 2.82), independent of the presence of CD [23]. Thus, although there is no doubt about the effect of CD and ODD on the liability for further SUD, the debate remains open regarding the place of ADHD as a risk factor for SUD in adolescence and later life.

Another interesting point is the association between trauma exposure in childhood/adolescence and further SUDs. It is well documented that children/adolescents who have been exposed to traumatic events have a higher prevalence of SUDs [29–31]. Although the occurrence of SUDs in a traumatized child/adolescent may be the result of the interaction between several variables, trauma exposure causes neuroendocrinological changes that, in turn, might be associated with higher drug propensity. De Bellis [32] mentions that in a developing brain, elevated levels of catecholamine and cortisol (as a result of a traumatic event, such as maltreatment or sexual abuse) may lead to adverse brain development which will result, through different pathways, in maturation failures in the frontal and prefrontal cortex. These stress-induced mechanisms will cause executive impairments which are clearly implicated in SUD liability, as will be discussed latter.

Neurobiology

The dopamine (DA) system has long been implicated in alcohol dependence and other substance dependences [33–36]. DA-regulated areas such as the basal ganglia and frontal areas are affected in SUD subjects [37]. Executive [38] and reward system (RS) functions [37] have a strong influence on SUD liability. Thus children with cognitive dysfunctions (such as ADHD or CD) might be in high-risk drug use situations, probably as function of poor judgments and a tendency to sustain a behavior despite negative consequences [39]. An adolescent with ADHD, for example, might have more difficulties in accurately evaluating the negative consequences of drug use or a high risk situation for drug use, which is an important mechanism in order to avoid drug use. If the adolescent does not properly realize that drug use is resulting in negative consequences, such as family problems, he might have more difficulty in changing to a healthier behavior due to his impaired cognitive flexibility. Furthermore, individuals with SUD may have dysfunctions in the brain RS. The RS is associated with motivation, salience of a stimulus [40], and delay capacity [41]. As a result, a youth with a RS dysfunction may choose a more immediate but ultimately worst reward rather than delayed gratification for future benefit(s) or may compulsively seek reward from drugs or alcohol at the expense of his immediate or future needs and despite immediate or future consequences. Impulsive behavior and choices are associated with drug use. Subjects with SUD may decide on choices with high immediate gains in spite of higher future losses [42]. Thus, for an adolescent with ADHD, it might be more important to get high, for example, than avoid the legal or academic consequences due to this behavior. This intriguing neurobiological 'environment' might be the result of different components, probably highly interrelated.

Brain imaging studies provide a good method for evaluating brain effects (both on morphology and function) of drug use. The vast majority of brain imaging studies in this field, however, have been conducted in adult samples. Nevertheless, there are some studies with adolescents documenting the drug effects on the brain RS and areas related to executive function, usually with consequences that are not only related to intoxication. For instance, blood oxygenation level-dependent (BOLD) functional MRI was performed in 24 chronic marijuana users (12 abstinent and 12 active) and control subjects during a set of visual attention tasks. Active and abstinent marijuana users showed decreased activation in the right prefrontal, medial and dorsal parietal, and medial cerebellar regions, but greater activation in various frontal, parietal, and occipital brain regions during the visual attention tasks (all with $p \leq 0.001$). Both earlier age at first use and greater estimated cumulative dose of cannabis exposure were related to lower BOLD signals in the right prefrontal region and medial cerebellum [43]. A pilot study with functional MRI found differences in the hippocampus between adolescents with cannabis use vs. just tobacco users vs. non-smokers [44]. Another study with MRI and PET evaluated the effects of age at first cannabis use on brain morphology. Subjects who started using marijuana before

age 17 years, compared to those who started later, had smaller whole brain and percent cortical gray matter volumes and larger percent white matter volumes. Functionally, males who started using marijuana before 17 years had a significantly higher cerebral blood flow than other males [45]. More brain imaging studies are needed in this age range, preferably with longitudinal designs and including both genders (girls are consistently underrepresented).

Genetics

Genetics has an important effect on the risk for SUDs, mainly in more severe cases, as evidenced in different studies [46, 47]. Studies with twins have shown heritability as a risk factor for the use of nicotine, caffeine, tranquilizers, sedatives, and also marijuana and cocaine dependence [19]. In relation to alcohol, Yates et al. [48] demonstrated that genetic factors influence the severity of the degree of dependence, while lighter degrees would be better explained by environmental factors. Considering cannabis, the heritability estimates range between 0.45 and 0.78 for abuse or dependence, respectively [49]. Regarding alcohol, twin studies have indicated that 20–30% of the variation in liability to alcohol initiation might be attributed to genetics, whereas 50–60% of the variation of alcohol progression may be associated with genetics. It is interesting that besides the direct predisposition to drug dependence, genetics can mediate the risk for SUDs by stimulating risk phenotypes for use of SP. In a community-based sample of 4,493 adolescents and young adults, a genome-wide search for quantitative trait loci described the molecular genetic basis of the comorbidity between dependence vulnerability and antisocial behavior (same region on chromosome 9q34) [50]. In relation to SUDs for cocaine, Guindalini et al. [51] demonstrated that the presence of allele 3 in a polymorphism at the DA transporter is associated with a larger risk of abuse of this substance (allele: OR = 1.2, 95% CI 1.01–1.37, $p = 0.036$; 3/3 homozygote: OR 1.45, 95% CI 1.18–1.78, $p = 0.0008$) [52]. Interestingly, the DA transporter was also implicated in ADHD vulnerability, which in turn might have an influence on adolescent SUD [28, 53].

Intrauterine Exposure

The intrauterine exposure to drugs also plays a role in SUDs liability. Significant alcohol consumption during pregnancy has been associated with attention deficit problems, impulsiveness and cognitive deficits, which are implicated as risk factors for alcohol-related disorders. Higher rates of alcohol dependence (15.9%) were observed in subjects without a first-degree family history of alcoholism but with intrauterine exposure to alcohol. Through multivariate analysis, controlling for family history, exposure to other substances (nicotine, caffeine, antibiotics, cannabis, among others)

and adverse environmental effects such as low socioeconomic level, intrauterine exposure to alcohol maintained a significant association with alcohol-related problems at the age of 21 years [54]. Similarly, it has been shown that intrauterine nicotine exposure is associated with higher ADHD rates [55], indirectly affecting SUD liability, since ADHD has been suggested as an independent risk factor to SUDs [28]. Smith et al. [56] examined the possible neurotoxic effects of prenatal cocaine exposure on the developing brain using proton magnetic resonance spectroscopy (^{1}H-MRS). The authors compared 14 cocaine-exposed children with 12 age-matched unexposed controls. Metabolite concentrations of N-acetyl-containing compounds, total creatine (Cr), choline-containing compounds, myoinositol, and glutamate + glutamine were measured in the frontal white matter and striatum. Children exposed to cocaine in utero had significantly higher Cr (+13%) in the frontal white matter. Recently, the effects of in utero cocaine and poly-substance exposure on the adolescent caudate nucleus were assessed through high-resolution MRI. The comparison focused on contrasting the control group with high-exposure subjects (mothers who used cocaine during pregnancy). Results indicated that the caudate (both left and right) was significantly larger in controls versus high-exposure subjects ($p < 0.0025$), implying cocaine exposure-related detriments to the dopaminergic system [57]. The effects of prenatal cannabis on response inhibition, assessed with functional MRI, showed that there was a significant increase in neural activity in bilateral prefrontal cortex and right premotor cortex during response inhibition with increased prenatal marijuana exposure and an attenuation of activity in the left cerebellum when challenging the response inhibition neural circuitry. Prenatally exposed offspring had significantly more commission errors than non-exposed participants. These findings were observed when controlling for present marijuana use and prenatal exposure to nicotine, alcohol and caffeine, suggesting that prenatal marijuana exposure is related to changes in neural activity during response inhibition that last into young adulthood [58]. Regarding alcohol exposure, a study examined brain metabolism using magnetic resonance spectroscopy (MRS) and searched for regions of specific vulnerability in adolescents and young adults prenatally exposed to alcohol. Ten adolescents and young adults with confirmed heavy prenatal alcohol exposure and a diagnosis within the fetal alcohol spectrum disorders were included. Three of them had fetal alcohol syndrome, 3 had partial fetal alcohol syndrome, and 4 had alcohol-related neurobehavioral disorder. The control group consisted of 10 adolescents matched for age, sex, head circumference, handedness, and body mass. Three-dimensional ^{1}H-MRS imaging was performed in the cerebrum and cerebellum. Metabolite ratios for N-acetylaspartate/choline, N-acetylaspartate/creatine and choline/creatine, and absolute metabolite intensities were calculated for several anatomic regions. In patients with fetal alcohol spectrum disorders, lower N-acetylaspartate/choline and/or N-acetylaspartate/creatine ratios were found in the parietal and frontal cortices, frontal white matter, corpus callosum, thalamus, and cerebellar dentate nucleus when compared with controls. There was an increase in the absolute intensity of the glial

markers choline and creatine. Results suggested that prenatal alcohol exposure alters brain metabolism in a long-standing or permanent manner in multiple brain areas [59]. Thus, drug use during pregnancy might result in long-lasting brain morphology and functional changes in the offspring. Interestingly, some studies reported changes in brain structures/functions that are well recognized as playing a role in SUD liability (frontal and caudate response inhibition); this is of special concern as these children might also have a higher genetic susceptibility to SUDs.

Age at First Consumption

The age at first consumption has been implicated in SUDs risk. A precocious beginning of PS use (around 13 years of age) is related to the fastest evolution toward SUDs [60]. A younger age at experimentation was a significant predictor of alcohol abuse between 17 and 18 years of age, and subjects who tried alcohol earlier were at a higher risk ($p < 0.001$) [61]. In spite of these findings, there is discussion in the literature whether the age at first consumption is an independent risk or just a marker of, for instance, greater impulsiveness or higher exposure to PS. However, animal studies have strongly suggested an independent effect of early exposure to different drugs and further long-lasting brain changes, usually in the direction of a higher sensitization to drug effects. For instance, nicotine self-administration by adolescent rodents had stronger and longer-lasting effects on nicotine intake in adulthood than initial self-administration by adult rodents [62]. Also, the exposure of mice to both methylphenidate (MPH) and 3,4-methylenedioxymethamphetamine (MDMA) during adolescence resulted in long-lasting neural adaptations, including sensitized responses to cocaine-induced reward and psychomotor stimulation following cocaine withdrawal. The animals received intraperitoneal injections of saline, MPH or MDMA during adolescence period. One month later, when already adults, cocaine-induced conditioned place preference (CPP) and locomotor activity were investigated. Previous MPH exposure caused significantly less CPP. However, 2 weeks later, after withdrawal from cocaine and extinction of CPP, cocaine was again administered and resulted in a significantly higher CPP in both MPH and MDMA groups in comparison to the saline group [63]. Long-lasting brain effects of early exposure to cannabis have also been documented. In this regard, the effects of repeated cannabinoid administration in adolescent and adult rats on DA were assessed in the mesoaccumbens. In this study, only the adolescent group developed long-lasting cross-tolerance to morphine, cocaine and amphetamine. These findings suggested a neuronal adaptation of dopaminergic neurons after sub-chronic cannabinoid intake at a young age, with consequences on the subsequent responses to drugs of abuse [64]. A different cocaine response, according to different stages of brain maturation, was also documented. Cocaine CPP was evaluated in early adolescent, late adolescent and young adult rats to test whether age-related differences in cocaine place preferences were

related to differences in the mesolimbic dopaminergic system. Measures relied on extracellular DA levels in the nucleus accumbens septi of the three 3 groups of rats via quantitative microdialysis under transient conditions. Results showed that adolescents differed from adults in basal DA. There were age-related differences in the extraction fraction, an indirect measure of DA reuptake. Together, these findings suggest ontogenetic differences in extracellular DA and DA reuptake and that these differences might be implicated in the higher adolescent vulnerability to addiction [65]. There are also data documenting the long-lasting effects of early alcohol exposure on further DA levels, helping to explain the underlying physiological mechanism in adolescent vulnerability to the rewarding properties of ethanol. Recently, it was tested whether chronic ethanol exposure during adolescence would alter nucleus accumbens septi DA levels in adult rat brains. Changes in extracellular DA levels in the anterior nucleus accumbens septum shell were measured via the no net flux paradigm. Findings documented greater extracellular DA levels in rats chronically treated with ethanol during adolescence in comparison with saline-exposed controls [66]. Similarly, the hypothesis was tested that ethanol consumption by alcohol-preferring rats during the peri-adolescent period would cause persistent alterations in the mesolimbic DA system. The results of the microdialysis experiments suggested that peri-adolescent ethanol drinking by alcohol-preferring rats increased basal DA neurotransmission and prolonged the response of DA neurotransmission to ethanol [67]. Another study indicated an age-dependent difference in the homeostatic alterations of mesolimbic systems in response to repeated ethanol treatment in rats, an effect that may manifest itself as differences in behavioral responsivity and conditionability to the drug and the drug's effects [68]. Thus, animal studies strongly support that: (a) the adolescent brain is more sensitive to drug effects, and (b) some long-lasting brain effects of drug exposure are age-dependent.

Gateway Theory

Despite concerns about the validity of the gateway theory for adolescents who use PS, this theory remains an important paradigm for understanding the development of drug use in adolescents. Certain types of drugs can predispose the pathway for SUDs towards more severe stages. A previous history of tobacco dependence is a factor for the regular use of cannabis [69]. In that study, 57.4% of the individuals who reported tobacco dependence confirmed regular use of marijuana, while only 12.5% of those who denied such dependence were regular users of marijuana ($p < 0.0001$). Besides, marijuana use was accepted as a trigger ('gateway theory') for use of other illicit PS. Another study considered the frequency in the use of marijuana as a predictor for SUDs between 16 and 19 years of age [70]. However, it is very difficult to conduct a study that really 'proves' the gateway hypothesis in its real meaning in the real world. According to the marijuana gateway theory, for example, the use of cannabis would

increase the risk of use of other drugs. Thus, studies should differentiate the effects of cannabis exposure per se from, for instance, the effect of a common propensity. In addition, if cannabis really increases the risk of other drug use, would this risk be conferred by some neurobiological effect (for example, sensitization) or due to environmental factors (increasing contact with drug use subcultures or with drug sellers, for instance)? Animal models help to answer this question, at least partially, as some strong environmental factors are eliminated in this method (no peer pressure or influence of drug sellers, for instance). In this sense, it was recently described that exposure to cannabis during adolescence later on caused a specific disturbance of the endogenous opioid system in rats. Striatal preproenkephalin mRNA expression was increased in the nucleus accumbens shell and the μ-opioid receptor and GTP-coupling was potentiated in the mesolimbic and nigrostriatal brainstem regions in cannabis-pretreated animals. μ-Opioid receptor function in the nucleus accumbens shell was specifically correlated with heroin intake. Ellgren et al. [52] concluded that their findings support the gateway hypothesis by demonstrating that cannabis exposure in adolescence has an enduring impact on hedonic processing resulting in enhanced opiate intake, possibly as a consequence of alterations in limbic opioid neuronal populations. However, the gateway theory is another question that remains open, and it is important to note how simplistic it would be to try to understand adolescent SUDs in a non-integrative model.

Treatment: General Aspects

It is well established that some treatment is better than no treatment for adolescents with SUDs. Even so, relapse rates are high [71], making the treatment of adolescents with SUDs a challenging task. Effort has been made in order to identify the characteristics of better treatment outcomes. It seems that longer treatment duration or time spent in treatment is associated with better results [72]. Also, some staff characteristics might interfere with treatment success [73, 74]. The therapist should be aware of adolescent cognitive and developmental characteristics. There is evidence supporting the use of several specific psychosocial interventions for adolescent SUD, such as cognitive behavior therapy, motivational therapy [75] and family therapy [76]. It is important to note that a very large number of adolescents with SUDs will have one or more coexisting psychiatric comorbidities which should be properly addressed [3]. Some comorbidities will require medication and there is some evidence for the use of lithium for bipolar comorbidity [77], bupropion for ADHD comorbidity [78] and for mood disorders comorbidities [79], and fluoxetine for depression comorbidity [80, 81]. There is a strong need for more pharmacological trials in adolescents with SUDs and other psychiatric disorders. Taking ADHD as an example, there is report of a 44% prevalence of ADHD among male adolescents with illicit SUD in a community-based study [28]. Despite the evidence that ADHD is associated with a worse SUD

prognosis for alcohol and cannabis [82, 83], few treatment studies have been conducted in this dually diagnosed population. Several evidence-based guidelines suggest that stimulants (e.g., MPH) should be the first option for treatment of ADHD [84], but ADHD treatment studies typically exclude individuals with drug use/misuse or SUD. Since ADHD [85], MPH [86] and most abused drugs [38, 87–89] are associated with dysfunctions and/or actions on the dopaminergic system, the clinical and neurobiological effects of MPH might not necessarily be generalized to this dually diagnosed population. Cocaine, for example, increases DA by blocking the striatal DA transporter [90], the same target of MPH. Moreover, there is a body of evidence describing that cannabis affects DA regulation [89, 91]. Thus the clinical effect of MPH might not be the same in the context of acute or chronic drug exposure, highlighting the need for treatment protocols derived from studies based on ADHD/SUD samples, and not just on ADHD or ADHD plus other comorbidities. Finally, although acamprosate [92] and naltrexone have been evaluated in adults with SUD [93], we were only able to find one published study with acamprosate in adolescents [94], and no treatment study with naltrexone.

Given the high prevalence, the severity of the associated outcomes and the difficulties in keeping an adolescent engaged in treatment programs for enough time, probably the most important issue in adolescent SUDs is the role of primary prevention. Effective preventive strategies involve different perspectives, such as governmental policies regarding drug use and recognition of early predictors of SUDs. This idea is corroborated by the fact that, in a significant group of adults with SUD, the onset of their SUD diagnosis was before the age 18 years [95]. In this sense, it is well known that adolescent SUDs have a multivariate etiology, with the influence of both biological and environmental variables [96, 97].

Conclusions

There is significant evidence for the role of neurobiological aspects in SUDs liability. The earlier the exposure at first drug use, the higher the risk of drug problems. This fact probably reflects a combination between a higher neurobiological propensity for SUDs in children and adolescents, in comparison to adults, and the effect of drugs in subjects with less developed brain processes and social skills due to young age or several other environmental, family and individual aspects. From a clinical perspective, it is very important to delay the age at first use of nicotine, alcohol and other drugs. Much attention should be given to those children with externalizing disorders, including high impulsivity as well as those with evidence of mood deregulation or internalizing disorders. If the adolescent already has a SUD diagnosis, specific treatment should be offered, preferably by professionals who are familiar with child and adolescent psychopathology, as well as intervention targeting comorbid psychopathology.

Conflict of Interest

Dr. Szobot: Janssen-Cilag – speaker's bureau. Dr.Bukstein: Shire Pharmaceuticals – consultant, research support, and speaker's bureau; McNeil Pediatrics – speaker's bureau, consultant; Eli Lilly – research support; Novartis – speaker's bureau.

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Molecular Genetics in Child Psychiatry

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Abstract

Genetic research into common complex disorders is at a pivotal point. Whole genome association studies currently underway, hold great promise for the identification of novel genes and causal mechanisms over the next few years. There has already been tremendous progress from the application of quantitative genetic, informing us about the aetiological relationships between different components of complex phenotypes such as autism and addressing the links between neurodevelopmental disorders and common comorbidities. Molecular genetic studies targeting candidate genes have clearly identified some specific genetic risk factors. In the post-genomic era the focus of research is increasingly turning towards the neuronal and cognitive processes that mediate genetic influences on behaviour and the translation of new knowledge into clinical practice. The degree to which genetic and other biomarker information will impact directly on clinical practice through the identification of novel drug targets and improved targeting of both medical and non-medical interventions remains unknown. However, genetic research is already having a major impact on the way that we conceptualise neurodevelopmental disorders and their links to frequently occurring comorbid symptoms and traits. The ease with which modern genotyping methods can be applied means that genetic information can be incorporated into almost any study design and promises rapid developments in our understanding of the complex interactions between genes and environment and their impact on child psychiatric disorders.

This chapter provides an overview of progress in the molecular genetics of child psychiatric disorders. We focus on the genetics of two of the most common disorders seen in child psychiatric clinics, autism and attention deficit/hyperactivity disorder (ADHD), while recognizing that progress has been made in other areas such as schizophrenia, bipolar affective disorder, tic disorders, anxiety, depression and obsessive-compulsive disorders, and a number of rare Mendelian conditions with psychiatric sequelae (e.g. tuberous sclerosis, fragile-X syndrome). In particular, substantial advances have been made in schizophrenia with the identification in recent years of

several novel genes involved in neurodevelopmental mechanisms and evidence that the genetic risks relate to combinations of psychotic and affective features that break down the traditional Kraepelinian dichotomy [1]; although studies of psychosis are usually completed in adult samples. Genetic studies are also transforming our views of neurodevelopmental disorders with the recognition that genetic risk factors are shared across traditional diagnostic boundaries and that diagnostic concepts such as autism may be more heterogeneous than previously recognized.

Advances in quantitative genetics, using family, twin and adoption study designs, have informed phenotypic strategies for molecular genetic analyses. These studies not only demonstrate the important role of genetic influences on many child psychiatric disorders, but also show the importance of quantitative approaches to clinical phenotypes in child psychiatry, and the degree to which there are shared and independent genetic effects within and across traditional diagnostic boundaries. Nearly all disorders in child psychiatry show heritability of 50% or more with varying degrees of shared and non-shared environmental influences. One of the most important advances in recent years is the recognition that gene–environment interactions are likely to be important and that these are included in the heritable component from twin studies, so that high heritability does by no means exclude an important role for the environment [2].

While many child psychiatric disorders tend to aggregate in families, they rarely show simple Mendelian patterns of segregation. Rather, they show complex patterns of inheritance that are widely considered to result from the action of multiple genes of small effect, possibly interacting with each other and environmental factors, rather than the effects of single genes seen in neuropsychiatric disorders such as tuberous sclerosis or fragile-X syndrome. For this reason it is unlikely that genetic information alone will prove useful for clinical diagnostic tests. However, discovering susceptibility genes is important in advancing our understanding of the molecular and neurobiological processes involved and the ways that genes modify our responses to the environment to cause or perpetuate psychiatric morbidity. There is now also an increasing interest in studies that investigate cognitive, neuroimaging or neurobiological endophenotypes that may more closely represent underlying mechanisms that mediate between genetic variation and behavioral symptoms [3].

As in all branches of medicine, genetic studies in child psychiatry require that the object of investigation can be measured in a reliable way. Within psychiatry the use of interview data and the application of operational diagnostic criteria generate high inter-rater reliabilities, and this has been the approach taken in most molecular genetic studies in child psychiatry, through the use of structured parental interview data in combination with data from other sources such as teachers. An alternative approach is to think of psychiatric symptoms as lying on a continuum in the same way that we study the genetics of blood pressure or cholesterol levels as continuous traits. In such an approach we can look for correlations between the presence of genetic risk factors and quantitative traits such as reading ability or levels of ADHD

symptoms that represent an underlying dimension of genetic risk. Genes of small effect that determine continuously distributed traits are described as quantitative trait loci and their existence is supported by twin studies that show high heritabilities for quantitative traits and continuity of genetic influences with extreme groups. The merits of using quantitative trait versus the categorical diagnostic criteria remains an area of ongoing debate [3, 4] but, to date, the focus in most molecular genetic studies of child psychiatric disorders has been on diagnosed clinical groups.

Quantitative Genetic Studies

These focus on the extent of phenotypic variation for a given disorder or trait amongst people with varying degrees of family relatedness. Family studies have been used to compare the rates of disorder in the relatives of affected individuals with the rates in control groups, but these were unable to parse familial effects into their genetic and environmental components. Although adoption studies can be used to disentangle these effects, twin studies are the most frequently used method that compare monozygotic (MZ) twin pairs that are genetically identical (sharing 100% of genetic variation) with dizygotic (DZ) twin pairs that only share 50% of their genetic variation. Disorders with a strong genetic basis would be expected to show high concordance rates within MZ twin pairs and much lower concordance within DZ twin pairs. In contrast similar concordance rates between MZ and DZ twin pairs would suggest that the familial environment makes the major contribution to co-twin similarity for a trait. Statistical methods usually involve model fitting that aims to determine the relative contribution of three different components: additive genetic effects (a^2); effects of shared environment (c^2), and effects of non-shared environment (e^2). Additive genetic effects, also termed heritability in the narrow sense, refers to the proportion of total phenotypic variance explained by additive genetic factors. It is important to note that no specific assumption is made about the nature of the environmental effects, and that the term 'shared environment' refers to those factors in the environment which cause individuals within a family to resemble each other; unique or 'non-shared environment' on the other hand, refers to those factors which cause members of a family to be different from each other, and also includes measurement error [5]. Hence, by calculating the correlations and co-variances for MZ and DZ siblings, twin studies are able to estimate heritability and environmental effects affecting phenotypic variance.

A complementary regression approach, first described by De Fries and Fulker, examines the genetic relationship between extreme groups and continuous ratings among co-twins and has been used to demonstrate the continuity of genetic influences between clinical disorder and quantitative traits in ADHD and autism [5]. Family and twin studies are now widely used to ask more complex multivariate questions about the familial and genetic relationships between two or more traits or disorders and can also be used to show genetic links between behavior and endophenotype

Table 1. The main differences between association and linkage

Linkage	Association
Co-segregation of genetic markers with disorder within families	Co-segregation of genetic markers with disorder within populations
Multiply affected pedigrees or affected sibling pairs	Case-control or proband-parent trios
Detectable over large genetic distances: >10 cM (around 10 million base pairs)	Detectable over short genetic distances: <1 cM (around 5–600,000 base pairs)
Power to detect large effects (approximate odds ratio >3, quantitative trait locus effects >10%)	Power to detect small effects (approximate odds ratio >1.2, quantitative trait locus effects >0.1%)
Detects in chromosomal regions spanning multiple genes	Detects one or a few very close genes, or localizes association signal to one region within a single gene
Linkage signals may arise from multiple different genetic variants co-segregating in different families	Association signals usually arise from a single genetic variant

measures such as performance on cognitive experimental tasks, for example between ADHD and reaction time in tasks of executive function [3].

Molecular Genetic Studies

The identification of genes that increase risk of a disorder is the preliminary step prior to more functional types of investigations. Both linkage and association strategies have been adopted to search for such genes, either scanning the entire genome with no a priori hypothesis, or investigating targeted candidate genes selected on the basis of prior information (table 1). The advantage of whole genome scan approaches is that they have the potential to identify novel genes or genetic mechanisms, which is a powerful strategy for psychiatric disorders where the underlying pathophysiology is, in most cases, very poorly understood.

There are many different kinds of genetic variants (also known as polymorphisms) in the human genome and a range of different genotyping methods to assay these. One of the most recent and exciting advances in genotyping involves exploiting the most common type of genomic polymorphism, known as single nucleotide polymorphisms (SNPs) that occur approximately once every 500–1,500 base pairs. Since the human genome consists of around 5×10^9 base pairs, hundreds of thousands of SNPs are needed to scan the entire genome for association with a particular disorder. Fortunately,

a new generation of high throughput assays using DNA micro-array technologies enables the simultaneous measurement of hundreds of thousand SNPs and this has led to the completion of numerous studies in the last year that have searched the genome for association with complex medical and psychiatric conditions. These methods have been very successful for a number of common complex medical conditions and it is only a matter of time before they bear fruit by identifying novel genes associated with child psychiatric disorders. Although whole genome association studies in disorders such as ADHD are currently being completed, these advances have come too late for inclusion in this article, but are expected to make major breakthroughs within the next few years. To date most of the genes known to be associated with child psychiatric disorders have been identified through association studies of targeted candidate genes.

Linkage Studies

Linkage studies seek to identify genetic markers that co-segregate with a disorder within families. Linkage approaches are very powerful for identifying genes of major effect and have been highly successful in identifying genes for disorders that follow Mendelian segregation patterns using extended pedigree approaches. Linkage studies for common complex disorders, such as child psychiatric disorders, where the effects of individual genes are much smaller, have been far less successful. Nevertheless, they have the potential to identify chromosomal regions containing genes that confer moderate to large risks, narrowing the search for the specific genes involved. The usual approach is to use large samples of affected sibling pairs, based on the premise that pairs of siblings affected with the same disorder will share susceptibility genes inherited from the same parent. By using markers spread evenly throughout the genome, one can determine whether affected siblings share parental alleles more often than by chance alone, in which case there is evidence of linkage between the chromosomal region involved and the clinical disorder. This approach can only identify broad regions containing susceptibility genes but will not directly identify the specific gene involved.

Association Analysis

Association is more powerful than linkage for detecting small genetic effects by searching for association between a specific genetic variant (allele) and a disorder or trait within the general population (rather than within families). Compared to linkage, association has the power to detect very small genetic effects and is usually based on the analysis of singletons or affected offspring–parent trios, rather than affected sibling pairs or family pedigree samples. The simplest approach is a case-control design in which the frequency of marker alleles in a group of affected individuals is compared to those in a sample of control subjects without the disorder. A statistically significant

difference suggests either tight linkage with a functional genetic variant that increases risk of the disorder (a phenomenon called linkage disequilibrium) or that the marker itself confers susceptibility for the disorder. Linkage disequilibrium describes the phenomenon where loci are so close together on a chromosome that they are not separated by recombination events over many generations. Genetic variants tend to form clusters or blocks in which every marker in the block is highly correlated with every other marker. The recognition of this block-like structure has been the basis behind the International HapMap project (http://www.hapmap.org) that has genotyped several million markers in a standard set of samples from several ethnic populations. This has enabled the identification of sets of markers that describe common genetic variation across the entire human genome and has formed the basis for contemporary studies that aim to scan genes, chromosomal regions or the entire genome for association.

One potential disadvantage of case-control studies is that the frequency of genetic variants may differ markedly from one population to another. For example the 7-repeat allele that is associated with ADHD has population frequencies that are exceedingly low in Asian populations, around 12–20% in European populations and very high in African populations. Population stratification differences between case and control samples can therefore give rise to both type I and II errors if case and control samples are not well matched for ethnic background. Although there are ways of testing for and adjusting for potential stratification effects, an alternative approach that is widely adopted in child disorders is the use of within family tests of association such as the Transmission Disequilibrium Test (TDT) or the Haplotype-based Haplotype Relative Risk (HHRR) analyses. The TDT is a test of association in the presence of linkage since it combines a linkage test by counting the number of transmissions from heterozygote parents to their affected offspring, with a test of association by counting the number of transmissions for a specific allele (whereas linkage consider the transmission of any allele within a family). Since the expectation is that a specific allele would be transmitted from heterozygote parents 50% of the time, any distortion of the 1:1 ratio of transmissions to non-transmissions is evidence of both linkage and association. Since this analysis does not rely on allele frequencies it is robust to stratification effects.

The HHRR is a different approach which creates a set of 'pseudo-control' data from the non-transmitted parent alleles. The affected offspring receives one allele from each parent (the case genotype), and the other two parental alleles that are not transmitted to the offspring form the control genotypes. This approach works since the non-transmitted parental alleles are perfectly matched to the genetic background of their offspring and represent the background allele frequencies from the population. No allele frequency differences are expected between the non-transmitted parental alleles and a well-matched independent control population. Although association is powerful, many more markers are needed to screen the genome for association than for linkage (in the order or 500,000–1,000,000 SNPs for whole genome association); and this gives rise to a considerable multiple testing problem and also explains the large number of false-positive findings reported in the literature. To

overcome this, stringent criteria need to be adopted in the region of $p < 1 \times 10^{-7}$. Since such low significance values are rarely found in individual studies, multiple replication and meta-analysis are required to confirm genetic associations. This has been possible for clinical categories such as ADHD, but presents a more serious problem for confirming associations with endophenotype measures, where individual studies tend to be relatively small, measures may lack reliability and different research groups use different measures. For these reasons there are currently no clearly replicated associations with endophenotype measures within child psychiatry.

Within child psychiatry, association studies have been used predominantly to test specific hypotheses derived from theoretical considerations, exemplified by the analysis of genes involved in dopamine metabolism and ADHD [6]. In contrast, in autism where the a priori hypotheses are less clear, molecular genetic studies have selected genes within regions identified on the basis of linkage or cytogenetic evidence.

Attention Deficit/Hyperactivity Disorder

ADHD has long been known to run in families, and adoption studies have found that ADHD is more common in the biological rather than the adoptive relatives of hyperactive children. Numerous twin studies conducted in different countries have demonstrated the importance of genetic factors for the disorder. In a recent review of the literature an average heritability of 76% was estimated when the results of 20 twin studies were pooled [7]. These studies also demonstrate that the heritability and the estimated contribution of shared and non-shared environmental factors may vary considerably according to who is rating the children, the instrument used for assessment, the construct definition, and its associations with other disorders [4]. The importance of rater effects is probably best demonstrated by the finding that whereas ADHD is one of the most heritable psychiatric disorders according to parent and teacher reports, no genetic contribution was found when teenage self-report data were used [8]. Clearly these factors may play an important role in molecular genetic studies and bias estimates of association and linkage.

Twin studies also find that substantial genetic effects underlie those with extreme symptoms of ADHD with DeFries-Fulker extremes analysis indicating the continuity of genetic influences between the clinical disorder and the quantitative trait in the general population [for review see, 4, 6]. It also appears that the two dimensions of ADHD according to DSM-IV, namely hyperactive-impulsive and inattentive, show substantial genetic overlap, although there are significant independent genetic effects as well [9], indicating the value of studies aimed at specific subtypes or symptom domains in ADHD. An empirical approach to deriving subtypes of ADHD has been attempted using latent class analysis, and independent transmission could be demonstrated for the derived subtypes in two independent samples [10]. The latent classes

map loosely onto the DSM-IV subtypes with the combined subtype forming a genetically distinct group, while the inattentive subtype is cleaved into a group sharing genetic influences with the combined type group and a separate 'pure' inattentive subgroup. The hyperactive-impulsive sub-group did not appear to share genetic influences with either of the other two clinical subtypes of ADHD.

Clinicians are familiar with high rates of comorbidity and the extent of overlap between ADHD and other developmental traits and disorders such as conduct problems, reading ability, autism and general cognitive ability. In each of these cases twin studies suggest that the clinical overlap results from overlapping sets of genes that have pleiotropic effects (i.e. multiple clinical effects of genes). However other mechanisms such as risk models or liability threshold models might also be important. The relationship between ADHD and conduct problems is particularly prominent within clinical settings and twin studies have found that the genes that underlie conduct problems overlap with those that influence ADHD symptoms [11]. One suggestion is that the co-occurrence of conduct problems and ADHD indicates a more severe form of ADHD, predicting an increase in the number of relatives with ADHD in relatives of comorbid ADHD cases compared to non-comorbid cases [11]. One difference however between ADHD and conduct problems is that in addition to genetic influences, conduct problems but not ADHD appears to be influenced by family environment. This suggests a risk model whereby the developmental trajectory from ADHD to the development of conduct problems is mediated by environmental risks acting at the level of the family.

Both linkage and association designs have been used in the search for genes that increase the risk for ADHD. As shown in table 1, genome-wide linkage studies have identified several regions potentially containing genes of moderate effect, although to date none of these have been clearly verified. Several independent studies have identified chromosome 5p as a site yielding significant linkage signals (table 1). This is of potential relevance to the dopamine transporter gene (*DAT1*), a recognized candidate gene for ADHD that lies within this region. In one study it was reported that genetic variation of *DAT1* might give rise to the linkage signal [12], but further work is required to scrutinize this finding. Specific genes associated with ADHD have yet to be identified that account for linkage signals within the other chromosomal regions.

In view of the marked clinical response of ADHD to stimulants, that has its main effect through blockade of the dopamine transporter, and other evidence implicating the role of monoamines in ADHD, the focus of most candidate gene studies in ADHD has been on genes involved in regulation of dopamine and related neurotransmitter systems. The candidate gene association approach has been widely adopted to the analysis of these genes, with the largest study completed to date providing a comprehensive investigation of 51 genes in a sample of more than 700 proband–parent trios [13]. Overall, such approaches have been successful in identifying several genes that appear to confer small but significant genetic risks for ADHD [6, 7] including those listed in table 2. However, it is important to note that, assuming a standard normal trait distribution and an additive genetic model, the proportion of

Table 2. Average odds ratios (OR) and corresponding 95% confidence (CI) from the pooled analysis of genetic variants associated with ADHD in more than one study [7]

Gene	OR	95% CI	Allele Frequency	QTL	Number of families to replicate with 80% power
DRD4	1.16	1.03–1.31	0.12	0.001	3,196
DRD5	1.24	1.12–1.65	0.35	0.004	728
DAT1	1.13	1.03–1.24	0.73	0.001	2,748
DBH	1.33	1.11–1.59	0.5	0.007	391
SNAP-25	1.19	1.03–1.38	0.5	0.003	1,043
SERT	1.31	1.09–1.59	0.6	0.006	466
HTR1B	1.44	1.14–1.83	0.71	0.010	315

The variance components to relative risk calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/vc2rr.html), was used to estimate the quantitative trait locus (QTL) effects for these findings. The programme calculates the threshold, assuming a standard normal trait distribution, such that the QTL variance for the discrete category based upon this threshold would be the same as the QTL variance for the continuous measure. Assuming an additive genetic model, the proportion of phenotypic variance explained by the genes associated with ADHD is approximately 3.2%. The number of families needed to replicate these findings with a nominal alpha of alpha = 0.05 and a power of 80% is listed. Modification from [3].

DRD4: Dopamine D4 receptor; DRD5: dopamine D5 receptor; DAT1: dopamine transporter; DBH: dopamine beta hydroxylase; SERT: serotonin transporter.

the variance explained by the genes discovered so far amounts to approximately 3.2% [3], which is only 4.2% of the estimated average heritability of 76%. Furthermore, of these findings only the associations with genetic variants within or near the dopamine D4 (*DRD4*) and D5 (*DRD5*) receptor genes have so far been clearly confirmed following a comprehensive meta-analysis of world data [14].

The 7-repeat polymorphism in exon III of the *DRD4* has been robustly shown to confer a small but definite increased risk for ADHD in meta-analytic studies [7, 14]. The interest in *DRD4* originates from the discovery of a highly variable region in the human *DRD4* that alters the protein structure of the receptor. In vitro evidence suggests that there is a differential response of the various alleles, with the 7-repeat allele leading to a blunted response of the receptor to dopamine stimulation [7]. Recent evidence suggests that, in addition to the 7-repeat allele, the shorter 5-repeat allele may also confer risk of the disorder, whilst the 4-repeat allele may have protective effects, as implied by significant odds ratios below zero [14].

The other gene for which there is good evidence of association to ADHD is the repeat polymorphism that lies close to the *DRD5*, with meta-analysis confirming the association between ADHD and a 148-bp allele of the polymorphism [14]. The functional variant that gives rise to the association has yet to be identified.

One of the most prominent targets for molecular genetic studies in ADHD has been the *DAT1*, a Na^+/Cl^--dependent neurotransmitter transporter which regulates dopamine re-uptake at the synaptic cleft and is the primary target for methylphenidate. The gene contains a 40-base pair variable number tandem repeat polymorphism located in the 3′-untranslated region of the gene, of which the 9- and 10-repeat alleles are the most common. It has been suggested that the 10-repeat allele may be associated with higher mesolimbic density of the dopamine transporter and therefore higher production or turnover of dopamine, although the evidence for this is conflicting [7]. Since it was first reported that the 10-repeat allele of *DAT1* might confer risk of ADHD there have been numerous studies with conflicting results. Furthermore, a recent comprehensive meta-analysis failed to show significant association with ADHD (OR 1.04, 95% CI 0.98–1.11) [14]. However, an accumulation of recent evidence has confirmed and extended previous findings on the association between ADHD and DAT1, suggesting that genetic variation of the promoter region may be involved [13], and that the 10-repeat is either marking another functional variant in the region or might be involved in intragenic interactions with other functional sites within the gene [12, 15].

Recent studies have also suggested a role for gene–environment interaction effects, in which genetic variants of *DAT1* on the risk for ADHD may be moderated by environmental risks, such as maternal alcohol or tobacco use during pregnancy and psychosocial adversity [16–18].

Several other genes, most notably perhaps the serotonin transporter and the synaptosomal-associated protein of a 25-kDa gene (SNAP25), have been found to be associated with ADHD in several studies. However, further work is required to establish their role in this disorder [7].

Future studies combining whole genome linkage and association data are expected to identify novel genes within the next few years. It will be of considerable interest to see whether these studies identify further genes influencing the regulation of the known neurotransmitter systems or whether novel neurochemical or neurodevelopmental mechanisms will be identified. Currently there are several thousand samples of ADHD being analyzed across different centers around the world and close collaborative links are being coordinated between the various research groups involved. With the advent of novel techniques to explore the entire human genome for association the basis for the identification of novel genes and their confirmation by replication is well under way.

Autism

Autism has long been known to aggregate in families and shows a high heritability. Twin studies of autism show concordance rates for MZ twins ranging between 60 and 90% whilst those in DZ twins do not exceed 10% [19]. The earliest twin study in the

field [20] was the first to indicate the much higher concordance rate in MZ compared to DZ twins of what the authors termed 'cognitive disorder' (mainly speech and language abnormalities). A follow-up of this study demonstrated that most non-affected MZ co-twins of twin probands with autism displayed social and communication impairments [21]. The high prevalence of early language and communication difficulties in MZ twins discordant for autism compared to their DZ counterparts, gave rise to the notion of a broad autism phenotype, although its exact boundaries are yet to be defined [22].

Increasing evidence suggests that autism may be usefully measured on a continuous scale. Furthermore, evidence from twin studies suggests that autism measured as a dimensional trait is highly heritable in boys and is moderately heritable in girls [23]. More recent evidence finds relatively low genetic correlation between the three domains of impairment in autism, namely social interaction deficits, communication problems, and rigid or repetitive behaviors, suggesting the existence of independent genetic effects on the three component traits of autism [24]. Extending these findings and using a DeFries-Fulker analysis showed that in those children with scoring at the extremes for autism-like traits, there was substantial genetic specificity for each of the three domains of clinical impairment [25]. These findings could obviously be highly relevant for gene-mapping strategies by indicating the presence of independent genetic and presumably therefore neurobiological processes for the major components of autism.

Currently, there are few clues as to the pathophysiology of autism. This makes it difficult to have a priori hypotheses about the genes that might be involved in genetic risk for the disorder, making a candidate gene approach a risky endeavor. For this reason, most clues about specific genes have come from the association of autism with cytogenetic abnormalities (aberrant chromosomal structures) and from linkage studies. It is estimated that cytogenetic abnormalities occur at a rate of about 3% in autism [26] and the most common anomaly involves chromosomal region 15q11–13. Deletions in this region are known to cause Angelman syndrome and Prader-Willi syndrome, depending on whether the maternal or paternal chromosome is affected. Those subjects with Prader-Willi syndrome as a result of maternal uniparental disomy display a phenotype with autism-like impairments [27], and this observation has led researchers to assess candidate genes on chromosome 15, such as the GABRB3 gene coding for a subunit of a GABA receptor. To date reported associations have not clearly confirmed [19].

There have also been a great number of linkage studies for autism in recent years and one of the regions most consistently implicated is a locus on chromosome 7q [for review see, 19, 22], which is also supported by meta-analytic evidence [28]. Further regions implicated in autism are on chromosome 2q and 17q [29]. These results have led to the investigation of candidate genes at the locus on chromosome 7. One of the best studied genes in this region is engrailed 2 (*EN2*), a homeobox transcription factor with an important role in cerebellar development. Recent evidence has indicated a

significant association between autism and two intronic markers within the *EN2* gene, providing considerable evidence for its involvement in autism [30], making this a very attractive gene for further study.

The finding of platelet hyperserotoninemia in a substantial proportion of patients with autism has prompted research interest in *SLC6A4*, the serotonin transporter gene. Although some results have been particularly encouraging, overall the findings remain inconclusive [31].

Of particular is the recent finding of significantly increased de novo copy number variation (CNVs) associated with autism spectrum disorders [32]. In a case control comparison CNVs were identified in 12 out of 118 (10%) of patients with sporadic autism compared to only 2 out of 196 (1%) of controls. The CNVs consisted of both deletions and increased copy number of regions containing in most cases several genes. Further work is needed to confirm the identity of the specific genes involved, but the data suggest that relatively rare variation in the copy number of many different genes contribute to the development of autism.

Concluding Remarks

Both quantitative and molecular genetic studies are making major contributions to our understanding of child psychiatric disorders. Current nosology is being challenged by genetic data. The delineation of clinical disorders and their relationship to normal behavior is expected to become clearer as specific genes associated with these disorders are identified. The increasing availability of sufficient samples and the recent advances in our ability to interrogate the human genome in its entirety herald a new era of post-genomic research, where the focus will turn increasingly to the mechanisms that mediate the association of genes with behavior. The degree to which this will impact directly on clinical practice through the identification of novel drug targets and improved targeting of both medical and non-medical interventions remain unknown, but is already having a major impact on our conceptualization of neurodevelopmental disorders and the links betweens these and associated behaviors. The ease of modern genotyping methods means that genetic information can now be incorporated into almost any study design and suggests that the rapid increase in our understanding of the complex interactions between genes and environment and their impact on child psychiatric disorders will continue to accelerate.

Note: Due to the limit on the permissible number of references, the authors only cite those original articles which are thought to be of immediate relevance to the reader, and, in most other instances, refer to overview texts; however, a more detailed list of original references is available from the authors upon request.

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Recent Developments in Neuropsychological Models of Childhood Psychiatric Disorders

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Abstract

The number of studies on the neuropsychology of childhood disorders has increased exponentially over the past decade. We report the results of an initial meta-analysis of key neuropsychological constructs included in studies of nine of the most prevalent childhood disorders. Results indicated that the neuropsychological etiologies of each of these disorders are complex and multifactorial. No single deficit is necessary or sufficient to explain all cases of any disorder, but preliminary evidence suggests that disorders may be distinguished by profiles across multiple neuropsychological processes. Slow processing speed and increased response variability are ubiquitous across disorders, but somewhat distinct profiles emerge on different aspects of executive functions. Attention deficit/hyperactivity disorder and Tourette's disorder are most strongly associated with inhibitory difficulties, whereas difficulties with cognitive flexibility are most pronounced in groups with autism spectrum disorders and childhood-onset schizophrenia. Working memory difficulties are significant in most groups, but these weaknesses are largest in groups with learning disorders and childhood-onset schizophrenia. Future research is needed to clarify further the relations among these heterogeneous diagnostic phenotypes and complex neuropsychological processes to facilitate studies that link these weaknesses to specific etiological risk factors.

The study of the neuropsychology of childhood disorders is at a fascinating point in its development. During the latter half of the 20th century, conceptual models were guided by the classical disease formulation set out in diagnostic manuals, or on neurological lesion models. These approaches built on a unitary concept of the neuropsychology

of psychiatric disorders, which implicated single core deficits and simple linear models of the pathways from originating cause to symptom expression and associated impairment. Consequently the search for common and shared core deficits has defined the paradigm and various unitary core deficit models have vied for supremacy in models of attention deficit/hyperactivity disorder (ADHD) [1], autism [2, 3], conduct disorder (CD) [4], and reading disorder (RD) [5].

More recently, there has been a major shift in research strategy and a new paradigm for the neuropsychology of childhood disorders is emerging. This is based on the growing realization that the disorders defined in diagnostic manuals are by and large not neuropsychologically homogeneous entities as suggested by the unitary models set out above. At a clinical level children with a common diagnosis by definition share important commonalities of symptoms and impairment. In contrast, at a neuropsychological level they may display quite varying profiles of weakness.

In this chapter we summarize results from a meta-analytic review of neuropsychological studies of nine of the most common childhood disorders. After reviewing evidence regarding the associations between each individual disorder and neuropsychological construct, the second half of the chapter focuses on questions regarding diagnostic and neuropsychological heterogeneity. The final section of the chapter then summarizes the implications of these results for future neuropsychological models of childhood disorders and highlights several important directions for future research.

Why Study the Neuropsychology of Psychopathology?

Virtually all mental disorders are necessarily defined based on observable or reportable behaviors. From a clinical perspective, the validity of a diagnosis hinges on a straightforward question: do the behavioral symptoms of the disorder impair an individual's functioning sufficiently that the risks of not treating outweigh the risks of treating? Previous studies have demonstrated that each of the disorders described in this chapter is valid in this sense [for a description of studies of the validity of ADHD see, 6].

Whereas a significant association with functional impairment is sufficient to demonstrate the validity of a disorder for clinical purposes, the validity of a behaviorally defined disorder will always be constrained by potential rater biases and other difficulties inherent in the measurement of behavior. The long-term objective of research on psychopathology is to understand all disorders at each of the four levels of analysis described by Pennington [7]: (1) behavior; (2) neuropsychology/cognitive processes; (3) brain development, and (4) etiology. Although the field is not yet at the point at which etiological or neuropsychological markers can be identified that reflect the diagnostic categories in the DSM-IV, neuropsychological assessment and its

findings have already inspired new literature suggesting intervention for children with particular neuropsychological profiles [8, 9]. Thus, clinical practice is already moving outside the behavioral classifications of the DSM-IV to recognize neuropsychological profiles as useful clinical tools in some instances. Yet there is considerably more potential here. Neuropsychological research has the potential to facilitate important advancements in these areas by helping to pinpoint the specific neural systems and processes which are compromised in childhood disorders, enabling more effective applications of interventions.

Neuropsychological methods may also be helpful to understand the pervasive diagnostic heterogeneity that characterizes many of the disorders and overarching behavioral categories defined in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, Text Revision (DSM-IV-TR) [10]. Here we focus on neuropsychological studies of diagnostic subtypes and comorbidity between different disorders, but a similar approach could be used to assess the impact of heterogeneity as a function of age, sex, socioeconomic status, or other variables of interest.

A Meta-Analytic Review of Neuropsychological Studies of Childhood Disorders

Overview

Over 400 studies have examined the neuropsychology and neurophysiology of ADHD alone, and hundreds of additional studies have tested the neuropsychological functioning of individuals with other developmental disorders. The sheer volume of the extant literature precludes a comprehensive review of all of these measures and constructs in anything less than a book length account [for overviews see, 11, 12]. Therefore, we focus here on five constructs that are important components of the most prominent theoretical models of ADHD and other childhood disorders. These constructs are executive functions (EFs), delay aversion, modulation of behavior in response to reward and punishment cues, response variability, and overall cognitive processing speed. To synthesize the extensive literature on the relations between these constructs and ADHD, our group and several others have completed meta-analytic reviews of published studies that administered measures of at least one of the constructs to groups with and without ADHD [13–21]. For this chapter we updated previous meta-analyses of ADHD by adding studies published since the initial reviews were completed and measures that were excluded from the initial reviews.

In addition to updating the ADHD meta-analysis, we also review studies of these five neuropsychological constructs in eight clusters of disorders with a modal age of onset during childhood or adolescence. These disorders include other disruptive behavior disorders such as oppositional defiant disorder (ODD) and CD, anxiety disorders, autism spectrum disorders, childhood-onset schizophrenia (COS) and other psychoses, juvenile bipolar disorder, major depressive disorder (MDD), learning dis-

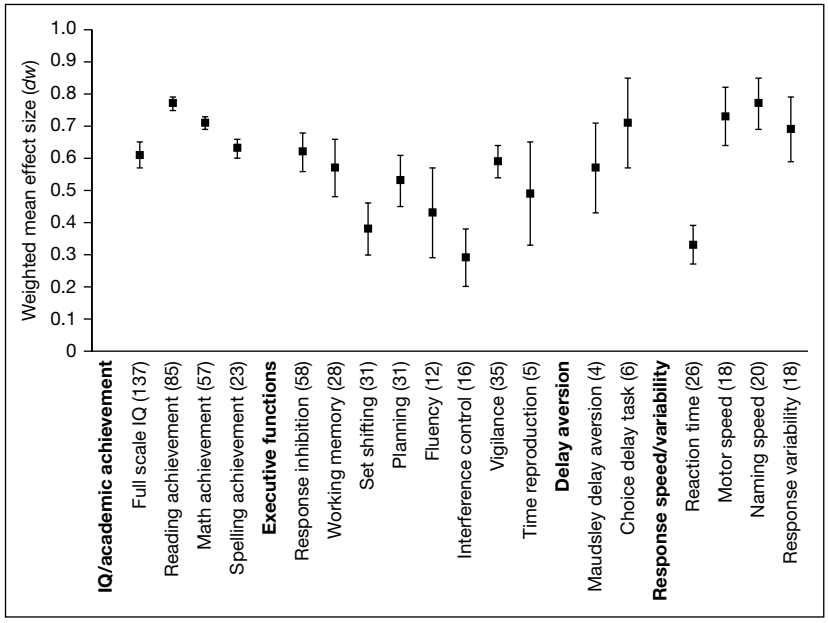

Fig. 1. Weighted mean effect size of the difference between groups with and without ADHD (error bars indicate the 95% confidence interval for the weighted effect size). Numbers in parentheses indicate the number of studies that included the measure. Effect sizes were taken from previous meta-analyses and updated with results from studies published subsequent to the meta-analysis. The topics of the initial meta-analysis were IQ [13] academic achievement [161], overall executive functions [13, 20, 21], the stop-signal task [15], verbal and spatial working memory [17], Stroop interference control [14, 19], delay aversion [59], and processing speed [20].

orders (LD), and Tourette's syndrome (TS)/tic disorders. Due to space constraints we do not include a comprehensive review of other neuropsychological constructs that are important for childhood disorders, such as motor skills, basic learning and memory processes, and speech and language abilities, but we describe the key results for these domains in the text.

In the initial section of the chapter we briefly describe the theoretical and empirical foundation of each of the five neuropsychological constructs, then summarize the results of studies of each disorder that included measures relevant to the construct (fig. 1; table 1). All of the results in figure 1 and nearly all of the results in table 1 are from studies of children or adolescents. If neuropsychological studies of children had not been completed for a specific construct, effects from adult samples were included and this was noted in table 1 (e.g., planning weaknesses in individuals with MDD). Studies of response to reward and punishment are not included in table 1 because these studies have used a wide range of tasks and experimental designs that are difficult to combine for a pooled analysis [for a comprehensive review see, 16], and delay aversion

Table 1. Meta-analysis of neuropsychological studies of childhood disorders: Effect size (d)[a] of the mean difference between groups with and without each disorder[b]

	Intelligence	Executive functions							Other cognitive processes	
		response inhibition	working memory	set shifting	planning	vigilance	fluency	interference control	response variability	processing speed
ADHD[c]	+++	+++	++	+	++	++	++	+	+++	+++
Anxiety	++ [134, 141]	+ [130, 134, 135]	++ [141[d]]	+++ [126, 155]	+ [141[d], 155]	no studies –	0 [116[d]]	no studies –	+++ [134, 135]	+ [116[d]]
Autism	++++ [127, 137, 158]	++ [76, 127, 158]	++ [127, 158]	++++ [127, 137, 158]	++++ [128, 137, 158]	+++ [76, 122]	+++ [127, 158]	+ [128, 137]	++ [76, 127, 158]	+++ [148]
Bipolar	++ [123, 131, 145]	++ [131, 145]	+++ [124, 138, 145]	++ [124, 131, 145]	++ [123, 124, 138]	+++ [124, 131, 145]	++ [117]	++ [124, 145]	+++ [145]	+++ [117, 124, 145]
MDD	++ [125[d]]	+ [36]	+++ [140[d], 154[d]]	++ [153[d], 154[d]]	+ [140[d]]	+++ [36]	+++ [36]	+++ [36]	+++ [36]	+++ [124[d], 153[d]]
LD/RD	++++ [30, 37, 139]	++ [30, 37, 135, 142]	++++ [30, 37, 42, 142]	+ [29, 139, 142]	+ [42, 139]	++ [29, 37, 42, 142]	+++ [42]	+ [29, 30, 37]	+++ [29, 30, 37, 142]	+++ [29, 30 37, 42]
ODD/CD	++ [134–136]	++ [46, 121, 134]	++ [51, 133, 150]	++ [132, 133, 156]	++ [132, 136, 156]	++ [121, 133]	+ [136, 156]	++ [133, 156]	+++ [46, 134, 135]	++ [132]
COS	++++ [35, 143, 146]	+ [35, 146]	++++ [22, 35, 143]	++++ [35, 143]	+++ [157[d]]	+ [35, 146]	+++ [143]	++ [125[d]]	++++ [149[d]]	+++ [35, 143]
Tics/TS	++ [137, 152, 158]	+++ [120, 152, 158]	+ [144, 158]	+ [120, 137, 158]	+ [137, 158]	+++ [152]	++ [120, 158]	+ [120, 137]	+++ [97, 152, 158]	+++ [119, 120, 144]

[a]Symbols indicate the estimated mean effect size (d) [159] for comparisons between groups with the disorder and comparison groups without a diagnosis. 0 = Null result with an effect size of <0.1; + = small effect (d = 0.1–0.3); ++ = medium effect (d = 0.4–0.6); +++ = large effect (d = 0.7–0.9); ++++ = very large effect size (d = 1.0–1.5); +++++ = extremely large effect size (d = 1.6+).

[b]The reference numbers below each estimated effect size indicate a representative subset of all studies which included that specific comparison. The full list of studies and effect sizes used to compute the estimates in the table is available from the first author upon request.

[c]ADHD effect sizes are based on the studies summarized in figure 1.

[d]Study of adults included because studies of children and adolescents have not been completed.

is not included in table 1 because only two studies have included childhood disorders other than ADHD. Studies of these constructs are summarized in the text.

The studies included in table 1 are a comprehensive list if a construct has been included in a small number of studies (e.g., response inhibition in children with anxiety disorders). In contrast, for many measures it was not feasible to list all studies due to space constraints (e.g., inhibition and set-shifting in groups with autism spectrum disorders and processing speed in groups with LDs). In those cases the estimated effect size is based on all available published studies, and a representative subset of all publications are listed in the footnote (please contact the first author for the full list of studies, measures, and effect sizes used to calculate the overall effects listed in table 1).

Executive Functions

For the past decade, prominent cognitive theories have suggested that symptoms of ADHD, autism, schizophrenia, and other childhood disorders arise in part due to a weakness in EFs, cognitive processes that serve to maintain an appropriate problem-solving set to attain a future goal [1, 22–24]. In a simplified model of cognitive control and decision-making processes, EFs represent 'top-down' cognitive inputs that facilitate decision making by suppressing irrelevant information and thus maintaining information about possible choices in working memory, then integrating this knowledge with information about reinforcement probabilities in guiding action. Although executive control processes involve several distributed brain networks, studies of primates and neuropsychological, neuroimaging, and lesion studies of humans suggest that the primary neural circuit includes the thalamus, basal ganglia, and dorsolateral and ventrolateral regions prefrontal cortex [7, 25].

Many theoretical models of ADHD have invoked the notion of 'executive control' as a single unified construct that encompasses many potentially separable cognitive functions [24]. However, exploratory and confirmatory factor analyses of EF tasks and results of a recent functional MRI study suggest that EFs may be more accurately characterized as a collection of related but separable abilities [26–30]. All of these studies suggest that EF tasks can be subdivided into measures of response inhibition, working memory/updating, and set-shifting, and several studies also found evidence of separable dimensions of vigilance, planning, and interference control, depending on which measures were included in the factor analyses. As a result, some theories of ADHD have posited a more focal weakness in a specific aspect of executive control such as response inhibition [1].

EF and ADHD

A significant difference was observed between groups with and without ADHD in 64% of the 215 comparisons in the 97 studies included in the meta-analysis (fig. 1). The weighted mean effect size across all EF measures fell in the range considered a medium effect ($d = 0.54$, 95% CI = 0.51–0.5), with the most consistent group differences and largest effect sizes observed on measures of motor response inhibition

(or response suppression), working memory, vigilance, and planning (weighted mean d = 0.53–0.62). Similarly, correlations between ADHD symptoms and dimensional EF measures are typically significant but small to medium in magnitude (r = 0.15–0.44) [29–32], and appear to be stronger for inattention symptoms than hyperactivity-impulsivity symptoms [30, 33, 34]. Taken together, these results clearly demonstrate that EF weaknesses are associated with ADHD in general, and inattention symptoms more specifically, but also indicate that the majority of the variance in ADHD symptoms is not explained by individual differences in EF.

EF and Other Childhood Disorders

Table 1 summarizes studies that administered EF tasks to groups with other disorders. Groups with each disorder exhibit significant weaknesses on measures of multiple EF domains, with corresponding effect sizes that are similar to those reported in the studies of ADHD. The most pervasive and severe EF weaknesses are exhibited by individuals with autism spectrum disorders and COS. Groups with high-functioning autism (HFA) perform worse than a comparison group on all EF measures, with the largest deficits on measures of planning and cognitive flexibility (set shifting). Groups with COS also exhibit pronounced weaknesses on measures of set-shifting, along with significant impairments in working memory and vigilance. In contrast, individuals with COS exhibit a much milder weakness on measures of motor response inhibition such as commission errors on a continuous performance test [35].

In contrast to the results for HFA, COS, and ADHD, EF weaknesses are milder and less consistent in groups with juvenile bipolar disorder, ODD/CD, and TS or other tic disorders. Moreover, in many studies the moderate EF weaknesses in these groups are due to comorbidity with ADHD, an issue that we discuss in more detail later in the chapter.

Studies of adults suggest that MDD may be associated with significant weaknesses in several EF domains, and one published study found that children with MDD exhibited weaknesses in vigilance, fluency, and interference control [36]. In contrast, initial studies suggest that anxiety disorders are not associated with EF weaknesses in most domains, with the possible exception of difficulty shifting cognitive set. These initial results are intriguing and fit well with theoretical models of internalizing disorders, but all require replication in additional samples of children and adolescents.

One of the most surprising findings from the past 5 years has emerged in studies of EF tasks in samples with RD [29, 30, 37]. The phonological deficit theory of RD is arguably the most compelling single-deficit theory for a childhood disorder. The phonological model suggests that reading difficulties occur due to a weakness in the ability to recognize and manipulate phonemes, the units of sound that are combined to form words [5, 7]. Individual differences on measures of phonological processing often account for over 50% of the variance in reading ability [38], and the effect size of the difference between groups with and without RD is large (d = 1.5–2.5) [30].

Phonological skills strongly predict early growth in single-word decoding abilities and a wide range of long-term academic outcomes [39], and the best validated treatments for RD improve reading ability by providing focused instruction and practice to improve phonological processing skills [40].

Against this historical background, initial studies that reported EF weaknesses in groups with RD suggested that these effects might be a secondary consequence of the linguistic impairments that characterize groups with RD [29]. Contrary to this hypothesis, however, more recent studies have consistently found that groups with RD exhibit weaknesses on a range of EF measures, including spatial working memory tasks that are specifically designed to minimize the extent to which they can be verbally encoded ($d = 0.7–1.1$) [30, 41, 42]. Therefore, these unexpected but consistent results across several studies suggest that RD is associated with significant EF weaknesses that are not simply a secondary consequence of a deficit in another domain.

In summary, these studies suggest that weak executive control is a ubiquitous correlate of nearly all childhood disorders. In contrast, EF weaknesses are neither necessary or sufficient to cause any of the disorders included in this review, and are instead one important component of the complex neuropsychology of childhood disorders.

Motivational Dysfunction

There has recently been renewed interest in the role of motivational dysfunction in ADHD and other childhood disorders [43]. Studies that manipulated reward and punishment contingencies have reported mixed results for ADHD and ODD/CD [for a comprehensive review of studies of ADHD see, 16]. Some studies found that response contingencies improved or normalized task performance in individuals with ADHD [44, 45], whereas several others found a main effect of reinforcement or response cost on the task performance of all groups, but no differential effect on individuals with ADHD or ODD/CD [46]. A third line of research found that when both reward and punishment were possible outcomes (i.e., one possible response received a reward and one response resulted in a penalty), individuals with elevations in ADHD or CD symptoms exhibited higher rates of impulsive behavior, whereas no group differences were detected in the condition with response-cost alone [47, 48]. Finally, several studies found that children with ODD or CD were more likely to continue to pursue a reward even when task probabilities indicated that punishment was becoming increasingly likely, consistent with the hypothesis that individuals with CD may be oversensitive to reward cues [49–51].

Taken together, these studies tentatively suggest that in contrast to children without ADHD or ODD/CD, individuals with ODD/CD may be differentially sensitive to reward and punishment cues in the environment. These studies do not rule out the possibility that ADHD may arise from motivational dysfunction, but the mixed results provide little conclusive support for this association with the possible exception described in the subsequent section.

Delay Aversion

An intriguing variant of the motivational hypotheses is the delay aversion model which suggests that children with ADHD have a motivational style that leads them to find delay extremely aversive [52, 53]. The model suggests that this style leads individuals with ADHD to make choices that will minimize delay even when presented with other options that take longer to complete but maximize long-term gains. Furthermore, if there is no choice except to tolerate the delay (for example, during a boring classroom session of a fixed duration), delay aversion may then be expressed as increased activity or inattention.

The delay aversion theory is grounded in the neurocircuitry of catecholamine-modulated brain reward circuits [54, 55]. These circuits are functionally segregated from the executive circuits described above and link the ventral striatum (in particular the nucleus accumbens) to frontal regions (especially the anterior cingulate and orbito-frontal cortex), reciprocated via the ventral pallidum and related structures through the thalamus. The amygdala is also implicated in this system, possibly playing a role in defining the motivational significance of incentives [56], and dopamine is a key neuromodulator [57]. This circuit is specifically implicated in signaling rewards, coding incentive value and regulating other behavioral processes involved in the maintenance of responding under conditions of delayed rewards [54]. The delay aversion model suggests that children with ADHD have fundamental impairments in the neural signaling of delayed rewards that lead to steeper discounting of the value of delayed rewards, leading the child to choose smaller reinforcers that will be delivered soon rather than larger rewards that will be delivered after a delay ([for a rat model relevant to the discounting of delayed rewards see, 58]).

Ten studies have tested the delay aversion theory by assessing how often children with and without ADHD select a small immediate reward rather than a larger delayed reward on simple laboratory choice tasks (fig. 1) [for a description of the meta-analysis of delay aversion see, 59]. The effect sizes for the two delay aversion measures (mean d = 0.57 and 0.71) are similar to the most discriminating EF tasks described in the previous section, albeit on a much smaller number of studies to date. Thus, although the magnitude of these effects suggests that delay aversion is also neither a necessary nor sufficient cause of all cases of ADHD, delay aversion and EF may contribute to a comprehensive model of ADHD and its cognitive heterogeneity.

Few studies have examined delay aversion in groups with disorders other than ADHD. One recent study of HFA and ADHD found that the group with ADHD was more likely to make the choice to minimize delay than the group with HFA and the control group, whereas the group with HFA did not differ from the comparison group [60]. Moreover, studies of several different disorders in adults have examined individual differences in delay discounting, a measure of the extent to which the subjective value of a future reward is reduced as a function of the delay before it will be received [61]. One study found that adults with schizophrenia had a significantly steeper

delay-discounting function than a control group without each disorder [62], indicating that the group with schizophrenia devalued future rewards more than individuals without the disorder. Similar results have been reported in studies of adults with substance abuse disorders and undergraduate students with significant social anxiety [63–65].

In summary, delay aversion appears to be an important component of the pathophysiology of ADHD, and a similar construct has shown promise in studies of adults with a range of disorders. In contrast, children with autism do not exhibit significant delay aversion, providing important support for the discriminant validity of the construct. Future research is needed to compare groups with ADHD to other groups that might be predicted to find delay especially aversive, such as ODD/CD and bipolar disorder.

Response Variability

Perhaps the most ubiquitous result in neuropsychological studies of childhood disorders is the finding that the reaction times (RTs) of individuals with a disorder tend to be slower and more variable than those of individuals from a comparison group [66–70]. Most previous studies have quantified response variability as the standard deviation or standard error of an individual's RT across all trials on a task, whereas more recently several authors have suggested that one of several more sophisticated analytic procedures may be optimal for the analysis of the complex temporal patterns present in RT data collected over hundreds of trials [66, 71, 72].

Differences between groups with and without ADHD replicate consistently even when the primary dependent measure is a relatively course measure such as standard deviation of RT [for review of 33 of 39 studies see, 67], and the mean effect size in these studies is comparable to or larger than the effects observed for EF tasks (weighted mean $d = 0.71$; fig. 1). Although fewer studies have examined response variability in other disorders, the results of the current meta-analysis suggest that all childhood disorders included in this review are associated with increased response variability with moderate to large estimates of effect sizes (table 1).

Until recently, interpretation of increased response variability was complicated by the absence of an explanatory theoretical model [43, 73]. An initial parsimonious hypothesis suggested that RT variability might simply be an inevitable consequence of slower overall response speed, and many studies have confirmed that measures of intra-subject variability are typically correlated with mean RT [67]. However, a closer analysis of individual trials revealed that increased response variability is due to a relatively small number of long RTs, a finding that is consistent with the possibility that these trials reflect momentary attentional lapses rather than slow RTs on most trials [66, 71]. Further support for this hypothesis is provided by studies that found that mean RT did not explain the relation between response variability and important external measures such as symptoms of psychopathology and performance on other cognitive measures [67, 74].

Taken together, these findings underscore the need for improved models of the pathophysiology of response variability. Recent theoretical models have proposed that increased response variability may be due to momentary attentional lapses that result from weak executive control [74] or interference from a 'default-mode' network that produces low frequency neuronal oscillations when the brain is in a resting state [66, 73]. Other models have suggested that increased variability may reflect chronic under-arousal or inconsistent regulation of arousal [75, 76], deficient extinction processes [58], or dysfunction in short-duration timing mechanisms [77, 78]. Finally, one of the most elaborated models incorporated neuropsychological data, psychopharmacological manipulations, and neurocomputational models to support the hypothesis that weaknesses in executive control may reflect reduced striatal dopamine, whereas increased response variability may be due to an independent process that is attributable to noradrenaline dysfunction [79].

The existing literature conclusively shows that response variability is associated with nearly all childhood disorders, and the initial success of new approaches suggests that additional research will be of considerable interest. Of particular importance will be studies that also measure constructs such as EF, delay aversion, and response to motivational contingencies, providing a direct test of whether response variability is independent of these other processes, interacts with weaknesses in one or more of these domains, or is simply a secondary consequence of another dysfunctional process.

Cognitive Processing Speed and Alerting

Along with increased response variability, groups with each childhood disorder included in this review exhibit general slow processing speed in situations in which responding quickly is important. Effect sizes are large for most disorders, with somewhat smaller effects for ODD/CD and anxiety disorders.

No theoretical model of a childhood disorder explicitly posits processing speed as a single core weakness that is a necessary or sufficient cause, although lowered cortical arousal is the most parsimonious neuropsychological explanation. Consistent with a low arousal hypothesis is the vigilance weakness on the continuous performance test that is present in nearly all groups (table 1), as well as consistent findings of increased slow wave activity on brain electrical recordings in individuals with ADHD [80]. Alternatively, slow response time could be attributed to poor response activation, a distinct process linked to left lateralized processing [81]. In either case, the magnitude and consistency of these effects indicates that a comprehensive model of the neuropsychology of ADHD must explain slowed processing. Future research is needed to test whether slow processing speed is related specifically to other measures of arousal, vigilance, activation or alerting, and then whether those domains account for findings in the realm of executive control, aversion to delay, or response variability.

Initial Conclusions from Neuropsychological Studies of Childhood Disorders

The results summarized in this section confirm that groups with childhood disorders differ from groups without a diagnosis in multiple neuropsychological domains, with average effect sizes that are medium to large (d = 0.30–0.80). These effect sizes are sufficiently large to be important for etiological theories of the disorders, but are not large enough to identify DSM-IV categories of children with adequate sensitivity and specificity.

Similar to studies of adult disorders [82], the nine childhood disorders included in this review are characterized by a generalized neuropsychological weakness across a range of cognitive processes, including intellectual ability, multiple aspects of executive control, processing speed, and response variability. In addition, the results of the meta-analysis provide tentative support for distinct neuropsychological profiles across disorders. For example, the largest effects for ADHD and Tourette's disorder were reported on measures of response inhibition, response variability, and processing speed, whereas cognitive flexibility appears to be relatively spared in these groups [83]. In contrast, groups with HFA and COS exhibited pronounced weaknesses on measures of cognitive flexibility and planning, but were less impaired on measures of response inhibition. Individuals with LD/RD were most impaired on measures that involved retention and rapid processing and manipulation of information, and groups with mood disorders and ODD/CD exhibited moderate nonspecific weaknesses on most tasks.

We discuss the implications of the similarities and differences in the neuropsychological profiles of the disorders in more detail later in the chapter. First, we briefly review studies of the impact of comorbidity, the co-occurrence of two or more distinct diagnoses in the same individual, on the neuropsychological profile of each disorder. These results help to clarify which neuropsychological weaknesses are independently associated with each disorder, providing important information regarding the interpretation of clinical heterogeneity in theoretical models of childhood disorders.

Comorbidity

Comorbidity is clearly the rule rather than the exception for DSM-IV-TR disorders in childhood and across the lifespan. For example, 70–90% of individuals with DSM-IV-TR ADHD meet criteria for at least one comorbid diagnosis [84, 85]. Disorders comorbid with ADHD include other disruptive behavior disorders (ODD 30–60%; CD 20–50%), LDs (20–40%), anxiety disorders (15–30%), and depression (15–30%) [84–88]. Rates of comorbidity are even higher when ADHD is assessed in groups that were first identified due to a diagnosis of Tourette's disorder (40–60%) [89, 90], COS (>80%) [91], or bipolar disorder (50–90%) [92].

These striking results clearly indicate that in addition to explaining the symptoms of a specific disorder of interest, neuropsychological models of childhood disorders must also account for the high rates of comorbidity with other disorders. However, surprisingly few neuropsychological studies of childhood disorders have controlled for comorbidity or tested its impact. Therefore, in the remainder of this section we present new data and review previous studies that tested the implications of comorbidity. Because space constraints do not permit a comprehensive summary of results for all possible pairs of comorbid disorders, the review is restricted to studies that examined comorbidity between ADHD and the other eight disorders.

The results summarized in tables 2 and 3 address two main questions that arise if a disorder is associated with a neuropsychological weakness when examined in isolation. The first question asks if a disorder is independently associated with the neuropsychological weakness after any significant comorbidity is controlled. If the effect is restricted to the comorbid group, it can be described more parsimoniously as a correlate of the comorbid disorder rather than as a neuropsychological weakness of the initial disorder per se. The columns on the left side of tables 2 and 3 summarize results from studies that addressed this first question for the neuropsychological constructs included in the meta-analysis.

Even if the initial disorder is associated with significant neuropsychological weakness when the comorbid disorder is controlled, the other disorder may still moderate this association. The columns on the right side of tables 2 and 3 summarize results of studies that tested if the relation between the primary disorder and neuropsychological performance was significantly stronger or weaker in the subset of individuals with the comorbid disorder.

Neuropsychology of ADHD after Controlling for Comorbidity

Because relatively few studies have systematically tested if the profile of neuropsychological functioning differs in groups with ADHD with and without comorbidity, we conducted analyses to test this question in the Colorado Learning Disabilities Research Center (CLDRC) twin sample, an ongoing study of the etiology of reading difficulties and ADHD [30]. Consistent with other community samples [93, 94], the majority of participants in our sample met criteria for the inattentive type ($n = 214$) or combined type ($n = 95$), and a much smaller proportion met criteria for the hyperactive-impulsive type ($n = 39$). Because results from our sample and others suggest that the hyperactive-impulsive type is not consistently associated with the neuropsychological weaknesses that characterize the inattentive and combined types [33, 95], the hyperactive group was excluded from these analyses. In addition, because the pattern of results was extremely similar for the inattentive and combined subtypes, these groups were combined to create a single ADHD group to simplify interpretation.

In our sample, the group with ADHD without RD exhibited weaknesses on nearly all neuropsychological measures in comparison to the control group (fig. 2a), indicating

Table 2. The effects of comorbidity on the neuropsychological functioning of individuals with ADHD

Comorbid disorder[a]	Studies that reported a significant ADHD effect when the comorbid disorder was excluded or controlled[b] (representative studies)	Studies that compared neuropsychological functioning in groups with ADHD with and without each comorbid disorder[b] (representative studies)
Anxiety	All tested measures[c,d]	The group with ADHD + anxiety was less impaired than the group with ADHD without anxiety on measures of response inhibition [130]
LD/RD	All measures[e] [29, 30, 32, 37, 41, 151, 159]	The group with ADHD + LD/RD was more impaired than the group with ADHD without LD/RD on measures of verbal fluency (fig. 2a), response inhibition [29, 142], processing speed [151] (fig. 2a), response variability [37, 159], vigilance [142], and working memory [30, 159]
Bipolar	Speed, working memory[f] [145]	After controlling for comorbid bipolar disorder, the ADHD effect was no longer significant on measures of processing speed [129], response variability [145], vigilance [145], and working memory [129]
ODD/CD	All measures[c] [32, 60, 72, 121, 127, 136]	The group with ADHD + ODD/CD was more impaired than the group with ADHD without ODD/CD on measures of response inhibition [158] The group with ADHD + ODD/CD was less impaired than the group with ADHD without ODD/CD on measures of response inhibition [147], planning [136], and vigilance [121]
MDD	All tested measures[d]	The group with ADHD + MDD was more impaired than the group with ADHD alone on measures of verbal fluency, response inhibition, processing speed, and working memory (fig. 2b)
Tics/TS	All tested measures[g] [144, 152]	The ADHD effect remained significant in all studies [144, 152]

[a]Although no studies have directly tested for mediator or moderator effects of autism spectrum disorders or childhood-onset schizophrenia in groups with ADHD, multiple studies have shown that ADHD is independently associated with deficits on all of the measures that were significant in table 1 and figure 1 when individuals with autism or schizophrenia spectrum disorders were excluded.

[b]The eight dimensions included in the table are fluency, planning, processing speed, response inhibition, response variability, set shifting, vigilance, and working memory. Delay aversion was not included in the table because few previous studies have examined the relation between ADHD and delay aversion while controlling other psychopathology. Interference control is not included because the initial main effect of ADHD was not significant in most studies.

[c] Results described in this chapter.

[d]No studies included a measure of planning.

[e]Results are summarized in figure 2.

[f]No studies included measures of delay aversion, fluency, or planning.

[g]Fluency and planning were not included in any study of tics/TS.

Table 3. Summary of studies that tested if the neuropsychological performance of other disorders differed as a function of comorbid ADHD

Primary disorder[a]	Studies that reported a significant effect of the primary disorder when ADHD was excluded or controlled[b] (representative studies)	Studies that compared neuropsychological functioning in groups with the primary disorder with and without ADHD[b] (representative studies)
Anxiety	None[c] [130, 134, 135]	
LD/RD	All measures [29, 30, 41, 139, 142, 159]	The group with LD/RD + ADHD was more impaired than the group with LD/RD without ADHD on measures of response inhibition [29, 142], response variability [142, 159], vigilance [37, 142], and working memory [37]
Autism	Fluency, shifting, working memory[d] [70]	After controlling for ADHD symptoms, the autism main effect was no longer significant on a measure of response variability [70]
Bipolar	All tested measures[e] [117, 124, 138, 145]	The group with bipolar disorder + ADHD was more impaired than the group with bipolardisorder without ADHD on measures of set shifting [138] and vigilance [138] After controlling for ADHD symptoms, the bipolar main effect was no longer significant on measures of set shifting[e] [133], processing speed[e] [145], response variability [145], or vigilance[e] [145]
ODD/CD	Variability, planning[f], shifting[f], vigilance, working memory [46, 150, 156]	After controlling for ADHD symptoms, the main effect of ODD/CD was no longer significant on measures of processing speed [132], planning[f] [132, 133], response inhibition [121], or set shifting[f] [51, 133]
Tics/TS	Inhibition[g] [120]	After controlling for ADHD symptoms, the main effect of Tourette's disorder was no longer significant on measures of verbal fluency [158], processing speed [144], response inhibition[g] [97, 152], response variability [97], vigilance [152], or working memory [144, 158]

[a]No studies have tested the effect of comorbid ADHD on the neuropsychological functioning of groups with COS or MDD.

[b]The eight dimensions included in the table are fluency, planning, processing speed, response inhibition, response variability, set shifting, vigilance, and working memory. Delay aversion was not included because few previous studies have examined the relation between ADHD and delay aversion while controlling other psychopathology. Interference control is not included because the initial main effect of ADHD was not significant in most studies.

[c]No simple main effect of anxiety was observed on measures of inhibition, planning, or processing speed. Measures of fluency, planning, and shifting were not included in any study of anxiety disorder that controlled for ADHD.

[d]Planning, speed, and vigilance were not included in any studies that controlled for ADHD.

[e]No studies included a measure of planning. In some studies the group with bipolar disorder without ADHD differed from controls on measures of processing speed, set shifting, and vigilance [112, 138], whereas in other studies these effects were explained by comorbid ADHD [133, 145].

[f]In some studies the group with ODD/CD without ADHD differed from controls on measures of planning and set shifting [156], but these effects were explained by comorbid ADHD in other studies [51].

[g]The main effect of TS on inhibition measures remained significant when ADHD was controlled in some studies [120] but not in others [97, 152].

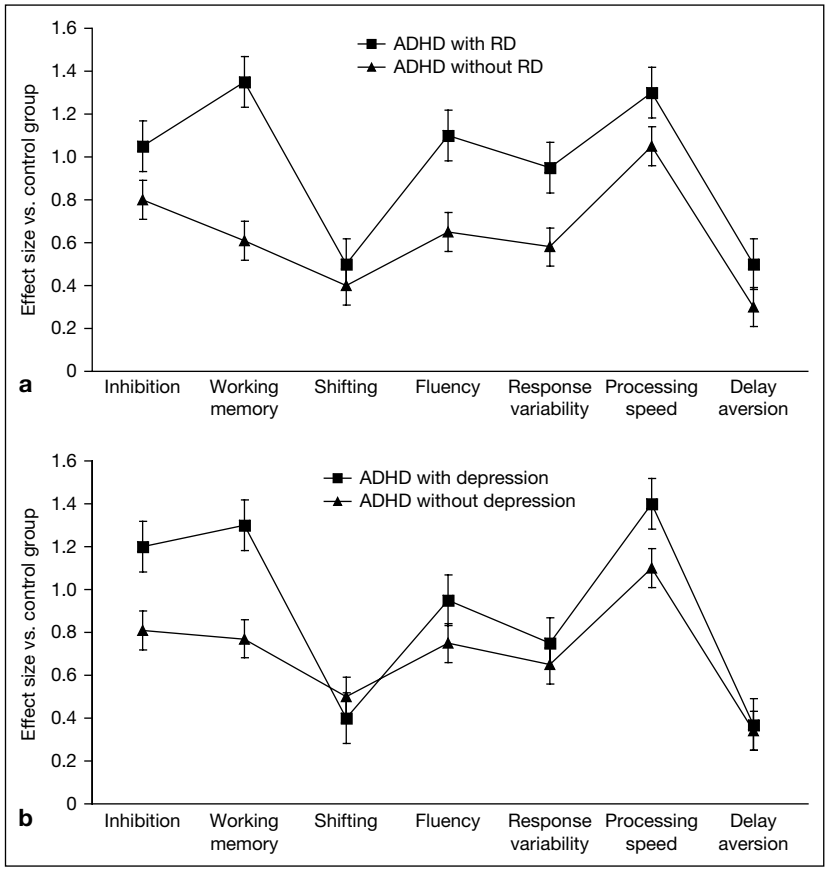

Fig. 2. Effect sizes in groups with ADHD with and without reading disability (**a**) and depression/dysthymia (**b**). Effect size = d [160], and error bars indicate the 95% confidence interval for each effect size. All measures were scaled so that larger positive effect sizes indicate that the comorbid group performed worse on the measure. RD was defined based on a cutoff score on a composite of the Peabody Individual Achievement Test Reading Recognition, Reading Comprehension, and Spelling subtests [30]. Depression/dysthymia was defined by parent and self-report responses on the DSM-IV Diagnostic Interview for Children and Adolescents (DICA-IV) [162]. Measures in composite scores were as follows [for a detailed description see, 30, 163]: Inhibition = Stop-signal reaction time and continuous performance test (CPT) commission errors; Vigilance = CPT omission errors; Working memory = sentence span, counting span, digits backward, CANTAB spatial working memory; Processing speed = rapid automatized naming, Stroop color and word naming, Wechsler Coding and Symbol Search, Educational Testing Service Identical Pictures test, Colorado Perceptual Speed; Delay aversion = Choice Delay Task.

that ADHD is associated with neuropsychological weaknesses that are independent of the influence of comorbid RD. On the other hand, the group with ADHD and comorbid RD performed more poorly than the group with ADHD without RD on nearly all neuropsychological measures in our battery. Similarly, several of the studies

summarized in table 2 found that the group with comorbid RD scored lower than the group without RD on measures of response inhibition, vigilance, working memory, and naming speed (table 2). These converging results suggest that comorbid RD may be a marker for a subset of individuals with ADHD with more severe neuropsychological difficulties.

To our knowledge no published studies have examined the influence of comorbid mood disorders on the neuropsychological correlates of ADHD. Analyses conducted for this chapter indicated that the group with ADHD with comorbid MDD or dysthymia was more impaired than the group with ADHD alone on measures of response inhibition, working memory, and processing speed (fig. 2b). Although we did not predict this pattern of results when we initiated the study, it is consistent with studies that reported weaknesses in executive control in children and adults with MDD (table 1). This pattern is also similar to the pattern reported in studies of ADHD with and without bipolar disorder, the other major mood disorder included in the review (table 2).

In contrast to the results for MDD and RD, comorbidity with CD or anxiety did not significantly change the ADHD main effect on any of the neuropsychological composites in our sample (d between groups with ADHD with and without the comorbid disorder = 0.0–0.2). Most previous studies also reported no significant differences between groups with ADHD with and without anxiety or ODD/CD, and those that did report a significant difference usually found that the group with a comorbid anxiety or disruptive disorder performed *better* than the group with ADHD alone (table 2). Similarly, available studies suggest that comorbidity with Tourette's disorder does not influence the neuropsychological performance of groups with ADHD (table 2), and a number of studies have demonstrated that ADHD is associated with a range of neuropsychological weaknesses when individuals with autism or COS are excluded a priori at the beginning of the study.

These studies indicate that no single comorbid disorder can account for the neuropsychological weaknesses associated with ADHD. However, the possibility still exists that the neurocognitive correlates of ADHD might be explained by a combination of multiple comorbid disorders rather than by ADHD per se. We tested this hypothesis by analyzing data from the CLDRC twin sample [30, 96]. All participants with ADHD who met criteria for RD, CD, generalized anxiety disorder, separation anxiety disorder, MDD, or dysthymia were excluded from analyses (approximately 70% of the initial sample met criteria for at least one of these disorders). After excluding this extensive list of comorbid disorders the remaining participants had slightly less severe ADHD symptoms and neuropsychological impairment, but still differed significantly from the control group without ADHD on all of the neuropsychological measures listed in figure 2 (mean d across all neuropsychological tasks = 0.6–1.1 in the group with comorbidity and 0.4–0.6 in the group without comorbidity).

Impact of Comorbidity with ADHD on Neuropsychological Functioning of Other Disorders

Table 3 summarizes studies that tested whether the presence of comorbid ADHD affected the neuropsychological performance of groups with other disorders. Groups with RD/LD, bipolar disorder, and ODD/CD exhibited neuropsychological weaknesses that are independent of ADHD (table 3, left column), but several studies also found that children in the comorbid group exhibited greater impairment than the group without ADHD (table 3, right column). The most striking results were reported in studies of Tourette's disorder, which consistently found that the neuropsychological weaknesses in groups with Tourette's disorder were almost entirely restricted to the subset of individuals who also met criteria for ADHD [97].

Conclusions Regarding Comorbidity

ADHD is associated with a range of neuropsychological weaknesses that remain significant when comorbid disorders are excluded or controlled. Similarly, groups with RD, ODD/CD, and bipolar disorder exhibit neuropsychological weaknesses that are independent of ADHD, although the presence of ADHD is often associated with more severe impairment. In contrast, neuropsychological weaknesses in groups with Tourette's disorder appear to be better explained by comorbid ADHD. Additional studies are needed to clarify the influence of comorbidity on the relation between ADHD and delay aversion, response variability, and response to reinforcement contingencies, and to test the influence of comorbidity between other pairs of disorders that do not include ADHD.

Conclusions and Implications for Theoretical Models of Childhood Disorders

Similar to findings for adult disorders [82], the nine childhood disorders included in this review are characterized by a range of neuropsychological weaknesses on measures of intellectual functioning, EFs, processing speed, and response variability, along with significant aversion to delay in groups with ADHD. Mean effect sizes are medium or large for most disorders ($d = 0.4–0.8$), indicating that each of these weaknesses is an important component of the overall neuropsychology of the disorder. On the other hand, the magnitude of these effect sizes and data from other previous studies [98] suggest that no single neuropsychological weakness is likely to be necessary or sufficient to cause all cases of any childhood disorder.

A comparison of results across different disorders revealed an issue with similar implications. Results of both the meta-analysis and individual studies that directly compared different combinations of comorbid diagnoses indicate that each neuropsychological weakness is associated with multiple childhood disorders. Taken together, these results argue against single-deficit theories that propose that all cases of a disorder are due to a single neuropsychological weakness that is unique to that disorder. Instead, it is likely that there is simply not going to be a 1:1 mapping of any

neuropsychological domains to all individuals with the specific behavioral disorders defined currently in DSM-IV.

Does the absence of a single necessary and sufficient core deficit for each disorder mean that the neuropsychological approach is not useful? On the contrary, several lines of evidence suggest that these complex neuropsychological results are simply a reflection of reality that was predictable based on the previous literature. Studies of ADHD have shown that individuals with childhood disorders may exhibit weaknesses in multiple neuropsychological domains, and the specific profile of neuropsychological weaknesses may differ among individuals who all meet diagnostic criteria for the same disorder [20, 98–100]. On the other hand, the ubiquitous comorbidity between nearly all pairs of disorders suggests that at least a subset of risk factors may be shared by multiple disorders. However, both of these findings could potentially be explained by weaknesses in diagnostic criteria rather than heterogeneity within and shared risk factors between valid diagnostic categories. Therefore, it will be important in future work to design studies in such a way that the natural boundaries of neuropsychological dysfunction can be mapped backwards onto behavior, rather than assuming that the behavioral categories are always valid in their current form. Support for that conclusion and for the neuropsychological findings described here is provided by studies of the genetic and environmental etiology of childhood disorders.

Although most childhood disorders are highly heritable (50–80%) [101–103], this does not imply that they result from a single major gene. In fact, molecular genetic data increasingly suggest that each of the disorders included in this review has a complex etiology that is likely to include many genetic and environmental risk factors that each increase susceptibility to the disorder a relatively small amount [104–106]. Moreover, multivariate twin studies suggest that at least a subset of genetic and environmental risk factors increase risk for two or more different disorders [101–103].

Though it is possible that each disorder could be due to a unique set of multiple risk factors that all influence a single neuropsychological weakness that is specific to that disorder, it is more likely that at least some of these risk factors may affect more than one disorder. Some may influence general risk factors that play a role in most childhood disorders, possibly by contributing to a weakness in a broadly distributed neural network that affects numerous other cognitive functions. Other more specific risk factors may increase risk for a cluster of related disorders by altering the function of a more specific neural network, such as the frontal-striatal network implicated in EF. It is likely that a third subset of risk factors will indeed be uniquely associated with each disorder, but rather than single core deficits, these unique risk factors will comprise one important component of a more complex multifactorial etiology.

Neuropsychological Profiles

A closer examination of the results of the meta-analysis illustrates how analysis of neuropsychological functioning in different domains may help to explain the similarities and differences across childhood disorders. Slow processing speed and increased

response variability appear to be general risk factors for most disorders, whereas weaknesses in different aspects of executive control may distinguish between disorders. Although all groups exhibited mild weaknesses on measures of inhibitory control and working memory, the effect size for response inhibition was largest in the groups with ADHD and Tourette's disorder, and the groups with a LD or COS exhibited a larger weakness in working memory than groups with other disorders. In contrast, groups with ADHD, LD, and Tourette's disorder exhibited minimal and inconsistent weaknesses on measures of set shifting and cognitive flexibility [83], whereas these were the most pronounced difficulties in the groups with autism (mean d = approximately 1.1 for measures of set shifting and planning) and COS (mean d = approximately 1.0).

Groups with anxiety disorders, mood disorders, or ODD/CD exhibited moderate weaknesses across many of the tasks. In contrast to the other disorders, however, the neuropsychological profile of these groups was relatively nonspecific. This pattern of results may be due to the fact that previous studies have focused primarily on cognitive aspects of executive control and processing speed, whereas these clusters of disorders might show larger effects on measures that more directly tap motivational circuits and processes involved in regulation of emotion.

Though much more work remains to be done, the current findings illustrate how neuropsychological methods have helped to constrain and refine overarching theories of childhood disorders. Given that neuropsychological deficits do not map cleanly onto current diagnostic categories, the neuropsychological level of analysis is likely to help to identify neuropsychologically distinct subgroups within disorders, as well as groups of individuals across disorders who exhibit similar neuropsychological difficulties. Both of these approaches may inform future remapping of diagnostic boundaries, and may provide a useful way to parse behavioral syndromes for targeted interventions and studies of genetic and environmental risk factors. Results of these studies will facilitate the development and refinement of complex multiple-deficit models of childhood disorders. We briefly describe two specific examples of such models below.

Multiple Deficit Models

The theoretical models that best fit existing data from neuropsychological and etiological studies explicitly hypothesize that each disorder is neuropsychologically heterogeneous. For example, a satisfactory theoretical model of ADHD must explain how multiple genetic and environmental risk factors lead to weaknesses in multiple EF domains, significant aversion to delay and possibly differential sensitivity to other motivational contingencies, and slower and more variable responses on both individual task trials and across entire measures. In addition, these models must account for the significant neuropsychological heterogeneity at the level of the individual child. Several multiple-deficit models have now been articulated by us and others [12, 53, 77, 107]. In the remainder of this section we describe just two examples of these models to illustrate ways that these models could be conceptualized.

Independent pathway models suggest that disruption in any one of two or more pathophysiological substrates can independently lead to the same final behavioral manifestation of a disorder. Therefore, independent pathway models propose *neuropsychological subtypes*. For example, Sonuga-Barke [99] proposed a dual-pathway model in which some individuals exhibit ADHD symptoms due to significant aversion to delay, whereas others have ADHD due to weak inhibitory control. In parallel using a temperament perspective, Nigg et al. [107] suggested that some cases of ADHD are due to an excessive approach system (appetitive), and others due to failures in cognitive control (executive system).

In contrast to independent pathway models, *multifactorial models* suggests that the symptoms of complex childhood disorders arise due to the additive and interactive combination of multiple dysfunctional processes. Because no specific weakness is a necessary or sufficient cause of the disorder, the exact cluster of weaknesses may differ among individuals, leading to neuropsychological and clinical heterogeneity. For example, individuals with weaknesses in executive control and processing speed may be most likely to meet criteria for ADHD, LD, or MDD, whereas the same EF weaknesses coupled with aversion to delay or disruption in other motivational processes might increase susceptibility to hyperactive-impulsive behaviors, disruptive behavior disorders, or substance abuse.

In one of the first direct tests of these models, Sonuga-Barke et al. [59] re-analyzed the dataset from the ADHD multimodal treatment study [100] to test the relations between delay aversion, response inhibition, and the DSM-IV-TR combined type. A cutoff score at the 10th percentile of a control group without ADHD was used to identify the number of children who exhibited deficient response inhibition, significant delay aversion, or significant dysfunction in both domains. A subset of the group with ADHD exhibited weak inhibitory control but not delay aversion (23%), and another group exhibited significant delay aversion only (15%), providing support for the dual-pathway model described by Sonuga-Barke [99]. In contrast, a higher proportion of the sample than would be expected by chance (23%) exhibited both delay aversion and weak inhibitory control, consistent with the predictions of the multifactorial model. Finally, 39% of the sample did not exhibit either significant aversion to delay or inhibitory difficulties, indicating that additional cognitive dysfunctions not captured by delay aversion or response inhibition represent either additional alternative pathways to ADHD or additional components in a multifactorial etiology. A similar pattern of results was obtained in parallel analyses of response variability and EF in three large independent samples [98], suggesting that this pattern is not specific to delay aversion and inhibition (18–27% of the group with ADHD exhibited no deficits, whereas 28–36% exhibited weaknesses on three or more measures).

In summary, the multiple-pathway and multifactorial models agree with earlier neuropsychological models that a comprehensive neurocognitive model of ADHD is almost certain to include dysfunction in multiple separable neural networks, but differ in not giving primacy to a single core deficit that drives the others. The reason for

not giving primacy is the modeling of heterogeneity into the conceptual framework. Additional research is needed to test if dysfunction in these different networks leads to distinct neuropsychological subtypes within each disorder, or if multiple dysfunctional processes act in combination to increase susceptibility to different disorders. Perhaps the most likely scenario is that both of these models may be partially correct, such that some cases of each disorder are attributable to a primary deficit in a relatively specific neurocognitive function, whereas other cases are caused by the combined effects of dysfunctions in multiple neural substrates.

Key Remaining Issues and Directions for Future Research

The transition from models positing a single primary deficit to multiple-deficit models represents a paradigm shift in the way that the neuropsychology of childhood disorders is conceptualized [99]. In this final section we summarize several key remaining issues for the field, then highlight future directions for studies of the neuropsychology of ADHD within a multiple-deficit framework.

Clinical Heterogeneity

The results of the current review indicate that additional research is sorely needed to clarify the meaning of the nearly ubiquitous comorbidity in childhood disorders. One approach that has been used frequently in previous studies is to apply stringent exclusion criteria at the beginning of a study to maximize the homogeneity of the sample. For example, many studies of different disorders have excluded participants who also met criteria for ADHD, LD/RD, ODD/CD, TS, mood disorders, pervasive developmental disorder, and mental retardation [for a detailed summary of these exclusion criteria in previous studies see, 70]. However, the a priori exclusion of a subset of individuals makes strong assumptions about the meaning of heterogeneity that are not easily justified based on existing knowledge, and may even be counterproductive. For example, whereas few would argue with the decision to exclude children with mental retardation from studies of the neuropsychological correlates of disorders in which most children have cognitive ability in the normal range, the justification for exclusion criteria based on other comorbidities is less clear. When we selected children with ADHD without any comorbidity for the analysis described earlier in this chapter, the neuropsychological effect sizes were less than half the size of the effects in the entire sample who met criteria for ADHD. Therefore, if we had made an a priori decision to exclude children with any comorbid disorder at the beginning of the study we would have excluded the subset of individuals with the greatest neuropsychological impairment and symptom severity – arguably the cases most in need of intervention and study and those with the most clear-cut case of ADHD.

The exclusion approach may be optimal if resource limitations or the study design mean that the final sample will be small. For example, neuroimaging studies are

required to carefully select which subset of participants to include due to the cost required to run each individual. In contrast, for most purposes the optimal approach is to include all individuals with a disorder for the initial sample, then to assess carefully putative diagnostic subtypes, comorbid disorders, and any other potential markers of heterogeneity. These markers can then be controlled statistically or used as exclusion criteria for specific analyses, facilitating a direct test of the impact of these variables on the neuropsychology of the disorder.

Direct Tests of Competing Neuropsychological Models

Most previous studies have examined the neuropsychological correlates of childhood disorders from a single theoretical perspective or with only one or two measures, making it difficult or impossible to test competing theories in the same study. Although effect sizes from multiple studies can be used to conduct preliminary comparisons between theories, interpretation of such comparisons is inevitably complicated by differences in study design and sampling procedures. Therefore, studies are needed that test multiple competing theoretical models in the same sample, such as the study by Rucklidge and Tannock [37] that showed that reading difficulties were predicted independently by letter naming speed and verbal working memory and studies that found that delay aversion and EFs independently predicted ADHD [100, 108].

New Methodological Techniques

Finally, perhaps the most exciting future direction for neuropsychological studies of childhood disorders is the increasing opportunity to incorporate new methodological approaches and multiple levels of analysis in a single study. In this section we briefly describe how neuropsychological studies might interface with five methods that show promise as tools for future research on the pathophysiology of childhood disorders.

Statistical Methods

The neuropsychological measures used in previous studies are complex tasks that involve multiple cognitive processes, making it difficult to determine which component of the task is responsible for a difference between groups. Moreover, the predictive power of many of these tasks is constrained by their relatively modest reliability in children. Both of these concerns may be mitigated in future studies by administering multiple measures of key constructs to facilitate the creation of latent trait or factor scores. These scores are based on the shared variance across multiple measures of a construct, separate from the variance associated with measurement error or other processes that are idiosyncratic to a particular measure. The potential utility of this approach is illustrated by results from the Colorado Longitudinal Twin Study that showed that the relation between inhibition and attention problems was stronger when inhibition was measured with a latent trait ($r = 0.44$) versus any individual inhibition measure ($r = 0.20–0.34$) [31].

Etiologically Informative Designs

Although individual differences in delay aversion appear to be primarily attributable to environmental influences [109], estimates of familiality and heritability are moderate to high for most measures of EF, processing speed, and response variability [109–111], and multivariate twin analyses suggest that common genetic influences account for most of the phenotypic covariance between these neuropsychological weaknesses and ADHD symptoms, reading difficulties, and symptoms of other disruptive disorders [96, 109]. Based on these results, studies have recently begun to test whether neuropsychological measures are useful as intermediate phenotypes (often called 'endophenotypes') that mediate or moderate the relation between specific genetic and environmental risk factors and the symptoms of childhood disorders [83, 112, 113]. Although this line of research is still early in its development, the endophenotype approach is likely to provide an important tool for the continued refinement of causal models of childhood disorders.

Neurocomputational Modeling

Sophisticated neurocomputational modeling techniques are likely to provide an extraordinary tool to understand the pathophysiology of complex disorders. Theoretical models of the neurophysiology of a disorder can be instantiated in computational models, then used to derive and constrain predictions to be tested using neuropsychological tasks. The neuropsychological results will then provide new data that the theoretical and computational models must explain, leading to further refinements to the models that can again be tested with revised neuropsychological tasks. The potential utility of this iterative approach is demonstrated in a recent paper that used a neurocomputational model and psychopharmacological manipulation to begin to tease apart the differential influence of dopamine and noradrenaline on different aspects of neuropsychological dysfunction in ADHD [79].

Brain Imaging

Similar to neurocomputational modeling, the collection of neuroimaging and neuropsychological measures in the same sample will allow these methods to inform and constrain one another. Theoretical models make specific predictions regarding the brain regions and neurotransmitter systems that are likely to be implicated in childhood disorders. Neuropsychological measures can then be developed that should recruit these specific regions of the brain to test these predictions using structural and functional MRI, event-related potentials, or other measures of neurophysiology [114, 115].

Treatment Response

The overarching goal of all neuropsychological research is to inform and improve clinical diagnostic procedures and subsequent interventions for childhood disorders. By including measures of neuropsychological functioning in treatment studies

along with other potential markers of clinical heterogeneity, it may eventually be possible to begin to predict the treatment that is most likely to be helpful for a specific individual.

Conclusions

A meta-analysis of nine of the most common childhood disorders indicated that the neuropsychological etiologies of most childhood disorders are complex and multifactorial. Comprehensive neuropsychological models of most disorders must incorporate increased response variability on single trials of cognitive tasks, slower overall processing speed across entire measures, and weaknesses in at least some aspects of executive control. No single deficit is necessary or sufficient to explain all cases of any disorder, but preliminary evidence suggests that disorders may be distinguished by profiles across multiple neuropsychological processes. Slow processing speed and increased response variability are ubiquitous across disorders, but somewhat distinct profiles are apparent on different measures of EFs. ADHD and Tourette's disorder are most strongly associated with inhibitory difficulties, whereas difficulties with cognitive flexibility are most pronounced in groups with autism spectrum disorders and COS. Working memory difficulties are significant in most groups, but these weaknesses are largest in groups with LDs and COS. Future research is needed to clarify further the relations among these heterogeneous diagnostic phenotypes and complex neuropsychological processes to facilitate studies that link these weaknesses to specific etiological risk factors.

Conflicts of Interest

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Electrophysiology in Child Psychiatric Disorders

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Abstract

Human brain activity reflects the wide time range of neural events. Measuring the brain's electric (EEG/ERP) and magnetic (MEG) fields resolves both fast and slow neural events through completely noninvasive recordings. EEG/ERP measures the dynamics of neural activations from milliseconds to hours for a wide variety of brain states and processes, even during sleep and in infants. Mapping and source estimation localizes these dynamic activation patterns in the brain with increasing accuracy. How recent EEG/ERP research on brain function has substantially contributed to the understanding of normal development and psychiatric conditions of children and adolescents is illustrated. The high time resolution is particularly important for measuring covert processes and distinguishing cause and effect in studies of perception, attention and executive control, memory, language, and emotion. The selected clinical applications in children and adolescents covers attention deficit/hyperactivity disorder along with its main comorbid disorders, specific language disorders and dyslexia. Future applications of EEG/ERP markers may clarify the interactions between brain states and transient functions, distinguish etiological pathways through patterns of genetic modulation, and predict clinical treatment response.

Over the past two decades, electrophysiological research has contributed substantially to the understanding of brain functions during normal development and their deviations in child and adolescent psychiatric conditions. This chapter will discuss methodological issues and consider the advantages and disadvantages. Recent advances in electrophysiological brain imaging using attention deficit/hyperactivity disorder (ADHD), autism, specific language impairments, and dyslexia will be illustrated as examples. Finally, future applications in research and clinical practice will be outlined.

Recordings of electric (EEG) and magnetic (MEG) fields make it possible to monitor the spatiotemporal dynamics of neural activation patterns associated with a wide range of cognitive processes and their development in real time. These methods enable the measurement of neural activations, from milliseconds (e.g., click-evoked brain stem, activity) to hours (e.g., sleep stages and cycles), associated with a variety of brain states and processes. These parameters can reliably be reproduced in a wide range of patient and age groups covering even infants, and they can give indices of pre-attentive, premotor and covert processing differences [for reviews see, 1, 2]. This makes them ideal for studying brain function during normal and deviant child development. Their excellent time-frequency resolution is particularly useful to clarify whether multiple deficits follow and cause each other, or are present simultaneously, which is not possible with slower metabolic methods. At the same time, the advances in source resolution now allow genuine dynamic EEG-based neuroimaging.

In contrast, neuropsychological performance data alone can only give indirect clues about covert processing. Different covert mechanisms leading to similar overt performance may appear indistinguishable, and deviant covert information processing may precede overt performance deficits or even underlie normal performance. In addition, many tasks tap more than one latent dimension of functioning [3]. Therefore, the construct validity of neuropsychological tasks is often uncertain. To uncover the neural bases of a cognitive process it is important both to identify the participating brain regions and determine the precise timing of the information processing within and among those regions [2].

Neuroimaging techniques based on cerebral hemodynamics or metabolism have excellent spatial resolution, but they lack the high temporal resolution of the EEG which allows accurate timing and sequencing of covert brain processes. Accurate localization, as is possible with functional MRI (fMRI), is necessary but not sufficient to understand brain function unless complemented by the high temporal resolution of EEG/MEG, because initial and re-entrant brain activation in the same brain region occurs within less than 100 ms and thus cannot be disentangled by slow time resolution of fMRI alone [4].

The EEG measures brain electrical activity using electrodes placed on the scalp. It directly reflects neural mass action, and mainly synchronized postsynaptic potentials of aligned neurons such as pyramidal cells in the cortex. Such spatiotemporal synchronization of neural networks results in net polarization of extended brain regions, which may be transient, slow, or oscillatory. Brain sources of scalp recordings can be estimated precisely from EEG or MEG topographies through source modeling. However, the inverse problem (i.e., estimating sources of the known scalp distribution) allows multiple solutions which fit the data equally well [2].

The resting EEG is recorded during relaxed wakefulness, typically with eyes closed. Clinically, relaxed wakefulness reflects a particularly important state of controlled

attention and arousal, where slower frequencies are generally associated with lower arousal or immaturity. The EEG is also an essential indicator of sleep stages and cycles and provides unique information regarding altered sleep physiology in psychiatric disorders [2].

EEG frequency analyses translate the high time resolution into a high frequency resolution. Numerous studies demonstrate that this frequency resolution is essential to characterize arousal, state regulation, and clinical features. Findings from EEG-based schizophrenia research can serve as an example. Drug-naïve first-episode adult schizophrenic patients exhibit increased slow as well as reduced medium frequency activity, with both dysfunctions localized in a similar frontal network [5]. Extensive EEG research has also elucidated developmental disorders such as ADHD and has related subtypes of ADHD to developmental models. While the spontaneous or resting EEG of ADHD children is often characterized by increased slow, and decreased fast activity [for review see, 2] as in younger children, at least one subtype of ADHD which is characterized by impulsivity and increased frontal β activity does not fit this developmental lag scheme [6].

In conclusion, EEG provides easy access to reliable measures of normal and deviant arousal and state regulation across a wide age range including infancy, where other functional brain mapping methods are of limited use. EEG studies also show that clinical deficits often affect multiple EEG frequency bands, and thereby reflect functional deficits in several distinct networks evident at the same time [2].

Event-related potentials (ERPs) are changes in the ongoing EEG or MEG which are time-locked (i.e., same latencies) and phase-locked (i.e., same amplitudes and polarities) to perceptual, cognitive, and motor processes. They are typically extracted from the ongoing EEG by means of signal averaging. Averaging not only eliminates the spontaneous background EEG 'noise', but also those event-related EEG modulations which are not phase-locked such as event-related synchronization and desynchronization. ERPs consist of characteristic sequences of components or 'microstates' (i.e., time segments with a stable topography) that span a continuum between early activity primarily determined by the physical characteristics of the eliciting stimulus (latency range 100–250 ms), and later components (latency range >250 ms) dominated by cognitive rather than physical characteristics of the stimuli [7]. These components are characterized by their topography, amplitude, latency, and their functional significance [2].

Auditory memory traces are measured through mismatch negativity (MMN), a frontally negative ERP component between 120 and 250 ms that is elicited by deviations in a repetitive auditory sequence. It can be considered as an outcome of an automatic 'comparison process' that contrasts incoming auditory input against the memory traces of the preceding sounds, and it is a valuable tool for investigating very early pre-attentive auditory discrimination and sensory or 'echoic' memory even in infants and children [8]. The development of language-specific memory traces has been demonstrated by the age of 1 year [9], although considerable topographic ERP

differences remain between children and adults [10]. The processing of language at the semantic and syntactic level is indexed by several ERP components. The N400 localized to the anterior medial temporal lobe [11] is regarded to be a sensitive index of semantic processing reflecting the neural mechanisms of semantic integration into context. ERP studies have documented that both lexical expectations facilitating early phonological processing and mechanisms of semantic priming facilitating integration into semantic context are already present in 19-month-olds [12]. Neural correlates of face recognition in the occipito-temporal brain, including the bilateral fusiform and right superior temporal cortices, are indexed by N170 [13]. This component can be used to assess developmental changes in face recognition already during postnatal development [14].

Later attentional and executive functions can be measured through the P300 type components following cues or targets in numerous tasks. The P300 components have been linked to attentional allocation, stimulus evaluation and context updating processes of working memory [15]. Reduced P300 amplitudes are a robust finding in a variety of psychiatric disorders, including schizophrenia [16], increased risk of alcohol and substance abuse [17, 18], and ADHD [19; for review see, 2]. Substance use disorder by age 19 years can significantly be predicted by P300 amplitude at age 10–12 [20]. P300 attenuation is usually measured for correctly detected targets only and is therefore not just a correlate of poor performance. The specific brain functions underlying inattention, impulsivity and impaired response control can be separated with adequate ERP tasks, for example the cued continuous performance test which yields different P300 components to cue, target, and NoGo stimuli. Control deficits in psychiatric disorders are also evident from altered ERP activity to performance errors and feedback. The initial error-related fronto-central negativity (ERN) peaks 100 ms after motor onset. It has been associated with performance monitoring, conflict inhibition and error processing, localized to the anterior cingulate gyrus, and is modulated by the lateral prefrontal cortex and the dopaminergic system [21]. The development of error processing is reflected in major differences between children, adolescents and adults regarding the time course of concomitant brain activation [22, 23]. The ERN amplitude is sensitive to mood and personality variables [24], suggesting that affective and motivational processes significantly influence performance monitoring and conflict processing. Recent data suggest that error- and feedback-related heart rate deceleration is a reflection of the same error-monitoring system that is responsible for the emergence of the ERN [25].

ERP parameters may reveal distinct information processing despite similar task performance. ERPs differentiate children with ADHD with and without comorbid conduct disorder or tic disorder [26–29], indicating that the presence of comorbidity in ADHD may alter brain electrical correlates, without necessarily affecting the level of overt behavioral performance. Recently, ERP correlates of irritability have been shown to discriminate children with severe mood dysregulation from children with narrow-phenotype bipolar disorder, suggesting that the pathophysiology of irritability

may differ among the groups and is influenced by oppositional defiant disorder severity [30]. ERP studies have also revealed distinct developmental trajectories of specific cognitive processes, e.g. of response inhibition vs. execution processes [31], or of conflict monitoring and response inhibition [32].

Recent Findings from ADHD, Autism, Language Impairment and Dyslexia

EEG/ERP research on ADHD has revealed a sequence of multiple activation deficits in posterior and anterior attentional networks within a sub-second range. Already early information-processing stages related to the initial orienting and stimulus evaluation are altered [for review see, 2]. Brain mapping indicates that children with ADHD exhibit increased early automatic attentional orienting (increased N1) before failing to allocate sufficient attentional resources in further processing stages (reduced P300, central processing, motor output) [19, 33]. This finding converges with shorter latencies of early auditory ERPs around 100 ms [34], and with a deviant topography of the visual N1 at around 200 ms in a stop task in children with ADHD [35, 36]. The latter results also indicate that a failure in early orienting can precede preparatory mechanisms and partly determine subsequent processing.

Impaired attention is reflected in a reduction of the P300 to cues which signal that the next stimulus may be a target, as replicated in several multicenter studies [19, 26, 37]. Importantly, these attentional deficits occur without concomitant responses or performance deficits, temporally precede inhibitory or executive control, predict subsequent performance, and do not depend on age and sex [19]. These covert attention deficits are more pronounced in ADHD children without comorbid externalizing behavior problems, despite a more severe psychopathology in the comorbid group [26, 38]. Electrophysiological evidence thus supports conclusions from recent family studies that the comorbid condition represents a separate pathological entity as in the ICD-10 classification system, rather than a sum of deficits from both pure disorders. Tomographic source solutions converge to posterior cue P300 sources [19, 37, 39]. This finding contrasts with the predominance of frontal deficits in metabolic studies of ADHD. It suggests under-activation of the posterior attention system in ADHD children, and involvement of central noradrenergic networks which modulate the P300 [40]. Further deficits of ADHD children during behaviorally silent waiting and preparation periods are implicated by reduced amplitudes of the contingent negative variation component [for review see, 2].

Inhibitory control deficits as reflected by reduced NoGo P300 are also found in ADHD [39, 41]. However, these are most prominent in ADHD children with comorbid externalizing disorders [27], unlike the covert attentional deficits. Also, they are preceded by state regulation deficits [35, 36] or accompanied by executive control deficits, particularly at slow event rates [42]. All these findings implicate a more general state or response regulation problem in ADHD. Consistent with this suggestion,

children with ADHD have a normal enlargement of their N2 component in NoGo as compared to Go trials [for review see, 2]. In contrast, the subsequent NoGo-P300 and its anteriorization are reduced in adults with ADHD [39]. This NoGo-P300 seems to reflect more general processes of response and conflict control beyond inhibition, and seems to be related to activations of the anterior cingulate cortex, and additional frontal and parietal regions in adults. Similarly, both attentional and inhibitory deficits are seen for ADHD children performing the Stop task, as their reduced activity to Go signals precedes an attenuated right frontal N2 activity to Stop signals [35, 36, 38].

Cognitive control processes as reflected in the ERN seem also to be deviant in children with ADHD [43, 44]. However, children with ADHD may also suffer from abnormal response strategy adjustments, reflected in deviant activity following the ERN [45].

In summary, ERP studies demonstrate that fast perceptual and attentional functions within the initial 150 ms of information processing are affected in ADHD, along with later deficits linked to attention and response control. The examples illustrate that the time resolution of EEG/ERPs is essential to clarify how altered modulation in sensory systems reflects a primary information processing problem, and not a secondary, late consequence of altered cognitive or emotional evaluation.

In young children with autism spectrum disorder (ASD), ERP studies have already revealed a similar slowing of face processing as in adults with ASD [46, 47]. These children's ERP amplitudes also fail to differentiate familiar from unfamiliar faces although they distinguish familiar from unfamiliar objects, suggesting that autism is associated with face recognition impairment early in life [48]. Furthermore, ERP studies have suggested that autism is associated with a disordered pattern of neural responses to emotional stimuli in 3- to 4-year-old children [49]. Conversely, recent fMRI studies failed to find any differences between adults with ASD and normal controls in fusiform gyrus activation during face processing, and concluded that face-processing deficits encountered in adults with ASD are not due to a dysfunction of the fusiform area [50]. This example indicates that structure and overall activation can be basically intact, even though the timing of the processes involved may be impaired; thus, measuring brain functions with a high time resolution can be crucial.

In developmental dyslexia, ERP studies documented that neurophysiological correlates of word recognition are attenuated [51, 52]. Auditory ERPs have also been used to study mechanisms of early language acquisition [53, 54], and for identifying children at risk of specific language impairment and related disorders [55]. MMN alterations are associated with the degree of phonological impairment [53, 56] suggesting a selective processing deficit at an earlier phonetic level as a possible source of the difficulties in learning to read. Several groups studied auditory ERPs to speech sounds in infants at risk of dyslexia and consistently found group differences. Children at risk had larger responses to standard sounds by the age of 6 months [57],

larger response to deviants by the age of 2 weeks [58], essentially absent mismatch responses to subtle speech contrasts by the age of 2 months [59], and a lower left lateralized mismatch response to speech at age 6 years [60]. Longitudinal studies have shown that infants' ERPs to speech sounds also predict (in a statistical sense) their subsequent language development, such as verbal memory at age 5 [61, 62] or reading skills at age 8 [62]. Studies on the development of coarse neural tuning for print indicate that fast brain processes specialize rapidly for print when children learn to read, and play an important functional role in the fluency of early reading [63]. ERP recordings indicate that printed words and other letter strings activate specialized visual functions within 200 ms in readers [64]. An initial delay of such visual tuning for print critically contributes to the development of dyslexia [65].

Electrophysiological Parameters as Potential Endophenotypes

For most child psychiatric disorders, specific pathophysiological pathways still have to be identified. Quantitative electrophysiological measures often show a higher heritability than neuropsychological variables, suggesting that they may provide useful endophenotype candidates which may disentangle phenotypic variation and facilitate the identification and functional characterization of susceptibility genes and other etiologic factors in etiologically complex disorders. Alpha band power recorded during cognitive activation is a strongly familial trait in ADHD [66].

For ERP, the average heritability is lower than for EEG (which reaches 79%) for alpha, but still at 60% for P300 amplitude and 51% for P300 latency, depending to some extent on task conditions [67]. A substantial proportion of genetic influences on P300 amplitude may be explained by strong heritability of theta and delta oscillations elicited during cognitive processing of stimuli contributing to the P300 [68, 69]. Functionally, P300 activity has been associated with quantitative trait loci at chromosomes 2, 5, 6 and 17 [18] and with specific genes involved in dopamine transmission (DRD2 polymorphism [70] and COMT polymorphism [71]). The utility of quantitative electrophysiological measures as endophenotypes of psychiatric disorders has been illustrated by the Collaborative Study on the Genetics of Alcoholism [for references see, 2]; associations between specific genetic polymorphisms (e.g., COMT, DRD4) and other ERP components (e.g., MMN, N170, novelty response) have been reported [72–74].

Future Applications in Clinical Practice

Electrophysiological measures may reflect treatment effects. Thus, Pliszka et al. [75] reported that methylphenidate may improve inhibitory control by enhancing brain mechanisms that trigger the inhibitory process and make stopping a motor act more

probable (reflected by increased N200), and by increasing attentional resources to the task when unsuccessful inhibitions occur (as reflected by increased NoGo-P3). These parameters also indicate changes in the pattern of brain activations due to attentional training. Short-term attention training had a specific effect on the scalp distribution of the ERPs that resembled the effect of maturation, thus supporting the direction of the behavioral data showing more adult-like performance after training [76]. There is growing evidence for neurofeedback as a valuable treatment module in neuropsychiatric disorders. Performance in self-regulation predicts clinical outcome. However, further controlled studies are still necessary to establish clinical efficacy and effectiveness and to learn more about the mechanisms underlying successful training [77–79].

Taken together, the functional significance of many EEG and ERP parameters has become biologically more meaningful and better grounded in neurosciences. ERP studies have helped (1) to clarify whether task processing and performance reflect the same underlying processes along development and in various disorders; (2) to illuminate the content validity of neuropsychological tests by revealing the modular architecture of more complex neuropsychological constructs; (3) to test alternative models of information processing, and (4) to constrain psychological theories [2]. Issues of specificity of findings associated with certain disorders and the impact of comorbid disorders have rarely been addressed. In addition, only few EEG- or ERP-based deficits have been replicated across a wide age range. Given these limitations, the clinical use of EEG/ERP as a tool to positively diagnose a certain child psychiatric disorder is clearly not warranted at this stage.

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Neuroimaging in Child Psychiatry

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Abstract

The focus of this chapter is on how MR-based neuroimaging techniques can be used to investigate the neurobiological basis of child psychiatric disorders. It is not a review of the literature, but rather discusses a number of examples to illustrate the utility of these techniques. First, we show how these techniques allow unprecedented access to the developing human brain as they can provide exquisitely accurate anatomical images as well as insight into the functional anatomy of the brain, without the use of ionizing radiation. Second, we explore how these techniques make it possible to explore human brain development in relation to the behavioral and cognitive developments that take place during childhood and adolescence, as well as their relevance to child psychiatry. Finally, we discuss neuroimaging studies of attention deficit disorder/hyperactivity disorder to illustrate how these techniques can be used to investigate the etiology of child psychiatric disorders.

This chapter discusses how neuroimaging techniques – magnetic resonance (MR)-based measures in particular – can be used to investigate the neurobiological basis of child psychiatric disorders. It is not a review of the literature, but will rather discuss a number of examples to illustrate the utility of these techniques. First, different MR techniques will be discussed that are commonly used in child psychiatry. Then MR investigations of typical brain development and its relevance to neuroimaging in child psychiatry will be discussed.

Brain development comprises multiple progressive and regressive events with different brain areas following individual growth trajectories [1–3]. For example, cortical gray matter follows a trajectory where a pre-adolescent 'peak' volume is followed by a post-adolescent decrease [4]. Furthermore, the age at which the peak occurs differs between cortical areas, suggesting a differential maturation rate between different regions. Furthermore, the peak occurs earlier in girls than in boys, suggesting that the rate of maturation differs between the sexes [4]. Such studies are relevant to child

neuropsychiatry: For example, Castellanos et al. [5] showed that brain development in boys and girls with attention deficit/hyperactivity disorder (ADHD) follows a very similar trajectory to that in typically developing children. Here, children with ADHD displayed a small decrease in brain volume that remained stable over time, suggesting that this neurobiological substrate of ADHD is non-progressive, at least after the age of 4 or 5 years (the age of the youngest subjects in this study).

In the final part of this chapter, we will illustrate how neuroimaging can be used to obtain information on the etiology of child psychiatric disorders. Examples from neuroimaging of ADHD will be used to illustrate the approaches discussed.

Neuroimaging Methods for Investigating Human Brain and Cognitive Development

MR techniques have introduced a new set of tools for capturing features of brain development in living, developing humans. The most common MR methods used in the study of human brain development include anatomical and functional MR imaging (fMRI). These methods have provided scientists with the opportunity to safely track the cognitive and neural processes underlying human development. Whereas anatomical MRI can be used to produce structural images of the brain useful for anatomical and morphometric studies, fMRI enables an in vivo measure of brain activity. fMRI measures changes in blood oxygenation in the brain that are assumed to reflect changes in neural activity [6] and eliminates the need for exogenous contrast agents including radioactive isotopes [7, 8]. Diffusion tensor imaging is a relatively new MR technique that can detect changes in white matter microstructure based on properties of diffusion [9]. Diffusion of water in white matter tracts is affected by myelin and the orientation and regularity of fibers, and provides an index of brain connectivity. These three methods have advanced the field of developmental neuroscience by providing evidence of changes in structural architecture and functional organization in the developing brain in vivo. However, they provide only an indirect measure of brain structure and function: for example, changes in the volume of a structure or amount of activity as measured by fMRI methods lack the resolution to definitely characterize the mechanism of change. Histological evidence suggests that brain development is a dynamic process of regressive and progressive changes. As such, MRI-based cortical changes observed with development may be a combination of myelination, dendritic pruning, and changes in the vascular, neuronal, and glial density. As such, the information from these methods about regional development is best combined with other evidence from postmortem and animal histological studies to enable us to further tease these processes apart. However, MR techniques have the great advantage of being noninvasive and, as such, they can be used to track development and learning more precisely within individuals over short or long intervals of time (i.e., days to years).

Structural Development

A number of structural MR studies have mapped the neuroanatomical course of human brain development. The findings are striking, as they parallel many of the postmortem histological findings, as well as behavioral and cognitive development. However, claims of causality between coincidental changes in brain and behavioral development is a common trap into which one could fall by simply assuming linear changes across systems and direct associations between these changes. Nonetheless, the synchrony in time course of the changes reported in MRI-based anatomical studies and cognitive development have driven more direct tests of these associations in functional images studies.

The most compelling reports of structural changes with development during childhood and adolescence have come from longitudinal MRI studies [4, 10, 11]. In general, the sequence in which the cortex matures parallels cognitive milestones in human development. Regions subserving primary functions, such as motor and sensory systems, mature first, with temporal and parietal association cortices associated with basic language skills and spatial attention maturing next. Higher-order association areas, such as the prefrontal and lateral temporal cortices, which integrate primary sensorimotor processes and modulate basic attention and language processes, appear to mature last. Specifically, MRI-based measures showed that cortical gray matter loss occurs earliest in the primary sensorimotor areas and latest in the dorsolateral prefrontal cortex. These findings are consistent with nonhuman and human primate postmortem studies showing that the prefrontal cortex matures at a more protracted rate than sensorimotor cortex in synaptic density [12, 13]. Cross-sectional studies of normative brain maturation during childhood and adolescence have shown somewhat similar patterns, suggesting that gray matter loss during this period reflects a sculpting process of the immature brain into the fully functioning mature one [3]. As such, the pattern of development observed with anatomical MR techniques appears to mirror ongoing neuronal regressive events, such as pruning and the elimination of connections.

Developmental changes in subcortical regions also occur during this period of development. One of the more reliable patterns reported is in subcortical regions to which association cortex projects. For example, both cross-sectional [2] and longitudinal studies [10] show patterns of development in portions of the basal ganglia to which the prefrontal cortex directly projects. Again, this pattern may reflect the gradual elimination of connections, with strengthening of others.

White matter volume increases in a roughly linear pattern, increasing throughout development until approximately young adulthood, paralleling changes in gray matter volume and density [2]. These changes presumably reflect ongoing myelination of axons by oligodendrocytes enhancing neuronal conduction and communication. Connections are being fine-tuned with the elimination of an overabundance

of synapses and strengthening of relevant connections with development and experience.

Functional Development

How do these structural changes relate to cognitive changes with development? The two coincide temporally by definition. In order to inform us about the functional organization of the brain, investigators linked neuroanatomical development to cognitive changes. For example, Sowell et al. [14] showed an association between prefrontal lobe structural maturation and memory function using neuropsychological measures. Similar associations have been reported between MRI-based prefrontal volume and specific measures of cognitive control – the ability to override an inappropriate response in favor of another [15]. Together these studies suggest that, perhaps not surprisingly, functional changes in brain development are reflected in structural changes. However, they provide only an indirect link between the two, whereas advances in current imaging methods enable a more direct assessment of this relationship using noninvasive measures.

fMRI enables a more direct investigation of structure-function associations and their development. Studies using this technique suggest different developmental trajectories for different brain regions. For example, cross-sectional studies have shown differential recruitment of subcortical as opposed to cortical regions with development [16–18]: Casey et al. [19] examined the development of neural systems involved in developing new stimulus-response mappings, while overriding preexisting ones. Here, the extent of activation in subcortical structures (hippocampus for new learning, striatum for overriding old responses) was far greater for children than adults, while their performance was significantly worse, suggesting that as these functions mature, the pattern of activation associated with them becomes more focal. This pattern occurred in parallel with greater recruitment of cortical regions with maturation. In a longitudinal functional MR study, we tracked the development of cognitive control longitudinally in a sample of children as they reached adolescence [20]. We showed a developmental shift in patterns of cortical activation from diffuse to focal activity. Sensorimotor regions uncorrelated with task performance were recruited less, while a region in ventral prefrontal cortex showed enhanced recruitment. Activity in this region is related to performance on this and other cognitive control tasks [15, 21–24]. In contrast, activation in structures such as the primary motor cortex remained unchanged for the simple comparison of responding (Go) versus not responding (NoGo) during performance of the task.

The developmental shift from diffuse to focal cortical activation may reflect the functional consequences of synaptic pruning and other regressive processes in combination with strengthening of relevant connections. However, few studies to date have related maturational changes in brain connectivity to their functional correlates. New imaging techniques such as *diffusion tensor imaging* are beginning to enable us to do exactly that [25, 26]. For example, Liston et al. [27] used this technique to relate

functional changes in fronto-striatal networks with the development of performance on a cognitive control task to changes in the connectivity between these structures. An automated fiber-tracking algorithm was used to delineate white matter fibers projecting from the ventral prefrontal cortex to the caudate nucleus. These two structures are known to contribute to cognitive control based on previous functional imaging studies [15, 20]. A posterior tract, not expected to contribute to this ability, was also delineated with this method as a control. Diffusion in prefrontal and posterior tracts became more restricted between the ages of 7 and 30 years. This shift was paralleled by an age-associated increase in efficiency in cognitive performance. Further, fronto-striatal radial diffusivities that are sensitive to changes in myelination, predicted individual differences in reaction time, when controlling for age and accuracy. This pattern was not observed in posterior tracts [27]. Collectively, these results indicate that maturation of prefrontal white matter and enhanced connectivity between fronto-striatal structures contributes to a developing capacity and individual variability in cognitive control.

A Developmental Approach to Neuroimaging in Child Psychiatry

These studies illustrate that if we are to explain changes in a dynamic system, then it is essential to examine developmental progressions in behavior and the brain, rather than examining behavior as a single snap shot in time. The importance of examining developmental trajectories is most obvious in understanding and determining whether atypical development is due to a developmental delay or deficit. A number of behaviors may be completely appropriate at one age but inappropriate at another. Clinical disorders, such as ADHD, may reflect exaggerated and/or residual processes that do not necessarily diminish or change with maturity. Understanding the normal progression in a specific behavioral or neural system will have a significant impact in determining the biological substrates of clinical disorders and targeting effective treatments and interventions. Although the majority of imaging studies to date have examined developmental progressions using a cross-sectional approach, examples such as those above show the importance of a longitudinal approach. This is especially important in biological systems given the extreme degree of individual variability in brain structure, relative to developmental variability during childhood and adolescence, the period of emphasis in this chapter [28].

MRI of Atypical Human Brain Development in Child Psychiatry

MRI is often used to study developmental disorders. The majority of these studies have focused on ADHD, the most common childhood disorder with a prevalence rate of approximately 5–8%. ADHD first manifests in early childhood, before the age of 7 and is characterized by age-inappropriate levels of impulsive, hyperactive of distractible behavior (i.e., cognitive control deficits). Children with ADHD have poor

performance on tasks that require inhibitory control, such as Go-NoGo and stop tasks. This finding has led some investigators to theorize that a deficit in inhibitory components of cognitive control may be central to this disorder [29]. This theory in turn implicates fronto-striatal circuitry in ADHD given its involvement in cognitive control [for review see, 30]. As discussed earlier, the development of fronto-striatal circuitry is protracted, as synaptic pruning and myelination of prefrontal fibers proceed slowly throughout late childhood and adolescence [2, 12, 15, 23, 25, 31, 32]. Children's capacity for cognitive control develops across the first decade with younger children more susceptible to interference on a variety of tasks in this domain [15, 33, 34]. Children recruit distinct and often larger, more diffuse fronto-striatal regions when performing cognitive control tasks than adults, suggesting development within and refinement of projections to and from these regions with maturation [for review see, 35, 36].

Structural Imaging Approaches to Understanding the Etiology of ADHD

Over two decades of structural MRI studies of abnormalities in ADHD have reliably shown smaller than normal brain volumes. In addition to an overall reduction in total brain volume, four major findings about regional differences are notable. Relative to controls, individuals with ADHD show: (1) smaller MRI-based volumes of the caudate nucleus; (2) smaller prefrontal volumes; (3) smaller vermis of the cerebellum, and (4) smaller white matter tracts. Longitudinal MRI-based anatomical studies of individuals with ADHD [5, 37] suggest that these neuroanatomical abnormalities are present early in childhood. As such, these differences appear to be due to early environmental and/or genetic effects. Investigators interested in the causal pathway to ADHD may then use such neuroimaging as an intermediate phenotype [38]. For example, we previously showed that some of the changes in brain structure associated with ADHD are heritable, as reductions in cortical grey matter were present in siblings with and without ADHD [39]. Furthermore, we showed that two ADHD risk genes directly impact fronto-striatal gray matter volumes [40]. A polymorphism in the dopamine 4-receptor (DRD4) has linked post-synaptic subsensitivity to dopamine [41], and variation in the dopamine transporter (DAT1) gene may be associated with the efficiency of the dopamine reuptake process [42, 43]. As such, both genes are of theoretical relevance to ADHD and both have been associated with the disorder in multiple studies [for review see, 44]. In our study, allele-specific effects were consistent with gene expression patterns in the brain, as the DRD4 genotype was associated with a reduction in prefrontal gray matter volume, and the DAT1 genotype was associated with reduced caudate nucleus volume [40]. This illustrates how we can begin to map the effects of ADHD risk genes on neurobiological measures. However, these studies are perhaps most informative when we can begin to show that gene effects are involved in translating genetic risk into neurobiology. For example, we recently investigated the impact of DAT1 genotype on brain activation patterns in individuals at genetic risk of ADHD, as well as subjects with ADHD and controls. We

found that the DAT1 genotype interacted with familial risk of ADHD in the striatum, suggesting that DAT1 gene effects in this region are involved in translating a genetic risk of ADHD into a neurobiological substrate. DAT1 genotype effects were specific to those individuals at familial risk of the disorder (affected and unaffected siblings). For controls, activity in this region was not different between carriers and non-carriers of the variant allele. The specificity of this finding points towards long-term possibilities for individualized treatment in ADHD: if the DAT1 genotype has differential effects on striatal activation, it may become possible to use this as a surrogate endpoint in individualized treatments targeting genotype/fMRI activation profiles [45].

Functional Imaging Approaches to Understanding ADHD

To date, more than 20 studies have used functional neuroimaging techniques to investigate brain activation patterns in ADHD in response to cognitive demands. Tasks that tax cognitive control have frequently been used, as problems in this ability are well established in ADHD [29]. These studies have shown that differences in cognitive control between subjects with and without ADHD are associated with differences in brain activation patterns [46–51]. In particular, they have demonstrated reduced activation in prefrontal areas as well as associated decreases in the recruitment of striatal regions during paradigms that require subjects to suppress prepotent tendencies as part of the task, such as Go-NoGo or Stroop paradigms [46–58]. In Go-NoGo tasks, subjects are required to respond to a stream of predictable stimuli by pressing a button. In the case of a rare NoGo stimulus, they are required to suppress this response. We used a version of this paradigm to show reduced fronto-striatal activation for children with ADHD compared to controls, even when performance was similar [48]. In the classic Stroop paradigm, subjects are required to name the color of ink in which a color word is printed, while suppressing the automatic tendency to read the word instead. For example, the word 'blue' printed in red ink should elicit the response 'red'. Several variations on this classic task have been developed, including a counting Stroop, where subjects are required to count the number of times a word appears on a screen, regardless of word meaning [46]. For example, the correct response to four appearances of the word 'one' would be 'four'. Bush et al. [46] used this paradigm to show hyporesponsiveness of the anterior cingulate gyrus in ADHD. This pattern of decreased activation in prefrontal and striatal areas in cognitive control tasks has led investigators to suggest that deficits in these regions are central to ADHD [for review see, 30, 59]. More recently, investigators have used tasks that investigate other aspects of behavioral control, such as paradigms that tap different aspects of attention [51, 60, 61], mental rotation paradigms [62] and paradigms tapping motivated behavior using reward anticipation [63]. Here again, investigators have reported deficits in striatal [51, 60, 62, 63] and prefrontal [51, 62] activation, as well as changes in activation in parietal areas [51, 61, 62]. These findings underscore the importance of fronto-striatal networks in

ADHD, as deficits in this network have now been associated with a wide range of cognitive tasks.

From Pathology to Recovery: The Role of Key Brain Regions May Change with Development

ADHD is remarkable amongst child psychiatric disorders, as many affected individuals experience a remission of symptoms by late adolescence [64, 65]. Recently, Halperin and Schulz [66] suggested that prefrontal regions may be involved in this spontaneous adolescent recovery, in addition to being involved in the pathophysiology of ADHD earlier in development. They showed enhanced activation in these regions in adolescents who had been diagnosed with ADHD during childhood [67]. Here, the observation of less activation for subjects in remission from the diagnosis [68, 69] led the authors to suggest that prefrontal function may be related to recovery in ADHD [66].

Towards an Integrated Theory of Cognitive Dysfunction in ADHD

In summary, functional MR studies of ADHD have shown changes in fronto-striatal circuitry. Interestingly, the only study to date to investigate neural functioning in a non-cognitive task did not show changes in these areas: Mostofsky et al. [70] investigated neural correlates of simple motor movements in ADHD and reported reduced activation in parietal and primary motor cortex only. If these findings can be replicated, they suggest that fronto-striatal involvement may be more specific to the cognitive and motivational deficits associated with ADHD, whereas motor clumsiness in this disorder may have a different basis. Alternatively, there may be other, undiscovered bases underlying both types of deficits in ADHD: recently, we reported deficits in fronto-cerebellar activation related to problems in detecting structure in the environment. We showed in two separate samples that children and adolescents with ADHD were behaviorally not able to benefit from trials, being predictable to the same degree as control subjects [71]. We used a variation of a Go-NoGo task, where the predictability of events was manipulated in two ways: expected or unexpected stimuli (Go and NoGo) were presented at expected or unexpected times. Behaviorally, children and adolescents with ADHD had increased variability in reaction times, and decreased benefit in reaction time when events were predictable. Differences in accuracy between groups were most reliable for temporally unpredictable trials. Furthermore, these behavioral changes were accompanied by decreases in fronto-striatal and cerebellar activation. Prefrontal areas were most impaired on unpredictable trials when stimulus identity was violated and cerebellum when timing was violated. These findings are consistent with the view that disruptive behaviors in inappropriate contexts, a major criterion in diagnosing ADHD, may be related to an impaired ability to predict temporal and contextual cues in the environment, thus hindering the ability to alter behavior when they change. Furthermore, they could be related to motor deficits in ADHD, if structure and timing of self-paced behaviors is similarly affected.

Conclusion

In this chapter, we have discussed how MRI techniques may be used to study child psychiatric disorders. These techniques enable unprecedented access to the developing human brain as they can provide exquisitely accurate anatomical images as well as insight into the functional anatomy of the brain, without the use of ionizing radiation. This not only permits the scanning of children, but also repeated scanning of the same individual over time. This makes it possible to explore human brain development in relation to the significant behavioral and cognitive developments that take place during childhood and adolescence and the relevance to child psychiatry. Neuroimaging studies of ADHD illustrate how these techniques can be used to investigate the etiology of child psychiatric disorders.

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