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Panayiotis Vlamos
Athanasios Alexiou *Editors*

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GeNeDis 2014 Information: Springer AEMB

GeNeDis 2014 Overview

The 1st World Congress on Geriatrics and Neurodegenerative Disease Research, GeNeDis 2014 focused on recent advances in Geriatrics and Neurodegeneration, ranging from basic science to clinical and pharmaceutical developments, providing also an international forum for the latest scientific discoveries, medical practices, and care initiatives. Leading scientists and experts, students, physicians and nurses, professionals as well as industries representatives, and many other participants discussed the latest major challenges, new drug targets, the development of new biomarkers, imaging techniques, novel protocols for early diagnosis of neurodegenerative diseases, bioinformatics methods, and several other scientific achievements. While the European Union aims to strengthen the research and innovation towards Horizon 2020, the translational research for healthy aging and neurodegeneration will remove any barrier on multidisciplinary collaboration. Novel approaches including biomarkers, stem cell therapy, protein misfolding, immunotherapy, as well as developments in our understanding of the genetics, the molecular mechanisms and signaling pathways contributing to neuronal dysfunction, nanotechnological products, and innovative computational methods will offer new research directions and strategies on future preclinical and clinical studies on neurodegenerative diseases and further improvement of quality services on rehabilitation and health education. Advanced information technologies have been discussed concerning the various research, implementation, and policy, as well as European and global issues in the funding of long-term care and medico-social policies regarding elderly people.

We can resume the major objectives of the 1st World Congress on Geriatrics and Neurodegenerative Disease Research, GeNeDis 2014 as follows:

- To promote the scientific and research results to the research community through sharing and exchanging ideas, experiences, and expectations focusing on Health Aging and Mental Wellness in the new digital era.

- To explore the beneficial (and not only) impact of scientific and technological achievements and future challenges that may affect the Health Aging and Mental Wellness process.
- To enhance the co-operation and the exchange of experiences and resources among organizers of events and the research community, increasing further the European dimension and added value of the activities of the Europe 2020 and HORIZON 2020.
- To increase the interest of all the stakeholders in contributing to the research in the field, while mental health is a basic human right, and is fundamental to all human and social progress. It is a prerequisite to a happy and fulfilled life for individual citizens, starting at birth, for functioning families and for societal cohesion.

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- Zouganelis George, Bournemouth and Poole College, United Kingdom

Keynote Lectures

- Professor Nikolaos Robakis, Professor of Psychiatry, Neuroscience and experimental therapeutics. First A.P. Slaner Professor for Alzheimer disease research. Mount Sinai School of Medicine, NYU, USA, Title: Molecular neuropathology of Alzheimer dementia and therapeutic approaches
- Professor George Paxinos, A.O., D.Sc., F.A.S.S.A., F.A.A., N.H.M.R.C., Australia Fellow, Neuroscience Research Australia, Barker St and Hospital Rd, Randwick, Sydney, Australia, Title: Brain, Behaviour and Evolution
- Professor Vasilis Ntziachristos, Chair Institute for biological and medical imaging (IBMI) Technische Universität München, Germany, Title: Biomedical optics and optoacoustics as a model for scientific discovery and economic growth
- Dr. Akihito Takashima, Department of Aging Neurobiology, National Center for Geriatrics and Gerontology, Japan, Title: Toxic tau aggregation in AD
- Professor Benjamin Wolozin, Department of Pharmacology Boston University Alzheimer's Disease Center, USA, Title: Stress granules and Neurodegeneration: A new paradigm for mechanisms of neurodegeneration
- Professor Panteleimon Giannakopoulos, Chairman of the Department of Mental Health and Psychiatry, University Hospitals of Geneva, Switzerland, Title: Mental health in a global world: moving from illness to individual vulnerability
- Dr. Efstathios Gonos, Director of Research IUBMB, National Hellenic Research Foundation, Institute of Biology, Medicinal Chemistry and Biotechnology, Greece, Title: Proteasome activation delays ageing and minimizes deficiencies underlying neurodegenerative diseases
- Dr. Ioannis Haranas, VDG Research and Development in Electromagnetic Theory Applications, Department of Mathematics, East Carolina University, USA, Title: Respiratory Particle Deposition Probability due to Sedimentation with Variable Gravity and Electrostatic Forces
- Professor Dimitrios Fotiadis, Unit of Medical Technology and Intelligent Information Systems, University of Ioannina, Title: Sequence patterns mediating functions of disordered proteins
- Professor Arno Villringer, Max Planck Institute for Human Cognitive and Brain Sciences, Germany, Title: The path from obesity and hypertension to dementia
- Professor Constantin Bouras, University Hospitals, Geneva, Department of Psychiatry, Switzerland, Title: Individual severity of AD-type lesions, Aß oligomers and comorbidity in the brain aging

Invited Talks: Workshops and Round Tables

- Professor Theodosia Vallianatou, Department of Pharmaceutical Chemistry, School of Pharmacy, University of Athens, Greece, Title: The impact of physicochemical and molecular properties in drug design. Navigation in the "drug-like" chemical space
- Professor Costas Demetzos, Faculty of Pharmacy, National and Kapodistrian University of Athens, Title: Advanced Drug Delivery nano Systems: perspectives and regulatory issues
- Dr. Paraskevi Sakka, Neurologist-Psychiatrist, Director at Hygeia Hospital, Neurodegenerative Brain Conditions – Memory Clinic, Chairwoman at Athens Association of Alzheimer's Disease, and Related Disorders, Greece, Title: Non-pharmacological treatments of dementia. The encouraging results of SOCIABLE

Chapter 1
Brain, Behaviour and Evolution

George Paxinos

Standard atlases using identical nomenclature enable scientists to navigate seamlessly between the brain of humans and experimental animals to test hypotheses inspired by human considerations and relate data from experimental animals to humans. In current atlas construction we make use of genes that are responsible for the segmentation of the brain in development (hox genes). Using evidence from transgenic mice and birds we are proposing a new plan for the organization and function of certain brain regions of mammals. The brainstem, for instance, can no longer be considered as a container of haphazardly arranged nuclei (as potatoes in a sac), but instead as regions which co-vary (start and end) with their neighbours.

The human brain features many more homologies with the brain of monkey (e.g. virtually all areas of the cortex are homologous), of the rat and of the bird than previously thought. Areas which are shown to be homologous are likely to have similar function as for example are 9/46 of the prefrontal cortex which is homologous in human and monkey and is involved in executive processing in working memory in both species.

Using MR images in mice and non-human primates we are attempting to provide 3D volumes of canonical brains against which transgenic varieties with clinical significance can be compared.

Finally, on the issue of evolution and survival, the brain is wonderful, but it is not omniscient. Both the dazzling technological success of our species and the worrisome environmental degradation it has produced are reflections of the function of our brains. The author concludes: If the brain were smaller than what it is, it would not have been able to support language and the development of science and technology which today threatens existence; if the brain were larger than what it is, it might have been able to understand the problem and possibly even solve it. The brain is just not the right size.

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Chapter 2
Searching for AD-Related Biological Vulnerability in Cognitively Intact People: A New Perspective for Mental Health

Panteleimon Giannakopoulos

Since the first description of the case of Auguste Deter, presented by Alois Alzheimer, there has been an exponential increase of our knowledge regarding neuropathological, cellular, and molecular substrates of Alzheimer disease (AD). The concept of AD pathogenesis has evolved from a static, binary view discriminating cognitive normality from dementia towards a dynamic view that considers AD pathology as a long-lasting morbid process that takes place progressively over years, or even decades, before the first symptoms become apparent operating in a continuum between the two aforementioned extreme states. Several biomarkers have been proposed to predict AD-related cognitive decline, initially in cases with mild cognitive impairment and more recently in cognitively intact individuals. These early markers define at-risk individuals that are thought to be at the preclinical phase of AD. However, the clinical meaning of this preclinical phase remains controversial. The fate of these cognitively intact individuals positive for some early AD biomarkers is still a matter of debate. Preclinical AD markers may represent a double-edge sword. On the one hand, they make it possible to define a group at risk for AD-type dementia (in terms of disease prevalence) but, on the other hand, this group may comprise an increased ratio of resistant individuals, which do not develop dementia despite substantial brain cerebral amyloidosis. Within the preclinical AD spectrum, a first group concerns presymptomatic cases that are positive for at least one amyloid marker (e.g., PiB-PET, low Aβ42 CSF level). All of these subjects could convert to MCI or AD-type dementia within 8–10 years. A second group includes cases with stable asymptomatic cerebral

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amyloidosis that will indefinitely remain cognitively stable, even though they have positive amyloid marker(s). Defining distinct biomarkers for these stable cases would enable more reliable predictions of clinical evolution at the individual level. Moreover, comparative analysis of these two groups could let us gain better insight into the nature of compensatory mechanisms as well as into the reasons of their failure that marks the beginning of AD-type dementia.

Chapter 3
The Path from Obesity and Hypertension to Dementia

Arno Villringer

Hypertension and obesity are two major risk factors for the development of vascular diseases such as coronary artery disease or stroke. Traditionally, it has been assumed that neurodegenerative disorders such as Alzheimer's disease follow different and independent pathogenetic routes towards brain damage; however, more and more evidence is being provided that hypertension and obesity also are related to the development of neurodegenerative disease. We are studying human cohorts in which these risk factors are being assessed and related to changes in brain structure and function.

Associated with obesity we find the following alterations in the brain: (1) In early stages (young subjects), the main correlate of increased BMI or leptin level is found in reward areas showing more gray matter density probably related to the "addiction" nature of obesity. (2) In elderly subjects, we find diffuse brain atrophy associated with obesity, and (3) also in elderly subjects we find diffuse changes in white matter integrity similar to the ones which are observed in aging and Alzheimer's disease. The latter influence of obesity on white matter seems more pronounced in women.

For hypertension, we find an increased rate of white matter lesions as well as signs of atrophy in anterior cingulate and surrounding areas of the prefrontal cortex. While the white matter lesions in subjects with hypertension may be related to vascular disease, all the other findings seem to be related to other pathogenetic processes. We conclude that—even in subjects who do not suffer from neurodegenerative disease (yet?) hypertension and obesity are related to brain alterations of which some are so similar to those seen in subjects with manifest neurodegenerative disorders that a common pathogenetic path seems likely.

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Chapter 4
Proteasome Activation Delays Aging and Protects Against Proteotoxicity in Neurodegenerative Disease

Efstathios Gonos

Aging and longevity are two multifactorial biological phenomena whose knowledge at molecular level is still limited. We have studied proteasome function in replicative senescence and cell survival (Mol Aspects Med, in press, 2013). We have observed reduced levels of proteasome content and activities in senescent cells due to the downregulation of the catalytic subunits of the 20S complex (J Biol Chem 278, 28026–28037, 2003). In support, partial inhibition of proteasomes in young cells by specific inhibitors induces premature senescence which is p53 dependent (Aging Cell 7, 717–732, 2008). Stable over-expression of catalytic subunits or POMP resulted in enhanced proteasome assembly and activities and increased cell survival following treatments with various oxidants. Importantly, the developed "proteasome-activated" human fibroblast cell lines exhibit a delay of senescence by approximately 15 % (J Biol Chem 280, 11840–11850, 2005; J Biol Chem 284, 30076–30086, 2009). Our current work proposes that proteasome activation is an evolutionarily conserved mechanism, as it can delay aging in various in vivo systems and it protects against proteotoxicity in neurodegenerative disease models. Moreover, additional findings indicate that the recorded proteasome activation by many inducers is Nrf2 dependent (J Biol Chem 285, 8171–8184, 2010). Finally, we have studied the proteolysis processes of various age-related proteins and we have identified that CHIP is a major p53 E3 ligase in senescent fibroblasts (Free Rad Biol Med 50, 157–165, 2011).

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Chapter 5
Decrease in Amyloid Deposition in Aging Brain—An Autopsy Study

Gabriel Gold, François Herrmann, Constantin Bouras, Eniko Kövari, and Aikaterini Xekardaki

Keywords Brain amyloid • Alzheimer's disease • Normal aging

During the last century a worldwide population aging was observed, thanks to improved living and medical conditions. It is not known whether these progresses have had any effect on cerebral aging.

In the present study we compared amyloid deposition in 1,599 autopsied cases aged 65 and over in an autopsy population between 1972 and 2006 (mean age 82 ± 8). Amyloid and NFT deposition were rated according to Thal and Braak staging, respectively. Linear regression models were used to assess period effects after adjustment for age, cognitive status, and neurofibrillary tangle (NFT) staging. Amyloid/NFT stage ratios were calculated to account for possible changes in AD prevalence/severity over time.

In the total population the mean amyloid stage was significantly related to year of death ($p = 0.001$). In non-demented cases, the amyloid stage decreased 24 %, from 1.88 ± 0.89 to 1.57 ± 0.81 ($p < 0.0001$). This change was most striking in the oldest-old population, as amyloid deposits in recent cohorts were similar to those seen in individuals who were 10 years younger at autopsy in earlier cohorts. The amyloid/NFT stage ratio decreased in both demented and non-demented cases confirming that more recent cases had less amyloid despite higher NFT densities. Analysis according to year of birth also revealed highly significant cohort effects.

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In conclusion: We describe a strong cohort effect on age- and disease-related neuropathological changes that may influence the performance of early amyloid-based AD markers. Our results also provide preclinical evidence supporting recently described decreases in AD incidence. These results, if confirmed in community-based studies, may lead to new strategies for the prevention of pathological brain aging.

Chapter 6
Neuropathological Changes in Aging Brain

Aikaterini Xekardaki, Eniko Kövari, Gabriel Gold, Adriana Papadimitropoulou, Ezio Giacobini, François Herrmann, Panteleimon Giannakopoulos, and Constantin Bouras

Abstract Neuropathological hallmarks of Alzheimer's disease (AD) include tangles (NFT) and beta amyloid (Aβ) plaques. Despite numerous neuropathological studies that assessed the relationship of cognitive decline with neuropathologic lesions, their correlation still remains unclear. NFTs and Aβ plaques have been widely implicated and described in normal aging. The number of NFTs in the CA1 and the entorhinal cortex seems to be more closely related to cognitive status, compared to the amyloid load whose role still remains controversial in the AD. In this review, we refer to our main studies performed in Geneva during the past two decades attempting to assess the correlation of pathology with clinical expression. The theory of cognitive reserve has been proposed for further understanding of interindividual differences in terms of compensation despite the presence of pathological lesions. The increasing prevalence of the AD, the limitations of actual treatments, as well as the high public cost reflect the imperative need for better therapeutic and early diagnosis strategies in the future.

Keywords Alzheimer's disease • Neurofibrillary tangles • Aβ plaques • Paired helical filaments • Substantia nigra pars compacta • Mini Mental State Score • β-Amyloid precursor protein

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6.1 Introduction

The population is growing older every year creating a big challenge for public health to cope with the amelioration of life quality with increasing age in the future. Prevention and early detection of heavy pathological entities in terms of public health cost and prognosis, such as the Alzheimer's disease, are necessary. Therefore, a lot of funding has been invested in the comprehension of pathophysiological mechanisms and early disease detection biomarkers during the past few years.

Cerebral aging is a very complex process involving molecular mechanisms' alterations, such as reduced mitochondrial function, increased oxidative stress, autophagy, the accumulation of ubiquitylated protein aggregates, as well as impaired signalling of numerous neurotransmitter and neurotrophic factor pathways [1]. The main neuropathological findings in the Alzheimer's disease have often been described in old individuals without cognitive impairment. Recent research has turned its interest on the trajectory of normal aging in the human brain, suggesting that there is a clinicopathological continuum between healthy aging and dementia. The hypothesis behind this new line of research is that the quantity and localization but not the nature of the lesions characterize cognitive deterioration and progression from intact cognition to mild cognitive impairment and to dementia [2]. We performed a number of clinicopathological studies in order to address the issue of the lesions' continuum in a very old population. When studying neuropathological correlates of centenarians we found that they were resistant to neurodegenerative process and had mild loss of neurons in the hippocampus, restricted to layer II of the entorhinal cortex [3–5].

Neurofibrillary tangles and amyloid plaques are the principal pathological hallmarks described in both normal aging and neurodegenerative diseases. Distinguishing demented and non-demented participants based on pathology has been revealed to be extremely difficult. We will further overview the basic pathological findings in the aging brain, their overlap with the ones in the Alzheimer's disease, as well as their clinical correlates.

6.2 Neurofibrillary Tangles: From Healthy Aging to the AD

Paired helical filaments (PHF) are one of the principal constituents in AD pathology. They are found in three distinct intraneuronal regions, forming the major part of the neurofibrillary tangle (NFT) [6]. Two different groups identified the core protein component of the PHFs, the tubule-associated hyperphosphorylated tau protein in 1986 [7–9]. The physiological role of the protein tau involves the microtubules' stabilization and their interaction with cytoskeletal filaments [10].

Braak and Braak described in 1991 a staging scheme concerning NFT lesions in dementia to differentiate different stages of disease [11]. They suggested that Braak I and II stages include the transentorhinal cortex with mild implication of the hippocampus and no implication of the neocortex, corresponding to clinically silent AD. Stages III and IV include more NFTs in the entorhinal and transentorhinal cortex, in the hippocampus and mild neocortical pathology corresponding to early AD. Stages V and VI involve high density of NFTs in the hippocampus, as well as the neocortex, and are linked to fully developed AD.

Several clinicopathological studies have examined the correlation of cognitive status and pathological findings [12–14]. Arriagada et al. were one of the first teams to describe the positive correlation between the number of neocortical NFTs and the severity of dementia [15]. Over the past few years the Geneva group has performed a series of clinicopathological analyses with demented and non-demented subjects [16–22]. NFT number was proved to be strongly related to cognitive impairment, especially massive NFT formation in the CA1 field, the entorhinal cortex, and the area 9 of the brain [23]. In line with our studies, other groups with large autopsy series have concluded that the density of NFTs in selected cerebral fields is strongly related to the cognitive status as tested by different neuropsychological tests [24–26].

Tomlinson et al. were the first to describe the presence of NFTs in cognitively intact elderly people [27]. Since then several other studies have indicated the presence of NFTs in normal brain aging [28–31]. Our group has performed a series of autopsies in demented and non-demented population during the past two decades. NFTs were found to exist in areas such as the entorhinal cortex, the CA1 field, as well as the temporal cortex [16]. The localization and number of NFTs correlate with cognitive decline. NFT numbers in the entorhinal cortex or area 9 could predict almost more than 87 % of the MMSE scores' variability [17].

We studied a particular subset brain in a subgroup of AD patients that develop parkinsonism [20]. They represent a percentage of approximately 30 % and present no Lewy body pathology at autopsy. Our sample included 22 patients with AD, 11 with parkinsonism and 11 without. All cases were carefully selected from a brain bank of 5,278 autopsies performed in the Geneva University Hospitals after neuropathological AD confirmation and parkinsonism. Post-encephalitic, idiopathic PD, potentially drug-induced parkinsonism, cases were excluded. The results showed that parkinsonism in AD is related to an important neuronal loss in the substantia nigra pars compacta (SN) and in the putamen. Tau deposition was a less important factor, with densities of NFTs in the SN correlating with parkinsonism but not in the putamen. These data suggest that a subgroup of patients with AD develop more subcortical extension with a probable worse prognosis in comparison with cortical only AD cases.

6.3 Amyloid Oligomers and Senile Plaques: From Healthy Aging to the AD

Amyloid deposits in the brain are the second pathologic hallmark of the AD. Amyloid β peptide is a 39–43 amino-acid peptide generated by enzymatic cleavages of the β-amyloid precursor protein (β APP) that is very sensitive to the proteolysis by a set of proteases called secretases. Secretases are responsible for the production of Aβ(1–40) peptide or Aβ(1–42/43) with a higher tendency to self-aggregate. Senile plaques consist of amyloid fibrils composed by aggregated Aβ peptides. Before developing fibrils, they aggregate into oligomers. Soluble non-fibrillar oligomeric assemblies are suggested toxic at the synaptic level [32]. To further elucidate the molecular entity underlying cognitive impairment and amyloid deposition we performed a neuropathological study to explore the relationship of mid-molecular weight Aβ oligomers with their regional distribution and their relationship with lesion development in controls and mild-to-severe AD patients. We found that mid-molecular weight Aβ oligomers had the same regional distribution with fibrillar amyloid pathology both in controls and AD. This suggests that the formation of oligomers is perhaps necessary for the formation of stable amyloid plaques (Mid range molecular weight Aβ oligomers in normal aging and AD: regional and clinicopathological correlations. Bouras, personal communication).

Numerous studies have focused on its role in the normal aging brain and the neurodegenerative disease. NFTs and amyloid depositions are very common in elderly people without any cognitive impairment, particularly in the oldest old [18], reference NFT. While the correlation of NFT number with the severity of cognitive decline has been confirmed by several researchers, a direct link for amyloid deposits still remains unclear. The use of amyloid ligand uptake in PET as one of the most important biomarkers for the early diagnosis of the AD still remains controversial. In fact, in the early stages of AD there is no or scarce deposition of amyloid in the frontal cortex. On the other hand, the soluble oligomers that are detected by PET should be present everywhere in the brain. In our recent study [20] we compared amyloid deposition in 1,599 autopsied cases aged 65 and more (mean age approximately 82.8 years) between 1972 and 2006 in Geneva to detect cohort effects on age- and AD-related neuropathologic changes. Amyloid-to-NFT stage ratios were used to account for possible changes in AD prevalence to severity over time. We found that the brains of older individuals in 2006 were 10 years younger in terms of amyloid deposition compared to people that died earlier. The amyloid/NFT ratio was decreased in both demented and non-demented cases confirming the decreased amyloid in more recent autopsied subjects despite the severity of presence NFT densities.

6.4 Vascular Disease

Vascular disease is the second most common dementia disease after AD [33]. We performed a series of studies to assess the repercussions of vascular burden in brain aging. A high percentage of AD cases (approximately 2/3) were found to present a mixed neuropathological profile with the coexistence of vascular pathology confined to microvascular lesions [34] or lacunes [35]. Cortical microinfarct scores statistically correlated with the clinical variability assessed by the CDR scale. Subcortical lacunes in the thalamus and basal ganglia predicted cognitive decline in the elderly in our second series of autopsy including 72 patients. Periventricular and deep white matter lesions seem to play a very modest role in cognitive decline. A lot of research has been done in the field to assess the criteria for mixed dementia, as well as the potential synergistic role of vascular and neurodegenerative disease when the amount of lesions is not sufficient to provoke disease [36, 37].

6.5 Discussion

Neuropathological lesions of AD have been widely described in cognitive intact elderly people by several authors. Which is the turnover point over which lesions become clinically evident? Why elderly people with extended neuropathological lesions manage to compensate them and remain cognitively intact? Through our experience in the field and the existing literature we notice that the appearance of NFTs and amyloid plaques after the age of 50 is inevitable. Despite this common feature only 10 % of the elderly population (after 65 years) manifests the symptomatology of AD. Each case though presents an individual profile in terms of lesions and clinical symptomatology with cognitive decline depending on the number of healthy remaining neurons. Epigenetics have been proposed as a potential molecular mechanism participating in the AD pathophysiology to explain interindividual differences [38, 39]. APP DNA methylation has been proved to be normally methylated and hypomethylated with age, resulting in increased Aβ production (reference Tohgi et al. reduction with age in methycytosine. Brain Res Mol Brain Res 70:288–292). Histone modifications have also been described in AD hippocampal neurons, as well as other brain regions implicated in the disease [40]. The theory of cognitive reserve [41] has been proposed during the past years as the most plausible hypothesis to explain interindividual variability in pathology and clinical expression of AD. Low educational level and occupational status have been described as risk factors for the AD [42]. Cognitive reserve is thought to be the moderator between pathological brain changes and clinical expression [41, 43]. Its pathophysiological basis still remains unclear. Perhaps the anatomical variability mainly in the entorhinal cortex may play an important role for the preservation of the cognitive functions. FMRI studies in elderly healthy controls could help us to further elucidate the underlying neural mechanisms. The need for more efficient therapeutic strategies is crucial given the actual poor results from clinical trials, as well as the increasing prevalence of the disease.

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Chapter 7
Artificial Humanoid for the Elderly People

Panagiota Simou, Athanasios Alexiou, and Konstantinos Tiligadis

Abstract While frailty and other multi-scale factors have to be correlated during a geriatric assessment, few prototype robots have already been developed in order to measure and provide real-time information, concerning elderly daily activities. Cognitive impairment and alterations on daily functions should be immediate recognized from caregivers, in order to be prevented and probably treated. In this chapter we recognize the necessity of artificial robots during the personal service of the elderly population, not only as a mobile laboratory-geriatrician, but mainly as a socialized digital humanoid able to develop social behavior and activate memories and emotions.

Keywords Assistive interactive robots • Elderly • Frailty • Geriatrics • Caregivers • Nursing homes • BioArt • MEMS • Artificial intelligence • Weak quantum theory

7.1 Introduction

According to the World Health Organization, worldwide more than 35 million people live with dementia. This number is expected to double by 2030 and more than triple by 2050. Dementia affects people in all countries, with more than half (58 %) living in low- and middle-income countries. By 2050, this is likely to rise to more than 70 %. Additionally in the same report, by taking into consideration the financial component of this growth, treating and caring for people with dementia currently costs the world more than US $600 billion per year. This includes the cost of providing health and social care as well as the reduction or loss of income of people with dementia and their caregivers [1]. In the knowledge of the great economic depression of nowadays, there are a few announced projects and

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collaborative programs on Active and Healthy Ageing worldwide, like the European Innovation Partnership 2020, in order to improve the sustainability and efficiency of social and health care systems and boost citizens and markets to respond and win to the ageing challenge. While prevention, screening and early diagnosis is the key access for the healthy growth, many IT multidisciplinary applications have been already used for care and cure of the elderly; that is, neuroinformatics can play a pivotal role in human brain research leading to innovations in neuroscience, informatics and treatment of brain disorders [2].

Assistive technologies like e-care systems, proactive service systems, household interactive robots for pathophysiological testing and entertainment, as well as surveillance systems are already been used collaboratively with nursing staff and family members to form a life support network for older persons by offering emotional and physical relief [3–5].

In this chapter we study the use of assistive robots in elderly healthcare and provide some aspects for the theoretical framework, of the under construction "Geroid" (Fig. 7.1), a complex artificial humanoid for medical assistant and bidirectional communication. We describe the main features and its ability to serve alone in elderly's homes or in nursing houses, offering integrated geriatric evaluation of certain frailty's symptoms or produce psychological or emotional stimuli to the elderly.

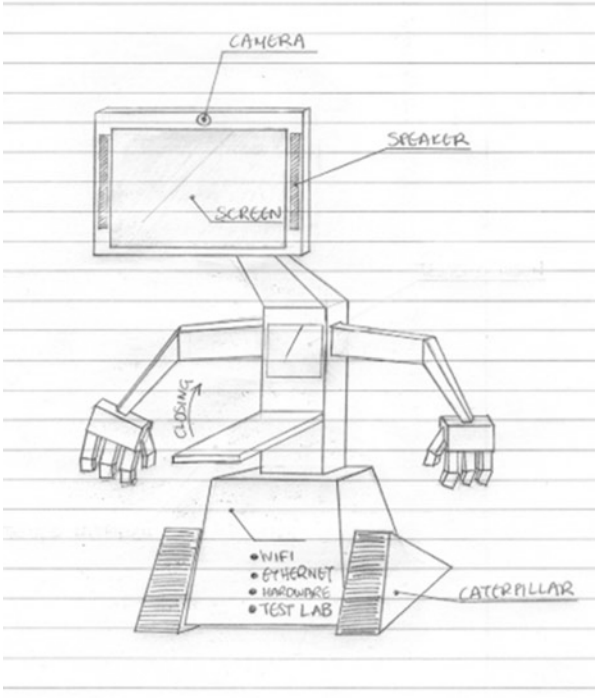

Fig. 7.1 "Geroid" (a blueprint 2014, courtesy of Alexiou A., Simos M., Simou P.)

With a short review, assistive robots for older persons can be categorized into rehabilitation robots and socially assistive robots [6, 7]. On the one hand rehabilitation robots provide physical assistance (artificial limbs, exoskeletons, smart wheelchairs, etc.) and the other socially assistive robots can either be companion-type robots or service-type robots [8]. While a few numbers of sociable oriented robots have been already produced and studied in elderly daily functions [9, 10], mostly satisfying the three basic rules of caregiving such as entertainment, security, and healthcare, obviously there is still a lot of issues to be addressed while the geriatric clinical medicine through frailty's symptomatic recognition is continuously evolving. Obviously interaction companions are clearly better than silence [11], but this is not enough, while good robotic behavioral design should be human centered, focusing upon understanding and satisfying the needs of the people who actually use the product [12].

7.2 Human Superiority and Ethical Decisions

The converging of science and technology has to serve humans, under the condition that humans serve always humanitarian ideas and principles [13]. According to humanism, human beings have the right and responsibility to give meaning and shape to their own lives, building a more humane society through an ethical orientation and free inquiry. The moral person guided from his evolving social behavior can easily comprehend and be committed to laws and principles that a scientific field, such as artificial intelligence (AI) set as a precondition, in order to improve the structural elements of human's biological existence [14].

A highly significant difference between human and humanoid concerns the humanoid's response to the finite number of programmed information and commands and the related finite number of actions and behaviors, even in the case of autonomous robots. On the opposite, human nature has the capability to adjust to any kind of complex mechanisms of thinking, perception and choice, capable to act according to critical judgment and very often through social or personal dilemmas or consciously actions not compatible (in many cases) to the society's rules.

When a caregiver is asked to provide care services to an elderly, may act sometimes voluntarily or spontaneously, depending on the circumstances, without referring to mechanical or predefined commands like a super intelligence system or application. While elderly, usually with high degree of frailty or dementia, may not be very cooperative with the care giver, the last one has to take initiatives several times that will save the life of elderly, without any kind of confirmation. Besides, humans under the interaction and familiarity with others can sense and understand any need or discomfort without be clearly concretize. But the human need to serve, even if there is no specific order or instruction, denotes choice and free will in most of the cases. The emotional help, the offer of joy and consolation, the willingness to listen or to tell a story, defines choice and care from the perspective of the caregiver. In few cases the choice of caregiver could be against the rules or regulations of the

nursing home, having always in minded that health care, security and entertainment must be offered for the benefit of the elderly.

Autonomous machines, interactive robots, and artificial intelligence's applications can be well programmed but unfortunately not educated or enriched with humanitarian or social principles. Let's assume the following imaginary occasion:

An elderly is directed to the bus-stop under conditions of particularly cold. It is just 20 m from a stop, near the traffic light and walks slowly and heavily.

The bus has already stopped at the specific bus-stop, embarking and disembarking passengers. The driver closes the doors and starts.

Approximately after 20 m the bus necessarily stops at the red light, exactly where the elderly stands. The elderly feels a great relief and make a sign to the bus driver to open the door.

Unfortunately the humanoid bus driver is already programmed and recognizes the specific bus-stops; therefore the door remains closed and after 1 min of waiting the traffic lights, the bus leaves.

Socially acceptable factors like the respect for the elderly fellow citizens and their potential frailty, the cold temperature, or any traditional or social accepted actions could not interrupt the humanoid's code.

The humanoid bus driver had no such choice, performing pre-scheduled commands according to a GPS coordinator. A human driver?

We consider as a crucial disadvantage the difficulty to establish a strong and reliable emotional relationship between elderly population and assistive robots, while robots cannot make ethical decisions [15] or analyze weighted data in order to extract critical thoughts and always benefit the elderly. Even in the case of independent or non-independent decision systems, we are not able to process emotions or transfer the moral and ethical way of acting and living, into humanoids. According to scientists (even the most optimistic), it is highly unlikely in the future for any type of super-robot to have these properties while engineers cannot apply mental processes in an executable level.

In our opinion, humanoid's progressive development is most likely to depend to the establishment of quantum processes in ICT systems, far away from the classic Turing Machine or the Von Neumann's architecture. It is clearly that either we refer to Plato Dianoia and Noesis (*Phaedo and Timaeus*) or Aristotle wisdom (*Nicomachean Ethics*), human intelligence and its subsystems, are more characterized via the quantum randomness, uniqueness and entanglement rather than the classic information bit.

Weak quantum theory (WQT) [16] can serve as the theoretical framework of modeling future interactive assistive robots in a more socialized and emotional way. A more successful way of applying the ordinary's quantum theory assumptions, in order to model and program psychiatrists' treatments into robots, seems to be characterized mainly form the terms of complementarity and entanglement [17], transference and countertransference [18]. Although for many medical doctors and theoretical scientists, the application of quantum axioms in medical evaluation and treatment seems impossible, Freud had already observed strange interpersonal experiences which he called transference and countertransference, where patients

transfer or activate past experiences into the present or even more a problematic pattern could be recognized.

It is obvious that Geroid and Elderly define such a concept of complementarity and a relationship of polarity between apparently opposing organisms.

7.3 The Interactive Autonomous "Geroid" for Elderly

There are few clinical studies and review papers [8] concerning behavioral and technological issues of assistive robots in elderly population. We can mention the studies of Van Dijk [19] who discovered that older persons' acceptance level and motivation to use technological devices rise, when they discover that the devices are convenient and have useful features, Venkatesh et al. [20] who resulted that women's computer self-efficacy is deemed to be lower, which makes it more difficult for them to see the advantages of using such devices, Czaja et al. [21] who claimed that education and technological experience influence access, acceptance and the usage of new technologies, Kidd et al. [11] who consider that robot must interact not only to a single elderly but mainly to interact to the overall social support network of the individual, Mitzner et al. [22], Schermerhorn et al. [23], and Gaul et al. [24] who discovered the influence of social factors like age, gender and background to the positive acceptance of the robot.

Several times assistive robots, as an extension of elderly physical existence, e.g., a robot chair, may offer independence against kinetically problems and increase the sense of security and self-confidence. Additionally, elderly can be emotionally strengthened, mentally improved and negate the frustration of disintegration of the aged human body. The positive psychology stimulates the body and stimulates the mood for life.

The mechanical supported elderly can feel stronger in the presence of technology and might be able to offer actively to its environment, by self-handling any personal daily activities and needs or even more offering to his own family, when residing with them. A friendly walking discussion and a sense of sharing social experiences and memories between a robot and its elderly owner, it is most likely to remind us science fiction movies, where robotic mechanical accessories serves as autonomous care units care, evaluating health conditions or simply entertain and keep active thinking and creativity of older people, even it is nowadays a reality. Obviously, if we overcome a few crucial aspects, such that the probable fear in a percentage of older adults to technological appliances [22], the gender differences on technology acceptance and usage [25], the correlation between education level, sociodemographic background, and usage of technological devices [21, 26] we can certainly support that assistive interactive robots offer a great relief to the elderly and empowerment of their dignity and positive self-regard.

Having in mind that dementia and frailty represent a complex entropy system of multidisciplinary factors like physiological, psychological, genetic, environmental, genetic, cardiovascular, comorbidity, and ageing biomarkers, "Geroid" has been

designed as a humanoid recognizable robot (not human). It is equipped with a media installation of personalized memories and knowledge, able to socially interact with his/her ("Geroid" can mimic voices and uses female or male speaking language) elderly companion, awakening the past and establishing a close relationship. Obviously the "Geroid" robot is able to recognize symptoms and body expressions and serve as a medical doctor, caregiver, and mobile laboratory. It can be adjusted in matters of religion and culture, nationalities issues, daily habits, and hobbies; therefore the elderly's background and any personalized memories are already "uploaded" in the "Geroid" from the familiar environment or the "Geroid" can recognize expressions and be educated in the case of unknown persons.

We believed that the "Geroid" must not mimic or attempt to act like another human animal or even more an animal, while there were a lot of cases where elderly were scared and felled awkward on its presence [27].

This artificial caregiver is not just a programmed super intelligent application. Is more likely to play the role of an artificial Medical Doctor, able to offer confidence and secure dealing with frailty symptoms, but also to represent a 24/7/365 familiar character programmed to share memories or to be linked via a common Wi-Fi access to a close relative.

Alexiou et al. (Fig. 7.1) have already designed "Geroid" (*under patent approval*) as a voice-controlled and -operated digital robot, with a dual module for gender recognition and expression and the representation of audio visual stimuli, using familiar voices, galleries of personal photos and videos, as well as artistic, cultural, social, economic or even political representations. As a complex Micro-Electro-Mechanical-System (MEMS), "Geroid" is able to satisfy difficult medical tasks like MRI or EEG and analyse frailty biomarkers without external assistant in order to lift or stabilize the elderly patient.

Apart from the operational scheduling of the "Geroid" we were very concerned about the appearance of the robot—caregiver. While our humanoid is definitely represents a BioArt product, its physical appearance and the possibility of emotional expression plays an important role for its acceptance from the elderly population.

Starting from the industry, robots are nowadays capable to participate in medical surgical treatment and even more to control personalized diagnosis and screening far away from hospitals or doctors' offices. The collaboration of engineers, medical doctors, caregivers, and artists will definitely establish a new inspired field of assistive robots, where a great technological gap have to be filled concerning the older generations of the previous century. It is has been already stated that BioArt can apply innovative techniques in cases of disabled people, and serves as an educational medium for the integration of AI products into society. BioArtists can share the knowledge of presenting the products of AI in an acceptable way for the human brain, providing also a set of principles and rules such as: aesthetics, behavioral properties, boundaries and functions, adaptation, and harmonization in customs [28].

Conclusion

Is it possible to define the degree of influence of human conscience, dignity, rights, and fundamental freedom by merging human and machine? Is it possible to achieve and control confidentiality and privacy on genetic or personal data, without of course increasing tremendously the high quality treatment cost [13]?

It seems that the necessity of creating metallic assistants-robots constitutes a spontaneous attribute of human culture and temperament with roots reaching back to the dawn of our civilization [28].

It is much more difficult to accept a not-human-compatible body, even in the case of an artificial servant. We need to educate society, in order to accept this new kind of relationships, where partner or companion is not human or even Transhuman, pet or an ordinary object (sometimes humans are associated with objects giving them human characteristics) but instead is a product or application of super intelligence's that provides cure, care, and social interaction.

Apparently, man can easily accept contact with organisms (alive or artificial) in which human features can be endowed. This makes him feel more comfortable in order to establish strong relations with a specific object.

Which are the main conditions in order to make a humanoid caregiver acceptable to the elderly population, concerning its exterior surface and the aesthetics of its functionalities? Do we have really to place beside the time defended and crummy elderly due to his comorbidities, a strong and immortal human (a dressed with human clothes remote-controlled Android System [29]), which is most likely to generate negative thoughts for his mortality, and perishable body or a humanoid-oriented voice-controlled robot (clearly metallic construction) that even the old human will see as an inferior structure?

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Chapter 8
Deprescribing Psychotropic Medications in Aged Care Facilities: The Potential Role of Family Members

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Abstract There is widespread concern in Australia and internationally at the high prevalence of psychotropic medication use in residential aged care facilities. It is difficult for nurses and general practitioners in aged care facilities to cease new residents' psychotropic medications when they often have no information about why residents were started on the treatment, when and by whom and with what result. Most existing interventions have had a limited and temporary effect and there is a need to test different strategies to overcome the structural and practical barriers to psychotropic medication cessation or deprescribing. In this chapter, we review the literature regarding psychotropic medication deprescribing in aged care facilities and present the protocol of a novel study that will examine the potential role of family members in facilitating deprescribing. This project will help determine if family members can contribute information that will prove useful to

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clinicians and thereby overcome one of the barriers to deprescribing medications whose harmful effects often outweigh their benefits. We wish to understand the knowledge and attitudes of family members regarding the prescribing and deprescribing of psychotropic medications to newly admitted residents of aged care facilities with a view to developing and testing a range of clinical interventions that will result in better, safer prescribing practices.

Keywords Psychotropic medication • Deprescribing • Aged care facilities • Older adults • Dementia

8.1 Introduction

On 30 June 2012, there were 166,976 Australians living permanently in residential aged care facilities, 52.1 % of whom suffered from dementia [1]. About a half of the residents of aged care facilities take one or more psychotropic medications (antipsychotics, antidepressants, benzodiazepines) [2–4]. For some, they are a worthwhile adjunct to psychosocial approaches in the management of behavioural and psychological symptoms of dementia (BPSD). For others, however, psychotropic medications no longer serve a useful purpose. Unnecessary medications are a major concern. They are costly and have adverse effects that are distressing and reduce the quality of life of older people [5]. Residential aged care facilities are complex organisations and seemingly simple tasks—namely reducing residents' medications—can present real challenges in this environment.

"Deprescribing" is a term that has been coined to describe the potentially complicated process of optimising medication regimens through reduction and/or discontinuation of inappropriate medications [6–10]. Deprescribing should ideally be a patient-centred process involving multidisciplinary collaboration. Engagement of general medical practitioners (GPs) is essential and pharmacists can play a key coordinating role [11–13]. Steps involved in deprescribing include review of all medications; identification of potentially inappropriate medications that could be ceased, replaced or reduced; prioritisation of the order in which medication changes should occur; planning of the deprescribing regimen together with patients and carers and provision of continuous monitoring, review and support in a manner analogous to medication prescribing [11, 14–17]. In undertaking deprescribing, it is important to acknowledge that there are patients who may continue to derive benefits from medications on an ongoing basis. Therefore, the goal of deprescribing should relate more to quality use of medications rather than cessation as an end in itself.

In this chapter, we first review the literature regarding psychotropic medication deprescribing among aged care facility residents, including the barriers to deprescribing and the limitations of current approaches. We then present the protocol of a novel study that will examine the potential role of family members

in facilitating deprescribing by filling in gaps in clinicians' knowledge of residents' psychotropic medication histories.

8.2 Psychotropic Medication Use in Residential Aged Care Facilities

Residential aged care facility residents are prescribed large quantities of antipsychotic and other psychotropic medications. In a recent study in Sydney, Australia, for example, 28 % of nursing home residents were prescribed an antipsychotic medication, 27 % took an antidepressant and 16 % took an anxiolytic or hypnotic [3]. These rates were actually higher than those reported by the same authors nearly 15 years earlier. Similar prescribing practices apply in the USA, the UK, Europe and Scandinavia [3].

Antipsychotic and antidepressant medications can alleviate distress in the case of residents with persistent, troubling psychotic symptoms, aggressive behaviours or melancholic depression but the numbers of residents with these sorts of syndromes are relatively modest and such high prescribing rates cannot be justified clinically [18].

All medications have unwanted, adverse effects. Psychotropic medications increase the risk of sedation, confusion, falls, fractures and loss of mobility and independence [19, 20]. They can also lead to nausea, dizziness and other unpleasant side effects. Antipsychotic medications in particular are associated with increased mortality in people with dementia and all second generation antipsychotics now carry a package warning to that effect [21]. Quantifying the positive and negative effects of these treatments in frail older people is difficult as most drug studies exclude aged care facility residents. On balance, however, it is probable that more residents of these facilities are harmed than helped by them. The broader community is disadvantaged too as some newer medications are expensive and falls with fractures lead to costly hospital admissions and increased care needs.

8.3 Principles and Practice of Deprescribing Psychotropic Medications

Deprescribing aged care facility residents' psychotropic medications is now widely recommended. Most published clinical guidelines state that antipsychotics should be withdrawn at least every 6 months on the grounds that even if the medication played a useful role when instituted (which is debatable), the behavioural and psychological symptoms of dementia usually remit with time, making long-term treatment unnecessary [22]. This advice is supported by evidence. In a recent Cochrane review of nine de-prescribing studies involving 606 people with

dementia, most were withdrawn safely from long-term antipsychotics without any detrimental effects. Caution is required though. There were suggestions in two of the nine reports that people whose agitation or psychosis had clearly improved with treatment were more likely to relapse when their treatment was stopped [23].

Despite widespread concern in professional and public domains, psychotropic medications are mostly continued for long term. In the only study of its type to date, we found in a longitudinal survey of seven aged care facilities in Melbourne, Australia, that medications were rarely changed or stopped. Contrary to expectation, most medications had been initiated prior to entry to the facility. Nearly one-third (27 %) of residents were taking an antipsychotic at the time of admission. Over the following 6 months, antipsychotics were started in another 5 % and stopped in 5 % of cases. Similarly, antidepressants were taken by 30 % of residents at entry point. They were started in another 6 % and stopped in only 5 % over a 6-month period [24]. A recent study using the National Prescription Database in Ireland also reported high rates of psychotropic medication use on admission to residential aged care. However, continuation of psychotropic medications following admission only partially explained the higher dispensing rates of psychotropic medications in aged care facilities [25].

8.4 Barriers to Deprescribing Psychotropic Medications

Managing medications initiated prior to aged care facility admission presents a real challenge. Most high-level care residents have moderate-to-severe dementia and cannot recall who started a treatment, let alone its rationale, duration or clinical benefit if any. The documentation that accompanies new arrivals is often sketchy and former GPs are rarely contacted for information. Current GPs might therefore feel reluctant to withdraw existing treatments. They have no knowledge of residents' former level of function and the adverse effects of medications may not be obvious. Furthermore, GPs and facility nursing staff may fear that "difficult" behaviours will re-emerge [26]. Deprescribing guidelines acknowledge that treatment optimisation requires knowledge of patients' medical and functional histories, medication histories and treatment response [27]. As things stand, GPs attending Australian residential aged care facilities will rarely have access to all this information, making it difficult for them to comply with the department of Health and Ageing guiding principles for medication management in aged care facilities [28].

To complicate matters, there are practical, systemic and cultural barriers to implementing change in organisations as complex as residential aged care facilities in which the responsibility for initiating, monitoring and adjusting treatments is dispersed across a range of personnel from a variety of professional backgrounds (although only a medical or nursing practitioner can actually change medications). These barriers can include regulatory arrangements, reimbursement systems, leadership style, structural influences (facility size, staff turnover, educational opportunities) and overt and latent shared norms [29].

8.5 Existing Approaches to Deprescribing Psychotropic Medications and Their Limitations

The approaches used to date to encourage de-prescribing have entailed legal compulsion, multi-disciplinary reviews and educational programs. Statutory directives have minimal effect. In the USA, federal regulations introduced in 1990 to limit antipsychotic medications to nursing home residents with specific psychiatric diagnoses and behavioural indications led to a reduction in psychotropic prescriptions—but only to the levels seen currently in Australia [30]. In New South Wales, Australia, a legal requirement to seek substitute consent before administering psychotropic medications to people who cannot give consent themselves is mostly ignored [31]. Legal sanctions that are not monitored or enforced are unlikely to be of value in changing practice.

Medication reviews by a geriatrician, pharmacist, nurse and GP proved more effective in a South Australian controlled trial involving 154 aged care facility residents with either a challenging behaviour or polypharmacy. Scores on a scale of medication appropriateness were significantly reduced in the intervention facilities, with no consequent worsening of behaviours [32]. Similar findings emerged in four other studies of pharmacist or multidisciplinary reviews of psychotropic prescriptions in Australian, British and Swedish long-term care facilities [33].

Educational initiatives have proved successful in most but not all trials [33]. In Queensland, Australia, pharmacist-led medication reviews coupled with nursing education led to reductions of 6 and 14 % in benzodiazepine and antipsychotic prescriptions, respectively. There were no differences, though, in residents' disability levels or hospital admissions over coming months [34]. Outreach visits by pharmacists were well received but had no discernable effects in a South Australian study [35]. By contrast, in Tasmania, Australia, a complex intervention in which community pharmacists initiated medication audits, feedback cycles, nursing education sessions and a multi-disciplinary conference led to cessations or reductions in doses for 37 % of residents taking an antipsychotic in intervention facilities compared with 21 % in control facilities. For residents taking a benzodiazepine, there were cessations or reductions in dose for 40 and 18 % of those in intervention and control facilities, respectively [36]. When prescriptions were checked a year later, benzodiazepine usage had dropped a little further in intervention facilities but the proportions of residents taking antipsychotics had returned to baseline levels [37].

8.6 Study Protocol

8.6.1 Study Rationale

Educationally directed efforts to induce deprescribing and maintain changes in practice may be too complex, time consuming and expensive to contemplate rolling out nationally without additional strategies in place to reinforce them. With this in mind, we wish to explore a new and complementary approach that taps family members' knowledge of residents' prescribing histories and their willingness to endorse deprescribing when provided with balanced information about this practice. Our study proposal is based on the following propositions:

1. It is understandable that clinicians are reluctant to stop a treatment when they have no knowledge of who started the treatment, their reasons for starting it and its benefits and adverse effects.
2. There are no simple, familiar clinical markers to guide psychotropic de-prescribing. If an antihypertensive or hypoglycaemic medication is stopped, residents' blood pressures or glucose levels can be monitored easily and treatments can be re-started if required. In the case of psychotropic medications, staff must accept a risk that psychiatric disorders or challenging behaviours of an unknown nature may re-emerge for at least a proportion of residents at some point.
3. In the case of residents with dementia who cannot provide this sort of information themselves, tracing information through former GPs, medical specialists and pharmacists is difficult, time consuming and not remunerable for GPs—though perhaps not impossible. This approach will form the basis of a separate future research initiative.

We are not proposing any particular intervention based on family members' responses. Instead, we wish to adopt a phased step-wise approach that has been recommended for evaluation of complex interventions [38]. This will involve first checking, by means of a modestly sized feasibility study, if family members' knowledge of psychotropic prescriptions and their attitudes to deprescribing have the potential to make a useful contribution to clinical practice. It is envisaged that this information will, in turn, inform the development of a definitive intervention that utilises the facilitators and addresses the barriers that have been identified in the feasibility study.

8.6.2 Research Questions

In an effort to circumvent the difficulties encountered in deprescribing psychotropic medications in aged care facilities, our project will address the following questions:

1. For aged care facility residents who take one or more psychotropic medications at the point of entry to high-level care, to what extent do family members know that these medications are being dispensed and can they recognise their names?
2. To what extent can family members provide information about the original prescriber of each medication; the original indication(s) for its use; the approximate duration of the prescription and their perception of its effectiveness?
3. If family members are given carefully balanced, evidence-based written information about the advantages and disadvantages of the relevant classes of medications, what views do they express about the pros and cons of continuing prescriptions and would they support efforts by the nursing staff and GP to attempt deprescribing?
4. What are family members' attitudes towards deprescribing, as indicated by their scores on an adapted version of the Patients' Attitudes Towards Deprescribing (PATD) Questionnaire (see description below)?

8.6.3 Study Design

We propose an exploratory study (using surveys and semi-structured interviews) of the knowledge and attitudes of family members concerning ongoing psychotropic prescriptions for 50 newly admitted high care residents of a convenience sample of aged care facilities in south-eastern Melbourne.

8.6.4 Study Procedures

Family members who agree to participate and provide written informed consent will be encouraged to seek information from other sources regarding their relative's medication history and to complete a semi-structured interview (of approximately 1-h duration) with a trained research assistant at a later time. This will take place either in person, in a private area of the aged care facility, or by telephone if preferred. Face to face interviews will be audiotaped for checking purposes if respondents agree. Other family members will be welcome to participate if they wish. It will be made clear prior to the interview that we are seeking family members' views purely for research purposes and that the research assistant (who will have no specialist knowledge in this area) will not be able to engage in discussion about individual medications.

The research assistant will present the family members with a list obtained from the aged care facility of all current regularly prescribed medications and all occasionally prescribed medications that have been dispensed at least once in the previous week. The list will include the medications' generic and all Australian brand names. The family members will be asked: (1) to nominate which medication names they recognise as the ones being taken by their relative (answers will be

recorded as "recognised" or "not recognised"); (2) if they know the name and identity (GP, specialist) of the original prescriber of each medication; (3) the reason (s) why each medication is prescribed; (4) the approximate duration of each medication prescription and (5) their rating of each medication's effectiveness on a 5-point scale (ranging from "very effective" to "very ineffective", or "don't know"). Responses will be recorded verbatim.

Next, family members will be presented with a short pamphlet (about 250 words) outlining the general benefits and risks of ongoing prescriptions of psychotropic medications and the principles of deprescribing. The pamphlet will state that, while some medications are required on a continuing basis, many no longer serve a useful purpose and are best stopped gradually, usually over a period of several weeks, to reduce side effects and costs. It will be made clear that medications can be started again if necessary. After a discussion about the advantages and disadvantages of deprescribing in general, using pre-prepared probes if necessary, respondents will be asked to rate their level of support for attempts to deprescribe each psychotropic medication on a 5-point scale ranging from "strongly support" to "strongly oppose" (or "don't know").

Finally, GPs will be given a list of all the psychotropic medications (with doses) being dispensed regularly to their patients and asked to nominate if any are used primarily for physical health reasons (e.g. antidepressants to treat pain or urinary incontinence).

8.6.5 Ethical Considerations

This study has been submitted for approval to the Monash University Human Research Ethics Committee.

This is a feasibility study, not a deprescribing initiative, and we do not expect medication deprescribing to occur on a large scale as a result of study participation. However, the information provided by family members could be of genuine clinical value and so, with their consent, we will pass this information on to the aged care facility nursing staff and GPs using a specially designed form. Furthermore, following their involvement in the study, family members may find themselves wondering whether review and adjustment of their relatives' psychotropic medications are needed. As a result, there may be more medication reviews, and more family requests for reviews, than would normally be the case, a possibility that facilities will be made aware of. Any such reviews would take place separate to the study, as part of residents' routine clinical care. GPs attending study facilities will be informed of the study and given the opportunity to opt out of it at any time. If they do so, we will not recruit family members of any of their patients (or cease further recruitment if GPs opt out of the study after recruitment has already commenced).

Although this possible increase in medication reviews may place additional demands on facility and GP resources, it may also contribute positively to improved

patient care. If GPs choose to make medication changes, one possible benefit may be the finding that residents no longer require certain medications, or only require the medications at lower doses.

On the other hand, reducing or ceasing psychotropic medication may be associated with a risk of re-emergence or worsening of previously well-treated behavioural and psychological symptoms of dementia. In this event, it may be appropriate to reinstate medication (that was reduced or ceased) to help re-settle these symptoms, in conjunction with utilising non-medication approaches to treatment. The researchers will be available to provide initial advice to the aged care facility and GPs if such a scenario arises. If direct specialist involvement is required to assist GPs in this process, guidance will be provided on how to refer residents to the local public Aged Persons Mental Health Service (which will have been given prior notice regarding the conduct of the study).

8.6.6 Setting

We will include the family members of between 2 and 5 residents from 10 to 25 aged care facilities in south-eastern Melbourne, giving a total of 50 residents. We will sample facilities broadly to ensure a mix of public and private facilities across a range of suburbs.

8.6.7 Recruitment

Because the residents concerned will have dementia, they will be unlikely to be able to give informed consent to the study. Instead, we will seek consent from their closest family member or legal guardian. This will be done in accordance with the ethical principles for involving people with cognitive impairment in research studies that are outlined in the Australian National Statement for Ethical Conduct in Human Research [39]. Family members of residents who meet the study's inclusion/exclusion criteria (see below), and are therefore eligible for study participation, will be identified by facility administrators and their contact details passed on to us with their verbal consent. The research team will subsequently contact the family members directly to describe the project and answer any questions. An explanatory statement for family members to read and a consent form for them to sign and return will subsequently be posted. Consent will be sought separately for the interview to be tape-recorded and for the information provided about psychotropic medications to be fed back to the nursing staff and GP.

8.6.8 Participants

8.6.8.1 Inclusion Criteria

We will include family members of residents who (1) have been admitted or transferred from another facility to high level care within the previous 3 months; (2) have a diagnosis of dementia entered in the clinical file and/or have a Mini-Mental State Examination (MMSE) score of $\leq$23 points; (3) continue to take one or more previously prescribed antipsychotic, antidepressant and/or benzodiazepine medications and (4) have a nominated primary contact person (usually a family member) who has sufficient English fluency to complete an interview.

8.6.8.2 Exclusion Criteria

We will exclude family members of residents who (1) have a diagnosis entered in the clinical file of schizophrenia, bipolar disorder, schizoaffective disorder or delusional disorder or (2) are judged by nursing staff to be so physically unwell that death is imminent.

8.6.9 Outcome Measures

8.6.9.1 Primary Measure

The primary measures of interest will be the proportions of family members who (1) can recognise the name(s) of the psychotropic medications dispensed to their relative and (2) can nominate the original prescriber of each medication, the original reason(s) for the prescription, the approximate duration of the prescription and their perception of its effectiveness.

8.6.9.2 Secondary Measures

The secondary measures of outcome will be (1) family members' attitudes to the deprescribing of these medications and (2) their scores on an adapted version of the Patients' Attitudes Towards Deprescribing (PATD) Questionnaire, a 15-item checklist developed in South Australia [8, 9]. This questionnaire—which has items like "I believe that all my medications are necessary"—has demonstrated content validity, construct validity and test-retest reliability. The authors of this tool have consented to its adaptation for use among family members of aged care facility residents.

8.6.10 Sample Size Justification

We anticipate that 50 interviews will be sufficient to capture a broad range of viewpoints concerning the major psychotropic classes. If we reach the point of data saturation, a smaller number of interviews may be required.

8.6.11 Feasibility

We have partnered with aged care providers to conduct many studies in local aged care facilities over a 20-year period. This research will build on established networks. The residential standards agency regards participation in research very favourably and so facilities derive direct and indirect benefits from collaborating with us. This particular project requires little staff input and presents no major resource issues for the participating aged care providers. The study will be conducted in accordance with Alzheimer's Australia guidelines for involving people living with dementia and their families in research [40]. This will help ensure that the study is both feasible and acceptable from a consumer and carer perspective.

One of the objectives of the study is to gauge family members' motivation to participate in such an exercise and their capacity to contribute useful information. We believe that many will find the topic of interest and so completion rates are likely to be high.

8.6.12 Statistical Analysis

8.6.12.1 Quantitative Analysis

The proportions of family members who recognise prescribed treatments will be tabulated by medication class (antipsychotic, antidepressant and benzodiazepine or other hypnotics) and compared with other selected major medication classes (e.g. antihypertensives).

The proportions of family members who can nominate the original prescriber (yes/no), indication (known/unknown) and ratings of the perceived effectiveness of treatments will be tabulated by medication class.

Comparisons between psychotropic classes, and between psychotropic and other classes, will be made using chi-square and t-tests for categorical and continuously distributed data, respectively.

8.6.12.2 Qualitative Analysis

Family members' comments to the semi-structured probes will be noted manually on a prepared template. Major themes will be extracted from these notes using a framework analysis method [41]. Responses will then be coded by two research staff independently followed by discussion and reconciliation of any disagreements. Thematic analysis will address attitudes towards deprescribing with special reference to positive and negative concerns, perceived barriers and facilitators, preferred processes and expressed needs for additional information, communication or support.

8.7 Discussion

If it emerges that few family members can have any useful information to add, and few of them have any views about prescribing practices, there may be no value in seeking their participation in the complex decision-making processes that deprescribing entails. Based on experience, however, we suspect that family members will often have useful knowledge and/or clear views about their relatives' ongoing pharmacotherapy. If this is true, there may be opportunities to include their knowledge and attitudes in the residential assessment procedures mandated by the Australian federal government.

If it transpires that most family members do not want psychotropic medications to be stopped, then efforts to encourage nurses and GPs to deprescribe them, without reference to relatives' views, will almost certainly prove counterproductive and a different strategy will be required.

The prescribing histories reported by family members will sometimes be incorrect but, to put this in context, errors can arise even when information is taken from competent patients or medical records [42]. Medical practitioners and pharmacists must always consider the possibility of error when reviewing prescriptions with patients or their proxies and the possibility of error is not in itself a reason to persist with a treatment, regardless of other considerations.

In conclusion, this pilot study will address one of many structural barriers to deprescribing (in this case, a lack of valid clinical data regarding psychotropic prescriptions). Multiple strategies might need to be adopted to change practice in real-world conditions and so this study is one of a suite of projects that we will attempt to implement in an effort to improve psychotropic prescribing practices in residential aged care settings. Development of evidence-based clinical practice guidelines for psychotropic medication deprescribing in aged care facilities is an anticipated longer term goal.

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Chapter 9
Findings Regarding the Relationships Between Sociodemographic, Psychological, Comorbidity Factors, and Functional Status, in Geriatric Inpatients

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Abstract **Objective** To assess the impact of socio-demographic and comorbidity factors, and quantified depressive symptoms on disability in inpatients.

Methods Observational cross-sectional study, including a number of 80 elderly (16 men, 64 women; mean age 72.48 years; standard deviation 9.95 years) admitted

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in the Geriatrics Clinic of "St. Luca" Hospital, Bucharest, between May-July, 2012. We used the Functional Independence Measure, Geriatric Depression Scale and an array of socio-demographic and poly-pathology parameters. Statistical analysis included Wilcoxon and Kruskal-Wallis tests for ordinal variables, linear bivariate correlations, general linear model analysis, ANOVA.

Results FIM scores were negatively correlated with age ($R = -0.301$; 95% $CI = -0.439$ -0.163; $p = 0.007$); GDS scores had a statistically significant negative correlation ($R = -0.322$; 95% $CI = -0.324$ -0.052; $p = 0.004$) with FIM scores. A general linear model, including other variables (gender, age, provenance, matrimonial state, living conditions, education, respectively number of chronic illnesses) as factors, found living conditions ($p = 0.027$) and the combination of matrimonial state and gender ($p = 0.004$) to significantly influence FIM scores. ANOVA showed significant differences in FIM scores stratified by the number of chronic diseases ($p = 0.035$).

Discussion and conclusions Our study objectified the negative impact of depression on functional status; interestingly, education had no influence on FIM scores; living conditions and a combination of matrimonial state and gender had an important impact: patients with living spouses showed better functional scores than divorced/widowers; the number of chronic diseases also affected the FIM scores: lower in patients with significant polypathology. These findings should be considered when designing geriatric rehabilitation programs, especially for home – including skilled – cares.

Keywords Disability • Multi-poly-pathology • Functional Independence Measure (FIM) • Geriatric Depression Scale (GDS) • Geriatric inpatients

9.1 Introduction

Given the shift of the world's population age structure, there is increasing interest among health care specialists, social care givers, and administrative organizations all over the world to promote independent living in late life and a healthy and active aging process. Depressive symptoms and functional limitations have a negative impact on patients' quality of life and well-being, as well as on their families who provide care and support [1].

Life changes and events such as bereavement, retirement, chronic conditions and disabilities, cognitive impairment, loss of active social roles, and financial strains are all potential risk factors for depression, although it is recognized that elderly do benefit from a high level of resilience and inner resources to cope with these challenges [1–3]. Projections suggest that by 2020, depression will become the second leading cause of health problems worldwide, as measured by disability-adjusted life years [4].

Reports on depressive disorder prevalence in old age are few and contradictory mainly due to methodological issues, given the multiple comorbid diseases and cognitive impairment in old age [5]. Some research findings confirmed a positive

correlation of depressive symptoms with age [6] while others reported a decreasing prevalence of depression and anxiety in older age [7, 8]. While some studies reported higher incidence of minor depressive symptoms, compared with ratings of major depression disorder in people aged 65 and over [9, 10], others stated that depression score tends to increase with age, unlike the prevalence of depression [11]. In European countries, the percentages of elderly suffering from depressive symptoms and disorders were estimated as high as 55.1 in females over 60 years old, 71.8 in females over 75 years old, 32.1 in males over 60 years old, and 37.5 in men over 75 years old [12].

Depression symptoms and disorders often coexist with chronic conditions in old age, worsening health outcomes and limiting functionality. The relationship between physical disability and psychological disorders is complex and difficult to elucidate, especially in elderly [13]. A strong association between functional disability and depressive symptoms in old age has repeatedly been reported [13–20]. Depressive symptoms are recognized as a limiting factor of functional independence in the elderly [21, 22], and some have hypothesized a reciprocal, potentially spiraling relationship between depression and disability [23–25]. Conversely, some authors have pointed out that the psychological well-being is significantly correlated with better functional status and survival in elderly [26, 27].

To our knowledge, there are no reported research data on the relationship between geriatric depressive disorders and functional status in Romanian elderly. We conducted an observational study, aiming to assess the correlations between functional status and quantified depressive symptoms, and sociodemographic and comorbidity factors, in geriatric inpatients.

9.2 Methods

This is an observational cross-sectional study, aiming to analyze the association of depressive disorders with functional limitations, in patients admitted for various chronic conditions in our Geriatrics medical unit. We have selected a number of 80 patients 50 years of age and older (64 women and 16 men, mean age 72.48 ± 9.95 years) living in independent communities and referred to our Geriatrics Division by their general practitioners, for various diseases, over a period of 5 months (May 2012 to September 2012). The subjects were included in the study after signing an informed consent and based on the following exclusion criteria: younger than 50 years of age, patients living in care homes, suffering from terminal illnesses and/or cancer, diagnosed with dementia, patients who have undergone a surgical procedure within the last 2 months, hemiplegic and/or tetraplegic patients, and other neurological or psychiatric disorders that might have averted the subjects from completing evaluation scales.

All patients were screened for the following major chronic conditions: hypertension, hypotension, chronic ischemic heart disease, congestive heart failure, chronic venous insufficiency, peripheral arterial disease, chronic obstructive

pulmonary disease, asthma, chronic bronchitis, obesity, diabetes mellitus and other metabolic diseases, impaired visual acuity, hearing loss, balance disorders, and liver and kidney diseases. A prior diagnosis was accepted by interviewing the subjects and asking for medical documentation. De novo diagnoses were made by specific clinical, biological, and imagistic investigations. The number of diagnosed chronic conditions was recorded for each subject.

For each patient, a set of sociodemographic data was recorded: marital state (married/widower/divorced), living conditions (alone/with family), education (illiteracy or elementary/secondary/tertiary or higher education), and provenance (rural/urban).

Functional status was assessed using the Functional Assessment Measure (FIM). FIM is a widely accepted instrument that uses a scale to measure one's ability to function with degrees of independence quantified from 1 (Total Assistance) to 7 (Total Independence)—based on the ability to perform motor activities such as: grooming, sphincter/s control, transfer/s, locomotion and cognitive ones, such as comprehension, expression, social interaction, or memory, among others (totally 18 detailed items). Usually, a FIM score is collected within 72 h after admission, within 72 h before discharge, and between 80 and 180 days after discharge [28–31].

Depression and anxiety symptoms were evaluated using the Geriatric Depression Scale (GDS) Long Form (30 items). First developed by Yesavage et al. [32], GDS is a validated, largely used instrument, based on a self-reported evaluation; each of the 30 questions requires a simple yes or no answer. While this tool cannot substitute a psychiatric evaluation and diagnosis, it is very efficient and reliable for the screening and assessment of depression in elderly [33].

Statistical analysis was performed using SPSS 16.0 for Windows. It included the Wilcoxon and Kruskal-Wallis tests for ordinal variables, linear bivariate correlations (the Pearson correlation coefficient), and general linear model analysis.

9.3 Results

Our study group included 80 patients, 64 (80 %) women and 16 (20 %) men, aged between 52 and 92 years. The main features of the group are detailed in Table 9.1.

In order to analyze the impact of socio-demographic and comorbidity factors on FIM scores, we stratified the patients by: gender, age (we defined four age groups: patients aged 52–61 years, 62–71 years, 72–81 years, 82–92 years), marital status, living conditions, provenance, number of chronic conditions (we defined four groups, according to the number of associated diseases: patients with 2–3 chronic conditions, patients with 4 associated conditions, patients with 5 chronic conditions, patients diagnosed with 6–7 chronic conditions), and education. Since FIM values were not normally distributed ($p = 0.000$ for one-sample Kolmogorov-Smirnov test) in our study group, we employed the Wilcoxon signed-rank test (for two samples) and Kruskal-Wallis test (for multiple samples), for comparison between categories (Table 9.2).

Table 9.1 Mean and median values for age, number of chronic conditions, GDS and FIM scores in the study group

	Mean ± SD	Median
Age	72.48 ± 9.95	74
No. of chronic conditions	4.63 ± 1.14	5
GDS score	13.40 ± 7.45	14
FIM score	119.78 ± 10.75	126

SD standard deviation

As shown in the table, age had a significant impact on FIM scores ($p = 0.001$), which were lower in older patients. FIM scores were significantly higher in married patients, as compared to divorced ones (0.017). Patients living alone had lower FIM scores than the ones living with family, but this difference was not statistically significant ($p = 0.102$).

To further document the relationship between age and functional independence, we assessed the linear correlation between age and FIM using the Pearson correlation coefficient (R). FIM scores were negatively correlated with age ($R = -0.301$; $R^2 = 0.091$; 95 % CI −0.439 to −0.163; $p = 0.007$) (Fig. 9.1).

To explore a possible relationship between depressive symptoms and functional status, we first assessed the linear correlation between GDS and FIM scores, and we found a statistically significant negative correlation ($R = -0.322$; $R^2 = 0.104$; 95 % CI −0.324 to −0.052; $p = 0.004$) (Fig. 9.2).

A general linear model ($R^2 = 0.693$), including all the other variables (age, education, living conditions, provenance, gender, matrimonial state, respectively, number of chronic conditions) as factors, found living conditions ($p = 0.027$) and the combination of matrimonial state and gender ($p = 0.004$) to significantly influence the FIM score, alongside with GDS score ($p = 0.014$).

Finally, we performed a discriminant function analysis to further study the effect of each variable on FIM scores. To this end, we created an auxiliary binary variable, defined as 1, if FIM $\leq$ 122 (28 patients) and 2, if FIM $>$ 122 (52 patients). The obtained standardized canonical discriminant function coefficients were, in order: 0.541 for age, 0.412 for gender, 0.362 for marital state, 0.310 for GDS, 0.295 for education, 0.241 for number of chronic conditions, 0.138 for provenance, and 0.120 for living conditions. The highest coefficients, reflecting the strongest relationships with FIM, were those corresponding to age, gender, and marital state.

In conclusion, our study confirmed that functional independence significantly decreases with age. Interestingly, we found that physical functional limitations were more severe in single (widowers and especially divorced) persons, particularly men, as compared to married patients. Patients with more severe depressive symptoms (higher GDS scores) had more important limitations to their functional independence (lower FIM scores).

Table 9.2 FIM values by categories

Categories		Number (%)	Mean ± SD	95 % CI for mean	*p*
Gender	Female	64 (80.00 %)	120.42 ± 10.80	117.72–123.12	0.270
	Male	16 (20.00 %)	117.19 ± 10.48	111.60–122.77	
Age group	52–61	14 (17.50 %)	124.64 ± 4.53	122.03–127.26	0.001
	62–71	20 (25.00 %)	121.05 ± 12.20	115.34–126.76	
	72–81	27 (33.75 %)	119.81 ± 10.16	115.79–123.84	
	82–92	19 (23.75 %)	114.79 ± 11.83	109.09–120.49	
Marital state	Widower	38 (47.50 %)	116.89 ± 1.98	112.87–120.92	0.017
	Divorced	4 (5.00 %)	115.25 ± 18.93	85.13–145.37	
	Married	38 (47.50 %)	123.13 ± 6.74	120.92–125.35	
Living conditions	Alone	20 (25.00 %)	117.30 ± 12.31	111.54–123.06	0.102
	With family	60 (75.00 %)	120.60 ± 10.16	117.97–123.23	
Provenance	Rural	19 (23.75 %)	122.05 ± 6.32	119.01–125.10	0.644
	Urban	61 (76.25 %)	119.07 ± 11.75	116.06–122.08	
No. of chronic conditions	2–3	14 (17.50 %)	123.93 ± 5.85	120.55–127.31	0.126
	4	23 (28.75 %)	119.43 ± 11.46	114.48–124.39	
	5	25 (6.25 %)	121.96 ± 8.71	118.37–125.55	
	6–7	18 (22.50 %)	113.94 ± 13.29	117.38–122.17	
Education	Illiteracy or elementary	24 (30.00 %)	117.92 ± 11.25	113.17–122.67	0.089
	Secondary	48 (60.00 %)	121.02 ± 9.44	118.28–123.76	
	Tertiary	8 (10.00 %)	117.88 ± 16.27	104.27–131.48	

CI confidence interval
p was generated using the Wilcoxon test, for two samples, and the Kruskal-Wallis test, for multiple samples

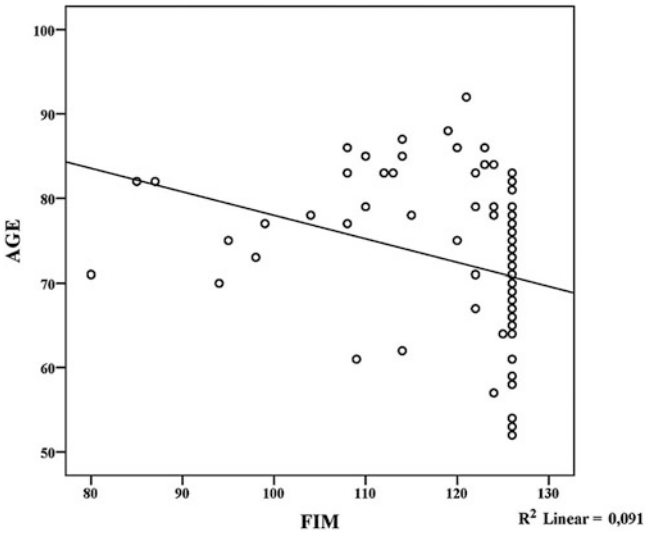

Fig. 9.1 The negative correlation between FIM scores and age

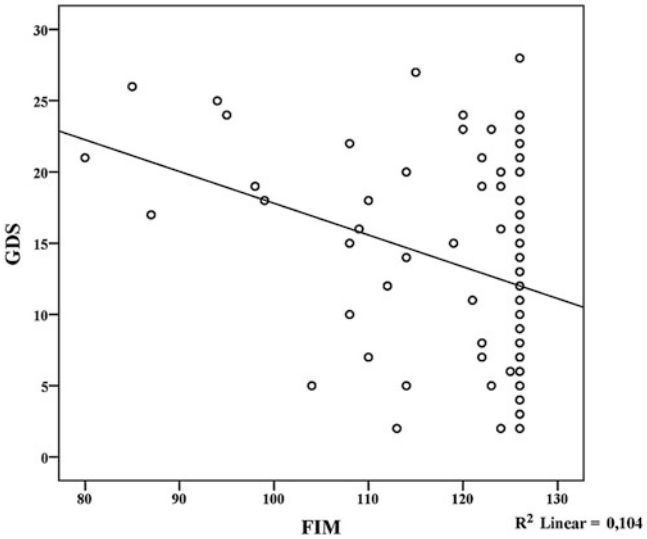

Fig. 9.2 The negative correlation between FIM and GDS scores

9.4 Discussion

Limitations of functional independence in elderly represent a serious socioeconomical concern [1]. It is therefore important to identify the risk factors for frailty and disability, to develop new preventive strategies.

Our study had some limitations: it included a small number of patients and being a cross-sectional study, did not allow establishment of a causal relationship between depression and disability, but our results obtained can offer interesting prospectives for subsequent longitudinal studies, with larger numbers of subjects to allow a rigorous analysis, by subgroups of interest.

As expected, we found a significant association between functional limitation and age in our group of community dwelling elderly. We also found a significant inverse correlation between GDS and FIM scores, suggesting that depression might contribute to functional capacity limitations. This relationship between depressive symptoms and functional decline in old age [14–22] and frailty [34] has been frequently described in literature. On the other hand, there is accumulating evidence to support the idea that that psychological well-being is correlated with better physical performance [26, 27, 35] and even better survival in elderly [26, 36, 37].

Some authors have described a bidirectional relationship between depression and disability in elderly, creating a vicious circle, where functional impairment leads to depression and this, in turn, enhances functional limitations [23–25].

The World Mental Health (WHM) Surveys are a conglomerate of general population surveys carried out in 17 countries across the world, which have used standardized diagnostic assessment of mental disorders and collected information on chronic physical disease prevalence and functional disability. Their results have shown that individuals with depression/anxiety disorders are more likely to be severely disabled than those with chronic physical conditions and the comorbid association tends to exert a synergistic effect on disability [19]. Another study, specifically targeting the geriatric population, has highlighted the negative effect of various degrees of depressive symptoms on functional status, but did not control for other chronic diseases [14].

In our study, marital status had an important impact on functional independence: patients with living spouses had significantly better functional scores than the widowers and divorced. These results are consistent with previously reported findings: recent data from the National Social Life, Health, and Aging Project (USA) showed that higher levels of loneliness were associated with more severe functional limitations [38].

Conclusions

Our study objectified the correlation between depression and functional status. Interestingly, education had no influence on FIM scores; the living conditions and the combination of marital state and gender had an important impact on functional scores: patients with living spouses showed better values than the divorced/widowers; the number of chronic diseases also affected FIM scores, which were lower in patients with increased polypathology. These findings should be considered when designing geriatric rehabilitation programs, especially for home care.

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Chapter 10
The Role of Chemical Engineering in Medicinal Research Including Alzheimer's

Georgios M. Kontogeorgis

Abstract Various disciplines of chemical engineering, especially thermodynamics and kinetics, play an important role in medicinal research and this has been particularly recognized during the last 10–15 years (von Stockar and van der Wielen, J Biotechnol 59:25, 1997; Prausnitz, Fluid Phase Equilib 53:439, 1989; Prausnitz, Pure Appl Chem 79:1435, 2007; Dey and Prausnitz, Ind Eng Chem Res 50:3, 2011; Prausnitz, J Chem Thermodynamics 35:21, 2003; Tsivintzelis et al. AIChE J 55:756, 2009). It is expected that during the twenty-first century chemical engineering and especially thermodynamics can contribute as significantly to the life sciences development as it has been done with the oil and gas and chemical sectors in the twentieth century.

Moreover, it has during the recent years recognized that thermodynamics can help in understanding diseases like human cataract, sickle-cell anemia, Creuzfeldt-Jacob ("mad cow" disease), and Alzheimer's which are connected to "protein aggregation." Several articles in the *Perspectives* section of prominent chemical engineering journals have addressed this issue (Hall, AIChE J 54:1956, 2008; Vekilov, AIChE J 54:2508, 2008).

This work reviews recent applications of thermodynamics (and other areas of chemical engineering) first in drug development and then in the understanding of the mechanism of Alzheimer's and similar diseases.

10.1 Introduction

The significant role of chemical engineering in medicinal research and biotechnology has been intensively recognized, especially during the last 20 or so years, with thermodynamics being one of the disciplines of importance [1–6]. In downstream biotechnology, the main interest is in the design of separation processes such as chromatography and crystallization. In the pharmaceutical industry there is interest

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in optimizing the selection of solvents, which is of major importance in the manufacturing process of many pharmaceuticals. Thermodynamics is also of importance in the understanding of the mechanisms of several diseases, like cataract, Creutzfeldt-Jakob ("mad cow" disease), and Alzheimer's, which are now believed to be caused by protein aggregation [4, 5, 7, 8]. This understanding may contribute to the discovery of new cure for such diseases.

Complex physicochemical interactions are a common denominator in most of the aforementioned applications due to the presence of the biomolecules and the often aqueous solutions in the presence of salts and polymers. Thermodynamics, e.g., solubility estimations, is often associated with complex phase diagrams which must be known as a function of temperature, charge, solvent type, pH, and ionic strength.

10.2 Medicinal Research and Solvent Selection

Screening for solvents and calculating the solubility of pharmaceuticals in the selected solvents are important tasks in the pharmaceutical industry [9–13]. The thermodynamic properties of pharmaceuticals and other biomolecules are of importance for rational design and optimizing separations such as crystallization, but they are also relevant to understanding the complex phenomena and interactions, e.g., aggregation, associated with certain diseases. Another important application is the controlled release of pharmaceuticals through polymeric capsules. In this case, the permeability of the pharmaceutical and its diffusion rate ultimately depend on the solubility of the pharmaceutical in the polymer [5].

Thermodynamics of pharmaceuticals is complex, because these are multifunctional chemicals, frequent use of mixed solvents and polymorphism. Nevertheless, there is much industrial interest, as shown in several publications from industrial colleagues [9–13]. Several computational thermodynamic models are now used for solvent selection in the pharmaceutical industry including QSAR, local-composition models, variations of solubility parameter concept, and quantum chemical approaches; for a review see Kontogeorgis and Folas [14].

Most of these approaches are essentially empirical in nature, requiring several adjustable parameters which are obtained from experimental solubility data that must be available prior to using the models. Moreover, these models do not explicitly account for complex interactions present in pharmaceutical mixtures, which are due to the strong intermolecular forces especially polarity and hydrogen bonding. We have recently developed [6, 15] for mixtures with pharmaceuticals a theoretically oriented model (called NRHB; non-random hydrogen bonding), based on an advanced theory, which explicitly accounts for hydrogen bonding and other complex interactions. The model is in a form of an equation of state and can thus be used both at low and high pressures, both for single and mixed solvents, wide temperature range and for both pharmaceuticals and polymers. Also, the model is combined with the concept of solubility parameter, which is widely used for the

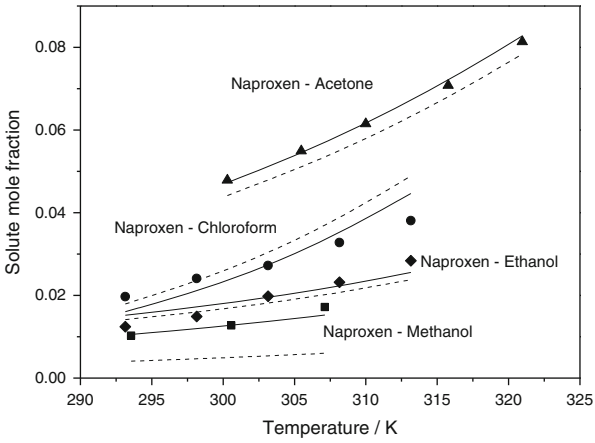

Fig. 10.1 Solubility of naproxen in various solvents. Experimental data (*points*), model predictions (*dashed lines*) and model correlations (*solid lines*) using a single temperature-independent parameter. From Tsivintzelis et al. [15]

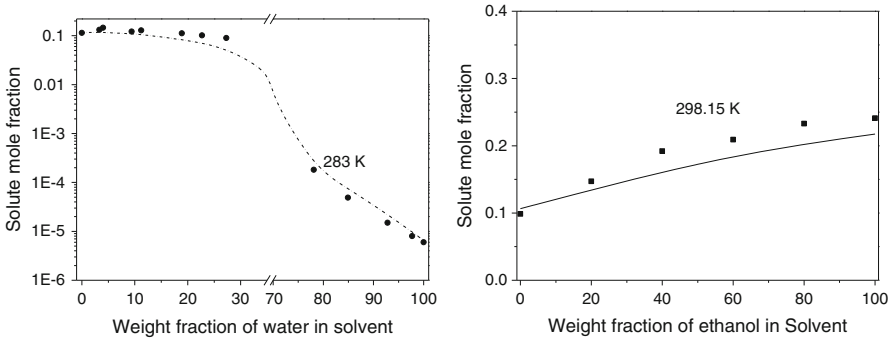

Fig. 10.2 (*Left*) Solubility of ketoprofen in the acetone–water mixture. Experimental data (*points*), and model predictions using binary interaction parameters from the corresponding binary systems. From Tsivintzelis et al. [15]. (*Right*) Solubility of ibuprofen in ethanol–propylene glycol mixture at 298.15 K. Experimental data (*points*), model predictions using binary interaction parameters from the corresponding binary systems (*line*)

screening of solvents in pharmaceutical applications. But the most important characteristic of NRHB is the adoption of a segment-type approach which ensures that all the involved hydrogen bonding interactions are accounted for and moreover that the parameters are obtained from low-molecular-weight compounds.

Thus, the new model (NRHB) has the potential of being an invaluable tool in pharmaceutical industry and related applications. The model is described in recent publications [6, 15] and some typical results are shown in Figs. 10.1 and 10.2. The results for mixed solvents are predictions and no new parameters are used. The method can be readily extended to new pharmaceuticals and solvents but should be of course tested prior to use. So far nine pharmaceuticals and intermediates have been considered, which contain a variety of hydrogen bonding forming groups.

10.3 Chemical Engineering in Alzheimer's Research

Peter Vekilov [8] writes that amyloid diseases will be of increasing importance in the coming years as Alzheimer's effects, in some form, touch about half of the people above 85 years of age and there will be more and more patients as life expectancy increases. Carol Hall states [7] that five million Americans (5–10 % of 65–74-year-olds and 50 % of 85-year-olds) have Alzheimer's, at a cost to society of $148 billion/year.

Alzheimer's in one of the many "amyloid" type diseases, which are now believed to be due to protein deposition or protein conformation change. The causes of amyloid formation are not fully understood. Several of the key proteins, e.g., APP (amyloid precursor protein) are present in both healthy and diseased people. APP is cleaved to form Alzheimer's proteins. In Alzheimer's these proteins aggregate to form fibrils but in healthy people they do not, and it is not clear why.

Actually, beyond Alzheimer's it is suggested that many more diseases are connected to "protein aggregation" or agglomeration, e.g., human cataract and sickle-cell anemia.

This "protein aggregation" can be understood in thermodynamic terms in various contexts; for example, it can be described by a liquid-liquid equilibria diagram. One example is illustrated in Fig. 10.3 showing the importance of thermodynamics (liquid-liquid equilibria in this case) as linked to protein aggregation. This figure shows the separation of g-crystallin in the eye. The broken line represents the body temperature. As the years go by and the eye ages, the protein concentration in the eye changes and one or more proteins may achieve a concentration that exceeds the saturation concentration and we may enter in the liquid-liquid equilibrium region [5]. The second (concentrated) liquid phase, partly crystalline, which is shown on the right remains in the eye as a dispersion and interfere with vision. This second phase may be responsible for cataract symptoms. Precipitation of this second phase may be avoided by adding a small amount of glutathione that forms a soluble complex with crystalline and keeps it in solution over more extended temperature ranges, as shown in Fig. 10.3 [5].

Experimental results such as the ones shown in Fig. 10.3 can provide methods to prevent cataracts in the human eye, a disease that strikes millions of elderly men and women throughout the world. Similar studies have been reported for fibril formation that is considered responsible for Alzheimer's disease [16].

10.4 Outlook

The role of chemical engineers in understanding the challenges in protein structure and contribution to amyloid diseases has been discussed in several recent publications in the *Perspectives* section of *AIChE J* [7, 8, 17].

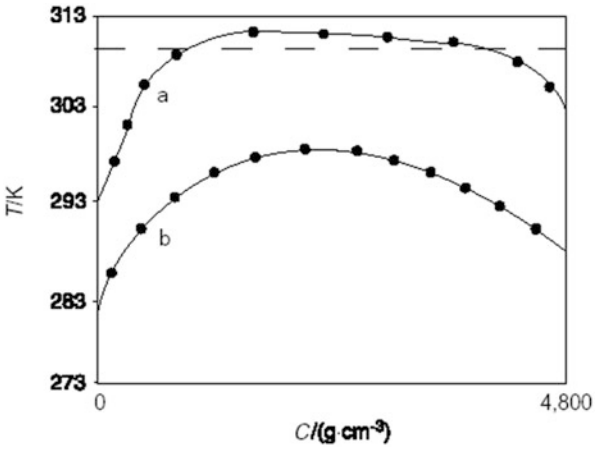

Fig. 10.3 Cataract formation and protein aggregation: Liquid–liquid separation of g-crystallin in the eye shown as temperature plotted against concentration. (*a*) Native g-crystallin; (*b*) g-crystallin/glutathione complex. The *broken line* denotes body temperature 310 K (37 °C). The *x*-axis represents a protein concentration from 0 to 4.8 g/cm^3. From Prausnitz [5]

It has been emphasized that the thermodynamics of the protein systems involved in the amyloid diseases is indeed very complex but understanding of hydrogen bonding phenomena [7] and use of tools such as osmotic second virial coefficients [17] can contribute in a quantitative understanding of Alzheimer's disease. For example, according to molecular-level computer simulations by Hall's group [7] the hydrogen bonding between backbone NH and CO and the hydrophobic interactions between side chains are the key driving forces for fibril formation in Alzheimer's. Hall [7] also reviews several ongoing and future trends in drug research related to Alzheimer's, including several recent drug efforts designed to reduce the amyloids responsible for the disease. Nevertheless, as she also states [7], there are still many unanswered questions about the structure of the amyloid fibrils, the reaction pathway of proteins during aggregation, the role of the environment and toxic steps or species during the aggregation process, and why these proteins behave differently in different people.

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Chapter 11
On the Comparison of a Novel Serious Game and Electroencephalography Biomarkers for Early Dementia Screening

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Abstract Patients with amnestic mild cognitive impairment are at high risk for developing Alzheimer's disease. Besides episodic memory dysfunction they show deficits in accessing contextual knowledge that further specifies a general spatial navigation task or an executive function (EF) virtual action planning. Virtual reality (VR) environments have already been successfully used in cognitive rehabilitation and show increased potential for use in neuropsychological evaluation allowing for

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greater ecological validity while being more engaging and user friendly. In our study we employed the in-house platform of virtual action planning museum (VAP-M) and a sample of 25 MCI and 25 controls, in order to investigate deficits in spatial navigation, prospective memory, and executive function. In addition, we used the morphology of late components in event-related potential (ERP) responses, as a marker for cognitive dysfunction. The related measurements were fed to a common classification scheme facilitating the direct comparison of both approaches. Our results indicate that both the VAP-M and ERP averages were able to differentiate between healthy elders and patients with amnestic mild cognitive impairment and agree with the findings of the virtual action planning supermarket (VAP-S). The sensitivity (specificity) was 100 % (98 %) for the VAP-M data and 87 %(90 %) for the ERP responses. Considering that ERPs have proven to advance the early detection and diagnosis of "presymptomatic AD," the suggested VAP-M platform appears as an appealing alternative.

11.1 Introduction

Most neuropsychological assessments of prospective memory and spatial navigation tasks bear little similarity to the events that patients actually experience as memories in daily life. The first aim of this study was to use a virtual environment, which was a virtual representation of an actual archeological museum in order to measure cognitive deficits in a realistic environment. We called this environment virtual action planning museum (VAP-M) and used it in order to characterize cognitive profiles in an ecological fashion, which includes memory for central and perceptual details, spatiotemporal contextual elements, and binding. This study included subjects from two different populations: patients with amnestic mild cognitive impairment (aMCI) and an age-matched group of healthy adults (non-impaired; (NI)).

It recently became evident through fMRI studies that changes of functional connectivity in prodromal and early Alzheimer's disease can arise from compensatory and/or pathological processes [28]. During those changes, people who are in the early stages of AD might get lost, forget where they put things, and have trouble driving, all of which are examples of impairments in executive functions and spatial cognition [28]. During the last 5 years, researchers investigated the potentials of virtual supermarkets to evaluate executive dysfunctions in several populations including MCI [14, 35]. On the other hand, spatial cognition tasks tap very broad networks in the MTL and the cortex, areas of the brain that are sites of the earliest pathological changes in AD and that are known to play an important role in episodic memory function. Thus, virtual reality tests of spatial cognition could be used to detect early deficits in AD [16]. Furthermore, VAP-M might enhance executive

function and thus late cognitive components, such as the late positive potential P300 [19, 35].

Not all 3D virtual reality environments however are created equal [26] and given an individual's stage of cognitive development, one environment can be more beneficial for cognitive screening than the other. For example, the route planning, verbal episodic memory, and visuospatial working memory tasks used in VAP-M were very similar to those used in an actual educational museum visit [1]. The modularity of the cognitive skills above also reflects the standards of current process-specific assessments [29]. The VAP-M screening environment is implemented as close as possible to the actual Archeological Museum of Aiani, at Kozani, Greece from where we took the layout and archeological artifacts. Consequently, this virtual navigation task is also meaningful for clinical decision-making about real-world behavior as well. This paper describes the comparative study of virtual reality reaction times and cognitive brain activity in order to define cognitive profiles and reliably detect abnormalities in older adults.

Therefore, in the present study we used event-related brain potentials (ERPs) derived from the electroencephalogram (EEG) in order to study more closely the correlation between virtual reality and the neuronal processes which are affected by the aMCI.

11.2 Methods

11.2.1 Virtual Reality Hardware Setup

Our Virtual Museum system has been developed in XML and VRML and is described in detail at Tsatali et al. [33]. The VR hardware consisted of a Pentium-based computer with 4 GB RAM, Intel Quad Core processor, and NVIDIA graphic cards with 512 MB memory. A high-definition (HD) 1080p home theater projector from Epson (Epson Inc, Tokyo, JAPAN) was used for the visualization. We chose the HD projector instead of other standard virtual reality visualization hardware, like the head-mounted display, because we wanted to minimize discomfort and simulation sickness [6, 32]. The sound environment was created through by a Sound blaster gaming sound card (Creative Inc, San Francisco, CA, USA). User interaction was supported by a wireless joystick from Logitech (Logitech International S.A, Apples, SWITZERLAND) and a common PC mouse (Microsoft Corp, Seattle, WA, USA).

The system originally allowed museum curators to build, manage, archive, and present virtual exhibitions based on 3D models of artifacts. The innovation of this study is that it modified the setup so that it allows cognitively impaired and healthy old people to explore virtual exhibitions implemented using very simple everyday interfaces (e.g., joystick, mouse) (Fig. 11.1).

Fig. 11.1 Users can "walk" freely in the virtual museum and interact with the artifacts. Once they select an artifact they can choose to zoom in, rotate it at the *X*, *Y*, *Z* axis, and read details in tags on the artifact itself

11.3 Procedure

11.3.1 Participants

We used a sample of 25 aMCI (18 females and 7 males) and 25 controls (20 females and 5 males) with a mean age of 64.3 years. The original criteria for mild cognitive impairment set out by Petersen et al. require that a person must present with a memory complaint, show evidence of objective memory decline in relation to age and education, demonstrate preservation of other areas of cognitive function and activities of daily life, and not fulfill criteria for dementia [22]. Because it has since become apparent that not everyone who demonstrates cognitive impairment short of dementia has a "memory" complaint, we used the recently expanded criteria that include people with non-memory complaints (single-domain non-memory MCI), as well as those exhibiting multiple domains of cognitive impairment who nonetheless fail to fulfill criteria for dementia (multiple domains slightly impaired) [21].

11.3.2 Neuropsychological Screening

Each participant was classified as normal or aMCI on the basis of a set of neuropsychologically based criteria for aMCI that differed in their characterization of objective cognitive impairment. Demographic data and neuropsychological scores are presented for each population in Table 11.1. The subjective **Cognitive Difficulties Scale** [17] was used to assess cognitive complaints in daily life. The CDS is a 39-item self-report measure that uses a Likert-type scale. For each item (e.g., do you have difficulty remembering the names of the people you know?), the

Table 11.1 Means and SDs of demographics and general neuropsychological abilities

	Older adults ($n = 25$)	aMCI patients ($n = 25$)	ANOVA/ ANCOVAS
Age (years)	77.2 (4.9)	78 (4.7)	$F(2, 49) = 5.5^{**}$
Level of education	5 (1.7)	5 (1.9)	
Gender (male–female)	(5:20)	(7:18)	
Depression			
Mini-GDS (cut-off <2/5)	.4 (.9)	.1 (.3)	$F < 1$
Global cognition			
MMSE	28.9 (.8)	26.7 (1.6)*	$F(2, 49) = 83.8^{***}$
CDS	21.9 (11.9)	42.9 (15.1)*	$F(2, 49) = 25.8^{***}$
Executive functions			
WCST	18.8 (8.7)	25.1 (7.9)	$F(2, 49) = 8.2^{**}$
TMTA (s)			
TMTB-A (s)	45.9 (13.4)	53.1 (24.1)	$F(2, 49) = 12.9^{***}$
Inhibition	158.4 (119)	66 (48)	$F(2, 49) = 3.79^{*}$
Forward span	6.1 (.3)	5.3 (1.3)*	$F(2, 49) = 14.9^{***}$
Backward span	3.6 (.9)	2.9 (.6)*	$F(2, 49) = 10.6^{***}$
Verbal memory			
Delayed recall	15.9 (.25)	13.3 (1.6)**	$F(2, 49) = 33.9^{***}$
Total recall (3 trials)	45.8 (1.3)	32.7 (8.2)***	$F(2, 49) = 77.9^{***}$
Delayed total recall	15.9 (.4)	11.6 (3)	$F(2, 49) = 95.1^{***}$
Intrusions	0	1.7 (1.4)**	$F(2, 49) = 28.1^{***}$
Perseverations	0	.7 (1.5)	$F(2, 49) = 9.9^{***}$
Recognition: hits/false recognitions	15.8 (.5)/(0)	13.5 (1)/11)	$F(2, 49) = 9.75^{***}$ $F(2, 49) = 5.1^{*}$

*$p < .05$, **$p < .01$, ***$p < .001$

participants have to choose among a range of five responses: "1" corresponds to "never" and "5" corresponds to "very often." We investigated executive functions and episodic memory using well-established tests. First, flexibility was measured with the **Trail-Making Test** (TMT) [38]. Short-term memory was assessed with the forward digit span, and working memory (the ability to simultaneously maintain and process information) was evaluated with the backward digit span of the **Wechsler Adult Intelligence Scale** (WAIS) [12]. To test verbal episodic memory, participants were given the word-learning test described by [39]. Global measure of cognitive function was assessed with the **Mini-Mental Status Exam** (MMSE) [4].

Inhibition and selective attention were assessed with a variety of tests including the **Stroop Color-Word Interference Test** [31]. More complex tasks of executive function were assessed by the **Wisconsin Card Sorting Test** [27], which surveys set maintenance and set shifting abilities as well as perseverative tendencies.

The assessment of **verbal episodic memory** was done with the Rey auditory verbal learning test (RAVLT), which is a well-validated word recall test [5]. Assessment of mood and emotional state is a critical component of the evaluation of the

aMCI patients as emotional distress can cause or exacerbate cognitive problems. Specific tests were chosen on the basis of the patient's overt expressions of emotions as well as his/her comments regarding current mood state, energy level, sleep habits, appetite, socialization with others, optimism, level of self-esteem, and overall sense of well-being. For most patients, the assessment of mood was comprised of interview data and responses to brief self-report measures, such as the **Geriatric Depression Scale** [37].

11.3.3 Electrophysiological Recordings

Participants received an Auditory ERP recording completed using a Nihon Kohden—Neuropack M1 MEB-9200 evoked potential/EMG measuring system. Event-related-potentials (ERPs) are used as a noninvasive clinical marker for brain function in human patients. Auditory ERPs are voltage changes specified to a physical or mental occurrence that can be recorded by EEG [18]. Different ERPs were used in order to pinpoint the functional processes which would be improved by the cognitive process training and which may be affected by retesting. The principal ERP components elicited after task-relevant visual stimuli are among others the N1, the anterior N2, the P2, and the P3b. The Auditory ERPs were recorded during an Electroencephalogram (EEG), with 15 electrodes (Fp1, F3, C5, C3, Fp2, F4, C6, C4, O1, O2, P4, P3, Pz, Cz, Fz) according to the 10–20 international system, referred to both earlobes. Ag/AgCl electrodes were attached to the scalp with adhesive cream in order to keep the electrode resistance below 5 kΩ. The horizontal and vertical EOG was measured by electrodes placed at the outer canthi (LO1, LO2) and above and below both eyes (SO1, SO2, IO1, IO2). The amplifier band pass was 0.01–140 Hz. EEG and EOG were sampled continuously with a rate of 2,048 Hz. Data was archived on a hard disk with triggers using post-session annotation.

Off-line, the EEG was downscaled to a sampling rate of 500 Hz by using the software Neuroworkbench (Nihon-Kohden, Japan). The epochs were 1,100 ms long ranging from 100 ms before and 1,000 ms after stimulus onset. All epochs with EEG amplitudes of more than ±120 μV or with drifts of more than 150 μV within 300 ms were discarded. For all participants and conditions at mean 48 epochs (Min = 17; Max = 53; SD = 7.3) of the epochs remained for averaging after artifact rejection and correction. The epochs were averaged according to the stimulus conditions (target trials versus nontarget trials) and referenced to linked earlobes (excluding the EOG electrodes). For stimulus locked averages only correct epochs were used, excluding trials with false alarms or misses. A digital low-pass filter was set at 17 Hz in order to reduce oversampling [13].

11.3.4 Experimental Procedure

Both groups (NI and aMCI) participated at the two different paradigms VAP-M and AERPs. The experimental procedure for the AERPs was in accordance with the standard auditory oddball paradigm. Subjects were engaged in a simple discrimination task based on two different tones with the target stimulus presented less frequently than the nontarget or standard stimulus. Briefly, a series of binaural tones at 70 dB sound pressure level (SPL) with a 10 ms rise/fall and a 100 ms plateau time was presented. The auditory stimuli were presented in a random sequence with target tones of 2,000 Hz occurring 20 % of the time and standard tones of 1,000 Hz occurring 80 % of the time at a rate of 0.5 Hz. The subject was required to distinguish between the two tones by responding to the target (i.e., mentally counting) and not responding to the standard. Participants were instructed to pay attention in distinguishing the tones, count the target tones silently, and report the total number at the end of the exam. Each patient was tested twice to ensure that the averaged response waveform was reproducible. Recording was terminated as soon as a predetermined number of responses to target stimuli, 30 trials, had been collected.

The peak amplitude and latency of the N1 potential were measured at the two occipital electrodes O1 and O2 were the potential showed its maximum. The N2 was quantified as the mean amplitude in the time interval between 240 and 300 ms at the electrodes FCz, Cz, and CPz where maximum amplitude resulted. A reliable measurement of the peak was not possible due to the overlapping P2, and P3b potentials. The P2 potential was quantified in amplitude and latency as the local maximum at the electrodes FCz, Cz, and CPz in the search interval between 200 and 400 ms where it showed the highest peaks. The peak amplitude and latency of the P3b potential were measured as the local maximum at the electrodes Cz, CPz, and Pz in the search interval between 400 and 700 ms where it showed the highest amplitudes.

When subjects participated at the VAP-M paradigm, they were instructed they will enter a virtual reality environment of an archeological museum, which contained 6 halls of archeological artifacts found at the region of Ancient Macedonia. The virtual layout and collection of archeological artifacts per hall was following the actual layout and collection of the real archeological museum, which was the basis for the virtual one. After the basic instruction there was a training period of 5 min, where the participants were free to explore an empty and get used to the interaction and input devices (joystick, mouse). Sometimes, the training session lasted until the participants felt familiar with the equipment.

The participants were then given pictures of five archeological artifacts and written directions on how to locate them in the different halls. They were given 2 min to try and memorize the pictures and directions and then had 12 min in order to locate the artifacts. The number of items to be located was based on the literature for multiple memory deficits and their relation to everyday functioning in individuals with mild cognitive impairment [29]. This part of the VAP-M exercise was

designed to assess mainly prospective memory, visuospatial working memory, and executive function.

The exercise had one additional level when completed, which was also based on the literature [24]. After a break of 5 min, the participants had to spell out any remembered details for the five archeological artifacts above as well as the associated spatiotemporal context. The experimenter would note all recalls on a structured grid of responses. There was no specific order in the recall of the components. Once the element was recalled, the participants could then provide contextual recall in any order. The participants were never probed. For each recall test, the instructions were associated with an example as follows:

- "Try to remember as many details as you can from the archeological artifact within 5 minutes" (color, shape, patterns, etc.) (what).
- "Situate the artifacts in time: were they at the beginning, the middle, or at the end of your virtual museum tour?" (when).
- "Situate the artifacts of the scene to each other" (e.g., the artifact XX was to the left of the first hall) (allocentric where).
- "Try to remember if you turned left or right after the artifact" (egocentric where).

The scoring of the categories above was done in two different ways: (a) measuring the reaction time as seconds needed to complete one answer (correct or wrong) per category above for each of the five archeological artifacts and (b) measuring how many errors the groups made for each of the five artifacts above. For example, one possible scoring example for one of the artifacts could be: There was a booth with a black vase (correct what); at the beginning of the virtual museum hall 1 (correct when), the vase was from white marble (wrong what); it was in front of the archeological site poster (1 allocentric where error); I turned right after this scene (1 egocentric where error). In total, 5 min was allowed for each artifact verbal recall. The total duration of the VAP-M exercise along with the training and the breaks was approximately 30 min. At the end of the exercise there was a total response time and a total errors score.

11.3.5 Statistical Analysis

Statistical analyses were performed by means of repeated measures ANOVAs with Greenhouse-Geisser corrected degrees of freedom. In case of significant main effects (if the factor included more than two levels) or interactions, additional ANOVAs were applied for post hoc testing of contrasts and simple effects. For response times (RTs; correct commission trials) the ANOVA included the within factor time (session one, session n) and the between factor group (VAP-M and NI). Separate ANOVAs were carried out for false alarms and for misses, because they are different types of errors either demanding a response or not. Both analysis included the factors time and group.

Six separate ANOVAs were carried out for the peak amplitudes and latencies of the N1, P2, and the P3b, respectively, including the between subject factor group and the within subject factors session (session one, session two), stimulus type (target, nontarget), and electrodes (O1 and O2 for the N1; FCz, Cz, and CPz for the P2 potential; Cz, CPz, and Pz for the P3b potential, resp.). An additional ANOVA was carried out for the N2 mean amplitudes including the between subject factor group and the within subject factors session, stimulus type, and electrodes (FCz, Cz, and CPz).

Finally, we adopted a generic classification scheme, suitable for dealing with multivariate data that incorporates standard pattern-analytic steps leading from feature ranking to train/test a learning algorithm (a detailed description can be found in [30]). In short, the derived measurements (related to the performance of a subject in either experimental paradigm) were treated as a set of features and ranked using the class separability criterion according to their importance in subsequent classification. Based on the most appropriate subset of features (e.g., at the ERP paradigm that is the area near the N2 and P3 peaks and for the VAP-M paradigm that is the area where the most errors occurred), we took a k value equal to 3 and built a k-nearest neighbor (knn) classifier with values normalized and distances in standard Euclidian space. Due to the small number of participants, we used a twofold cross-validation scheme with two sets: (a) training set and (b) test set and we repeated the cross-validation process for ten (10) times in order to get the mean data. We then measured the performance of the classifier in terms of sensitivity and specificity. The performance measures were accompanied with the appropriate visualizations (scatterplots). The advantage of using a common algorithmic procedure for analyzing subjects' performance in both VAP-M and ERP experimental procedures facilitated the direct comparison of the two different prognostic tools.

11.4 Results

11.4.1 Neuropsychological Tests Performance and VAP-M

We conducted analyses of Bravais–Pearson correlations to determine the features that the classical verbal memory tests (Ray Auditory Verbal Learning Test—RAVLT) and a daily complaint scale such as the CDS share with VAP-M. These correlations were computed separately for each group and were also controlled for the level of education and gender. All scores used to calculate correlations were raw scores. We took the total score of all errors and RTs (when, where, allocentric, and egocentric details), for each of the five artifacts of VAP-M test. We found that the more complaints that the patients had about their cognitive experiences in daily life, the more impaired they were on VAP-M (Table 11.2).

Moreover, when we looked at the correlations of the CDS score with each VAP-M condition (total RT and total errors), we observed that aMCI patients'

Table 11.2 Intercorrelations between the VR test and CDS and between the RAVLT memory test and CDS

	VAP-M		RAVLT
	Total RT	Total Err	
CDS			
Normal		0.7	
aMCI	0.86	0.89	0.65

Only significant correlations are presented ($p < .05$)

VAP-M scores in the passive condition were negatively correlated with the CDS. Moreover, we observed that scores on the RAVLT test were not correlated with the CDS except for the aMCI group, where learning of the verbal test was negatively correlated with the CDS.

11.4.2 Behavioral and Cognitive Performance During the VAP-M Recall Task

The ANCOVA on VAP-M total reaction time and total error scores revealed a strong effect of group on the behavioral performance ($F(1, 50) = 79.9$, $p < .001$), indicating that aMCI patients' recalls were impaired compared to healthy control participants. An effect of group on the reaction times ($F(1, 50) = 24.1$, $p < .001$) was observed, indicating that aMCI patients' total recall time was impaired. An effect of group was also observed for total error scores ($F(1, 50) = 33.1$, $p < .001$) indicating that aMCI patients performed more errors compared with healthy older participants.

With regard to spatial memory recall in specific, an effect of group on the egocentric total error score ($F(1, 50) = 41.6$, $p < .001$) was observed, indicating that aMCI patients' (mean of 3.5) recalls were deficient compared with healthy older adults (mean of 4.3). Again, an effect of group on the allocentric where score ($F(1, 50) = 28.9$, $p < .001$) was observed indicating that aMCI patients recalled significantly less allocentric spatial information than healthy older adults.

In general, we found that the aMCI patients' performances in VAP-M were inferior to that of the healthy controls. The performance of a common classifier was proved enhanced when VAP-M reaction time and errors-related scores were fed as features. The situation is demonstrated vividly via Fig. 11.2. The sensitivity of the classifier was 100 % and the specificity 98 % for the VAP-M paradigm (regarding the NI vs. aMCI discrimination).

11.4.3 Event-Related Potentials Data

For the ERP characteristics we used the mean prolonged latencies as indicated at the literature, e.g., [15]. However we excluded any errors/misses of the target

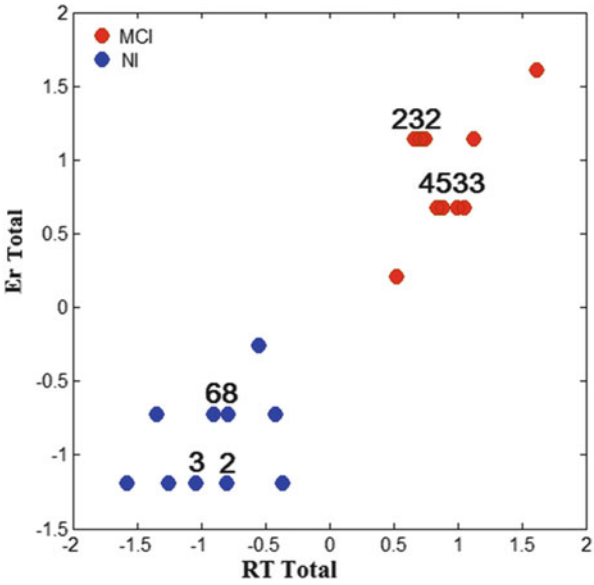

Fig. 11.2 VAP-M scatterplot based on the discriminating variables (RT total and Er total). Some dots are overlapping so the number of the overlapping dots is given above; the total is always 25 dots per group. Perfect classification can be easily accomplished even with simple classifiers (e.g., 100 % correct classification was achieved with a knn classifier [using $k = 3$])

stimuli because we found that the handling of the response button introduced a lot of noise to the signal we then had to process. The classic multidimensional scaling (MDS) technique was then employed to summarize all these comparisons within a 2D display (in a format similar of Fig. 11.2). The two groups appear well separated, and with the $k = 3$, a knn-classifier with performance of 89 % correct classification was achieved. Since excluding the error/misses above reduces the generality of our approach, we used the same classifier for ten repetitions per group in order to better generalize the performance and we reached a sensitivity of 88 % and specificity of 90 %.

11.5 Discussion

This pilot study results confirm that aMCI patients experience a profound genuine deficit of episodic memory, in line with the progression of hippocampal atrophy reported in the literature [2, 7, 20, 23, 25]. Furthermore, we saw that the aMCI patients were impaired compared with the control group at recalling central information. The same is observed with standard verbal memory tests as well [40, 2, 41, 20].

With regard to VAP-M, the aMCI patients were impaired in comparison with the control population for the delayed recall of egocentric memory (memory for the position of archeological artifacts regarding the position of our body) and allocentric spatial information (memory for spatial relationships between archeological artifacts independent of the position of the body). More specifically,

spatial allocentric memory errors were found to be particularly useful for characterizing aMCI patients, which according to the literature [8] provide a potential diagnostic cue for aMCI pathology. This cognitive ability is considered to depend mainly on the hippocampal areas, which suffer more damage in aMCI than in healthy aging [9, 36]. There is yet another virtual reality study, which showed that reduced volume of the hippocampus, the precuneus, and parietal regions predicts, respectively, the allocentric and egocentric memory impairment of patients with aMCI [34].

Another finding of the study above is that aMCI patients who converted to dementia 6 years later showed initially reduced hippocampal volume and impaired allocentric memory compared with aMCI patients who did not convert to dementia, whereas reduced parietal volume was not associated with the probability of conversion [34]. Although the above results suggest that allocentric assessment by means of virtual reality is a promising cue for early prediction of AD, more allocentric tasks should be developed in order to better understand the allocentric impairment demonstrated in aMCI. For example, one virtual reality exercise can be a mapping recall where participants were asked to draw a map of the environment or recognition of snapshots from a novel perspective compared with the encoding perspective.

Our study evaluated recall of temporal memory was by asking participants to specify whether the item occurred at the beginning, the middle, or at the end of the VAP-M halls. Another recent study demonstrated that differences in the precision of the temporal demands of a task led to the activation of different neuroanatomical regions [11]. On the standard temporal memory test, e.g., recalling the order in which stimuli were originally presented, accuracy was predicted by activity in the parahippocampal cortex, whereas on a coarse temporal test, e.g., when during the course of the experiment the stimulus appeared, accuracy was predicted by activity in several regions of the prefrontal cortex and in the hippocampus. The VAP-M temporal assessment is similar to a coarse temporal test, where aMCI patients retain some capacities that depend on relatively preserved frontal regions. The recall of sequential events is supposed to be strongly related to hippocampal function [10] and would thus be sensitive to aMCI.

While our analyses were focused specifically on the P3 latencies and the generalization of the results was low because we excluded the missed target data, we believe that our data are still broadly consistent with the posterior anterior shift in aging model and suggest that the increased frontal engagement of the aMCI group may arise in part from a need to overcome inefficient early perceptual processing of task stimuli. Future studies with larger sample sizes would be desirable to explore the potential relationship between early spatial memory deficits within VAP-M and the ERP marker identified here.

Conclusion

The rationale guiding the present study was the accumulation of knowledge about the relationship between realistic spatial memory assessment, ERPs, and the need to find a valid and nonthreatening way of diagnosing aMCI. The Virtual Reality tool, VAP-M might, therefore combined with ERPs, provide an additional tool to improve the early screening of MCI while avoiding the difficulties of neuropsychological tests. In particular, neuropsychological studies would benefit to use virtual tests and a multicomponent approach to assess episodic memory and encourage active encoding of information in patients suffering from mild or severe age-related memory impairment.

Overall, our results are in accordance with the notion that virtual reality is promising for early screening of patients with suspected AD. Our results confirm that the deficit of allocentric and egocentric spatial memory in particular, typically reflecting hippocampal damage, can be screened with virtual reality and used as a diagnostic cue for aMCI [3]. Overall, VR studies are likely to create more multi-sensorial and self-relevant situations than typical laboratory conditions. Overall, our study clearly demonstrates the feasibility of using VR technology to study the memory deficits of patients with aMCI. Our next study is trying to better understand the interaction of VR technology with neurophysiological biomarkers such as the ERP responses, using data-mining techniques.

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Chapter 12
On the Observed Specific and Non-specific Effects of Complex Therapeutic Interventions: Truly Separate or Complementary?

Lionel R. Milgrom

Abstract Specific and non-specific effects observed in randomised controlled trials (RCTs) are generally treated implicitly as ontologically separate and purely additive. Building on the notions of Heisenberg uncertainty and complementarity from the *discourse* of quantum theory, and using a simple arithmetic argument, it is demonstrated how this separation enables results of RCTs (particularly of complex interventions) to be treated in a convenient but ultimately incorrect manner. Conclusions drawn from RCTs (that justify—and are justified by—a reductionist approach to therapeutic efficacy) should therefore be open to question.

Keywords Evidence-based medicine • RCTs • Specific and non-specific effects • Complex interventions • Abelian and non-abelian groups • Quantum theory

12.1 Introduction

Systematic reviews and meta-analyses of double-blind randomised placebo-controlled trials (RCTs) represent the "gold standard" of evidence-based medicine (EBM) by which therapeutic interventions—conventional medical and complementary and alternative (CAM)—are judged scientifically acceptable.

[*Source*: SUNY Downstate Medical Centre. Medical Research Library of Brooklyn. Evidence Based Medicine Course. A Guide to Research Methods: The Evidence Pyramid: http://libguides.methodistcollege.edu/content.php?pid=175181&sid=1474687]

This is thought to enable purely objective clinical decisions to be taken: other forms of evidence and clinical decision-making tend to be either downgraded or

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ignored (the diagram above represents the current hierarchy of research design types used when making this judgement call).

EBM, however, was originally envisaged as ". . ..an approach to health care that promotes the collection, interpretation, and integration of. . .. *patient-reported, clinician-observed*, and *research-derived evidence* (author's emphasis). The best available evidence, moderated by patient circumstances and preferences, is applied to improve the quality of clinical judgments". [1]. Thus, RCTs were thought of as just one part of an evidence "package", derived from multiple sources [2].

But EBM early on became narrowly focussed on one kind of evidence, a case made forcibly by Cartwright when raising questions about the limitations of the RCT [3–5]. Rawlins in his 2008 Harveian Oration to the Royal Society of Medicine (2008) expressed similar doubts, suggesting "RCTs, long regarded as the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of hierarchies of evidence is inappropriate; and hierarchies are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence base" [6].

Indeed, EBM's limited evidential focus has exercised some clinicians, not only for its perceived overbearing attitude towards clinical decision-making [7], but also for its intolerance towards what has been called "therapeutic pluralism" [8]. In addition, EBM has been found to be logically inconsistent because its ". . ..strict distinction between admissible (based on RCTs) and other supposedly inadmissible evidence is not itself based on evidence, but rather, on intuition.... Ultimately, to uphold this fundamental distinction, EBM must seek recourse to (bio)political ideology and an epistemology akin to faith" [9].

EBM's ascendency has led to a tendency to question (and in some cases ridicule [10]) the value of complex interventions and procedures (e.g. acupuncture, psychotherapy, physiotherapy and homeopathy) that may be thought not to lend themselves readily to the strictures of the RCT protocol. This in turn has generated interest in how the RCT protocol might itself be a source of interference in the therapeutic process [11–13].

In addition, EBM's change of emphasis during the 1990s arguably has led to a resurgence of positivism and scientism [14] as readily accessible (and media friendly [15]) interpretations of science which, though long criticised in the physical sciences [16–24], go relatively unchallenged in more public arenas, and still hold sway in the bio-medical sciences.

Scientism in medicine, Leggett [25] predicted, would among other things lead to loss of a patient's individuality as correct management of disease becomes equated with proper management of the patient. By effectively reversing Osler's famous dictum, "A good physician treats the disease; a great physician treats the patient" [26, 27], scientism saddles medicine with a burden French physician and philosopher of medicine Georges Canguilhem warned of "Medicine is the science of the limits of the powers that the other sciences claim to confer upon it. . .." [28]. Emphasising this point in his obituary to Canguilhem, *Lancet* editor, Richard Horton wrote, ". . ..To allow our conceptions about a 'disease' to be governed only by the amount of objective data that can account for that condition is to undermine

the project of medicine....We seek biological meaning, but that end point may not be what our patients seek: indeed, it may be what they fear" [29].

Apart from down-grading or ignoring other forms of evidence, another effect of EBM's narrow evidential focus is to saddle the medical research community with the ultimately Sisyphean labour of subjecting ALL medical procedures and therapies to the RCT, so they can be judged fit for clinical use. This could be counter-productive as "....Of around 2500 treatments covered 13 % are rated as beneficial, 23 % likely to be beneficial, 8 % as trade off between benefits and harms, 6 % unlikely to be beneficial, 4 % likely to be ineffective or harmful, and 46 %, the largest proportion, as of unknown effectiveness.... the figures above suggest that the research community has a large task ahead and that most decisions about treatments still rest on the individual judgements of clinicians and patients" [30].

12.2 Efficacy vs. Effectiveness

"Efficacy" refers to how a drug/procedure works *in an ideal or controlled setting*, e.g. a clinical trial, particularly an RCT. Thus, efficacy measures a drug's performance usually over a limited period of time, under tightly controlled conditions.

"Effectiveness," on the other hand, gives an indication of how well an intervention might work *under more real-life conditions*. From clinical trials, the intervention might well have been judged efficacious, licensed for use and then made available for consumption. So, effectiveness considers how easy the intervention is to use over longer time periods, how beneficial it might be to the population of users at large and its possible side effects. These parameters are usually determined via observational studies that are not randomised.

Thus, in biomedicine "efficacy" is a narrower definition than "effectiveness", but as is increasingly being realised, both are required in order to gain a more complete understanding of how the behaviour of interventions in the laboratory translates into real life [31].

Thus, antidepressants (e.g. Prozac, aka Fluoxetine) are considered *effective* medications by many doctors and patients [32] and, regardless of their known side effects (in the case of Prozac, these can include suicidal tendencies [33, 34]), they have succeeded in earning pharmaceutical companies large profits. However, except perhaps for the most severely depressed patients, in trials against placebo, the *efficacy* of antidepressants has been shown to be clinically insignificant [35]. Indeed, in severely depressed patients, their efficacy is thought to be due more to decreased responsiveness to placebo, than increased responsiveness to the antidepressant medication.

The placebo effect has dogged the pharmaceutical industry since it began clinical research into new antidepressants [36]; the more so as it has now been demonstrated in an RCT on the treatment of irritable bowel syndrome that even when participants knew they were receiving placebo pills, they still got better [37]!

12.3 The Implicit Assumption in RCTs

Several limitations of the RCT have been identified, including the difficulty in generalising from internal to external validity. Thus Cartwright notes that "RCTs have high internal validity but the formal methodology puts severe constraints on the assumptions a target population must meet to justify exporting a conclusion from the test population to the target" [3]. Rawlins goes further: ". . .RCTs are often called the gold standard for demonstrating (or refuting) the benefits of a particular intervention. Yet the technique has important limitations of which four are particularly troublesome: the null hypothesis, probability, generalisability, and resource implications" [6]. However, in this chapter we concentrate on a slightly different question: Is there an implicit assumption inherent in RCT ideology that is a further limitation?

This was suggested by Weatherley-Jones et al. while reviewing the placebo-controlled trial as a test of CAMs. What they found was that built into the RCT methodology lay the assumption that specific and non-specific effects of an intervention are treated as separate, non-interacting phenomena [11]. Specifically, RCT ideology assumes implicitly "the healing process during treatment is an additive effect of the natural course of the disease, the nonspecific effects of the therapeutic intervention (e.g., consultation), and the specific effects of the treatment. As a placebo is not considered to have any specific effect, effects seen in a placebo arm of a trial are due to the additive effects of the natural course of the disease, and the non-specific effects of the therapeutic intervention". Similar doubts have been expressed about the appropriateness of applying the RCT methodology to other so-called complex interventions (e.g. acupuncture and psychotherapy) [38]. So, it is interesting to couch the above quotation in more algebraic terms. We shall term the verum arm of the trial *A*, and the placebo arm as *B*:

The specific effect of the intervention is then easy to determine simply by subtracting the totality of *B* from the totality of *A*, i.e.

$$\mathrm{A} - \mathrm{B} = (1 + 2 + 3) - (1 + 2) = 3$$

The question then is to what extent this implicit assumption of independence and ontological separability of specific and non-specific effects of an intervention is really justified. First, it is instructive to consider what it means to say specific and non-specific effects of a treatment are purely additive.

12.4 Specific and Non-specific Effects: Abelian and Non-abelian Groups

In abstract algebra, an abelian group (named after the Norwegian mathematician Niels Henrik Abel [39] is one in which the result of applying the group operation to two group elements is independent of their order. Under these circumstances, the group elements are said to commute. For example, abelian groups generalise the well-known commutative arithmetic of integers under the operations of addition and multiplication; thus,

$$a + b = b + a, \text{ and } a \times b = b \times a.$$

This can be generalised as $a*b = b*a$ or $a*b - b*a = 0$ where the symbol "*" represents the group operation.

Consequently, if specific and non-specific effects are to be identified as members of an abelian group, then under the group operation of addition, they will commute, and so can be treated separately, and additively like ordinary numbers. As we saw above, this would facilitate drawing conclusions about the specific effects of an intervention from the results of an RCT simply by subtracting the results of the placebo arm of the trial from those of the verum arm.

A non-abelian group, on the other hand, is one in which there are at least two elements a and b such that applying the group operation [40] *is* dependent on their order, i.e.

$$a * b \neq b * a \quad \text{or} \quad a * b - b * a \neq 0$$

Such groups are said to be non-commutative. Now processes generally consist of a series of operations whose order matters, leading to different observable outcomes depending on how they are combined. An obvious example is the process of making bread: changing the operational sequence by which bread is made is the difference between an observably good wholesome loaf and an inedible abomination. Thus, the process of bread making might be considered non-abelian: the order of operations matters in producing the observed desired result—an edible loaf.

The point is this: the RCT is also a process consisting of operations whose order matters. Therefore, it may be considered non-abelian, and so its observables, i.e. specific and non-specific effects, do not commute under the operation of addition. Contrary therefore to the simplifying assumption implicit in the RCT, specific and non-specific cannot be considered as ontologically separate, additive and commutative like numbers.

Thus, conclusions drawn from RCTs appear to be founded on a contradiction: while in essence specific and non-specific effects of an intervention are non-abelian, they are treated as if they are abelian. The question then is does it matter.

12.5 "Complex" Interventions and RCTs

Although there is no sharp delineation between what constitutes a simple or complex intervention, the latter is usually described as one containing multiple interacting components, and non-linear causal pathways. Complex interventions are often contrasted in the health literature with supposedly "simple" interventions, in particular medical interventions, which are generally thought to have simple linear pathways linking the intervention and its outcome [41]. That said, there are still debatable issues surrounding evaluation of what constitutes simple and complex interventions, developing methodologies to test them, and generating new theories to explain them, some of which have yet to find practical applications [42].

Nevertheless, the treatment of specific and non-specific effects as ontologically separate, non-interacting phenomena [11] has led to investigations into how the RCT protocol could act as a source of interference in CAM therapeutic processes. Thus, using the idea of three-way quantum entanglement [43] as a metaphor, a non-local holistic relationship between patient, practitioner and therapeutic intervention has been envisaged which is thought of as being "collapsed" by and during the RCT observational process [12, 44].

In addition, the orthodox quantum theoretical framework has been generalised by relaxing its restricting conditions, so that complementarity and entanglement become useful concepts in much broader contexts. This relaxed, more generalised version of orthodox quantum theory is called weak quantum theory (WQT) [13, 45, 46].

From these theoretical investigations, it is clear that the mathematical *discourse* of quantum theory, as demonstrated by Heisenberg's uncertainty relations, could have a parallel in the nature of RCT specific and non-specific effects, and so requires an algebra of observables that too is non-abelian.

Though counter-intuitive (and apparently unlike macroscopic physical systems), there is a definite operational limit on how accurately pairs of conjugate observables (e.g. position and momentum; energy and time) of a microscopic quantum system can be measured simultaneously [47]: the more accurate the measurement on one, the less accurate will be the measurement on the other. There is, however, another related facet of quantum theory that needs to be considered in the context of this discussion.

12.6 The Notion of Complementarity in Quantum Theory

Central to quantum theory is the idea of complementarity [48], a principle first enunciated in 1928 by Danish physicist Niels Bohr. Depending on the experimental setup, the behaviour of light and subatomic particles is sometimes wavelike, sometimes particle-like (i.e. photons, electrons, atoms and even whole molecules express wave-particle duality). However it is impossible to observe *both* the wave *and* particle aspects of such phenomena *simultaneously*. Together, however, they

present a more complete description of phenomena than either of the two taken alone [49].

This means that what is observed (be it particle or wave) is intimately dependent on the kind of experiment performed. In other words, the answer obtained depends on how the (experimental) question is asked. Consequently, the idea of complementarity in quantum theory posits observer and observed as fundamentally and irrevocably connected. Indeed, this is why one cannot even say the act of observation changes that which is observed: without an observer there is no observation in the first place.

This leads to one of the more startling suggestions to emerge from quantum theory that, in its history, several quantum physicists from Max Planck [50] onwards have proposed, namely that via consciousness, *observation in part creates the universe* [51]. This arises through a re-evaluation of one of materialistic science's key positivist assumptions, that everything physical is measurable or observable.

Such an assumption appears eminently reasonable, except when one is confronted by the findings of quantum theory. Thus, "without forsaking the requirement of empirical evidence for knowledge of physical characteristics, it is possible for quantum properties (e.g., a particle's wave function) to be physical but not directly observable or measurable" [52]. In fact, all that a wave function contains within it is what can possibly be *known* about a system by observation, *not its ontological reality separate from the observer*. The reasons for this are in part embedded in quantum theory's formalism which describes quantum properties like wave functions, in terms of an abstract space generalised mathematically from the ordinary 3-D space "out there" and separate from us that is taken for granted in everyday life.

When it comes to dealing with the theory and practicalities of quantum entanglement [53], modern interpretations of quantum theory have even more profound consequences for conventional science's purely materialistic positivist interpretation of reality. Thus, to quote physicist Anton Zeilinger (2004) [54], "....information or knowledge, in some instances, can have a more fundamental meaning than an objective reality". More specifically, information defines to some extent what *can be* reality, because it is the act of measurement that changes the quantum state. D'Espagnet [55] goes further, concluding that we most definitely do NOT live in the strongly objective reality we appear to see around us and supported by materialistic science. Indeed, it is only when the quantum state is taken too realistically that paradoxes emerge; the most famous being the unusual fate of Schrödinger's gedanken feline [56].

Such paradoxes disappear, however, if the quantum state is interpreted simply as a *representation of knowledge*. To quote Zeilinger again, "....on a much deeper level we may say that reality itself is beyond our reach. We can only concern ourselves with what can be said about reality" [54]. This implies that the origin of effects such as quantum entanglement is essentially epistemological rather than ontological in origin, echoing Kantian [57], even postmodern concerns [16–21] about the impossibility of ascertaining what reality "really is". In effect,

developments in the realm of quantum information technology [53] are reopening profound questions about the nature of reality that positivist materialistic science may have temporarily silenced [14].

12.7 Quantum Theory? In Biomedicine?

Apart from being treated as non-abelian, could there be a complementary relationship between specific and non-specific effects as conjugate observables from RCTs of complex interventions, as there is between quantum theoretical conjugate observables, e.g. position and momentum of a particle? Certainly, Weatherley-Jones et al. [11] hinted at this, and it has been made more explicit elsewhere [13, 44, 58, 59]. The suggestion here is that perhaps a form of quantum theoretical *discourse* might reasonably describe the effect of RCTs on the therapeutic process, particularly in complex interventions.

An immediate objection to this line of argument resides in the philosophical difference between the classical physics of macroscopic systems and the physics of microscopic quantum systems. In the former, experiments over hundreds of years have confirmed that a commutative abelian algebra adequately describes the relationship of simultaneously observed conjugate observables.

This is not the case for microscopic quantum systems. Heisenberg showed that because it is impossible to simultaneously measure with the same high degree of accuracy conjugate observables such as position and moment of a quantum system, the algebra to describe them had to be non-abelian. Importantly, the extent to which this algebra does not commute depends on an incredibly small universal number called Planck's constant h [47].

Quantum physics is also inherently statistical. Thus, the measured outcome of an experiment will generally not be the same if the experiment is repeated several times. Only the statistical *mean* of the measured values, averaged over a large number of runs of the experiment, is a repeatable quantity. Quantum theory does not predict the result of individual measurements, only their statistical mean. This predicted mean is called the *expectation value*, and, importantly, is represented not by a number but by a linear mathematical operator.

Clearly, as RCTs deal with what can only be described in the physical sense as "macroscopic" systems, the adoption of a quantum theoretical-like non-abelian algebra of conjugate observables would appear to be unnecessary, if not a case of "special pleading" for complex interventions like homeopathy to be considered scientifically (even ethically and morally [60]) more acceptable [61].

However, homeopathy is not the only complex intervention. Via weak quantum theory (WQT), complementarity and entanglement have been shown to extend far beyond the specific meanings ascribed to them by the orthodox quantum theory of the microscopic world, into engineering, the cognitive sciences and psychology [45]. WQT achieves this by generalising orthodox quantum theory via stepwise relaxation of some of its restricting conditions while at the same time maintaining its non-commuting algebra of conjugate observables.

Thus, WQT shares with orthodox quantum theory holistic correlations and entanglement if, in multi-component systems, *observables pertaining to the whole system are incompatible with observables pertaining to its parts*, but differ fundamentally in that:

- Complementarity and entanglement are not restricted to a particular *degree* of non-commutability of observables; that is, there is no need for Planck's constant, and the degree of non-commutability varies from case to case.
- Incomplete knowledge of a system, or perturbations caused by observation, is an epistemological rather than ontological reason for complementarity and indeterminacy.
- WQT has no interpretation in terms of probabilities, and the mathematical operators representing expectation values tend to be non-linear: as noted earlier, in orthodox quantum theory, these mathematical operators are linear.

As such, WQT and other metaphorical applications of quantum theory mentioned here [12, 44, 58, 62] effectively free complementarity and non-local entanglement from their confinement within the microscopic domain of atomic and subatomic physics, to find more formal recognition in our everyday macroscopic world. How these insights can be used to describe the effects of RCTs on the therapeutic process concerns the rest of this chapter.

12.8 Discussion

Random allocation of an intervention (verum) and placebo (to rule out practitioner or patient bias) is not how complex or indeed any other interventions are practiced in real life. Here both practitioner and patient ideally develop a therapeutic relationship in which both tend to *know* what is happening. The blinding inherent in the RCT protocol however causes practitioner and patient to be caste into a relationship in which they *know that they do not know* what is happening, with concomitant disruption of the therapeutic context in which an intervention takes place, at the very least affecting effect sizes.

As a "complex" intervention is by definition one with multiply interacting components [41], then the assumption that specific and non-specific effects of an intervention can be treated as separate, non-interacting phenomena is, most likely, an oversimplification. One might ask therefore what the effects of specific and non-specific effects being non-abelian and complementary might be.

Several researchers have investigated this. For example, in double-blind pathogenic trials, Walach et al. [13, 63] noted that homeopathic remedies (even at ultra-high dilutions beyond Avogadro's number) produce more symptoms typical for a remedy than non-typical symptoms. Intriguingly, however, these workers' results suggested something much more bizarre: *a non-classical pattern where symptoms of a remedy in the verum arm of the trial appeared to be mimicked to a lesser degree in the placebo arm*.

Interestingly, there has been some confirmation of this result by another research group [64], which raises an interesting question. Could there be non-classical "leakage" of information between trial arms, indicating some form of non-local entanglement between them? Certainly, this has been considered [12, 13, 44–46, 58, 62, 63, 65], in which case, treating specific and non-specific effects of an intervention as independent of each other seems at the very least misguided, especially as it is clear that non-specific effects play a significant role in the healing process [66, 67].

Indeed, the separation of the therapeutic process into specific and non-specific effects might be seen to be, by its very nature, artificial and arguably, an artefact of the RCT methodology. This is because in real life, *there is no such separation*. Let us examine a case in point.

As a "complex" intervention, homeopathy has the added problem [68] of accounting for its beneficial effects in trials [69, 70] within the currently accepted biomedical model of drug action. For example, Brien et al. reported that a trial involving a 5-armed RCT methodology over a 7-month period found that adjunctive homeopathic treatment in patients with active yet relatively stable rheumatoid arthritis (RA) produced sizeable clinically relevant benefits [71]. However, these were attributed solely to the innately empathic nature of the homeopathic *consultation* (i.e. a non-specific contextual effect), not to the specific effects of any single or complex homeopathic remedy, the authors concluding, "Given the magnitude of these effects and the lack of reported side effects, the impact of the homeopathic consultation is of clinical relevance to patients and clinicians alike".

Support [72] for this partial "endorsement" of homeopathy asserted that Brien *et al*.'s results should be taken at face value; that is, any beneficial effects are due to the consultation not to any homeopathic remedies, which in any case are implausible and ineffective.

Such a conclusion is premature, given the self-confessed shortcomings of this trial (crucially, it was underpowered in several of its key arms concerning the use of homeopathic remedies [44]). However (and contrary to the conclusions of Weatherley-Jones et al. [11] and what is being proposed here), Brien et al. assume that specific and non-specific effects are separate and non-interacting and may be treated as abelian. If we are to take Brien et al.'s results "at face value", given what has been discussed earlier and results from other RCTs, there is another interpretation of their results: that what is being observed is complementarity between specific and non-specific effects of the intervention, so they have to be treated as non-abelian.

Thus, Brien et al. found no clear differences in their RCT due to homeopathic remedy type (complex or individualised, which they then discount) while observing beneficial non-specific effects of the consultation. It is possible that what is being happening here is that these non-specific effects coincided with uncertainty in observing the specific effects of the remedies. In contrast, and as Weatherley-Jones et al. have pointed out, observing specific effects of homeopathic remedies in RCTs leads to uncertainty in observing the non-specific effects of the consultation.

Conclusion

Though it is far too early to draw any firm conclusions, what this seems to be suggesting (and contrary to Brien et al. [71]) is that *RCTs that attempt to isolate the effect of the medicine seem to lose sight of the consultation*, *while RCTs that attempt to isolate the effect of the consultation seem to lose sight of the medicine*. It is this that resonates with the complementarity inherent in quantum theory.

In the orthodox quantum theory of physics we cannot observe both wave and particle aspects of a quantum system simultaneously, but together they present a fuller description of phenomena than either of the two taken alone. Similarly, what RCTs of complex interventions might well be demonstrating is *we can know about the therapeutic intervention or the consultation as parts of a complementary pair of phenomena making up a whole*, *but we cannot know both with equal certainty at the same time*. In other words, what this seems to be implying is a biomedical restatement of Heisenberg's uncertainty principle for the therapeutic process.

Of course (as posited by weak quantum theory and other quantum theoretical metaphors of the therapeutic process), the degree of uncertainty here would not be anywhere near as mathematically precise as that predicted by the orthodox quantum theory of the microscopic world. However, it would be a direct consequence of the non-commuting, non-abelian complementary relationship of specific and non-specific effects postulated in this chapter. More experiments will need to be performed however before any such biomedical version of Heisenberg's uncertainty principle could be confirmed.

Nevertheless, this raises an interesting possibility. The separation of the results of an intervention into specific and non-specific effects and their resulting complementarity might well be the result of choosing to observe a whole, integrated, irreducible, real-life phenomenon (aka, the therapeutic process) through the limiting prism of blinded RCT methodology. Though adopting such a reductionist viewpoint might appear to make life easier for how the efficacy of therapeutic interventions is interpreted, it is doubtful whether ignoring the inherent contradiction this implies offers any deeper insights into how they work, or furthers understanding of their effectiveness in "real life".

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Chapter 13
The Effects of Aging on Sleep Architecture in Healthy Subjects

Georg Dorffner, Martin Vitr, and Peter Anderer

Abstract This chapter presents normative data on healthy sleep, as measured by polysomnography (PSG), from "supernormal" subjects across the age range from 20 to about 90 years. The data originates from the SIESTA project database established in the late 1990s. While that data has been published and used in research in many ways, the novelty of the current analysis is (a) the focus on normative data following the latest sleep staging standard (AASM 2012), and (b) the results after narrowing down the data set by excluding outliers due to disturbed sleep pattern that can occur in a sleep lab and are thus not examples of "normal" sleep. Results demonstrate interesting dependencies of sleep architecture on age, in particular a reduction in total sleep time and changes in sleep stage distributions toward lighter sleep, which differ in detail between the two genders.

13.1 Introduction

Normative data based on polysomnographic (PSG) measurements in the sleep lab play an important role in sleep research and medicine, but have been underrepresented in literature. Dedicated normative PSG studies mainly exist for children, e.g., [1]. Reliable data from normal sleep in the healthy adult population, in particular in an unmedicated elderly population, has not been available to a

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sufficient extent. Existing reviews of sleep data [2] show that age and gender are the two most important factors influencing overall sleep architecture. Therefore, any research that aims at comparing sleep variables to a normative control population needs to have access to normative data grouped by gender and age group. If this is not done, estimates for variability might be unnecessarily large affecting the resulting power of the study. Also, diagnostic decisions can be improved when age and gender matched normative data are available.

The SIESTA project (1997–2000, funded by the EU commission in its fourth research framework), among other goals, aimed at collecting such normative data across all adult age ranges. The exclusion criteria for selecting normal healthy controls were any significant medical disorder interfering with the aim of the study, a mini mental state evaluation (MMSE) score <25, a Pittsburgh Sleep Quality Index (PSQI) global score >5, a usual bedtime before 22.00 or after 00.00, an anxiety (SAS) raw score >33, a depression (SDS) raw score >35, a history of drug abuse, subjects requiring psychoactive medication and/or other drugs that might interfere with the study assessments (e.g., beta blockers), and subjects who work at night.

The study resulted in data from a total of 196 normal subjects from eight European sleep laboratories [3], which has been widely used in research. Danker-Hopfe et al. [4, 5] used the data to determine interrater variability on sleep scoring for both the old "Rechtschaffen & Kales" standard [6] and the more recent standard by the American Academy of Sleep Medicine [7], respectively. Danker-Hopfe et al. [8] described sleep variables according to [6] in terms of percentile charts. Anderer et al. [9] developed the now well-known computer-supported scoring system Somnolyzer 24×7 based on the data. Several groups have used the database in their sleep research, e.g., [10].

13.2 Goals of This Study

This chapter focuses on a reanalysis of the SIESTA data on healthy normal based on the following aspects:

- A description of all variables of sleep architecture based on the modern AASM scoring rules [7]
- A retrospective exclusion of extreme values (outliers) with respect to sleep latency, sleep efficiency, and wake after final awakening

The motivation behind the latter aspect is the following. Aside from the well-known first night effect in sleep labs [11], also in target nights (second night after adaptation) sleep can be unusually bad even for perfectly normal sleepers. Such sleep should not be considered "normal" in order to not unduly increase the variance of norm data.

By focusing on sleep latency, efficiency, and wake after final awakening, outliers with respect to early, mid-, and late insomnia will be accounted for.

13.3 Materials and Methods

The basis for our analysis was the 196 data sets from the healthy subjects in the SIESTA database. In order to exclude outliers, the data was split into the three age groups 20–40, 40–60, and above 60. For each group, outliers (more than two standard deviations from the mean) with respect to the either variable sleep latency, sleep efficiency, and wake after final awakening were eliminated.

Sleep staging was performed by the validated computer system Somnolyzer 24×7 [12] based on the AASM scoring manual [7], followed by a visual expert review of the results, before sleep architecture variables were calculated. However, one major problem inherent in the data needed to be addressed first: while the AASM standard prescribes signals from frontal (F), central (C), and occipital (O) EEG electrodes according to the international 10/20 system, the protocol behind the SIESTA data foresaw frontopolar (Fp) positions instead of frontal ones. In other words, strictly speaking the data was not ready to be scored according to AASM 2007.

Luckily, the SIESTA protocol also allowed each participating site to record additional EEG leads. As a result, a subset of 40 PSG recordings contained signals from both frontal and frontopolar leads. This data subset was therefore used to validate the hypothesis that Fp leads can be used instead of F leads in a deviation from the prescribed montage to replicate sleep staging according to the AASM. Somnolyzer 24×7 was run twice on each recording of that subset, once with F3-A2 and F4-A1 (A ... mastoid positions), as is standard, as inputs, and once with Fp1-A2 and Fp2-A1 as fake frontal inputs instead. Only if the resulting pairs of major sleep variables did not show any significant difference between the two montages (paired t-test, alpha $= 0.05$), the subsequent analysis was to be continued.

The main sleep variables were then analyzed by ways of linear regression with age as an independent variable. In order to derive normative data, the variables were further described in terms of mean, variance, median, 25 % and 75 % percentiles for each of the following age intervals separately: [20, 30), [30, 40), [40, 50), [50, 60), [60, 70), $\geq$70. These variables included:

- Total sleep time (TST, in minutes): The time spent in any sleep stage
- Sleep latency (SLAT, in minutes): The time from lights out to the first occurrence of a sleep stage
- Wake in total sleep period (WTSP, in minutes): The total time spent awake between sleep onset and final awakening
- Sleep stage N1 (in % of TST): Light sleep characterized by slowing EEG frequencies and slow eye movements
- Sleep stage N2 (in % of TST): Stable mid-deep sleep characterized by sleep spindle activity in the EEG
- Sleep stage N3 (in % of TST): Deep or slow-wave sleep, characterized by slow delta waves (1–2 Hz)
- Sleep stage R (in % of TST): Rapid eye movement (REM) sleep, characterized by high-frequency EEG, rapid eye movements and low muscle tone.

13.4 Results

The comparison between the two montages (one including frontal electrodes, the other including frontopolar electrodes instead) on a subset of 40 recordings indeed showed no significant differences in the main sleep variables (all paired *t*-tests were non-significant, all correlation coefficients between target variables derived from the analyses using frontopolar and frontal electrodes were >0.99). This warranted the further analysis of the entire data set in terms of sleep variables according to the AASM standard using frontopolar leads instead of frontal leads for the scoring.

After exclusion of outliers in the three age groups a total of 160 data sets remained, with an age distribution depicted in Table 13.1. Even though patients with an age >80 are included, their number is too low to warrant a separate age group.

Figures 13.1, 13.2, 13.3, 13.4, 13.5, 13.6, and 13.7 show the age dependency of the main sleep variables as scatterplots, together with estimated regression lines and their confidence intervals. Table 13.2 shows the corresponding coefficients in terms of variable change per decade.

13.5 Discussion

All results confirm that sleep architecture is strongly age dependent, and that there is also a difference between male and female sleepers. In line with earlier observations (e.g., in [2]) the data shows a clear reduction in total sleep time with age (about 8 min per decade for males and 10 min for females). For both genders this is mainly explained by an increase of wake within the total sleep period (i.e., between sleep onset and final awakening), rather than by sleep latency (time until falling asleep) or wake after final awakening, for which there is no significant dependency.

Concerning the four major sleep stages the picture shows interesting gender differences. While both genders show a tendency toward increasing light sleep in favor of deep sleep, the detailed changes in architecture are different. For males, N1 is increased by about 2 % per decade explained mostly by a corresponding decrease of slow wave sleep N3 (-1.7 %). N2 remains unchanged. In contrast, females exhibit a smaller increase in N1 (1.1 %), accompanied with an increase in N2 (0.9 %), both apparently explained by a decrease in REM sleep R (-1.4 %), while slow-wave sleep shows no change.

Based on the age groups mentioned above, age- and gender-dependent norm data can now be provided for PSG research following the AASM standard,

Table 13.1 The distribution of finally selected "supernormal" subjects

Age group	20–30	30–40	40–50	50–60	60–70	≥70	Total
Male	11	11	13	11	11	17	74
Female	15	13	15	10	10	23	86

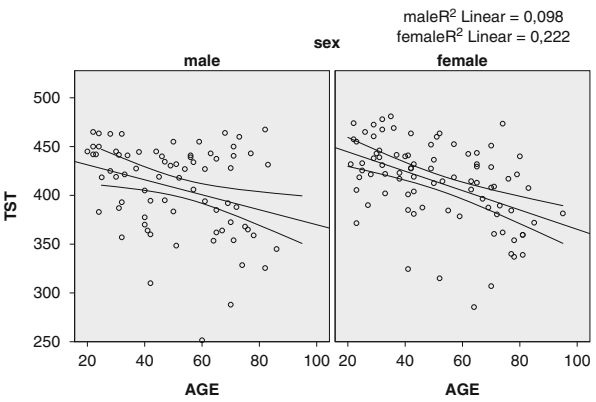

Fig. 13.1 Age dependency of total sleep time (TST, in minutes) for male (*left*) and female (*right*) subjects. *Lines* show the estimated regression lines with 95 % confidence intervals

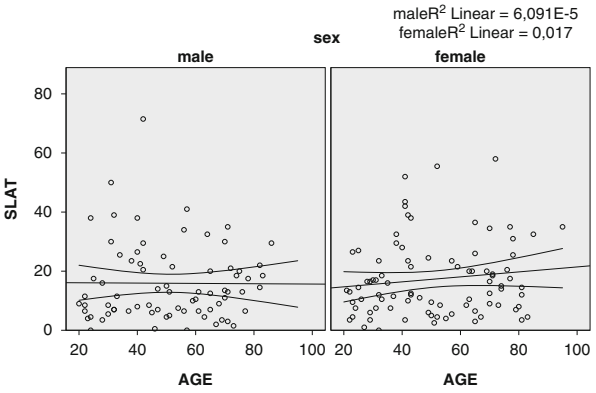

Fig. 13.2 Age dependency of sleep latency (SLAT, in minutes) for male (*left*) and female (*right*) subjects. *Lines* show the estimated regression lines with 95 % confidence intervals

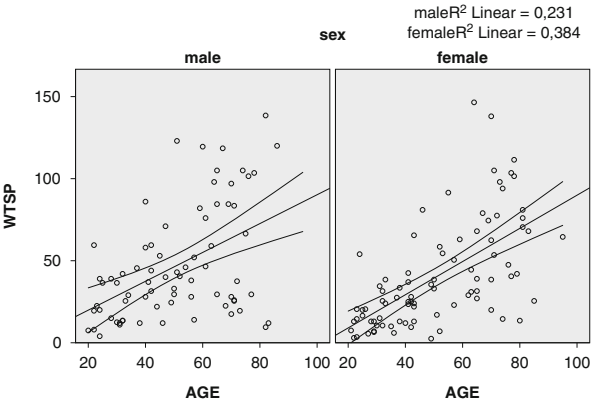

Fig. 13.3 Age dependency of wake in total sleep period (in minutes) for male (*left*) and female (*right*) subjects. *Lines* show the estimated regression lines with 95 % confidence intervals

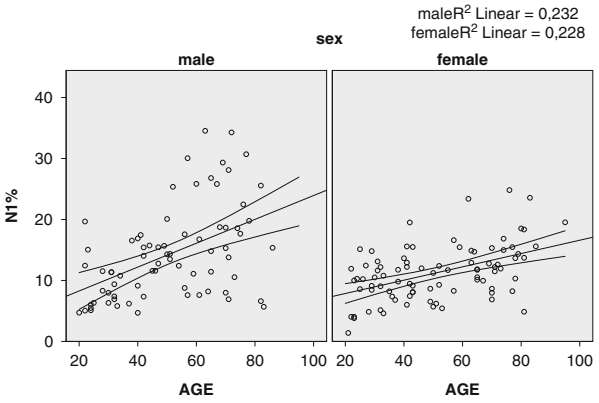

Fig. 13.4 Age dependency of stage N1 (in % of TST) for male (*left*) and female (*right*) subjects. *Lines* show the estimated regression lines with 95 % confidence intervals

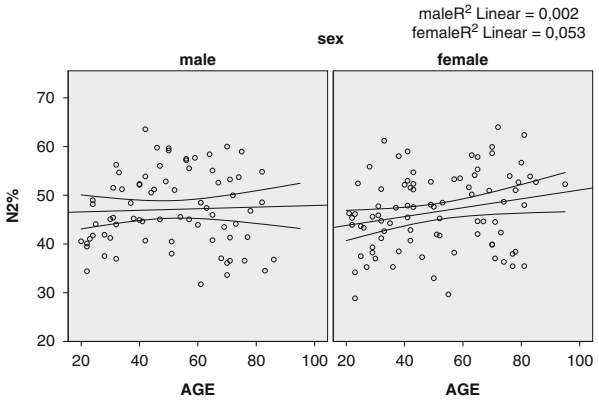

Fig. 13.5 Age dependency of stage N2 (in % of TST) for male (*left*) and female (*right*) subjects. *Lines* show the estimated regression lines with 95 % confidence intervals

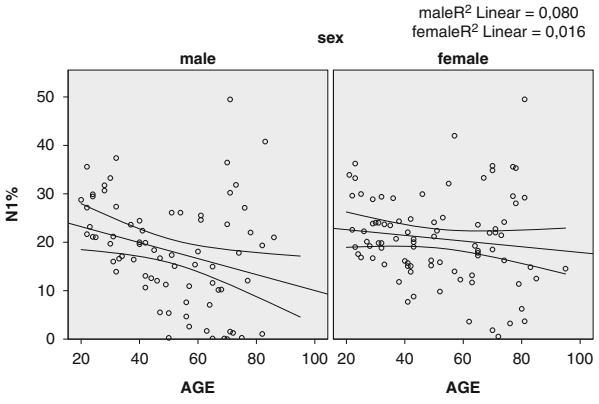

Fig. 13.6 Age dependency of stage N3 (in % of TST) for male (*left*) and female (*right*) subjects. *Lines* show the estimated regression lines with 95 % confidence intervals

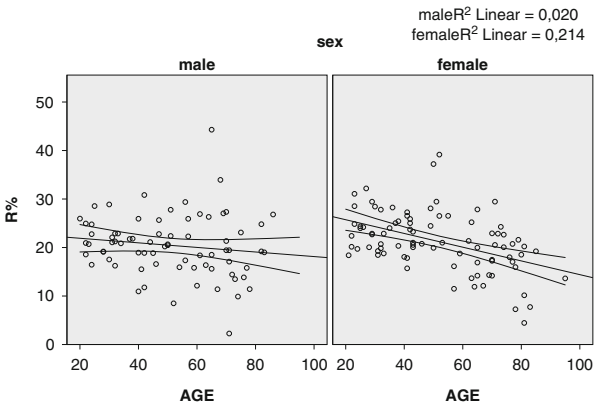

Fig. 13.7 Age dependency of stage REM (in % of TST) for male (*left*) and female (*right*) subjects. *Lines* show the estimated regression lines with 95 % confidence intervals

Table 13.2 Slope of regression line for each variable (in units of that variable) per decade with age as independent variable

Coefficient *k*	Male	Female
TST (min)	−7.7	−9.9
SLAT (min)	n.s.	n.s.
WTSP (min)	8.8	10.1
N1 (%)	2.0	1.1
N2 (%)	n.s.	0.9
N3 (%)	−1.7	n.s.
R (%)	n.s.	−1.4

"n.s." stands for "not significant"

providing a useful tool for powering clinical studies involving data from healthy subjects. Since the remaining number *n* in each group is not larger than about 11–13, coarser age groups might need to be selected for some project. Such normative data is not shown here due to space limitations, but can be made available upon request.

Conclusion

The data depicted and analyzed in this chapter is one of the few truly normative data sets on healthy human nocturnal sleep, as measured by polysomnography, and is compliant with the most modern standards of sleep scoring. Therefore, the "true" influence of age on normal, restorative sleep can be extracted more clearly. The results have shown that age does significantly alter sleep architecture by way of reducing total sleep time and shifting sleep stages toward lighter sleep even in subjects without any subjective sleep complain. The detailed changes in sleep architecture differ between the genders. These findings are not only important for assessing results in sleep research, but can also provide age- and gender-dependent normative data that can be used to power clinical trials in a more realistic and appropriate manner.

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Chapter 14
The Quantum Human Central Neural System

Athanasios Alexiou and John Rekkas

Abstract In this chapter we present Excess Entropy Production for human aging system as the sum of their respective subsystems and electrophysiological status. Additionally, we support the hypothesis of human brain and central neural system quantumness and we strongly suggest the theoretical and philosophical status of human brain as one of the unknown natural Dirac magnetic monopoles placed in the center of a Riemann sphere.

Keywords Frailty • Human brain • Central neural system • Excess entropy production • Magnetic monopole • Dirac string • Quantum information • Nonlinear mirror • Riemann sphere • Weak quantum theory • Complementarity • Entanglement

14.1 Introduction

The use of term frailty meets an increasing interest among the geriatricians and the medical doctors that treats elderly population (mainly aged over 65) and as a syndrome can be defined as a state of vulnerability to stressors resulting from a decrease in functional reserve across multiple systems and compromising an individual's capacity to maintain homeostasis [1]. Obviously frailty is a multiparametric clinical condition associated with a large scale of symptoms such as social and demographic factors, physical function, cognitive status and other social, environmental, and behavioral factors. While our knowledge concerning aging and systems biology is rapidly increasing, mathematical and biophysical modeling of frailty remains yet an open problem. The use of thermodynamics principles for irreversible processes has to be adjusted in a new way of studying geriatrics frailty.

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Additionally, nowadays several studies are under way concerning the analytically mapping of human brain, the modeling of all the subcellular processes and the way that cognition's disorders could be manipulated and treated in an effective way.

A latest research concerning the rapid way of human brain to process images and direct the eyes to their next target, conducted by neuroscientists at the Massachusetts Institute of Technology, seems to support our presented hypothesis theory [2]. During this clinical study, a series of 6 or 12 pictures presented at between 13 ms and 80 ms per picture to individuals, with no interstimulus interval and the results were consistent with feed-forward models [2]. As the authors concluded, a possible role for such rapid visual understanding would be to provide nearly instantaneous conceptual activation that enables immediate action when necessary, without waiting to refine understanding by reentrant processing or by the kind of conscious reflection that requires a stable recurrent network [2]. It is obvious that this two-way human brain processing must be operated in a simultaneous manner, almost synchronized, and be formalized by quantum and not classic information.

In this chapter we support that the application of the synchronistic theory [3], the modeling of synchronistic phenomena as entanglement correlations [4, 5], and the notation of complementarity in cognitive studies [6] through the formalisms of the Weak Quantum Theory (WQT) [7] are the necessary general framework for the establishment of a holistic human brain theory.

14.2 Measuring Frailty with Human Entropy

While the term "frail elderly" as a Medical Subject Heading term is defined as "older adults or aged individuals who are lacking in general strength and are unusually susceptible to disease or to other infirmity," we derived to a different formulation of the Hershey's original Excess Entropy Production (EEP) equation [8]. By taking into consideration the latest geriatrics clinical surveys, we propose a more complex system, for the representation of human aging, unlike the simple daily protein equilibrium that is the protein consumption minus the protein required [8].

Based on the Canadian Study of Health and Aging (CSHA) [9], we characterize human health as a dynamic system where frailty's progression depends on the overall human entropy. Categorizing the 70-item of the (CSHA) Frailty Index, we defined seven main groups of risk factors such as psychological, genetic, environmental, cardiovascular diseases, aging, comorbidities, and neurodegenerative lesions, where its subsystem entropy contributes to the overall system, often resulting to irreversibility even with a small accident or a symptom's presence. Increased entropy in any of the frailty subsystems may not lead immediately to a specific chronic disease or a case of morbidity. There is a chaotic combination of several factors, which have to be examined, in an individualized level, in order to calculate non-reversible healthy conditions.

Let us recall the basic equations for the internal entropy production for a chemical reaction system [10]:

$$\frac{\mathrm{d}S}{\mathrm{d}T} = \frac{Ar}{T}$$

where S is the internal entropy content; A is the chemical affinity, a chemical driving force; r is the reaction velocity, a chemical flow; T is temperature; t is time; and its general formulation is

$$\sigma(S) = \frac{\mathrm{d}S}{\mathrm{d}t} = \sum_{j=1}^{n} J_j X_j$$

where $a(S)$ is the internal entropy production at any time t, J_j is a flow for the component j, and X_j is a driving force for component j.

According to Hershey and Lee [11] EEP approaches a minimum or zero as the system approaches an equilibrium or stationary state and EEP describes the rate of approach of excess entropy (EE) to the final state, where

$$\mathrm{EEP} = \frac{\mathrm{dEE}}{\mathrm{d}t} = \frac{\mathrm{d}\left(\delta^2 S\right)}{\mathrm{d}t} = 2\sum_{j=1}^{n} \delta J_j \delta X_j$$

and

$$\mathrm{EE} = S - S^0 = \frac{1}{2}\delta^2 S$$

where S_0 is the entropy of the system in the reference state, δS is the first entropy deviation from the reference state, $\delta^2 S$ is the second entropy deviation from the reference state, and $\delta S = 0$ if the reference state is an equilibrium or stationary state of maximum entropy [12].

We analyzed the EEP equation of Hershey and Lee [8] and replace the [*Protein*] factor with the personalized [*Frailty*] value, where

$$Frailty = \sum_{i=1}^{n} a_i E_i, \qquad i = 1 \ldots 7$$

a_i is the energy coefficient and E_i corresponds to the i frailty's subsystem, expressed as an energy value. Therefore EEP can be rewritten as follows:

$$\mathrm{EEP} \cong \frac{(\delta[Frailty])^2}{[Frailty]}$$

where [*Frailty*] is the linear combination of the overall human quantum information of being healthy or not, that is,

$$|f\rangle = nh|0\rangle + h|1\rangle,$$

where $|nh|^2$ is the probability that elderly is not healthy, $|h|^2$ is the probability that elderly is healthy, $|nh|^2 + |nh|^2 = 1$, and $\delta[Frailty]$ is the daily total energy charge that human body produces in subcellular level minus the minimum energy required to result in a global irreversible process.

14.3 Signals Quantum Transmission in Human Body

We will start this third section with some basic mathematical terminology [13–16] based on the assumption of modeling the central nervous system (CNS) as a Riemann sphere with two states. One such system is described by the two-dimensional complex Hilbert space H^2.

We assume state $|\uparrow\rangle$ as the (1,0) and state $|\downarrow\rangle$ as the (0,1). While these two states are orthogonal we obtain $\langle\uparrow|\downarrow\rangle = 0$ and after their normalization we get $\langle\uparrow|\uparrow\rangle = 1 = \langle\downarrow|\downarrow\rangle$.

The overall system state results from the linear combination of the basis states $(\psi, \varphi) = \psi \cdot |\uparrow\rangle + \varphi \cdot |\downarrow\rangle$. The inner product of the general state $(a, b) = a \cdot |\uparrow\rangle + b \cdot |\downarrow\rangle$ will be computed from the $\langle (a, b)|(\psi, \varphi)\rangle = \overline{\alpha} \cdot \psi + \overline{b} \cdot \varphi$.

We assume also the following projective Hilbert space PH^2 where $\psi \cdot |\uparrow\rangle + \varphi \cdot |\downarrow\rangle = |\nearrow\rangle$ (Fig. 14.1).

According to the above, a synapse between a presynaptic neuron and a postsynaptic cell, for the transmission of an electrical or chemical signal will be equal to

$$\text{(True) or (1) for } |\nearrow\rangle$$
$$\text{(False) or (0) for } \langle\swarrow|$$

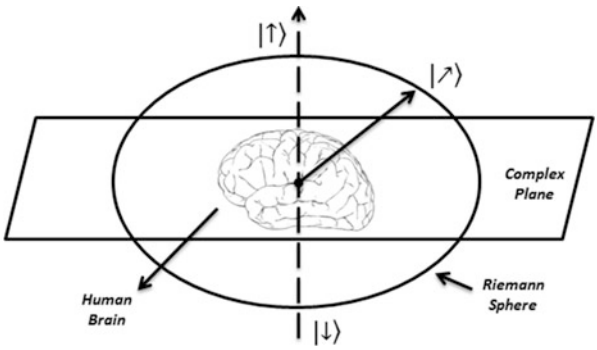

Fig. 14.1 The quantum brain in the center of a Riemann sphere

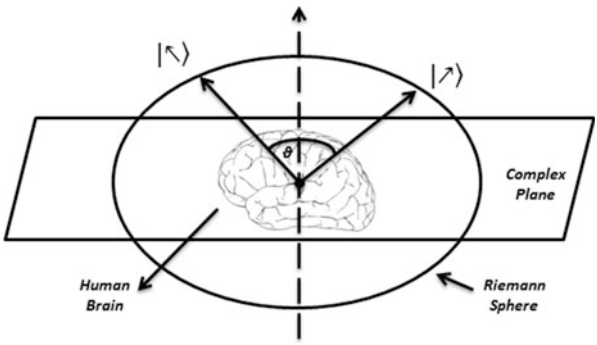

Fig. 14.2 The probability of measuring initial $|\nwarrow\rangle$ to a different direction $|\nearrow\rangle$

Assuming state $|\nearrow\rangle$, the probability of (True) during measure ($M\nearrow$) will be

$$\text{Prob} = \frac{|\psi|^2}{(|\psi^2| + |\varphi^2|)}$$

If we have a random state in the original direction $\langle\nwarrow|$ and measure the possibility of its existence in another direction $|\nearrow\rangle$ then the likelihood of (True) results from the relation

$$\text{Pr} = \frac{1}{2}(1 + \cos\theta),$$

where θ is the angle between $\langle\swarrow|$ and $|\nearrow\rangle$ in the three-dimensional Euclidean space (Fig. 14.2).

The Laplace operator in two dimensions of Euclidean space is given by $\nabla^2 = \partial^2/\partial x^2 + \partial^2/\partial y^2$, and must be transformed in curled metric as $\mathrm{d}S^2 = g_{ab}\mathrm{d}x^a\,\mathrm{d}x^b = \mathrm{d}\theta^2 + \sin^2\theta \cdot \mathrm{d}\varphi^2$ with spherical coordinates (θ, φ).

The Cartesian coordinates in the three-dimensional space can be presented in the form

$$\begin{aligned} x &= \sin\theta \cdot \cos\varphi \\ y &= \sin\theta \cdot \sin\varphi \\ z &= \cos\theta \end{aligned}$$

Additionally, Laplacian operator with partial derivative is given by

$$\nabla^2 = g^{ab}\nabla_a\nabla_b = \frac{\partial^2}{\partial\theta^2} + \frac{\cos\theta}{\sin\theta}\cdot\frac{\partial}{\partial\theta} + \frac{1}{\sin^2\theta}\cdot\frac{\partial^2}{\partial\varphi^2}$$

and ∇^2 Eigenvalues are

$$\nabla^2\Phi = -l \cdot (l+1) \cdot \Phi$$

where Φ the correspondence Eigenfunction with values $l = 0, 1, 2, \ldots$

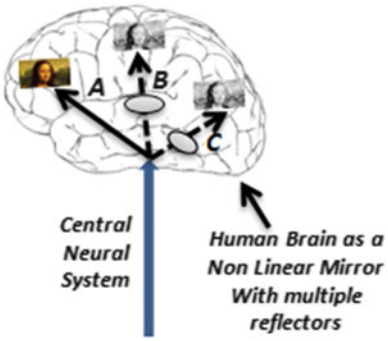

Fig. 14.3 Human brain as a nonlinear mirror with multiple reflectors

Given the complexity and randomness of energy production pathways, mainly by the activation of specific proteins and the quality of the mitochondrial dynamics, we conclude that any signal transmission requires energy production through non-conventional sources and non-discrete steps.

We therefore support that the human brain behaves like a nonlinear mirror, capable of generating and diffusing the incident signals from the CNS at different points, by moving forward and back in space and time, without creating actual copies of memories or reality's shots. Generated information behaves as if it is reflected by a spatial and temporal mirror and corresponds to authentic confirmation signals (without damage or distortion) in acknowledgment to the different brain subsystems receivers, acting as copies of the original signals (Fig. 14.3).

It is obvious that human brain does not create exact copies of the environmental reality i.e. optical images are derived inverted in the brain. In fact via quantum entanglement, a quantum state can be moved from one point of the nervous system to the brain and vice versa. While entanglement correlations cannot be used for transmitting signals or controllable causal influences [4, 5], Jung and Pauli [3] established the synchronicity theory in order to describe the so-called paranormal phenomena, not as results of any causal influence of mind on matter or other minds but as "meaningful coincidences" or correlations mediated by correspondences of sense and meaning [17]. Quantum information must be safety transferred in human body and shared equally with the past and to the future. Therefore the assumptions of weak quantum theory (WQT) [7] through the terms of complementarity and entanglement [6] can give us the necessary theoretical framework of explaining brain functionality and the conjunction between CNS and human brain parts.

14.4 CNS as a Dirac String

Our main objective is to establish the idea of a human brain isolated magnetic monopole existence [18–21], in order to pull electrons carriers' signals from the CNS. We use the initial Schrödinger wave equation $(\partial + M^2) \cdot \psi = 0$, which can be transformed to $(\partial + iM) \cdot \psi = 0$ for electron, using the Dirac operator.

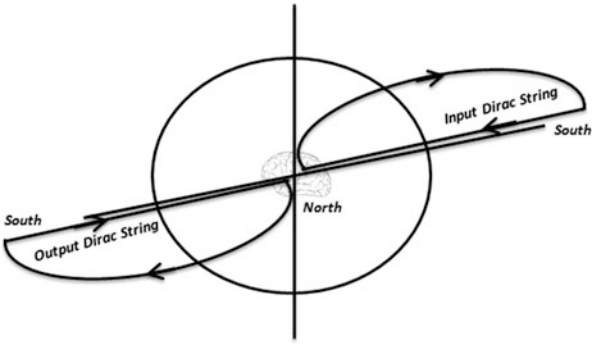

Fig. 14.4 Dirac strings across the CNS

The wave functions satisfying the Dirac equation will also satisfy the wave equation for particles with rest mass $\hbar \cdot M$. The Dirac equation might take the form of a Schrödinger equation:

$$i\hbar \cdot \frac{\partial \psi}{\partial t} = (i \cdot \hbar \cdot \gamma_0 \cdot \gamma \cdot \nabla + \gamma_0 \cdot \mu) \cdot \psi$$

where the parenthesis is the Hamiltonian operator; using the Hamiltonian, we express the interactions of the electron with the electromagnetic field generated by the magnetic monopole brain.

$$\text{Neural Cells} \xleftrightarrow{\text{synapses and electrons}} \text{Human Brain}$$

Therefore many Dirac strings are created for every neural pathway from one point of the CNS to another and to the brain, which are operated independently and often lead to undesirable side effects. These Dirac "brain bridges" give to the CNS the capability of accelerate synchronistic phenomena due to external stimuli or tissues-organs requests. As a conclusion the following theorem is resulting:

Theorem 1. Brain Magnetic Monopole (BMM) The magnetic power of the brain magnetic monopole is inversely proportional to the value of the electric charge flowing in each nervous Dirac string. The electric charge needs quantisation and must be equal to an integral multiple of a specific value of the electron charge.

This brain magnetic power will be given by the equation

$$P_{\mathrm{B}} = \frac{A}{|q|} = \frac{A}{N \cdot |q_{\mathrm{e}}|}$$

where $N = 1, 2, 3, \ldots$, $|q_{\mathrm{e}}| = 1.6 \times 10^{-19} C$, A is a physical constant expressed in $\frac{C \cdot J}{s}$ and depends on brain reflectance and its ability to act as a nonlinear mirror, creating evidence of information transference and countertransference as well as producing synchronistic phenomena through entanglement correlations (Fig. 14.4).

Conclusion

While new and extremely challenging evidences on brain ability to react on different environmental stimuli are published, in this chapter we propose a multiple formulation of human brain as a Dirac magnetic monopole, of CNS as Dirac string and of frailty evaluation as a thermodynamic problem. Merging biology with modern physics and mathematics, we support the hypothesis of the quantumness of CNS signals, through the formulation of human brain into a Riemann sphere in order to support the efforts of human brain mapping through a general and integrated theory.

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Chapter 15
The Vital Force "Reincarnated": Modeling Entelechy as a Quantized Spinning Gyroscopic Metaphor for Integrated Medicine

Lionel R. Milgrom

Abstract The ancient concept of the Vital Force receives a modern incarnation as a metaphorical multidimensional spinning gyroscope. The consequences for a different understanding of health and disease are examined in the context of integrated medicine.

Keywords Vital Force • Gyroscope • Wave functions • Homeopathy • Conventional medicine

15.1 Introduction

Integrative healthcare assumes that for the sake of our patients, conventional medicine and complementary and alternative medicine (CAM) find some common ground. The problem, however, is that conventional medicine is dominated by reductionism, a purely mechanistic epistemology, and scientism [1–10]. Thus, only physically identifiable manifestations of disease are considered "real," as they are the ones observable via the five senses.

Many CAMs (e.g., homeopathy) adopt a more holistic epistemology, which embraces the venerable notion of entelechy: that an essentially embodied but nonphysical (and therefore not directly observable) Vital Force (Vf) propels an organism towards self-fulfillment, e.g., health [11].

One way to meld these opposing epistemologies is to model entelechy using the multidimensional discourse of quantum theory. This is because, ". . .. it is possible for quantum properties (e.g., a particle's wave function) to be physical but not directly observable or measurable." Also, "a wave function contains within it all

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that can possibly be known about a system by observation, not its ontological reality, separate from the observer" [12]. Based on these insights, this paper proposes a metaphor for the Vital Force (Vf) as a multidimensional quantized spinning gyroscope [13].

15.2 The Vital Force (Vf) and Complexity

The Vital Force (Vf) bears striking similarities to *qi* or *chi* of Chinese acupuncture and *Prana* of Asian spiritual practices. From conventional medicine's reductionist viewpoint, the Vf is treated with contempt because "it doesn't have any identifiable source . . . obey any kind of (physical) law, it can't be defined; it is simply postulated ad hoc to explain whatever effects or alleged effects need explaining: it can't be pinned down or put to the question; its function is to provide the illusion of meaning without substance. . . . It can't be disproved because it is too amorphous and vague a concept [14]."

However, complex systems are known to self-organize, are open, and possess a wholeness that cannot be attributed solely to any particular part or subsystem [13]. Nondeterministically, the Vf might be considered as an emergent property of billions of living cells, which generates an all-pervading field that by feedback so organizes the totality's elements that it reinforces itself. This field would not originate in any one cell or body part, and being resultant of the whole organism, resists any dissipative entropic influence [15].

Such a holistic view of the Vf bares phenomenological comparison with conclusions derived from quantum physics [12, 16]. Thus, the Vf is not directly ascertainable: it is only observed indirectly through the symptoms it produces [17]. Similarly, in quantum theory, the *wave function* (a multidimensional mathematical descriptor of a quantum system's state) may only be inferred from the effects it produces in our reality [12, 18]. This is because of the multidimensional mathematical language used to describe wave functions [19].[1] Thus, trying to visualize a multidimensional quantum state in usual three-dimensional (3-D) terms [20, 21] leads to loss of information—like trying to squeeze a three-dimensional cube into a two-dimensional plane: information invariably gets lost, notably, in this case, the cube's three-dimensionality—and one reason why quantum entanglement seems so paradoxical [12].

[1] This uses complex numbers of the type $a + ib$, where a and b are real and $i = \sqrt{-1}$, is imaginary, i.e., a solution of $\sqrt{-1}$ does not exist within the scope of the real numbers. The use of complex numbers allows access to mathematically higher dimensional spaces than are available to the set of real numbers, which are a sub-set of complex numbers.

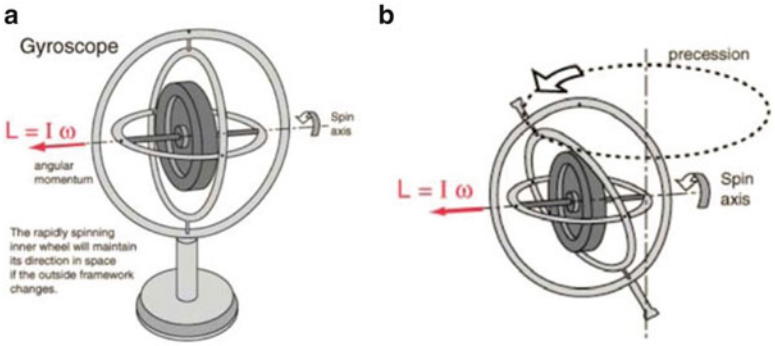

Fig. 15.1 (**a**) A type of gyroscope made by suspending a relatively massive rotor inside three rings called gimbals. Mounting each of these rotors on high-quality bearing surfaces insures that very little torque can be exerted on the inside rotor. (**b**) If a gyroscope is tipped, the gimbals try to reorient to keep the rotor spin axis in the same direction. If released in this orientation, the gyroscope will precess in the direction shown because of the torque exerted by gravity on the gyroscope

15.2.1 A Gyroscopic Model of the Vital Force

Based on the above conjectures, it is possible to develop a metaphor of the Vf as if it behaved like a gyroscopic entity. This utilizes the well-known properties of spinning tops and gyroscopes to illustrate the actions of the Vf in response to disease and remedies [13] (Figure 15.1 represents a more complex form of gyroscopic mounting but the same principles apply).

Thus, once set spinning at high speed, the angular momentum generated causes tops and simple gyroscopes to stand erect with respect to the Earth's gravitational field and will strongly resist any external lateral forces that try to topple the gyroscope (Fig. 15.2).

If those forces are strong enough, they will cause it to wobble about its spinning axis before the gyroscope settles back into its upright position. Also, any object attached to the rapidly spinning flywheel will be thrown outward. As the flywheel slows, the gyroscope wobbles again but now tilts over and rotates slowly about a vertical axis. This slow rotation of the gyroscope's spinning axis is called precession: The slower the flywheel spins, the faster the precession of the whole gyroscope, until it eventually topples over completely. A precessing gyroscope resists lateral forces far less strongly.

A healthy Vf may be likened to a fully upright (multidimensional) gyroscope with a rapidly spinning flywheel with one major exception: changes in the Vf "gyroscopic" angular velocity of precession do not occur smoothly but *in jumps*, i.e., *it is quantized*. Imagined as physical but not observable when healthy, the Vf gyroscope "spins" unobserved in an upright position. When diseased, however, the Vf "precesses," betraying the physical part of its existence by "throwing out" symptoms in our reality.

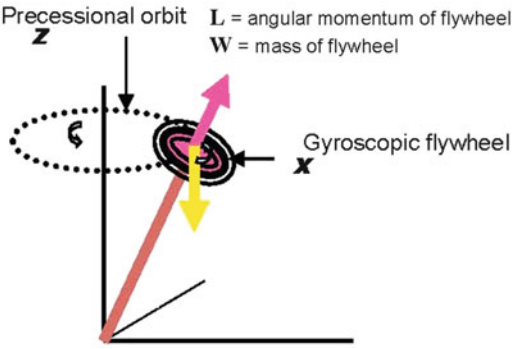

Fig. 15.2 Schematic of simple gyroscope and its forces, $L =$ angular momentum of flywheel, $W =$ mass of flywheel

Lateral forces, therefore, are akin to those stressors that can push the organism into disease states that are resisted easily by a healthy Vf and thrown off centrifugally to the organism's extremities. Acute disease expression may be likened to the wobbling of the Vf gyroscope after being acted upon by a strong force, prior to the Vf gyroscope resuming its healthy upright stance. A weaker Vf, however, is more like a gyroscope whose flywheel has slowed down so that it is less stable in an upright position. In this situation, the Vf is less able to resist those stressors that push the organism over into disease states.

Consequently, as the Vf begins to precess (i.e., express symptoms of disease): the greater the amount of precession, the more chronic the disease state and the greater its symptom expression will be. And the slower the Vf gyroscope's "flywheel" spins, the less able it is to throw off the disease.

Within this qualitative metaphor, the therapeutic homeopathic remedy can be seen as the force that, when applied to the Vf gyroscope's flywheel, causes it to speed up, spin faster, and throw off the disease state. Also, the term "disease" may be applied to those inherited and environmental stressors that could exert a braking effect on the Vf gyroscope's flywheel. These would include constitutional factors that could give rise to "friction in the bearings" (e.g., inherited imperfections in the Vf gyroscope's manufacture) and environmental factors giving rise to "friction on the fly-wheel" (e.g., poor diet, housing, and air quality, and dysfunctional relationships.) [13].

Further, in this metaphor, diseases and therapeutic modalities are envisaged as torque-like "vectors" that, respectively, "brake" or "accelerate" the quantized Vf gyroscope's rate of spin. The former causes the Vf to "precess," eliciting symptoms in our reality: the latter corrects precession by accelerating the Vf, which "throws off" the disease and restores health. This metaphor therefore, illustrates how diseases and therapeutic modalities have a mirror-like relationship, and suggests conventional medicine's homeostatic immune system might be seen as a physical projection of CAM's more general multidimensional Vf.

15.2.2 Developing the Vf Gyroscopic Model

1. *Assumptions*: so, to recap, the model of the Vf in terms of a quantized gyroscope [22] is based on three main assumptions:
   (a) *An individual's Vf can be imagined as behaving like a gyroscope*: *The faster it* "spins" *on its axis*, *the more easily it resists the effects of disease*. From this perspective, a Vf vector, **Vf** can be equated algebraically with the precessing angular momentum, $\mathbf{L_s}$ of a gyroscope. And like the magnitude of $\mathbf{L_s}$, L_s, the magnitude of **Vf**, *V*f, is inversely proportional to a gyroscopic precessional velocity, Ω so that, $\Omega = 1/V\text{f}$. Thus within certain limits, and just like a real gyroscope, the faster the Vf's angular velocity of precession (i.e., the slower its rate of spin about its "axis" and therefore the smaller its angular momentum), the weaker the *V*f.
   (b) *These changes in gyroscopic angular momentum corresponding to changes in the Vf's state of health do not occur smoothly but in a stepwise* ("quantized") *manner*. What this means is that, unlike a real mechanical gyroscope, the theoretical Vf gyroscope is not observed to experience gradual decreases and increases of its spin angular momentum. Similar to the way orbiting electrons in atoms are thought to jump instantaneously between energy levels when absorbing and emitting quanta of energy, the Vf jumps between states of health depending on its reaction to "quanta" of diseases and remedies.
   (c) *This idea can be extended to define mathematical operators that describe how these changes in a Vf's angular momentum/state of health are brought about by disease states and remedies*. In fact, these mathematical operators may be written algebraically in a manner similar to angular momentum shift operators used in the QT to describe the physics of electrons in atoms [23]. These are called Vital Force shift operators, and they elicit responses from the Vf that increase (i.e., remedy) or decrease (i.e., disease) its angular momentum/state of health. These Vf shift operators are derived from complementary complex number combinations [19] of the primary and secondary symptoms expressed by the Vf as experienced by the patient [22].
2. *Vf* "gyroscope" *wave function*: the totality of observed primary symptoms we shall denote as equal to $k_1\Sigma\sigma_1$, while the totality (hence the sign Σ, which means "sum") of observed secondary symptoms expressed by a Vital Force (Vf) shall be denoted as equal to $ik_2\Sigma\sigma_2$. Thus the Vf shift operators may be defined as:

$$V_+ = k_1\Sigma\sigma_1 + ik_2\Sigma\sigma_2 \text{ and } \mathrm{V}_- = k_1\Sigma\sigma_1 - ik_2\Sigma\sigma_2$$

   where $i = \sqrt{-1}$, and k_1 and k_2 are, for the time being, arbitrary constants of proportionality. This representation of the shift operators economically incorporates the complementarity of primary and secondary symptoms.

The terms "primary" and "secondary symptoms" here refer to the essential dual biphasal nature of the remedy as has been noted by previous authors [24, 25]. "Biphasal" means that a remedy is observed to exhibit the so-called primary symptoms followed by more lasting secondary symptoms. A closely related concept here is that of "hormesis" meaning a generally favorable biological response to low exposures to toxins and other environmental stressors. Such toxins/stressors demonstrating hormesis thus have the opposite effect in small doses as in large doses [26].

These primary and secondary effects are generally taken to be of equal value, although some authors have favored the longer-lasting secondary symptoms as being more useful to the physician because they are thought to have more to do with the response of the Vf to the remedy (in conventional medicine, these secondary effects might be equated roughly with so-called side effects).

The primary–secondary sequence can reverse depending on many factors, including susceptibility, potency, and time phases [25]. However, what it is important to realize is that it is not so much the sequence, but the fact that the remedy produces a *complementary duality* of symptoms: It is only by observing this complementarity that a remedy's totality of action can be fully understood. This duality is contained within the algebraic derivation of the Vf shift operators in terms of complex numbers [19, 22].

In terms of the Vf gyroscope model presented here, the constant k_2 may be thought to contain within it expressions of the energy and the "moment of inertia" of the Vf gyroscope. A similar analysis of k_1 shows it to be related to the power of Vf to resist external influences (i.e., disease): The larger k_1 is, the less the Vf "gyroscope" is troubled by external influences.

Following on from this, it is possible to derive a "wave function" Ψ_{Vf} for the Vf, which relates it solely to the totality of secondary-symptom observables (i.e., $\int \Sigma\sigma_2 = S_2$) and bears striking similarities to the wave function for a quantized rotating object [22] (see Fig. 15.3).

$$\Psi_{\mathrm{Vf}} \;=\; A\left(\mathrm{e}^{ik_2 S_2} \;+\; \mathrm{e}^{-ik_2 S_2}\right) \;=\; 2A\cos k_2 S_2$$

In addition, this analysis was able to show that remedies (**Rx**) may also be represented by wave functions of the form $\Psi_{\mathrm{Rx}} = \mathrm{e}^{-\mathrm{i}k_2 \Delta S_2}$ (where ΔS_2 refers to the overall change in the totality of secondary symptoms wrought by the remedy). Thus when the remedy is completely curative, $\Delta S_2 = S_2$ and $\Psi_{\mathrm{Rx}} = \mathrm{e}^{-ik_2 S_2}$.

If the remedy does not cause any change in secondary symptoms, then $\Delta S_2 = 0$, and $\Psi_{\mathrm{Rx}} = \mathrm{e}^{-ik_2 \Delta S_2} = \mathrm{e}^0 = 1$.

3. *The effect of the correct therapeutic remedy*: the effect of the correct therapeutic remedy Rx at the right potency is given by the product of Ψ_{Vf} and Ψ_{Rx} which leads to a boost to Vf written as $\Psi_{\mathrm{Vf+\Delta Vf}}$:-

   So, $\Psi_{\mathrm{Vf+\Delta Vf}} = \mathrm{A}(\mathrm{e}^{\mathrm{i}k_2 S_2} + \mathrm{e}^{-\mathrm{i}k_2 S_2})\mathrm{e}^{-\mathrm{i}k_2 \Delta S_2}$.

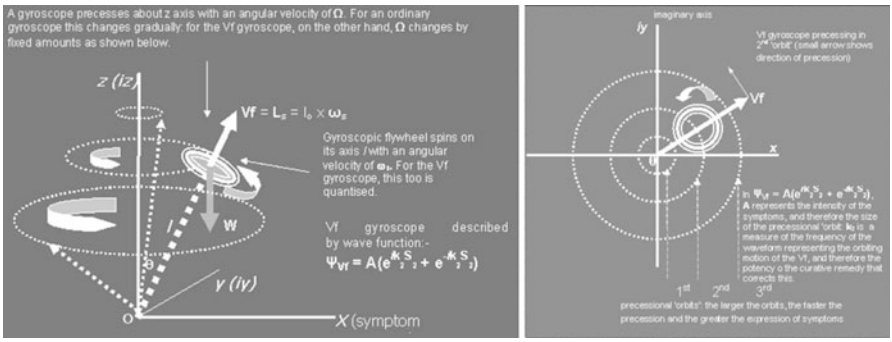

Fig. 15.3 Schematic of Vf "gyroscope" precessing in fixed quantized "orbits" of decreasing health. This shows that the wave function is related solely to a set of observables—the totality of secondary symptoms, S_2

Consequently, when the remedy is completely curative, $S_2 = 0$ and $\Delta S_2 = S_2$ and substituting, we get.

$$\Psi_{\mathrm{Vf}+\Delta\mathrm{Vf}} = 2A$$

Which means no more symptoms are shown = a healthier, faster spinning, 'upright' **Vf**. The conditions, however, have to be precise: *the right Rx at the right potency*.

4. *Homeopathic aggravation*: here the patient (**Px**) aggravates or "proves" the remedy (i.e., produces symptoms of the remedy)? This is the situation when the remedy cures, i.e., $S_2 = 0$ but now $\Delta S_2 > S_2$.

   So, substituting in $\Psi_{\mathrm{Vf}+\Delta\mathrm{Vf}} = A(\mathrm{e}^{ik_2 S_2} + \mathrm{e}^{-ik_2 S_2})\mathrm{e}^{-ik_2 \Delta S_2}$ we get....

$$\Psi_{\mathrm{Vf}+\Delta\mathrm{Vf}} = 2A\mathrm{e}^{-ik_2 \Delta S_2},$$

   i.e., the Rx has removed the original Sx but now added some of its own, aka "proving" Sx. This is equivalent to speeding up the Vf gyroscope too quickly: it wobbles violently before settling into its new higher, healthier rate of spin.

5. *Curative remedy at the wrong potency*: not all the symptoms are cleared, and this is the situation when $S_2 \neq 0$ and now $\Delta S_2 < S_2$.

   So, substituting in $\Psi_{\mathrm{Vf}+\Delta\mathrm{Vf}} = A(\mathrm{e}^{ik_2 S_2} + \mathrm{e}^{-ik_2 S_2})\mathrm{e}^{-ik_2 \Delta S_2}$ we get....

$$\Psi_{\mathrm{Vf}+\Delta\mathrm{Vf}} = A\left(\mathrm{e}^{ik_2\left(S_2 - \Delta S_2\right)} + \mathrm{e}^{-ik2\left(S_2 - \Delta S_2\right)}\right) \backslash$$

   i.e., not all the Sx are removed and the Vf is still precessing. Thus the right Rx has to be given at the right potency for complete cure to proceed. This is not easy: so safest way to proceed might be to remove Sx gradually. This might be a possible rationale for Hahnemann's invention and use of the LM potencies.

6. "Mirror-image" *relationship of diseases and remedies*: the remedy equation can be rewritten in polar form using Euler's transformation:

$$\Psi_{\mathrm{Rx}} = \mathrm{e}^{-ik_2\Delta S_2} = \cos k_2\Delta S_2 - i\sin k_2\Delta S_2$$

where k_2 is related to *remedy potency*. This shows the remedy can be represented as a *complex number* with a real (i.e., $\cos k_2\Delta S_2$) and an imaginary (i.e., $i\sin k_2\Delta S_2$) part. If disease is intimately related to the remedy (at the right potency) that cures it—they are like mirror images of each other. So in mathematical terms, the disease is the complex conjugate—"mirror image"—of the remedy which will be:

$$\Psi_{\mathrm{Dx}} = \mathrm{e}^{ik_2\Delta S_2} = \cos k_2\Delta S_2 + i\sin k_2\Delta S_2$$

Therefore, multiplying remedy and disease "wave functions" essentially cancels them out, i.e.,

$$\Psi_{\mathrm{Rx}}.\,\Psi_{\mathrm{Dx}} = \mathrm{e}^{-ik_2\Delta S_2}.\,\mathrm{e}^{ik_2\Delta S_2} = \mathrm{e}^{0} = 1$$

which is the same as writing $(\cos k_2\Delta S_2 - i\sin k_2\Delta S_2).(\cos k_2\Delta S_2 + i\sin k_2\Delta S_2) = 1$

The remedy Rx can be regarded as acting as an *accelerating torque* speeding up the Vf "gyroscope," while the disease Dx acts as a braking torque slowing it down. So, the right remedy at the right potency "cancels" out the effect of the disease.

15.2.3 A Model for the Homeostatic Immune System

Conventional medicine has no concept of an all-pervading Vf. In homeopathy, the goal of treatment is to help the Vf to throw off the disease (e.g., as in the Vf gyroscopic model). In contrast, conventional medicine recognizes a homeostatic immune system: its drug regimes, however, are less concerned with supporting it and more concerned with alleviating symptoms. In homeopathy, this is believed to be the cause of conventional drug side effects, as the Vf reacts against the drug's initial suppression of symptoms [24].

Depicting the Vf and remedies as wave functions implies a certain periodicity in their properties and behavior. This can indeed be exhibited by the Vf in its expression of symptoms, with their strength varying according to periodic modalities, such as the time of day.

Interestingly, there is some experimental evidence that biologically active substances at different serially diluted (and agitated) potencies will have periodic effects on their substrates. For example, Schiff reports alternating effects of different ultradiluted potencies of anti-immunoglobulin E (aIgE) on the decolorization of stained basophils, in most cases when the aIgE had been diluted and agitated beyond molecular existence [27]: some potencies enhance decolorization while others retard it. Schiff claimed this as evidence for the water memory effect.

Accordingly, k_2 values determine the periodicity of the Vf and remedy wave functions. As this constant is also associated with remedy potency (which is

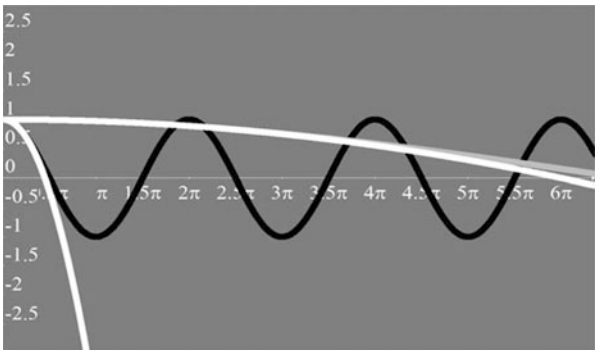

Fig. 15.4 Plots of the real part of $\Psi_{Rx} = e^{-ik_2\Delta S_2} = \cos k_2\Delta S_2 - i\sin k_2\Delta S_2$ ($k_2 = 1$; *black curve*: $k_2 = 0.075$; shallow *gray curve*), and $\Psi_{Rx} = \cos\ k_2\Delta S_2 \approx 1 - [k_2\Delta S_2]^2/2!$ ($k_2 = 1$; steep white curve: $k_2 = 0.075$; shallow *white curve*)

inversely proportional to material dose), it is interesting to investigate the possible effects of very low remedy k_2 values on the periodicity of Ψ_{Rx}.

From the previous section, we saw that the remedy wave function can be written in polar form:-

$$\Psi_{Rx} \ = \ e^{-ik_2\Delta S_2} \ = \ \cos k_2\Delta S_2 - i \sin k_2\Delta S_2$$

which means that the remedy wave function is represented as a *complex number* with a real ($\cos k_2\Delta S_2$) and an imaginary ($i\sin k_2\Delta S_2$) part. The real part is periodic and is shown as the black and gray lines in Fig. 15.4.

Crucially, what this means is that because k_2 is associated with remedy potency, and by representing the remedy as a wave function, *it should remain effective regardless of its material dose* (*potency*), *assuming it is correctly matched according to the law of similars*, i.e., *the prediction of homeopathy* (black and gray lines in figure).

Now, in mathematics, periodic functions can be expanded as power series, e.g.,

$$\cos\theta \ = \ 1 - \theta^2/2! \ + \ \theta^4/4! \ - \theta^6/6! \ + \ \ldots.(-1)^n\theta^{2n}/(2n)!$$

where $\theta = k_2\Delta S_2$. This means that as θ becomes very small, (i.e., as k_2 tends to 0) then in the remedy wave function, the imaginary part *is* in$\theta \approx 0$ and $\cos\theta \approx 1 - \theta^2/2!$ We can see in Fig. 15.4 (the white lines) that when this happens $\cos\theta$ is no longer a periodic wave function.

Low remedy potency in homeopathy means the remedy is in a material dose. Thus, as k_2 tends to 0 *because* $\cos k_2\Delta S_2 \approx 1 - (k_2\Delta S_2)^2/2!$ *is NOT a wave function*. In fact, as Fig. 15.4 shows, as k_2 tends to 0, the shallow gray and white lines are virtually indistinguishable. So, by making this approximation, we can see why only being used to dealing with remedies in material doses, conventional medicine might

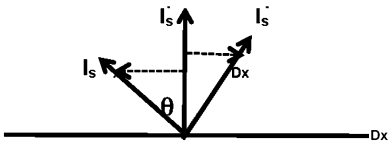

Fig. 15.5 Force diagram model showing the homeostatic immune system (**I_s**) disturbed by disease (**Dx**) and remedy (**Rx**) The line represents the totality of symptoms *n* expressed by I_s: to the right are disease symptoms; to left remedy "side effects"

conclude that *the remedy will NOT be effective in a non-material dose*, *as homeopathy claims*.

Conventional medicine has no concept of an all-pervading Vf. In homeopathy, the goal of treatment is to help the Vital Force to throw off the disease (e.g., as in the Vf gyroscopic model). In contrast, conventional medicine recognizes a homeostatic immune system: Its drug regimes, however, are less concerned with supporting it and more concerned with alleviating symptoms. In homeopathy, this is believed to be the cause of conventional drug side effects, as the Vf reacts against the drug's initial suppression of symptoms [24].

This situation in conventional medicine is represented simplistically by the force diagram in Fig. 15.5.

Here, a disease "vector" (**Dx**, dotted arrow to the right) acts on a homeostatic immune system "vector" (**Is**) by "deflecting" it to the right through angle φ. A drug "vector" is then prescribed (**Rx**, dotted arrow to the left) to alleviate symptoms, correcting the original angle of deflection, only to produce side effects, and a deflection in the opposite direction by angle θ.

It can be shown using a simplified mathematical derivation for the behavior of a homeostatic immune system under these circumstances, that:-

$$I_s = K(1 - \theta^2/2 + \theta^4/2.2! - \theta^6/2.3! \ldots)$$

Where K is a constant of integration. For low values of θ, this relationship approximates to:-

$$I_s = K(1 - \theta^2/2)$$

Which bears a close relationship to the equation above, $\cos k_2 \Delta S_2 \approx 1 - (k_2 \Delta S_2)^2/2!$. In other words, *the mathematical models used to represent the Vf and the homeostatic immune system deliver similar approximations for very low drug potency* (i.e., for values of $k_2 << 1$ when a remedy/drug exists in material molecular form: see nearly coincidental gently sloping gray and white lines in Fig. 15.6). Only when the remedy is becoming ultradiluted (as k_2 becomes substantial), according to these models, do the predictions of conventional medicine and homeopathy diverge.

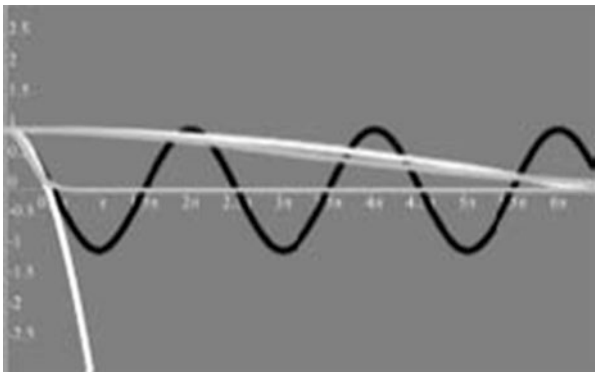

Fig. 15.6 Plots of the real part of $\Psi_{Rx} = e^{-ik_2\Delta S_2} = \cos k_2\Delta S_2 - i\sin k_2\Delta S_2$ ($k_2 = 1$; *black curve*), and $\Psi_{Rx} = \cos\ k_2\Delta S_2 \approx 1 - [k_2\Delta S_2]^2/2!$ ($k_2 = 1$; steep *white curve*: $k_2 = 0.075$; shallow *white curve*) and $I_s = K(1 - \theta^2/2 + \theta^4/2.2! - \theta^6/2.3!...)$ ($k_2\Delta S_2 \approx \theta$; $k_2 = 1$, steep *gray curve* flattening to 0: $k_2 = 0.005$; shallow *gray curve*)

Conclusion

In this paper, a model has been developed which depicts the Vf and potentised remedies as periodic wave functions. It turns out that at low potency (i.e., the remedy is at a physical material dose), these functions can be approximated in such a way as to lose their periodicity and therefore deliver predictions concerning the effects of highly diluted remedies that are in line with those of conventional medicine (i.e., they should have little or no effect).

In order to expand on this conclusion, another simple model was proposed, in which the conventional medical notion of a homeostatic immune system was treated as a simple force vector, deflected alternately by disease and remedy vectors. Thus, disturbance one way elicits symptoms of disease, while the disturbance the other way elicits symptoms of the remedy (i.e., "side effects."). The mathematical treatment of this simple model generates a solution whose interpretation is conventional medicine's prediction concerning the lack of efficacy of highly potentised substances. This, however, is the same prediction drawn from the Vf gyroscopic model concerning the efficacy of highly potentised remedies, when it is approximated to very low potency.

At this very early stage it might appear presumptuous, but parallels could be drawn here with the relationship between Newtonian and Einsteinian mechanics: The latter delivers the former when it is suitably approximated to velocities much smaller than light. Thus, Newton does not contradict Einstein: Rather, Newtonian mechanics is an approximation of Einsteinian mechanics, applicable at low velocities only. Similarly, it could be that there is no contradiction between conventional medicine and homeopathy: rather

(continued)

(continued)

conventional medicine may perhaps be better understood as an approximation of homeopathy when remedies are given at low potencies in material doses. Thus, although this is only a preliminary model based on several admittedly unproven assumptions, more sophisticated mathematical treatments than the ones presented here might in future provide a platform for the possible unification of conventional medicine with homeopathy. Given the increasing skepticism being directed at homeopathy, it would indeed prove ironic if eventually conventional medicine turned out to be a subset of a much broader paradigm that included homeopathy [28–30]!

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Chapter 16
Brain Reserve and Cognitive Training in the Elderly

Paraskevi Sakka

Given the precipitous forecast for dementia prevalence over the coming years, effective preventive strategies are of great importance.

Recent evidence linking mental activity and dementia risk invokes "brain reserve" as the mediating agent. 10–40 % of persons who satisfy post-mortem criteria for AD show no signs of cognitive impairment ante-mortem. Does brain reserve protect against amyloid load? Brain reserve has acquired several interpretations. The so-called hard version emphasizes a genetically based phenomenon, for example increased brain size or neural density. Another concept uses a "soft" analogy which is a flexible brain reserve compensating for neural dysfunction by motivating a great number of potential neural pathways. The latter, being the most reliable one, focuses on behavioural level by assessing frequency and range of participation in complex mental activities. Consequently, persons who have developed a wide spectrum of cognitive strategies for coping with complex problems perform very well in psychometric tests.

Many recent international cohort studies show an overall dementia risk reduction for high mental activity levels compared to low ones. Interestingly the effects of education, occupational complexity and cognitively active lifestyle are equally significant. However the question remains whether active lifestyle is a protective factor for dementia or low activity levels in fact represent an early symptom of insidious dementia.

There is a long history of studies investigating the effects of cognitive training in late life. Exercising on a specific cognitive task does improve performance in that task. But there is the issue of effect transfer and the challenge of effect durability. In recent years there are clinical trials indicating that advanced mental programmes

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can slow the decline not only in the trained mental domain but also in more general indices relevant to dementia.

Use of computer-based multi-component cognitive training allows for measurable and effective interventions for healthy and mild cognitively impaired elderly. Our team has developed such a computerized programme, SOCIABLE, which proved effective in improving and maintaining the cognitive abilities in three groups of elderly (cognitively intact, suffering from mild cognitive impairment and with mild Alzheimer's disease).

Chapter 17
Non-pharmacological Treatments for People with Dementia

Eleni S. Margioti

Worldwide, as a consequence of increased longevity, dementia prevalence is growing dramatically and Alzheimer's disease is considered the epidemic of the twenty-first century. Approved drugs for dementia exhibit moderate efficacy and offer temporary improvement to patients. Caregivers and medical professionals have been searching for more effective interventions.

Considering the difficulty in developing disease-modifying drugs for Alzheimer's disease and other forms of dementia, it might be time to think over the possibility of holistic approaches. The complementary and alternative medicine (CAM) for dementia includes off-label use of drugs, Chinese herbal medicine, food supplements, physical exercise, leisure activities, lifestyle, and non-pharmacological cognitive interventions.

The plasticity of the human brain is the main reason that explains the growing interest in non-pharmacological treatments for dementia. They are important because they maximize the positive outcome of pharmacotherapy, have no side effects, and are easily adjusted to individual and family needs.

In my presentation I will discuss the positive results of published randomized controlled studies of non-pharmacological interventions that have targeted the symptoms of dementia (cognitive stimulation therapy, cognitive training, cognitive rehabilitation, reminiscence therapy, physical activity, speech and language therapy, occupational therapy, interventions for families and caregivers). Other approaches like snoezelen/multisensory stimulation, reality orientation, bright light therapy, validation therapy, music therapy, aromatherapy, and animal-assisted therapy will also be briefly reported.

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Finally, I will present the results of a study conducted in our day care center for people with dementia in Athens. It is a multicomponent therapy consisting of various sessions such as cognitive enhancement, music, physical exercise, and computerized reminiscence. As expected, those who seem to benefit more from these therapies are people with mild cognitive impairment or people in the mild stage of dementia. Social and interpersonal skills are also improved and participants seem to be taking more initiative. Their mood has also been positively affected.

Given the encouraging outcome of these therapies, we believe more day care centers for people with dementia should be established so that more could benefit!

Chapter 18
SOCIABLE: A Surface Computing Platform Empowering Effective Cognitive Training for Healthy and Cognitively Impaired Elderly

Eva Danassi

SOCIABLE is a multinational, multicenter ICT project piloting a radically new approach for the support of mental activity of elderly people which builds upon novel perceptive mixed reality interfaces based on surface computing devices. A consortium of ICT and medical experts developed the cognitive training software targeting specific domains such as memory, attention, language, executive function, constructional praxis, logical reasoning, and orientation as well as affection and functional abilities. The project also included a back-office application facilitating medical experts in monitoring users' cognitive performance during the program and designing individualized sessions of increasing difficulties when needed.

We present the results of the SOCIABLE pilot clinical trial. 315 users from four European countries and seven pilot centers were assigned into three groups according to their performance in the neuropsychological assessment: (1) cognitively intact elderly, (2) elderly suffering from mild cognitive impairment (MCI), and (3) patients with mild Alzheimer's disease (AD).

They participated in 24-hourly, twice-weekly sessions of computerized cognitive training for 3 months, individually or in groups, in day care centers or at home. The equipment used consisted of a multi-touch Microsoft surface or all-in-one personal computers.

In order to assess the efficacy of the program, cognitive, affective, and functional assessment was performed pre- and post-intervention and 3 months after the end of the program (follow-up). In addition participants' performance was compared to that of a control group. The data collected were analyzed through a repeated measure analysis of variance 3×2 ANOVA with as within factor the assessment (0, 3, 6 months) and between factor the group (experimental vs. control).

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After the completion of the intervention, statistical significant improvement was observed in the score of most neuropsychological tests. Functionality was also improved, while depression scores remained unchanged. Improvement was maintained for 3 months after the end of the program for the group of the cognitively intact elderly and persons with MCI. The positive effects were not preserved in the group of AD patients.

It can be speculated that such a personalized and multicomponent training regime, like SOCIABLE, could be more effective in maintaining the cognitive abilities in the elderly than the classical approach. More research is needed through well-designed trials.

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