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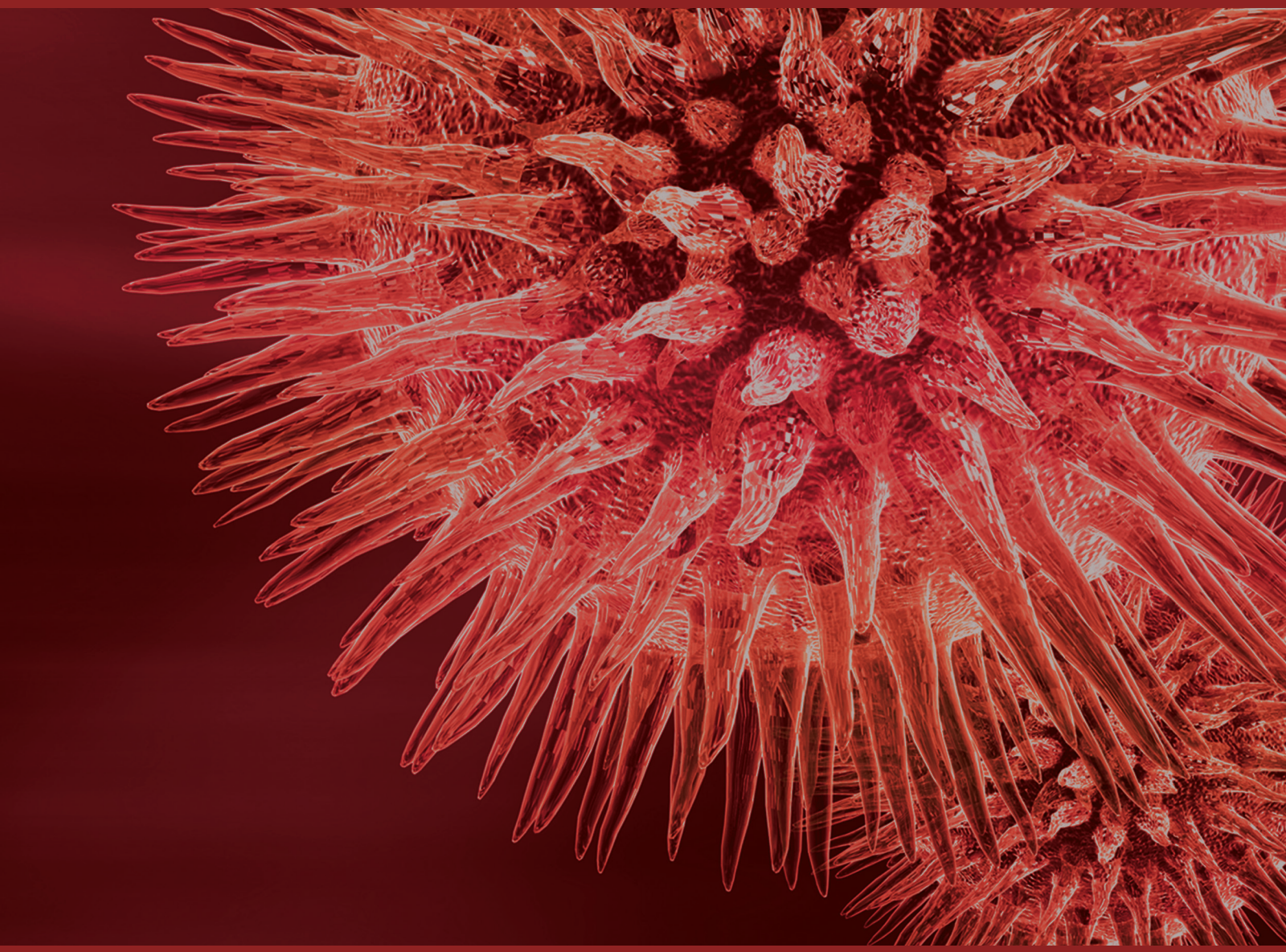
Successful Cognitive Aging: Between Functional Decline and Failure of Compensatory Mechanisms

Guest Editors: Slavica Krantic, Éric Boulanger, Bernard Mignotte, Emmanuel Moyse, and Charles Ramassamy



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Editorial

Successful Cognitive Aging: Between Functional Decline and Failure of Compensatory Mechanisms

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This special issue is focussed on the nature of "successful brain aging", as opposed to neuropathological cognitive defects, and the underlying compensatory mechanisms resulting in compensation of age-related dysfunctions in a homeostatic manner.

The biological definition of ageing posits that it consists of "a progressive accumulation of deleterious changes in cells and tissues that increase the risk of disease and death" [1]. For any attempt to assay the impact of aging *per se* on cognition in humans, the major problem lies in the selection criteria for subjects to be included in the study. "Disease-free" or "healthy" old subjects are recruited through public call to volunteers, after their appropriateness has been checked by assessment of the participants' general mental health via a battery of cognitive tests and cerebral MRI. However, it has to be stressed that, clinically, ageing *per se* is not a pathology; in other words, ageing is obligatorily normal. These considerations associated with the mean longevity in developed human societies led to introducing the following categorization among elderly people: young-old (6th-7th decades of age), middle-old (7th-8th decades), and oldest-old (above 85 years). The operational "generic" definition of "old subject" in geriatric medicine is nowadays "dependant or at risk of dependency"; it usually applies above 75 years.

To study the ageing on selected cohorts, two principal methods are used: transversal or longitudinal studies. The "transversal approach" implies comparison between aged and young subjects, as in laboratory animal studies of aging mechanisms at the cell and tissue level [2]. Old animals have the same genome and were bred in the same conditions as the young individuals and though constitute the control references with regard to the ageing process, which is obviously not the case for humans. Young subjects cannot be considered as controls for aging-related features of 50-year-older subjects. The life conditions of old subjects at youth differed from those of subjects recruited as the young controls by numerous aspects impacting health and cognitive performance (diet, war-related stress, cognitive training, and activity). According to the French hospital statistics indeed, the subjects admitted in geriatric departments in 1990 had a 15-year lower mean age and were less healthy than those admitted in 2015. This bias is known as the cohort effect. Therefore, the more accurate analysis of ageing relies on a "longitudinal approach" in a cohort of subjects, using regularly spaced examinations across the ageing duration, that is, two-three decades. This implies a progressive attrition of the studied cohort, because of personal moving, decease, and disease onset that causes the case exclusion. This is the bias of attrition known to select preferentially the less dependent persons. In summary, transversal methods tend to exaggerate the effect of ageing and longitudinal methods tend to minimize it.

To define the impact of ageing on cognitive functions, that is, the average evolution of cognitive performances "as

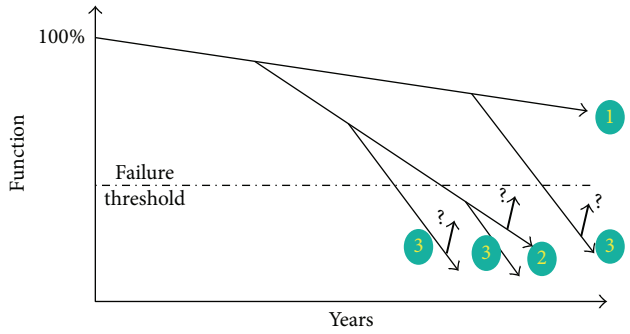

Figure 1

a function of chronological age in disease-free humans," which is frequently termed "across normal ageing," we need to define what is "normality" among old humans and especially with regard to cognition [3]. Ageing is commonly recognized to include a progressive decline of physiological efficiency in all organs, which can be schematized as a negative slope in the graphical plot of function index against age increase [4]. Medical observations show that, for all organs, clinical manifestations of deficiency appear when this slope crosses 30–50% of maximal (100%) values of optimal subject's functionality; this is termed "failure threshold." This may be also applicable to the nervous system. In Parkinson's disease thus, the first clinical symptoms seem to appear when 30–70% of the mesencephalic nigrostriatal dopamine neurons are lost [5]. These data suggest that the organs and functions encompass a functional reserve. However, the age-related negative slope of physiological functionality displays interindividual variations that are more and more expressed as chronological age advances. Some subjects in the sixties of age suffer much heavier physiological deficiencies than most of older ones. Therefore, a strictly chronological categorization of elderly humans is excessively reductionist. In particular, some subjects remain free of any chronic disease and display little or none physical or intellectual limitations up to advanced ages, which has been defined as "successful ageing" [6]. A more numerous part of elderly has some physical or intellectual limitations without real handicap and can be classified as "usual ageing."

To provide better comprehension of the complexity of an old individual, a French author proposed analysis of geriatric medical situations following a rule including 3 axes (see [7], Figure 1). Axis 1 represents the physiological ageing as a decline of the capacity to adaptation or reduction of a "static reserve" but this slope never attains the level of incapacity. Axis 2 represents the chronic diseases like Alzheimer's. This axis has a part upstream of the dotted line representing the deficiency (i.e., dementia in this case) which may correspond to the prodromal period of the Alzheimer's disease (AD). Axis 3 represents an affection (usually acute) which is totally ageing-independent but exacerbates the deleterious impact of factor 2. Regarding clinical studies of ageing impact on cognitive functions, since AD is usually diagnosed at late stages only, any group of "disease-free" aged subjects will include a number of prodromal AD patients whose memory performances are already weaker than healthy subjects. This fact strengthens the advantage of the longitudinal approach as compared to the transversal one.

Bouchon's axis 1 (Figure 1) can be influenced by genetic or environmental factors. Genetic factors include accumulation of genes that provide predisposition to longevity and though could be protective against cognitive decline across ageing. As a corollary, axis 1 may correspond to *the cognitive reserve concept*, which is born of observations demonstrating that some patients appear more resistant to the brain pathology, such as AD. Indeed, the dementia incidence is significantly lower in subjects with higher educational level and diplomas than in the general population [8]. Among the environmental factors affecting Bouchon's axis 1, longitudinal cohort study [8] indicated that the practice of leisure activities demanding planification, such as gardening, traveling, odd jobs, and knitting, decreases the risk of dementia [9]. This notion has been strengthened in the "Nun study" by correlating educational level with the results of regular neuropsychological tests [10]. It turned out that, in the global nun population, the cognitive impairment was significantly correlated with the severity of AD neuropathology, as quantified in postmortem brains by Braak's staging. By contrast, higher literary quality of autobiographies has been correlated with decreased risk of dementia [11]. However, a small subgroup displayed Braak's stages V-VI with intact memory and mild cognitive impairment, that is, AD histopathology in advance over cognitive decline, suggesting that these subjects (displaying the highest cognitive reserve) were spared [10]. An early and sustained practice of the most complex cognitive functions would thus allow building up reserves against ageing-related cognitive declines. In this light, cognitive reserve represents the capacity of individuals to resist cognitive alterations, including neuropathological ones. This concept has been further supported by a recent analysis of cognitive impairments among a population of AD patients [12]. This analysis indicated that when the cognitive reserve is weak, decline manifestations appear more progressively and slower than in subjects with high cognitive reserve [13], probably because in subjects with low cognitive reserve decline appears when lesion level is already very high. Obvious question is how to define and measure cognitive reserve for clinical purposes, how to achieve that most of people acquire the highest cognitive reserves, and how to prolong utilization of these reserves.

Bouchon's "factor 2" (Figure 1) reflects the breakpoint in the cognitive decline curve corresponding to clinically diagnosed AD, corresponding to around 70 years of age. This is precisely the age category that is currently increasing the most, according to demographic statistics [14]. The 70-year-old population encompasses a large proportion of subjects displaying *mild cognitive impairment* (MCI), that is, who complain about memory impairments but do not meet clinical criteria of AD in the absence of significant influence on daily living activities. Previous longitudinal studies have revealed that above 50% of MCI subjects convert into AD within 5 years, suggesting that MCI represents a predementia (or prodromal) stage of the disease rather than physiological ageing [15]. The chronological relationship between prodromal stage and demented stage of AD has been evaluated in

the PAQUID study [8]. Retrospective analysis performed in this study showed that subjects who had been diagnosed with dementia of AD displayed significant cognitive alterations (as compared to those without diagnosis of AD) around 13 years before the onset of clinically defined AD [16]. The remaining subjects of the cohort yielded a mean cognitive decline curve which was significantly different from the mean cognitive decline curve of the latent AD subpopulation. This led to updating AD concept and proposing a new set of diagnostic criteria for the research [17]. On these bases, any aged person who complains about memory deficits should be examined for biological diagnostic of MCI using CSF biomarkers or PET scan. Among the MCI patients that are identified as prodromal state of AD with the help of these new markers, those with high risk to develop AD are distinguished from those at lower risk by the highest cognitive reserve.

In keeping with Bouchon's rule, additional pathologies impinging on brain functions could precipitate the evolution from prodromal stage of AD to dementia. The majority of clinical dementia cases among elderly people are indeed accounted for by mixed brain pathologies rather than pure neuropathologies [18]. Bouchon's "factor 3" (Figure 1) in cognitive ageing corresponds to interference of acute pathologies (infectious, metabolic, traumatic, etc.) that render a person at the prodromal stage of AD more susceptible to experiment a delirium [19].

The contributions in this special issue deal with all of the above discussed aspects of aging. The contribution by M. Suwa et al. (Takatsuki Hospital, Osaka, Japon) discusses the predictive value of cerebral white matter intensity for cognitive impairment in neurologically "healthy" subjects displaying at least one atherosclerosis risk factor (age range 55–84 years) and how dietary intervention by sufficient polyunsaturated fatty acids intake may positively impact on the cognitive impairment. The work by Y. Os et al. from Maastricht University (Netherlands) focuses on cognitive intervention strategies and shows that these strategies change the brain activation process even in cognitively impaired persons; whether such cognitive interventions may be effective to delay conversion to dementia remains an open question. In a transversal study of neurologically "normal" young (18–35 years), mid-aged (36–55 years), and old (56–75 years) subjects, L. R. Demenescu et al. from the University Hospital of Aachen (Aachen, Germany) report how emotion recognition deficits emerge with increasing age. E. Bauer et al. from the University of Giessen (Giessen, Germany) and Evangelic Hospital (Bielefeld, Germany) assessed how the level of cognitive performance may impact on task load within left rostral prefrontal cortex; their data indicate that both parameters (age and performance level) affect the load-dependent activation within rostral prefrontal cortex. M. Silagi et al. (University of São Paulo "São Paulo, Brazil") present the evidence on the central mechanisms which compensate for the auditory deficits in sentence comprehension during the course of the normal aging. A.-M. Kirova et al. (Skidmore College, USA) highlight the mechanisms relevant to working memory and executive function decline across normal aging, MCI, and Alzheimer's disease. As the general light-motive of all these studies, it appears that cognitive ageing consists likely much more in a decrease of cognitive reserve than in functional losses.

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We would like to stress that this special issue would not have been possible without tight and fruitful collaboration between all guest editors. We are in particular indebted for the expertise, time, and help that Professors Bernard Mignotte, Charles Ramassamy, and Erick Le Bourg invested in this special issue.

Marc Verny
Emmanuel Moyse
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Research Article

Healthy Aging and Compensation of Sentence Comprehension Auditory Deficits

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Objectives. To analyze the effect of aging on sentence auditory comprehension and to study the relationship between this language skill and cognitive functions (attention, working memory, and executive functions). *Methods*. A total of 90 healthy subjects were divided into three groups: adults (50–59 years), young-old (60–69 years), and old-old (70–80 years). Subjects were assessed using the Revised Token Test. The measures used for performance analysis were number of correct answers (accuracy) and execution time of commands on the different subtests. *Results*. Regarding accuracy, groups showed similar performance on the first blocks, but the young-old and old-old performed worse than adults on blocks 9 and 10. With respect to execution time, groups differed from block 2 (i.e., the groups differed for all blocks, except for block 1), with the worst performance observed in the old-old group, followed by that of the young-old group. Therefore, the elderly required more time to attain performance similar to that of adults, showing that time measurements are more sensitive for detecting the effects of age. Sentence comprehension ability is correlated with cognitive test performance, especially for global cognition and working memory tests. *Conclusions*. Healthy aging is characterized by the ability to compensate for difficulties in linguistic processing, which allows the elderly to maintain functional communication.

1. Introduction

It is generally agreed that aging causes language disorders in the elderly, but this issue has not received sufficient research attention. With advancing age, disparities in cognitive performance and language among individuals increase. Studies have shown that the aging process causes heterogeneous changes in language and have sought to explain the reasons for the decline observed in certain functions and the sparing of others [1, 2].

There is extensive literature about changes in oral production with aging. It is known that vocabulary begins to decline starting at 50 years of age, whereas phonetic-phonological skills remain largely intact until very old age [3, 4]. Regarding language comprehension, a smaller number of investigations seeking to establish the effects on auditory processing deficits are observed. Auditory comprehension of sentences, especially of complex phrases, is an aging-related complaint [5], but the underlying causes of this decline and why some elderly subjects do not develop this deficit remains unclear.

Hearing deficits, both central and peripheral, are important factors to consider in language comprehension in the elderly [6, 7]. Moreover, the neural network of language comprehension processing is intrinsically related to other cognitive functions networks, such as working memory, attention, and executive function [8–10].

One of the mechanisms that could explain cognitive-linguistic heterogeneity manifested in normal elderly is cognitive reserve [11]. Brain networks are associated with cognitive reserve in adults, and compensation mechanisms can be observed in older elderly [12], as a result of the plasticity of the central nervous system [13].

Studies involving neuroimaging show inter- [14] and intrahemispheric reorganizations [15] associated with compensation during the aging process. Compensation becomes evident when images are correlated with stability or superiority of cognitive performance on several tasks, including language tasks [16].

One of the most widely used tests for assessing auditory sentence comprehension is the Token Test (TT) [17], which was devised to evaluate auditory memory and syntactic comprehension. The TT explores the ability to retain a significant number of items grouped into sections.

The TT has been the subject of several studies and is available in short versions [18–20], which have proven to be as effective as long versions for the detection of pathological conditions such as aphasia [18, 21–23] and neurodegenerative diseases [24–26].

Studies on the effects of sociodemographic variables in subjects without brain injury show a strong educational effect on performance in the TT, but the effect of aging is controversial, depending on the version of the test employed, the scoring system used, and the age range studied, with decline being most evident beyond 65 years of age [21, 27–30].

The study by Kim et al. [31] is notable for having used a response time measurement (measured from the end of the command until the initial touch of the piece, at natural speed) to verify the correlations between age and test performance, stating that these time measurements can be more sensitive for detecting the effects of aging.

Against this background, the main objective of this study was to compare the performance of adult, young-old, and old-old subjects in auditory sentence comprehension using the Revised Token Test (RTT) [22]. To study the effect of aging on this linguistic task, we used the number of correct answers (accuracy) and execution time of commands in the different subtests of the test.

An additional aim was to study the correlation of sentence comprehension ability with cognitive functions. The cognitive tests used for correlation with RTT were the Mini-Mental State Examination (MMSE) [32, 33] (global cognitive screening), semantic verbal fluency (FVS) [34] (semantic memory and executive functions), direct digit span [35] (attention and information storage capacity), and reverse digit span [35] (working memory and mind control for the operationalization of information).

The present study made differential use of the time measure and the execution time measure, because it is assumed to be more sensitive for detecting performance differences between age groups and allows researchers to observe the use of cognitive strategies for the implementation of full commands (manipulation of the tokens) and not only the timing between the giving of the command and the initial touch, for measuring the reaction time and response time. To the best of our knowledge, no studies using this form of time measurement for evaluating performance on the TT are available.

This study began with the hypothesis that auditory comprehension is a vulnerable skill in aging, but a subgroup of the healthy population retains performance similar to that of younger people. Elderly who maintain high performance do so through compensation mechanisms, which are related to the recruitment of cognitive functions that sustain language (e.g., attention, executive function, and working memory).

2. Materials and Methods

2.1. Ethics. This study is part of the larger project "Aging Maintaining Functions: elderly in the 2020s" run by the Department of Physical Therapy, Speech Therapy and Occupational Therapy, School of Medicine, University of São Paulo, Brazil. The study was supported by the National Council of Scientific and Technological Development (CNPq; process number 557887/2009-7) and was approved by the Research Ethics Committee of the University Hospital of the Medical School, University of São Paulo (registration CEP-HU/USP: 1005/10; SISNEP CAAE: 0034.0.198.000-10). After receiving complete information about the procedures, participants signed the consent form.

2.2. Participants. The study sample comprised 90 healthy subjects of both genders, aged 50 to 80 years, with over 5 years of formal education who were native Brazilian Portuguese speakers without cognitive complaints, with functional hearing and vision, with no motor deficits. Participants were equally divided into three groups according to age: Group 1, adults (50–59 years); Group 2, young-old (60–69 years); and Group 3, old-old (70–80 years).

2.2.1. Inclusion Criteria. To be eligible for study enrollment, participants had to meet the inclusion criteria for studies in neuropsychology described in the Mayo Older American Normative Studies (MOANS) [36]. These criteria primarily include an absence of cognitive complaints or psychiatric/neurologic disorders, no recent use of psychoactive drugs, and no alcohol dependence.

The subjects were submitted to cognitive tests and asked about communication functionality in everyday life. Inclusion in the study was conditional on obtaining scores consistent with normative values for the Brazilian population on the following tests:

(i) Mini-Mental State Examination (MMSE) [32, 33]: it is used for cognitive screening, with a minimum score of 25 points for individuals with 1–4 years of education, 26 points for 5–8 years, 28 points for over 8 years, and 29 points for over 11 years of education.

(ii) Adapted Cognitive Change Questionnaire (QMC) [37]: it includes questions about changes in performance of complex activities of daily living. The adopted cut-off score was 2 points.

(iii) Geriatric Depression Scale-15 [38, 39]: it is used to detect depressive symptoms that could impact cognitive performance. The adopted cut-off score was 5 points.

(iv) Functional Assessment of Communication Skills for Adults (ASHA-FACS) [40, 41]: the social communications domain was used for scoring. The test consists of 21 questions on the implementation of tasks independently, with different levels of assistance (minimum, minimum-moderate, moderate-maximum, and maximum) or impossibility of fulfillment. The final score is obtained by calculating the arithmetic mean of the scores attained on each question, with a maximum of 7 points.

All groups performed audiometric exams, with hearing thresholds of up to 40 dB horizontal line (HL) (at 500,

1000, and 2000 Hz), a symmetrical hearing configuration, and the presence of a V wave evoked with a click stimulus in the auditory brainstem response (ABR) (difference of up to 0.2 ms between the ears).

The subjects also underwent evaluations with an ophthalmologist and physiotherapist for exclusion of visual and motor abnormalities that may have compromised the tests run.

2.2.2. Exclusion Criteria. Subjects with scores below the cut-off score on cognitive tests, depressive symptoms, and other psychiatric or neurological disorders were excluded. Subjects who failed the auditory, visual, and motor tests were also removed from the sample.

2.3. Procedures

2.3.1. Revised Token Test (RTT). To compare the performance of adults, young-old, and old-old subjects auditory sentence comprehension, we used the Brazilian Portuguese version of the RTT. The test consists of 50 commands grouped into ten sections. The task entailed manipulating tokens of different shapes, sizes, and colors: 20 tokens of five different colors (blue, red, green, white, and black), two formats (squares and circles), and two sizes (small and large).

Semantic content and cultural factors are minimized because the requested information is reduced to the size, shape, and color of the tokens.

However, there are a progressive number of requests, and extent of information, in order to recruit working memory. Subtests 1 to 4 have simple and composite imperative statements that assess understanding of color, size, and shape. Subtests 5 to 8 require comprehension of prepositions related to visual-spatial content in the handling of one part (active part) over another (inactive part). In the last two subtests (9, 10), there is an increase in both information and linguistic complexity by introducing prepositional phrases, adverbial clauses, and compound sentences combined in heterogeneous commands on many dimensions, as shown in Table 1. Adequate performance of commands requires the cognitive support of attention, working memory, executive function skills, and language processing at different levels [22].

The test was applied individually in a quiet environment, as recommended in the original manual. Pretest instructions were given to familiarize the subjects with the concepts of color, shape, and size. All commands were given aloud by a speech therapist experienced in language assessment who was a native speaker of Brazilian Portuguese.

The commands were given at a normal speech rate for Brazilians living in São Paulo [42] and at an intensity of 60–70 dB sound pressure level (SPL) or approximately 50 dB hearing level (HL). Regarding prosody, the presentation of each unit in each command had no special inflection or pauses between units; that is, the prosodic features (speed, fluency, emphasis, intonation, and articulation) were constant across commands.

2.3.2. Cognitive Evaluation. To study the relationship between cognitive functions and sentence comprehension ability, the score and the total execution time in the RTT were correlated with the following tests:

Table 1: Examples of the complexity of RTT commands in each block.

Block	Examples
1	Touch the black circle
2	Touch the big green circle
3	Touch the green square and the black square
4	Touch the big green square and the little black square
5	Put the black circle above the white square
6	Put the big red square in front of the big white circle
7	Put the black circle to the left of the white square
8	Put the little green circle to the left of the big red square
9	Instead of the green square, touch the black square
10	Touch the big black square unless you have touched the little red circle

(i) Mini-Mental State Examination (MMSE) [32, 33]: it is used for cognitive screening. The examination presents temporal and spatial orientation, immediate memory, attention and calculation, delayed recall, language (reading, writing, naming, and repetition) subtests, and design copy for assessing visuospatial skills.

(ii) Semantic verbal fluency (FVS), animal category [34]: it evaluates semantic memory and executive functions. Subjects were instructed to list as many animals as they could in one minute.

(iii) Digit span in direct and reverse order [35]: the subjects should repeat increasing sequences of numbers in direct and reverse order. The direct sequence evaluates attention and information storage capacity, whereas the reverse sequence assesses working memory and mind control for the operationalization of information.

2.4. Data Analysis. Performance on the RTT was analyzed with respect to number of correct answers (accuracy) and execution time of commands. For number of correct answers, one point was awarded for each correct answer. The analysis considered the sum of correct answers under the total score and on each subtest. The analysis of execution time (time difference between end of command and full completion of action: touching or manipulating the pieces) was timed and measured in seconds. The analysis considered the sum of the times taken on each block and the total time.

For descriptive analysis, means and standard deviations of all demographic variables and performance on cognitive tests and on the RTT for the three age groups were calculated. Comparison of means for continuous data was performed using one-way ANOVA, given the Gaussian distribution of the data. When the difference between groups was statistically significant, a post hoc (Bonferroni) test was applied for pairwise comparison.

Table 2: Demographic and cognitive characteristics of the sample.

Variable	Group 1 mean (SD)	Group 2 mean (SD)	Group 3 mean (SD)	p value	Multiple comparisons (<0.05)
Age	54.3 (3.3)	64.3 (3.1)	74.3 (5.4)	<0.001*	G1 × G2 × G3
Education	10.9 (3.5)	10.8 (3.5)	10.8 (3.8)	0.991	ns
Gender					
M	5	10	7	0.530	ns
F	19	14	17		
MMSE	28 (1.1)	27.5 (1.8)	27.7 (1.7)	0.511	ns
CCQ	0.2 (0.5)	0.1 (0.3)	0.4 (1.0)	0.584	ns
GDS	1.8 (1.4)	1.3 (1.2)	1.2 (1.0)	0.214	ns
SVF	17.4 (5.2)	16.6 (4.7)	17.7 (3.8)	0.691	ns
DS-DO	5.6 (1.3)	5.6 (0.9)	5.8 (0.9)	0.670	ns
DS-RO	3.5 (1.1)	3.5 (0.9)	4.0 (1.4)	0.603	ns
ASHA-FACS	6.9 (0.0)	6.9 (0.0)	6.9 (0.0)	0.252	ns

SD = standard deviation; F = female; M = male; MMSE = Mini-Mental State Examination; CCQ = Cognitive Change Questionnaire; GDS = Geriatric Depression Scale; SVF = semantic verbal fluency; DS-DO = digit span in direct order; DS-RO = digit span in reverse order; ASHA-FACS = Functional Assessment of Communication Skills for Adults.
*Statistically significant difference.

Table 3: Performance of groups on the RTT as measured by number of correct answers (accuracy).

Subtest	Group 1 mean (SD)	Group 2 mean (SD)	Group 3 mean (SD)	p value	Multiple comparisons (<0.05)
1	5.0 (0.0)	4.8 (0.6)	5.0 (0.0)	0.199	ns
2	4.9 (0.2)	4.7 (0.7)	4.8 (0.5)	0.596	ns
3	4.7 (0.6)	4.8 (0.3)	5.0 (0.0)	0.051	ns
4	4.6 (0.9)	4.7 (0.5)	4.6 (0.5)	0.778	ns
5	4.4 (0.9)	4.2 (1.1)	4.2 (1.0)	0.726	ns
6	4.0 (1.1)	3.9 (1.4)	3.8 (1.0)	0.843	ns
7	4.5 (0.7)	4.2 (1.1)	4.5 (0.6)	0.520	ns
8	4.2 (1.3)	4.1 (1.0)	4.1 (1.1)	0.972	ns
9	4.2 (0.5)	3.6 (0.7)	3.3 (0.8)	<0.001*	G1 × G2 G1 × G3
10	3.8 (1.0)	3.1 (1.3)	2.8 (1.4)	0.024*	G1 × G2 G1 × G3
Total	44.5 (5.0)	42.6 (5.4)	42.4 (4.8)	0.319	ns

SD = standard deviation.
*Statistically significant difference.

The distribution of subgroups according to gender was compared by Pearson's chi-square test. Pearson's coefficient was calculated to determine the association between performance on the RTT and cognitive performance. The same test was also used to verify the correlation between number of correct answers and execution time on the RTT.

A 5% level of statistical significance was adopted for all analyses. Analyses were performed using the statistical software program BIOESTAT 5.0 [43].

3. Results

3.1. Demographic, Cognitive, and Communicative Functionality Characteristics. The demographic characteristics of the sample and performance on the cognitive tests are presented in Table 2. All groups differed with respect to age, but there was no statistically significant difference for the other variables, including education, which shows that the groups were well matched and homogeneous, allowing for the observation of aging effects.

3.2. Age Effect on RTT: Number of Correct Answers (Accuracy) and Execution Time. The performance of the groups, as measured by the number of correct answers on each subtest and total RTT, is presented in Table 3. All groups showed similar performance on most subtests (1 to 8), but adults differed from young and old-old on the last two subtests (9 and 10).

Table 4 shows the performance of the groups regarding execution time for each subtest and for the total test. The groups showed similar performance on subtest 1. The old-old group required a significantly longer time to perform

Table 4: Performance of groups on the RTT as measured by execution time.

Subtest	Group 1 mean (SD)	Group 2 mean (SD)	Group 3 mean (SD)	p value	Multiple comparisons (<0.05)
1	3.7 (2.1)	6.4 (4.2)	7.5 (4.6)	0.057	ns
2	5.1 (2.2)	7.0 (3.3)	9.2 (6.1)	0.006*	G1 × G3 G2 × G3
3	6.4 (3.5)	9.4 (7.5)	11.2 (7.9)	0.047*	G1 × G3
4	9.7 (4.9)	11.7 (8.1)	14.1 (6.6)	0.048*	G1 × G3
5	23.1 (7.7)	28.5 (10.6)	31.3 (11.1)	0.017*	G1 × G2 G1 × G3
6	26.2 (7.0)	30.8 (10.2)	37.5 (13.9)	0.002*	G1 × G3 G2 × G3
7	20.3 (7.0)	24.0 (10.3)	26.9 (8.0)	0.034*	G1 × G3
8	18.4 (8.0)	33.4 (11.5)	33.7 (9.7)	0.018*	G1 × G2 G1 × G3
9	15.6 (8.5)	22.1 (10.0)	24.7 (9.2)	0.003*	G1 × G2 G1 × G3
10	18.8 (10.1)	23.2 (8.5)	25.4 (8.4)	0.047*	G1 × G3
Total	148.7 (37.4)	190.1 (52.1)	211.9 (55.4)	0.002*	G1 × G2 G1 × G3

SD = standard deviation.
*Statistically significant difference.

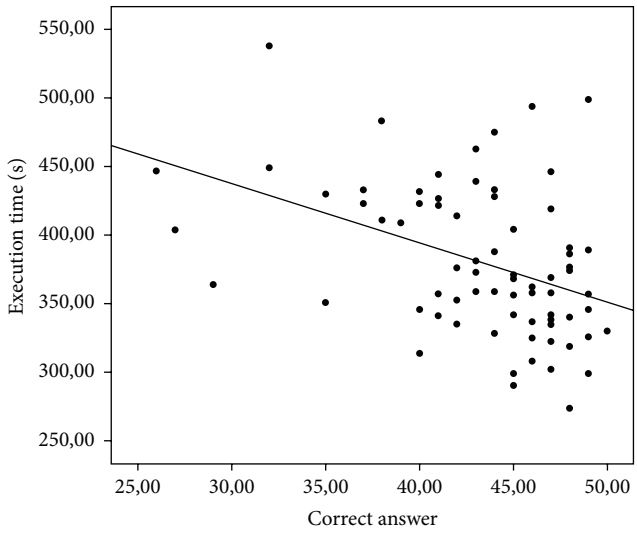

Figure 1: Correlation between number of correct answers (accuracy) and execution time on each RTT subtests.

the RTT test than did the young-old and adult groups. The old-old subjects differed from adults on all subtests (except for subtest 1) and from the young-old on subtests 2 and 6. The young-old group showed a longer execution time than adults on subtests 5, 8, and 9 and a longer total time.

Although the number of correct answers did not differentiate the groups with respect to total score, Pearson's correlation coefficient revealed that the variable number of correct answers had a statistically significant negative correlation with execution time ($p < 0.001$); that is, the longer the execution time, the lower the number of correct answers on the test, as shown in Figure 1.

Table 5: Correlations between performance on RTT and cognitive test performance.

	Performance on RTT	
	Total correct answers	Total execution time
MMSE	$r = 0.344$ ($p = 0.003$)*	$r = -0.102$ ($p = 0.392$)
SVF	$r = 0.157$ ($p = 0.186$)	$r = -0.114$ ($p = 0.336$)
DS-DO	$r = 0.308$ ($p = 0.008$)*	$r = -0.089$ ($p = 0.456$)
DS-RO	$r = 0.400$ ($p = 0.005$)*	$r = -0.022$ ($p = 0.853$)

MMSE = Mini-Mental State Examination; SVF = semantic verbal fluency; DS-DO = digit span in direct order; DS-RO = digit span in reverse order.
*Statistically significant difference.

3.3. Correlations between Performance on RTT and Cognitive Tests. Although the three groups exhibited no differences in education, in MMSE, or on the communication functionality questionnaire, some variables were correlated with group performance as a whole on the RTT, as shown in Table 5. There was a significant correlation between total number of correct answers on the RTT and MMSE score, digit span in direct and reverse order, and education (positive correlations).

4. Discussion

The results of this study show an age effect on auditory sentence comprehension, only for more complex commands. For number of correct answers, the groups exhibited similar performance, differing only on the last two subtests (adults performed better than the young-old and the old-old). However, the measurement of execution time differentiated the groups with respect to subtest 2. In general, the time required to complete the task increased with age. Additionally, there

was a correlation between the number of total correct answers on the RTT, education, and performance on the cognitive tests: MMSE (global cognitive measures), direct digit span (attention), and reverse digit span (working memory).

The differentiation of the groups based on the number of correct answers on subtests 9 and 10 shows the increased burden of working memory in these blocks, such as increasing linguistic (syntactic) complexity by introducing a variety of grammatical constructions into statements. The results showed a reduction in performance (lower scores and longer execution time) proportional to the increase in the extent and syntactic complexity of the stimulus.

One of the most important abilities required to understand longer utterances is working memory, which stores verbal information, allows for comprehension of speech sequences, and organizes responses [8, 9]. According to McNeil and Prescott [22], the RTT provides a direct measure of short-term memory, especially the phonological loop of working memory, comprehension of various types of sentences and their transformations, and understanding of specific vocabulary and certain semantic relations (conditional phrases).

According to the language model proposed by Shalom and Poeppel [44], language processing can be divided into three main processes: analysis, storage, and synthesis, which require the involvement of large brain networks. All three processes appear to be linked to performance on the RTT because the test commands must be analyzed, interpreted based on phonological, syntactic, and semantic processes, and summarized using motor output (which requires visuospatial analysis, planning, coordination, and working memory), perhaps explaining the correlations with cognitive test performance.

A number of studies have consistently shown a decline in working memory with age and how this skill can interfere with the performance of language comprehension tasks [9, 45, 46]. Aging may affect the ability to process large amounts of information, a difficulty that may require additional strategies when applying concurrent tasks, such as listening and manipulating elements [47].

One explanation for the equivalence of the performance of older adults is that they have realized compensation because the working memory (also evaluated in the RTT) is extremely vulnerable to aging. In our study, even the old-old adults showed scores similar to those of adults.

A feature of the RTT is that it allows information to be grouped into meaning units (chunks) for retention and command execution. According to Gilchrist et al. [10], in retention tasks, words tend to be grouped; they are not processed separately, and the same applies to the retaining command of the propositions. In the case of the TT, commands gather propositions whose words are composed in an unpredictable way and therefore do not allow for clustering; there is no syntactic or semantic plausibility. Thus, the words are processed as separate items, which burdens the working memory.

Results reported in the literature regarding the effects of aging on the accuracy of responses on the TT are conflicting. Wertz et al. [21] applied only part 5 of the TT and found a correlation with age and a gradual decline in performance after age of 40. Emery [27] observed a decline in individuals aged 30–93 years, with lower scores in the elderly (75–93 years). By contrast, Peña-Casanova et al. [28] evaluated subjects between 50 and 94 years of age and found little effect of age on TT performance. Snitz et al. [29] assessed elderly over 65 years and showed that performance on the Indiana University version of the TT was associated with younger age. Yang et al. [30] showed that seniors aged 65 years and older performed worse on the TT than did other groups.

The conflicting data can be explained by the different scoring systems used and different age groups studied. With respect to an analysis of execution time on the RTT, the elderly required more time to process information and compensate for possible auditory processing difficulties but exhibited similar results to adults regarding the number of correct answers for the majority of the test.

In this respect, Kim et al. [31] argued that the binary scoring system of hit-error (accuracy) used in scoring the TT is not sensitive enough to detect the effect of aging and established a performance measurement based on response time rather than accuracy. The authors found significant correlations with age above 65 years and noted that time measures can be more sensitive for measuring differences in verbal comprehension in this population.

The facilitation of auditory comprehension, particularly when there is more time to engage the compensation mechanism for signal processing deficit to perform tasks related to this language skill, corroborates data reported in the literature [16].

Similar compensations were observed in studies involving functional magnetic resonance imaging, where performance in sentence comprehension was associated with brain activity in certain areas. Older people, who exhibited similar performance to young people, showed additional activity in those areas where activity is typically found in young people. The elderly activated areas of the right hemisphere related to articulatory recapitulation of the phonological loop [15]. The present study provides evidence for this same phenomenon in the elderly subjects assessed. Therefore, it should be recognized that some aspects of the functioning of working memory resist aging-related loss, such as those related to vocal and subvocal rehearsal, and can support compensation for sentence comprehension.

Similarly, our results show that measures of time, especially execution time, are more sensitive for consistently detecting the effects of aging, regardless of hit analysis (binary or multidimensional), and the differences are evident even in young elderly (from 60 years). The fact that elderly required more time to complete the task but showed similar performance to younger individuals in subtests 1 to 8 of the RTT, which contained commands with simple or coordinated propositions, suggests the integrity of less complex syntactic processes [22].

Aging compensation mechanisms are related to cognitive reserve. Cognitive reserve theory recognizes that factors such as education, parental education, occupation, and reading habits may help maintain the performance of the elderly, particularly, naming, grammar comprehension,

and vocabulary tasks [11]. Among these factors, education is highlighted because it is closely related to working memory skills [48] and recruited in the comprehension of syntactically complex sentences. [11]. It is possible that the education factor has provided the elderly maintenance skills necessary for the performance of the RTT, although they needed an increased runtime strategy.

The RTT has been an interesting tool to study the effect of aging on the auditory sentence comprehension. The addition of temporal measures and the correlation with other cognitive tests can refine the reasoning about the underlying processes of syntactic comprehension. This perspective indicates the need for additional studies.

Moreover, the analysis of execution time helps inform the possibilities for cognitive stimulation in the elderly, such as the development of programs related to processing in temporal aspects of working memory.

The main limitation of this study was the absence of reaction time analysis, computerized records, or even videos that allow for qualitative and quantitative refinement of observations such as the nature of test errors. Another important limitation was the absence of functional imaging studies to confirm and describe the nature of the compensation processes.

This study raises the prospect of further investigations, such as studies on the relationship between performance on the RTT and other language parameters, for example, naming, repetition, and written language.

5. Conclusions

Young-old and old-old subjects showed similar performance to adults in auditory comprehension task as measured by the number of correct answers on RTT, while differing from adults on the last two subtests. However, elderly required more time to respond to commands. This behavior shows that the execution time measurement is sensitive for detecting the effects of age. Sentence comprehension ability was correlated with performance on cognitive tests, particularly, attention and working memory. Healthy aging is characterized by the ability to compensate for difficulties in linguistic processing, which allows the elderly to maintain normal function in everyday life situations.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

Authors' Contribution

The authors contributed equally to this paper.

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Research Article

Neural Processing of Emotional Prosody across the Adult Lifespan

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Emotion recognition deficits emerge with the increasing age, in particular, a decline in the identification of sadness. However, little is known about the age-related changes of emotion processing in sensory, affective, and executive brain areas. This functional magnetic resonance imaging (fMRI) study investigated neural correlates of auditory processing of prosody across adult lifespan. Unattended detection of emotional prosody changes was assessed in 21 young (age range: 18–35 years), 19 middle-aged (age range: 36–55 years), and 15 older (age range: 56–75 years) adults. Pseudowords uttered with neutral prosody were standards in an oddball paradigm with angry, sad, happy, and gender deviants (total 20% deviants). Changes in emotional prosody and voice gender elicited bilateral superior temporal gyri (STG) responses reflecting automatic encoding of prosody. At the right STG, responses to sad deviants decreased linearly with age, whereas happy events exhibited a nonlinear relationship. In contrast to behavioral data, no age by sex interaction emerged on the neural networks. The aging decline of emotion processing of prosodic cues emerges already at an early automatic stage of information processing at the level of the auditory cortex. However, top-down modulation may lead to an additional perceptional bias, for example, towards positive stimuli, and may depend on context factors such as the listener's sex.

1. Introduction

During adulthood, emotion recognition ability declines with advancing age. This process is independent of stimulus modality, that is, visual, auditory, and bodily expression modalities [1–5]. The decline is more pronounced for negative emotions, while the ability to discriminate positive emotions was preserved over age [6]. The neural correlates of this aging process and contributions from sensory processes are little known.

Only few studies examined age-related changes at the neural level of automatic processing of emotions, and the findings are inconsistent. In a combined functional magnetic resonance imaging (fMRI) and event-related potentials (ERP) study by Williams and colleagues [7], no significant age-related changes in the temporooccipital components emerged, suggesting preservation of emotional facial encoding across lifespan. Using a go/no go task with positive, negative, and neutral facial expressions (task irrelevant stimulation), Hilimire et al. [8] found pronounced early negativity at occipital sites and positivity at frontocentral sites to positive emotions in older adults. In young adults, a similar pattern emerged for negative emotions. The authors concluded that aging is characterized by enhanced early processing of positive emotions [8].

Indeed, most research on the aging of emotion processing focused on facial expressions; for example, see [8–11]. Less is known about age-related changes underlying automatic encoding of emotion within the auditory modality and, in particular, their neural correlates. The present study

Figure 1: Illustration of the experimental design. In a passive oddball design, standard stimuli were applied, that is, a random dissyllabic utterances from female speakers in a neutral voice. Twenty percent of the stimuli were deviant events, that is, either sad, happy, angry, or male utterances. SOA: stimulus onset asynchrony.

investigated the effect of aging on the neural response of automatic processing of prosody change detection using an oddball paradigm, that is, mismatch responses [12, 13]. In this fMRI variant of mismatch negativity [14, 15], participants were presented with deviant events (emotions and gender neutral prosody) embedded in a stream of standard sounds (female voice with neutral prosody), while they were watching a silent movie [16]. Due to the reported decline of the recognition of negative emotions in aging adults, we studied encoding of negative prosody at early sensory level across different age groups. Although, some studies reported reduced response in the elderly [9, 17, 18] suggesting reduced encoding of negative emotions, others reported no significant difference to negative emotions [19] or novel faces [20]. We hypothesized that responses to negative prosody at the superior temporal gyrus (STG) will decrease over age (hypothesis 1). Positive emotion recognition has been found preserved across aging [6]. According to the positivity bias hypothesis [8], we expected even increasing responses to positive deviants with age (hypothesis 2). Finally, women detected emotional cues better than men [21–23] and their ability to discriminate emotions was preserved with aging [5]. Thus, we hypothesized an age by sex interaction with reduced response amplitudes to prosodic cues in older men compared to women (hypothesis 3).

2. Materials and Methods

2.1. Participants. Fifty-nine participants were recruited through advertisement in a local newspaper and at RWTH Aachen. Two participants were subsequently excluded due to a low response rate (two or less answers) in the auditory screening test and two more at the participants' request. The participants were recruited for three age groups: young (age range 18–35 years), middle-aged (36–55 years), and older adults (56–75 years). Inclusion criteria were age range 18–75 years, no psychiatric and neurological disorders, no MRI contraindication, normal or corrected to normal visual and auditory acuity, and native German speaker. We used cutoff at the age of 75 because the prevalence of hearing loss increases for older subjects in 50–80% of the population [24]. Also, accumulating MRI contraindications may render the older sample nonrepresentative. Each participant completed a screening test for hearing ability, in which pure tones of 430, 2000, and 4096 Hz were presented to either left or right ear with varying intensity (software Presentation v14.2, http://www.neurobs.com/ [5]). Correct source localization indicated intact hearing. Structured Clinical Interview for DSM-IV German version (SKID-PIT Light [25]) screened for the presence of any Axis-I disorder. Edinburgh Handedness Inventory [26] assessed hand preference. Except for one participant who was ambidextrous, all the others were right-handed. The current affective state was assessed with Positive and Negative Affect Schedule (PANAS [27]) and depressive symptom with the Beck Depression Inventory revised version II (BDI II [28]).

The local ethical committee approved the study and it was performed accordingly to the Declaration of Helsinki. All participants gave written informed consent after receiving a full explanation of the experiment.

2.2. Stimuli and Design. Disyllabic pseudowords created following German phonological rules, spoken by one female and one male speech therapists, were selected from a validated database [16], based on accuracy rates (>80%). These pseudowords were spoken with angry, happy, sad, and neutral prosody. Stimuli were normalized to the same peak intensity. We chose happiness as the positive basic emotion and anger as the negative emotion with comparable arousal. The second negative emotion, sadness, was added as low arousal emotion comparable to the neutral condition.

We employed a passive oddball paradigm with 80% standard (frequent) stimuli and 20% deviants. Standard stimuli were pseudowords uttered by female neutral voice. Deviants were pseudowords uttered with either angry, sad, and happy prosody by a female voice or neutral prosody by a male voice (gender deviant). Stimuli were presented binaurally in a randomized sequence, although controlling that one deviant type was not presented twice one after each other and that there were minimum two and maximum nine standards between two deviants. Stimulus onset asynchrony (SOA) was 1.2 seconds (Figure 1). Two runs were conducted in 8 minutes and 80 seconds each with 400 stimuli presented per run. We used Presentation v14.2 (http://www.neurobs.com/) program for stimuli delivery and experimental control. Sound loudness was individually adjusted at the beginning of the scanning. A silent movie was presented during audiostimulus presentation. These movies were cut from a nature documentary ("Earth," 2007, Disneynature), so that they will have a neutral content. Participants were instructed to pay attention to the movie and to try to ignore the sounds. To ensure that participants will direct their attention toward the movie, they were told that at the end of the scanning they completed a short questionnaire about these movies. Thus, participants

were required to rate the emotion induced by these movies using a 5-point Likert-like scale where 1 was very negative, 3 was neutral, and 5 was very positive.

2.3. Behavioral Testing. After functional imaging of the oddball paradigm, participants performed a prosodic emotion recognition task employing angry, happy, sad, fearful, disgusted, and neutral utterances. 108 different stimuli were selected from the same database [16] and presented in a random order. Three male and three female speakers were selected, yielding 18 stimuli for each emotional category. Stimulus length was normalized to 700 ms. The interval between two successive stimuli was maximum 8 seconds or until a response was given. Participants selected one of the response keys that best described the emotion uttered. The six emotion labels were continuously displayed on the screen.

Emotion recognition data analysis was performed in SPSS 10.0.0 (SPSS Inc., Chicago, Illinois, http://www.spss.co.in/). Missing responses were excluded from the analysis. Repeated measurement analysis of variance was conducted testing for group effect on the reaction time. Accuracy was a categorical variable (true/false) and analyzed using a Generalized Linear Model (binary response with a probit link function; Wald chi-squared test) with emotion and age-group as predictors. We repeated the analysis examining for a sex effect with sex and age-group defined as between-subject factors and emotion defined as within-subject factor. In case a significant effect was observed, post hoc tests were conducted using Bonferroni correction. The significance level was set to $p < 0.05$ and estimated marginal means (EMM) and standard errors (SE) are reported.

2.4. fMRI Data Acquisition and Analysis. Neuroimaging data were acquired on a 3-Tesla MAGNETOM Trio MR Scanner (Siemens, Erlangen, Germany) using a 12-channel head coil. Functional images were acquired in the axial plan using T2*-weighted gradient echoplanar image (EPI) with repetition time (TR) being 2000 ms, echo time (TE) being 28 ms, flip angle being 77 degrees, matrix size being 64 × 64, voxel size being 3 × 3 mm, slice thickness being 3 mm, slice gap being 3.75 mm, 34 slices, and field of view being 192 × 192 mm. Two functional runs were conducted and each run comprised a total of 250 volumes. A high-resolution anatomical scan was acquired using a T1-weighted 3D sequence (TE = 2.52 ms; TR = 1900 ms; TI = 900 ms; flip angle = 9°; FOV: 256 × 256 mm^2; 1 mm isotropic voxels; 176 sagittal slices).

Prior to analysis, structural and functional data were visually inspected to ensure that no gross artifacts were present. Data preprocessing and analysis were performed using Statistical Parametric Mapping (SPM8, Welcome Department of Cognitive Neurology, UK, http://www.fil.ion.ucl.ac.uk/) implemented in MATLAB 7.10. The first nine volumes of each functional session were discarded to ensure signal stabilization. Functional images were slice timing corrected; realigned to the first volume of the first session to correct for within- and between-sessions motion; coregistered to the anatomical image; normalized into Montreal Neurological Institute (MNI) space using an affine fourth-degree b-spline interpolation transformation, and resliced with a resolution of 3 × 3 × 3 mm. Movement parameters for each participant were inspected using an exclusion criterion of more than 3 mm or 3-degree rotation in any direction. Finally, functional images were spatially smoothed with an 8 mm full width at half maximum Gaussian kernel.

First level analysis employed the general linear model in an event-related design. Each deviant was modeled as a stick function convolved with the canonical hemodynamic response function (HRF) and its temporal derivative (TD) as implemented in SPM8. Separated regressors were created for each deviant type. Standard stimuli were implicitly modeled in the design. Statistical parametric maps for the HRF and the TD were generated using *t*-tests to identify regions activated during each deviant type, that is, anger, happiness, sadness, and gender, relative to the standard (frequent) stimuli.

Second level analysis, first, investigated global changes in response amplitudes with age. Therefore, regression analysis assess tested a linear effect of age on the neural response to the different deviant responses. Second, to investigate nonlinear and hemodynamic effects, the contrasts entered into a mixed-model analysis of variance with deviant type and basis functions (HRF and TD) defined as within-subject factor and age-group defined as between-subjects factor. The factor depicting basis functions was defined as a two-level factor with unequal variance across the levels and sphericity not assumed. Further, we tested for a sex effect employing a two-way analysis of variance with sex and age-group defined as between-subjects factors and basis functions defined as within-subject factor for each deviant type.

Significant threshold for the main effects was set to $p < 0.05$ after family-wise error (FWE) correction for multiple comparisons across the whole brain. *F*-tests assessed interactions of group by deviant type (on HRF only) and group by deviant by basis functions. To test for group effects, the FWE correction was applied to the region of interest (ROI) encompassing bilateral superior temporal lobe including the auditory cortices (bSTL; WFU-Pickatlas [29]).

Voxel-based morphometry implemented in VBM8 toolbox with default parameters controlled for age-related structural changes on differences in hemodynamic responses. The high-resolution T1 images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and nonlinear transformation ("warping" [30]). The gray matter maps were smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum. The total brain volume (TBV) was calculated as the sum of gray matter and white matter density extracted from the segmented images and entered as a linear covariate of no interest in the mixed-effect model as described above. Due to group difference on years of education and depressive symptoms, we repeated the mixed-effect model analysis controlling for BDI scores, years of education, and TBV.

3. Results

3.1. Demography and Neuropsychology. Table 1 displays the characteristics of the groups. A group effect was found on

Table 1: Demographics and neuropsychology.

	Young adults (18–35 yrs; $n = 21$)	Middle-aged adults (36–55 yrs; $n = 19$)	Older adults (>55 yrs; $n = 15$)
Age	26.62 (3.48)	47.26 (4.86)	61.33 (5.75)
Females (%)	52	53	40
Right-handed (%)	100	96	100
Years of education	17.29 (1.79)	14.68 (3.45)	11.53 (2.72)*
BDI[1]	1.14 (1.88)	2.56 (2.64)	3.20 (2.76)*
PANAS[2]	19.17 (6.63)	13.47 (5.36)	17.27 (10.03)
Movies' rating	3.5 (0.55)	3.77 (0.83)	3.26 (0.56)
TBV[3]	1.60 (0.17)	1.53 (0.13)	1.47 (0.09)*

Notes. [1]Beck Depression Inventory; [2]Positive Affect and Negative Affect Scale (global score); [3]total Brain Volume; yrs = years of age. Means (standard deviations) or percentages (%) are presented. Stars (∗) indicate significant difference between groups ($p < 0.05$).

Table 2: Behavioral data of prosody recognition.

	Young adults (18–35 yrs; $n = 21$)	Middle-aged adults (36–55 yrs; $n = 19$)	Older adults (>55 yrs; $n = 15$)
RT mean ± standard deviation			
RT angry (sec)	2.04 ± 0.40	2.43 ± 0.59	2.91 ± 0.61
RT fearful (sec)	2.44 ± 0.36	2.63 ± 0.50	3.21 ± 0.49
RT disgusted (sec)	2.61 ± 0.50	2.81 ± 0.56	3.42 ± 0.55
RT sad (sec)	2.53 ± 0.47	2.90 ± 0.61	3.63 ± 0.80
RT happy (sec)	1.94 ± 0.40	2.11 ± 0.47	2.68 ± 0.53
RT neutral (sec)	1.84 ± 0.41	2.10 ± 0.57	2.99 ± 0.52
RT angry (sec)	2.04 ± 0.40	2.43 ± 0.59	2.91 ± 0.61
Accuracy estimated marginal mean ± standard error			
All emotions	0.78 ± 0.02	0.72 ± 0.02	0.56 ± 0.03*
Angry	0.84 ± 0.02	0.78 ± 0.02	0.61 ± 0.03*
Fearful	0.77 ± 0.02	0.69 ± 0.02	0.57 ± 0.03*
Disgusted	0.65 ± 0.03	0.56 ± 0.03	0.33 ± 0.03*
Sad	0.57 ± 0.03	0.59 ± 0.03	0.45 ± 0.03*
Happy	0.88 ± 0.02	0.79 ± 0.02*	0.62 ± 0.03*
Neutral	0.89 ± 0.02	0.84 ± 0.02	0.69 ± 0.03*

Notes. RT = reaction time, yrs = years of age. Stars (∗) indicate significant difference between groups ($p < 0.05$), such as older adults had reduced accuracy for angry, sad, disgusted, happy, and neutral prosody than young and middle-aged adults, and significant difference between middle-aged and young adults for happy prosody.

educational level ($F[2, 54] = 19.74$, $p < 0.005$), depressive symptoms ($F[2, 53] = 3.52$, $p = 0.04$), and brain volume ($F[2, 51] = 3.73$, $p = 0.03$). Young adults had more years of education than middle-aged and older adults ($p < 0.05$). Older adults scored higher on BDI and had reduced brain volume than younger adults ($p < 0.05$). No significant group effect was found on mood (global PANAS score: $F[2, 45] = 2.81$, $p = 0.07$), handedness: ($\chi^2[2, N = 55] = 1.93$, $p = 0.38$), and gender: ($\chi^2[2, N = 55] = 0.68$, $p = 0.77$). There was no group effect on emotional movie rating ($F[1, 52] = 0.68$, $p = 0.41$); independent from age, participant rated the movies as neutral.

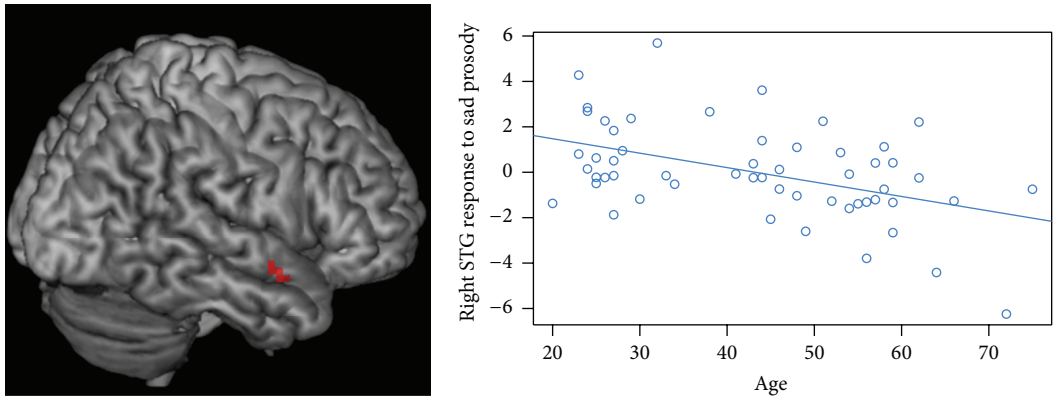
3.2. Behavioral Data. Behavioral data of six participants were lost because of technical problems related to computer crashes or because the experiment was stopped prior to its completion. Reaction time (RT) and emotion recognition accuracy data partially confirmed the previously published findings [5] and are summarized in Table 2. Significant effects were found for emotion ($F[5, 41] = 26.03$, $p < 0.05$) and group ($F[2, 45] = 21.74$, $p < 0.005$) on the reaction time. Post hoc test showed that older adults were significantly slower in responding than young and middle-aged adults (all $p < 0.005$). Group by emotion interaction failed significance ($F[10, 84] = 1.59$, $p = 0.12$). Repeating the analysis with age and sex between group effects, we found no significant effect of sex ($F[1, 42] = 0.13$, $p = 0.72$) or group by sex interaction ($F[2, 42] = 1.37$, $p = 0.26$).

Significant effects on accuracy were found for group ($\chi^2[2] = 197.04$, $p < 0.005$), emotion ($\chi^2[5] = 330.12$, $p < 0.005$), and group by emotions interaction ($\chi^2[10] = 20.53$, $p < 0.05$). The main effect of group indicated that in overall

Table 3: Age by sex interaction of prosody recognition.

Mean accuracy ± standard error	Young adults (18–35 yrs; $n = 18$)		Middle-aged adults (36–55 yrs; $n = 18$)		Older adults (>55 yrs; $n = 12$)	
	Female	Male	Female	Male	Female	Male
Angry	0.88 ± 0.03	0.80 ± 0.03	0.79 ± 0.03*	0.77 ± 0.03	0.63 ± 0.06*	0.60 ± 0.04*
Fearful	0.79 ± 0.03	0.76 ± 0.03	0.76 ± 0.03	0.61 ± 0.04*	0.80 ± 0.05	0.49 ± 0.04*
Disgusted	0.68 ± 0.04	0.63 ± 0.04	0.55 ± 0.03*	0.57 ± 0.04	0.30 ± 0.05*	0.34 ± 0.04*
Sad	0.62 ± 0.04	0.52 ± 0.04	0.63 ± 0.03	0.53 ± 0.04	0.45 ± 0.06*	0.44 ± 0.04
Happy	0.97 ± 0.01	0.81 ± 0.03*	0.81 ± 0.03*	0.77 ± 0.03	0.72 ± 0.05*	0.59 ± 0.04*
Neutral	0.85 ± 0.03	0.92 ± 0.02	0.83 ± 0.03	0.86 ± 0.03	0.75 ± 0.05	0.67 ± 0.04*

Notes. Stars indicate significant differences between age groups (∗) and sex (⟨∗⟩; $p < 0.05$). yrs = years of age.



(a) (b)

Figure 2: (a) Right STG [$x = 57$, $y = 2$, $z = -14$] response to sad prosody showing a negative correlation with age. (b) The responses at the right STG consistently decrease with age.

emotions young adults performed better than middle-aged and older adults and middle-aged adults performed better than older adults (all $p < 0.05$). The group by emotion interaction indicated that old adults perform worse than young and middle-age adults, for all prosodies except fearful, in which case they performed worse only relative to young adult. All $p < 0.004$; 95% Wald confidence interval [CI]: range from [0.06, 0.22] in middle-aged versus older adults for sad to [0.21, 0.37] in younger versus older adults for disgusted prosody; Table 2. Significant difference between young and middle-aged adults emerged for happy prosody ($p = 0.001$, 95% Wald CI [0.04, 0.15]).

Repeating the analysis including the sex variable, main effects were found for sex ($\chi^2[1] = 25.88$, $p < 0.005$), group ($\chi^2[2] = 158.34$, $p < 0.005$), and emotion ($\chi^2[5] = 325.45$, $p < 0.005$). Significant interactions were found for group by emotion ($\chi^2[10] = 30.90$, $p < 0.005$), emotion by sex ($\chi^2[5] = 27.28$, $p < 0.005$), and group by emotion by sex ($\chi^2[10] = 28.24$, $p < 0.005$), but not for group by sex ($\chi^2[2] = 2.71$, $p = 0.26$). In post hoc tests, female participants performed better than male participants on recognizing fearful and happy prosody (all $p < 0.05$). Table 3 displays the accuracy per emotion of age by sex groups. Overall, males and females showed a similar decline of emotion recognition performance with age, except for fearful, neutral, and sad prosody where an effect of sex by age was observed (see Table 3). Within the age group, sex differences were found for fearful and happy prosody, with a significant better performance for females (Table 3).

3.3. fMRI Results. Linear-regression analyses revealed a significant negative correlation between age and right STG responses to sad prosody (cluster peak at MNI = [57, 2, −14]; cluster size at $k = 17$ voxels; peak at $Z = 4.11$; $p = 0.016$ after FWE correction for bSTL volume; Figure 2). No significant correlation emerged between age and responses to happy, angry prosody, or male voice at this threshold.

In the mixed-effect model, processing of deviants elicited responses at bilateral STG only (right [66, −16, 1], $k = 641$, $Z > 8.0$ and left [−60, −10, −2], $k = 406$, $Z > 8.0$, and $p < 0.05$ FWE whole brain correction). Thus, bSTL could be used as a further conservative limitation of the investigated brain volume. A main effect of deviant type emerged in bilateral STG (right [66, −22, 1], $k = 25$, and $Z = 3.88$ and left [−54, −7, −5], $k = 50$, $Z = 4.45$, and $p < 0.05$ FEW correction for bSTL). No significant main effect of age groups emerged in this threshold.

A significant group by deviant type interaction emerged in the right STG ([54, 8, 1], $k = 16$, $Z = 4.15$, and $p < 0.05$ FWE correction for bSTL; Figure 3(a)). No brain areas outside bSTL showed significant effects. To further characterize this interaction, F-tests determined the group effect within each

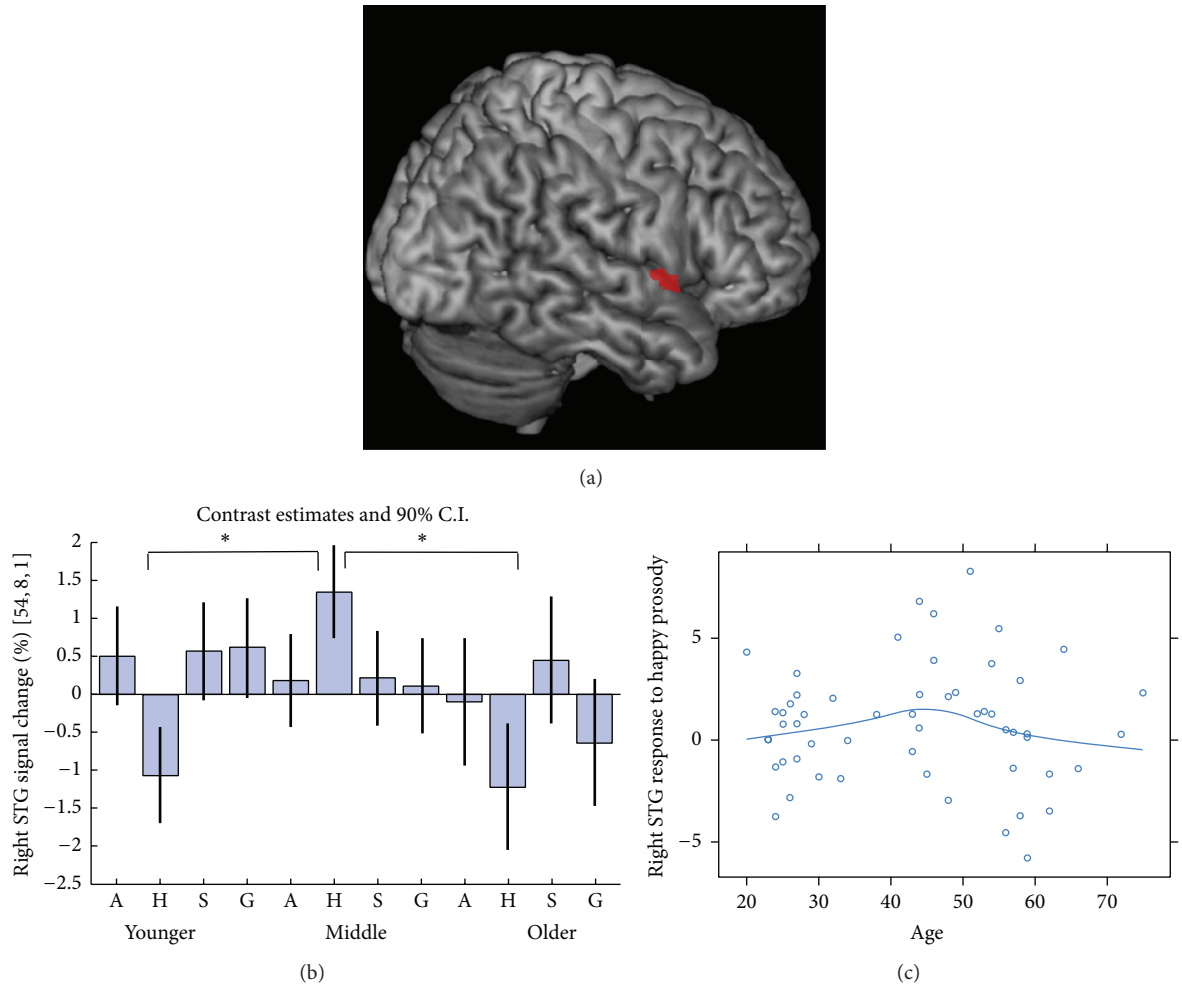


Figure 3: (a) Group by deviant type interaction at the right STG ([$x = 54$, $y = 8$, $z = 1$], $p < 0.05$ few correction for bSTL). (b) Bar plots depict % bold effect and the 90% confidence interval (C.I.), gray lines, in right STG within each group and for each deviant. Stars indicate significant groups differences ($p < 0.05$). (c) The relation between age and right STG response to happy prosody reveals an inverted U-shape. A: angry, H: happy, S: sad, and G: gender (male).

deviant type. Only for happy prosody, a significant group effect emerged (right STG $[57, -13, 7]$, $k = 34$, $Z = 4.48$, and $p = 0.002$, FWE correction for bSTL). In post hoc t-tests, responses to happy deviants were larger in middle-aged adults than in young and older adults ($Z > 4.48$, $p < 0.05$; Figure 3(b)). No significant difference on right STG response to happy prosody was found between young and older adults. Indeed, as already suggested by the regression analysis in Figure 3(c), response amplitudes and age seemed to vary in an inverted U-shape fashion.

Further, we investigated if there is a significant group by deviant interaction on the response shape including HRF and time derivate. Bilateral STG yielded a significant group by deviant type by basis function interaction (right $[51, 2, 1]$, $k = 34$, $Z = 4.66$; left $[-66, -37, 19]$, $k = 24$, $Z = 4.29$, and both $p < 0.05$ in bSTL).

Regarding sex differences, no significant sex by age-group interaction emerged in the STG responses.

Repeating the analysis controlling for age-related structural changes using the total brain volume as covariate of no interest, the effects remained comparable, in particular, the group by deviant interaction at the right STG ($[54, 8, 1]$, $k = 16$, $Z = 4.15$). The group by deviants effect was significant, even after controlling for depressive symptom, education (years), and TBV ($[57, 8, 1]$, $k = 23$, $Z = 4.37$, and $p_{\text{FWE}} < 0.05$ small volume correction), whereas the main effect of deviants was at a trend level ($p_{\text{FWE}} = 0.09$ small volume correction).

4. Discussion

This study examined age-related neural changes underlying automatic processing of emotional prosody. Our previous behavioral data partially corroborate previous findings of an emotion recognition deficit with aging [5] and further specified a sex by age interaction, for fearful and happy prosody recognition. Regarding the neural correlates of automatic sensory processing, right STG responses to sad deviants decreased linearly with age, whereas responses to happy deviants were maximal between 35 and 50 years of

age. These responses emerged in the right STG only and were not affected by the sex of the listener. The sad voice with low arousal may be particularly prone to reflect an age-related decrease in auditory processing. For the other emotions, top-down modulation may introduce mood bias or selective effects. In combination with the differentiated pattern of emotion recognition accuracy, we conclude that early auditory processing reflects only some of the changes affecting the categorization task. In particular, sex effects may affect other neural networks reflecting social cognition or learning history.

Emotion recognition abilities decrease with age. Behavioral data showed a general decline of emotion recognition ability and a slower reaction time with age. Older adults were found significantly less accurate in recognizing angry, sad, disgusted, happy, and neutral prosody than middle-aged and young adults and fearful prosody relative to young adults. These findings are in agreement with previous reports indicating a general emotion recognition deficit with age [1, 5]. Further, we found that females were in general more accurate at recognizing emotions from prosody than males. Considering age with sex interaction, older females performed better than older males in recognizing fearful prosody, and young females had a higher performance in recognizing happy prosody than young males. For the other emotions, both males and females showed a comparable decline of emotion recognition ability with age.

Age-related changes on the neural correlates of sensory acuity have been previously reported. Reduced visual [31–33] and auditory primary sensory areas [34] activation was reported with advance in age. The present study adds to the literature by indicating a modulatory age effect on automatic encoding of prosody. These findings are in line with previous studies form visual modality indicating decreased sensory areas response to emotional stimuli [8, 31–33]. Hilimire and colleagues [8] reported stronger negativity at occipital sites for sad face in young compared to older adults, whereas for happy faces stronger negativity was reported in older adults relative to young adults. Kensinger and Leclerc [35] suggested that automatic emotion processing is preserved with aging, whereas an age effect results in a more controlled emotional processing, such as emotion regulation and emotional memory involving a different neural mechanism showing an effect of age [11]. In our study, employing an event-related oddball paradigm, frontal areas did not emerge. However, auditory responses to sad prosody perception declined like emotion recognition ability with age. Thus, emotion recognition impairment might be related to decline of sensory ability with aging.

The age-related changes may not be specific to arousal or valence. Anger and happiness are emotions with high arousal, whereas sadness and anger are negative emotions. Our findings do not indicate a generalized age effect specific to arousal or valence but rather variations specific to basic emotions, as previously shown for audiovisual emotions in aging [36] and in neurodevelopmental disorders [37]. Valence and arousal may modulate rather higher level of stimulus processing and cognitive control.

The middle part of the STG is associated with "automatic integration" of emotional cues from voices irrespective of the attention focus or task demand [38, 39]. Thereby, the right hemisphere showed higher sensitivity towards prosody perception [39]. In a mismatch paradigm magnetoencephalography study, detection of emotions and gender elicited bilateral mismatch responses in the temporal cortex, including superior, middle, and inferior temporal gyri [16]. An earlier response (about 100 ms poststimulus latency) emerged predominantly in the right hemisphere for emotions detection and not for gender [16]. The present study not only does replicate the previous finding about the relevance of middle STG in sensory processing of emotional prosody, but also revealed an aging effect.

No significant sex by age interaction emerged at the neural level. Conceivably, automatic encoding of emotional prosody declines similarly in males and females with advance in age. Reports on sex differences of neural mechanism of auditory preattentive processing are variable. One study reported no sex difference in the amplitude, latency or duration, and phonetic change detection [40]. Other researchers reported stronger mismatch negative amplitude to emotional versus neutral prosody in young females indicating that females recruit additional processing resources to changes in emotional prosody [22]. The latter authors concluded that sex-related differences emerged at an "early, automatized stage of information processing." (page 638 [22]). Donges et al. [23] reported a greater sensitive towards positive facial expression in females using an affective priming paradigm in young healthy participants and no sex differences for negative emotions. Thus, it was suggested that females have an enhanced sensitivity towards emotional cues [21]. The lack of sex differences on the neural mechanism of automatic emotional prosody processing might be due to the longer temporal integration window of the fMRI in our study relative to electroencephalography or magnetoencephalography, which were applied in the above mentioned studies. However, the automatic encoding of emotional prosody seems to be overall equally preserved in both females and males across lifetime.

Although the sample size in the present study is similar to previous research, some caution is appropriate regarding the implication of the results due to the limited sample size. Cognitive abilities were not assessed in the current and therefore our interpretation is limited to sensory processing. However, reaction time is considered an index of cognitive abilities [41] and the overall decrease of reaction time parallels the abilities that reduced with age. Due to the set-up of the design, that is, passive oddball, we could not investigate whether prosody during scanning was perceived clearly. The volume of the sounds was individually adjusted, so that each participant could hear the sounds properly during the scanning. The passive oddball paradigm is well established and reflects sound discrimination in the absence of higher cognitive functions, for example, active attention toward the stimuli. We did find a main effect of deviants, as well as deviant by age interaction in the sensory cortex, which indicates that changes in prosody stimuli were encoded at the sensory level.

5. Conclusion

This study suggests that automatic encoding of emotional prosody is influenced by age. Although we observed a general decline in emotion recognition with aging, automatic sensory encoding deficit with aging seems to be specific to sad prosody. Indeed, the initial decline of response to happy stimuli was recovered in the elderly. Cognitive control, continuous learning experience, and in particular a positivity bias may interact with a decline of emotion detection across lifespan.

Conflict of Interests

The authors declare no conflict of interests regarding the publication of this paper.

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Review Article

Cognitive Interventions in Older Persons: Do They Change the Functioning of the Brain?

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Background. Cognitive interventions for older persons that may diminish the burden of cognitive problems and could delay conversion to dementia are of great importance. The underlying mechanisms of such interventions might be psychological compensation and neuronal plasticity. This review provides an overview of the literature concerning the evidence that cognitive interventions cause brain activation changes, even in damaged neural systems. *Method*. A systematic search of the literature was conducted in several international databases, Medline, Embase, Cinahl, Cochrane, and Psychinfo. The methodological quality was assessed according to the guidelines of the Dutch Institute for Health Care Improvement (CBO). *Results*. Nineteen relevant articles were included with varied methodological quality. All studies were conducted in diverse populations from healthy elderly to patients with dementia and show changes in brain activation after intervention. *Conclusions*. The results thus far show that cognitive interventions cause changes in brain activation patterns. The exact interpretation of these neurobiological changes remains unclear. More study is needed to understand the extent to which cognitive interventions are effective to delay conversion to dementia. Future studies should more explicitly try to relate clinically significant improvement to changes in brain activation. Long-term follow-up data are necessary to evaluate the stability of the effects.

1. Introduction

Aging is accompanied by changes in our cognitive functioning based on structural and functional changes in the brain [1, 2]. Many older persons complain about diminished cognitive functioning [3]. Cognitive complaints and cognitive deficits are often a burden for older persons and their family [4–6]. Cognitive deficits could also be a precursor for dementia. In that case it is important to intervene in an early stage to prevent or delay conversion to dementia and to minimize the impact of these objective or perceived cognitive problems [5, 7].

Pharmacological interventions are of limited efficacy, may have serious side effects, and are only available for patients with a clinical diagnosis of dementia [8]. Cognitive interventions have gained a lot of attention over the last years. The main goal of cognitive interventions is to stimulate the cognitive system or offer compensatory methods to address difficulties with cognitive functioning [7, 9]. Clinicians acknowledge the benefits of cognitive interventions such as changing a patient's sets of beliefs, affective states, or behavioural patterns and compensating for cognitive losses [10].

A literature review performed by Buschert and colleagues in 2010 highlights the effectiveness of cognitive interventions in improving global cognitive functioning, daily activities, quality of life, and diminishing behavioural problems in patients with Mild Cognitive Impairment (MCI) or dementia [8]. A review of randomized controlled trials on this topic in persons with MCI concluded that there is evidence for intervention success in overall cognition, overall self-ratings, episodic memory, and executive function/working memory.

The quality of the evidence is limited due to several methodological issues such as a small amount of long-term follow-up measures with generally small effect sizes. Moreover there are differences in design, sample sizes, and types of intervention [11].

Cognitive stimulation in a social setting such as reminiscence with reality orientation is associated with benefits in cognitive functioning as well as quality of life, well-being, communication, and social interaction skills [9]. In healthy elderly, cognitive interventions lead to fewer negative emotional reactions towards cognitive functioning [3, 12, 13], improvement in coping with reported cognitive failures [12, 13], and better objective cognitive functioning [13, 14]. Another important goal of cognitive interventions is intervening at an early stage of cognitive decline to slow or prevent progression to dementia. Cognitive interventions could even have the potential to delay the onset of Alzheimer's Dementia (AD) by 5 years in those patients at risk for AD [8]. The evidence for the efficacy of cognitive interventions is promising yet inconclusive due to differences in design, outcome measures, interventions, and sample sizes. The low costs, absence of adverse effects, and the possibility to delay the onset of Alzheimer's dementia make cognitive interventions attractive [8]. Some even stated that neurobiological outcomes might be used as a sensitive biomarker for the efficacy of cognitive training [15].

The mechanisms underlying the effectiveness of cognitive interventions are not well understood. A better understanding of these mechanisms can help us tailor our cognitive interventions and possibly improve the effectiveness.

One mechanism might be psychological compensation. Cognitive interventions would then improve coping strategies to deal with the still existing cognitive problems [3]. In clinical practice, the working mechanism and goals of cognitive interventions are explained to participants in terms of this psychological compensation. But recent neural models suggest that neuronal plasticity may also underlie the effectiveness of cognitive interventions [5, 8, 16–18]. Cognitive interventions might increase cognitive reserve that is reflected in changes in brain activation patterns [4, 8]. Cognitive reserve, the capacity of an adult brain to cope with brain pathology in order to minimize symptomatology, is linked to efficiency (less activation of brain networks) in healthy elderly. On the other hand, in pathological aging, cognitive reserve enhances the recruitment of compensating brain networks particularly the frontal areas, hippocampus, and the precentral gyrus [1, 19].

The aim of this paper is to review the evidence that cognitive interventions cause brain activity changes. Eventually, early intervention in prodromal stages to delay conversion to pathological aging is the ultimate goal. Therefore the effects of cognitive interventions on brain activity changes are studied in the brain of healthy older persons and in the brain of older persons suffering from pathological aging. To relate changes in brain activation to intervention effect, evidence of changes in performance, function, behaviour, and cognition are also reviewed.

2. Methods

2.1. Search Strategy. A systematic literature search of articles published from 1993 to March 2012 was conducted in Medline, Embase, Cinahl, Psychinfo, and the Cochrane Database. Medical Subject Headings (MeSH) terms, thesaurus terms, and an age selection > 60 years were used in the search (search terms used in selection of studies) as follows:

(1) Psychinfo: cognitive impairment OR dementia OR age selection set on > 60 years, Medline and Cinahl: cognition disorder OR dementia OR aged OR elderly, and Embase: cognitive defect OR dementia OR aged OR elderly;

(2) Psychinfo: behavioural therapy OR cognitive therapy Medline, Cinahl, Embase: behavior therapy OR cognitive therapy;

(3) Psychinfo: magnetic resonance imaging OR tomography OR electrophysiology, Medline and Cinahl: magnetic resonance imaging OR electroencephalography OR tomography, and Embase: nuclear magnetic resonance imaging OR electroencephalogram OR tomography.

Reference lists of the retrieved studies were searched to identify any relevant articles that had not yet been included. To be selected for this review, papers had to meet the following criteria: (i) the study had to involve the healthy elderly, the healthy elderly with cognitive complaints, and the elderly with Mild Cognitive Impairment or elderly with dementia; (ii) the study had to contain a cognitive intervention; (iii) the study had comparisons of brain activity measurements before and after the intervention; (iv) the study had a full report available; (v) the articles were in English. A flowchart of the inclusion process is shown in Figure 1.

2.2. Selection of Studies. The search resulted in 735 papers. One reviewer (YvO) screened all titles and abstract for suitability. Six hundred ninety-six studies were rejected because of duplication, lack of full data, lack of brain activity measures, or lack of a cognitive intervention. The remaining 39 studies were obtained in full text and assessed by two reviewers (YvO, MdV). There was full agreement on the exclusion of 23 papers because they did not meet all inclusion criteria. A manual search of the reference lists of the included studies resulted in 3 additional papers. A total of 19 studies met all inclusion criteria. Figure 1 shows the flowchart of the selection process of the papers.

2.3. Methodological Quality. The methodological quality of the included studies was assessed according to the guidelines of the Dutch Institute for Health Care Improvement (CBO). The CBO aims to improve healthcare by providing guidelines for evidence-based interventions both nationally and internationally (CBO, http://www.cbo.nl/). For randomized controlled trials, the following aspects were evaluated: randomization, blinding of randomization, blinding of participants, blinding of outcome assessors, baseline comparability,

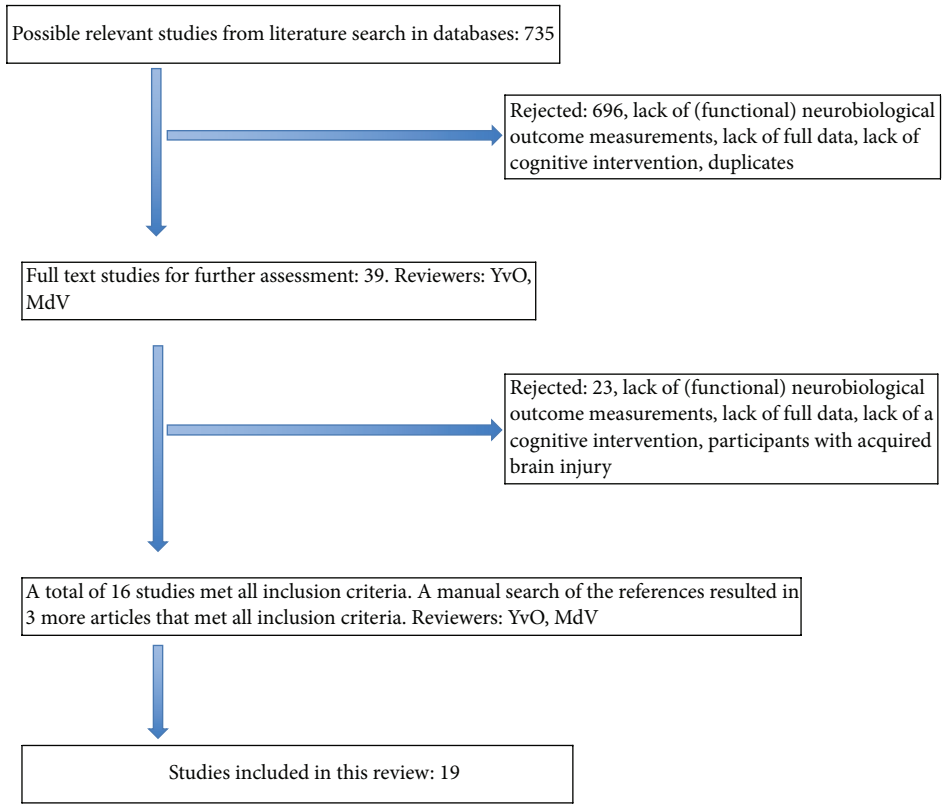

Figure 1: Flowchart of the search strategy.

loss to follow, use of intent-to-treat analysis, comparability of intervention, and a judgment of the validity and applicability of the study. Because it is impossible in cognitive intervention trials to blind the therapists to the intervention, this item was not included as one of the quality criteria. With regard to studies that did not contain a randomized controlled design, the following aspects were evaluated: definition of study population, selection bias, intervention description, outcome definition, blinded outcome assessments, completeness of the dataset/follow-up, loss to follow, confounders, and a judgment of the validity and applicability of the study.

Eventually, the overall quality of the individual studies was rated in a level of evidence, ranging from A1 to D. A1 is a systematic review of at least two independent, randomized double-blind studies of sufficient quality and size. A2 is a randomized double blind study of sufficient quality and size. B is a comparative study, which does not meet all the criteria of an A2 study. C is a noncomparative study and D is the opinion of experts (http://www.cbo.nl/). Two reviewers (YvO and MdV) independently assessed the methodological quality of the studies. The level of agreement was 96%. After a consensus meeting, both reviewers reached full agreement on the quality ratings. The quality ratings of the studies are displayed in Tables 1 and 2.

3. Results

3.1. The Healthy Elderly

3.1.1. Study Characteristics. Six studies focused on healthy older adults [18, 20–23, 30]. Two studies investigated the effect of the method of loci, a mnemonic technique, on brain activation [18, 30]. The intervention duration varied between these two studies from one day [30] to five weeks [18]. The neurobiological outcomes were different; the one-day intervention used Positron Emission Tomography (PET) measures and a memory test as outcomes [30]. The other study used magnetic resonance imaging (MRI), Magnetic Resonance Spectroscopy (MRS), performance on a memory test, and level of depression and anxiety as outcomes. One study lacked a control group [30], and the other study had a randomized controlled trial (RCT) design with a small sample size.

A third study [20] used a RCT design and studied the effect of a multicomponent intervention in 17 older persons with mild subjective memory complaints. Eight of them took part in the intervention that consisted of a diet, relaxation exercises, brain-teasers, memory strategies, and cardiovascular physical training. The PET and MRI data, performance on cognitive tasks, and scores on the subscale

Table 1: Methodological quality of randomized controlled trials.

RCT	The healthy elderly					MCI		Dementia				
	Valenzuela et al. 2003 [18]	Small et al. 2006 [20]	Erickson et al. 2007 [21]	Brehmer et al. 2011 [22]	Belleville et al. 2014 [23]	Rosen et al. 2011 [16]	Hampstead et al. 2012 [24]	Heiss et al. 1994 [25]	Akanuma et al. 2011 [26]	Förster et al. 2011 [27]	van Paasschen et al. 2013 [28]	Baglio et al. 2014 [29]
Randomized	1	1	1	1	1	1	1	1	1	1	1	1
Blinded randomization	0	0	1	0	1	1	1	0	1	0	0	1
Blinded participants	0	0	0	1	1	1	1	0	0	0	0	0
Blinded outcome assessors	0	0	0	0	0	1	0	0	1	1	0	1
Baseline comparability	0	1	1	1	1	1	1	1	1	1	1	1
Loss to follow	1	1	1	1	1	1	1	1	1	0	1	1
Intention-to-treat analysis	0	1	0	0	0	1	1	0	1	1	1	0
Comparability intervention	0	0	0	1	1	1	1	1	0	1	0	1
Validity and applicability	1	1	1	1	1	1	1	1	1	1	1	1
Total	3	5	5	6	7	9	8	5	7	6	5	6
CBO classification	B	B	B	B	A2	A2	B	B	B	B	B	B

The CBO classification reflects the level of evidence. A1 is a systematic review of at least two independent randomized double blind studies of sufficient quality and size. A2 is a randomized double blind study of sufficient quality and size. B is a comparative study, which does not meet all the criteria of an A2 study. C is a noncomparative study and D is the opinion of experts (http://www.cbo.nl/).

Table 2: Methodological quality of observational studies.

Observational studies	The healthy elderly	MCI			Dementia		
	Nyberg et al. 2003 [30]	Clare et al. 2009 [31]	Hampstead 2011 [32]	Belleville et al. 2011 [33]	Nagaya et al. 2005 [34]	Tanaka et al. 2007 [35]	Spironelli et al. 2013 [36]
Definition study population	0	1	1	1	0	1	1
Selection bias	0	0	0	1	0	0	0
Intervention description and allocation	1	1	1	1	1	1	1
Outcome definition	1	1	1	1	1	1	1
Blinded outcome assessments	0	0	0	1	0	0	0
Completeness dataset/follow-up	0	1	1	1	0	1	1
Loss to follow	0	1	1	1	1	1	1
Confounders	1	0	0	1	0	0	0
Validity and applicability	0	1	0	1	0	0	1
Total	3	6	5	9	3	5	6
CBO classification	C	C	C	B	C	C	C

The CBO classification reflects the level of evidence. A1 is a systematic review of at least two independent randomized double blind studies of sufficient quality and size. A2 is a randomized double blind study of sufficient quality and size. B is a comparative study, which does not meet all the criteria of an A2 study. C is a noncomparative study and D is the opinion of experts (http://www.cbo.nl/).

self-awareness of memory ability of the Mood and Feelings Questionnaire (MFQ) were collected.

A fourth study [22] evaluated the benefits of 25 sessions of computerized working memory training on neuropsychological tests varying in level of similarity to those practiced in the training. FMRI measures were studied to evaluate differences in brain activity post intervention. The strength of this study is the use of an active control group that also received a working memory training but with a fixed low level task load. The intervention group received an adaptive training with increasing task load.

Two studies [21, 23] studied the effect of repeated practice with performance feedback on brain activity. Both used single and dual tasks to study focused and divided attention. Belleville and collaborators [23] added a condition in which participants were instructed on the modulation of their attention to the tasks. They were interested if the training format would influence brain activity patterns after intervention. To investigate this hypothesis, all 48 community dwelling older adults were randomly assigned to one of the three intervention conditions, for example, single task, dual task, or top down control of attention. In the other study the 34 older participants were randomly assigned to either a waiting list or the intervention.

The intervention consists of 5 [21] or 6 [23] sessions. Both used fMRI and MRI as neurobiological outcomes. The reaction time and accuracy of the task performances were collected and served in both studies as behavioural data. Moreover both studies statistically examined the relation between performance gains and brain activity changes after intervention.

3.1.2. Findings. The six studies differ in the type of intervention, sample size, design, neurobiological outcomes, and the presence of more clinically relevant outcomes to measure intervention success (Table 2). All *six* studies found brain activity differences after intervention.

Participants in the study of Valenzuela et al. learned the same mnemonic (method of loci). They showed increases in brain activation in the hippocampus [18] and the left occipital parietal cortex and left retrosplenial cortex [30]. These areas are known to be associated with the cognitive domains that were targeted in the intervention. Post hoc relation between performance improvement and brain activity changes was identified in the Nyberg study. Only the older adults who also improved on a memory test showed these brain activity increases [30].

The study of Small and colleagues (2006) demonstrated decrease in the dorsolateral brain activation after intervention and an improvement in verbal fluency. There was no significant intervention effect on subjective measures of self-awareness of memory performance and a memory task [20].

There are three studies that explicitly tried to link intervention related performance gains to brain activation changes. Participants that profit the most from an adaptive working memory training showed the largest activation decreases in regions known to be involved in memory and attention processes (e.g., right inferior frontal, right inferior parietal, left fusiform region, and insula) and the largest activation increases in the caudate [22]. Another study provided evidence that training induced dual task performance improvement was related to increased activity in the left ventral prefrontal cortex and decreased activity in the dorsolateral prefrontal cortex. Compared with an adult sample, age related differences in brain activity were reduced after intervention [21]. The study of Belleville and colleagues [23] found significant correlations between performance and training related activity. They provide evidence that type of intervention influenced the loci and type of brain activity. Repeated practice in single tasking was associated with a

decreased activity in the inferior and middle frontal gyri bilaterally and the left thalamus. The computed correlations revealed that a better performance in single tasking was correlated with decreased activity in the right inferior and middle frontal gyrus. Repeated training in dual tasking resulted in greater activity in the prefrontal cortex during dual tasking. There were no significant correlations between performance gains and brain activity changes for this condition. For the strategic control of attention condition, dependent on the type of instruction, increased activity after training in the right middle frontal gyrus or the right cerebellum was seen. An improved ability to modulate attention according to task instruction was correlated with a greater activity in Brodmann area 10 [23].

However, how the brain activity changes in all studies were related to clinical relevant improvement is not clear, due to a lack of such outcomes and a fail to link brain activation changes to clinically meaningful improvement [18, 20–23, 30]. The stability of the intervention effects was unclear and long-term follow-up measures were lacking [18, 20–23, 30].

3.2. Patients with MCI

3.2.1. Study Characteristics. All five studies [16, 24, 31–33] that focused on MCI patients used fMRI to investigate the influence of a cognitive intervention on brain activity. However the targets of the cognitive intervention as well as the design of the studies differed.

The most recent study with an RCT design evaluated the effects of a mnemonic strategy training on object location associations and brain activation in the hippocampus via fMRI. A matched control group was also exposed to the same lists of object location associations, but without learning the mnemonic. Eighteen participants had a diagnosis of amnestic MCI. A group of 16 healthy controls were allocated to the same treatment conditions. Both diagnostic groups were comparable in terms of prognostic factors, and intervention success was evaluated by a modified change score for learning object location associations [32].

One study used an episodic memory training of 6 weeks (mnemonics and psychoeducation) with proven effectiveness for a MCI population. Fifteen participants with the diagnosis amnestic MCI and 15 matched healthy controls took part in the intervention. The data on visual memory, MRI, and fMRI were collected at baseline and after intervention. Brain activity was studied during encoding and retrieval of a memory test. A double baseline was used to study the possibility of a repetition effect. Furthermore preexisting brain activation differences between both groups were investigated by comparing fMRI data at baseline [33].

Another study [16] randomly assigned 12 MCI patients to a cognitive intervention or an active control group. The computer-based cognitive intervention aimed to improve processing speed and accuracy of auditory processing. It was a time consuming intervention. Participants used the cognitive training five days a week for a hundred minutes per day for two months. The active control group made computer-based exercises with comparable time intensity. Pre- and postintervention fMRI data and a memory test were administered [16].

A face-name association learning task was used as an intervention in an earlier study of Hampstead and colleagues [32]. They studied the effect of this face-name association learning in six amnestic multidomain MCI patients. The fMRI was administered before and after the 5 training sessions. They compared fMRI results of trained with untrained lists in different sessions to compensate for repetition effects of fMRI. Furthermore they computed a functional connectivity analysis [32].

In a single case design, the effect of a goal oriented cognitive rehabilitation was studied in a person with amnestic MCI. Besides fMRI data, performance on a memory tests and an anxiety and depression questionnaire were collected. Finally, the progress in personal rehabilitation goals was evaluated. A face-name association learning task was administered during the fMRI [31].

3.2.2. Findings. Despite the differences in methodologies, types of intervention, and sample sizes in the studies (see Table 3), all investigations found evidence for neurobiological changes in brain activation after intervention.

In an RCT study with an active control group, an intervention related increase in brain activity in the hippocampus was seen, whereas the active control group showed a decreased activity in the hippocampus. Participants that underwent the auditory processing training also improved on a memory test and the training tasks [16].

The other RCT study that evaluated a mnemonic training, found evidence for an intervention related increased activity in the left hippocampal body and the right hippocampus during retrieval of the trained stimuli. For retrieval of the untrained stimuli there was an intervention related increased activity in the right hippocampal. Performance improved after training for the trained stimuli, not for untrained stimuli [24].

In an earlier multiple cases study by the same author, increased connectivity and increased activity in frontal, parietal, temporoparietal areas and precuneus were seen after a face-name association learning training. The six participants also improved on trained and untrained memory tasks [32].

A study that evaluated the effect of an episodic memory training found increased activity in frontal, temporal, and parietal areas. Some areas were already active at baseline; other areas were new, alternative areas. Only increased activity in the right inferior parietal lobe correlated with improvement on a memory test [33].

A single case study found evidence for a pattern of brain activity increases and decreases after a goal oriented cognitive training. Decreases were seen in sensory areas during both encoding and retrieval, such as the higher visual areas, left fusiform gyrus, left medial occipital gyrus. Increased activity was seen in frontal areas, temporoparietal junction, parahippocampal gyrus, and right globus pallidus. Both subjective memory satisfaction and subjective memory performance improved after the intervention [31].

Table 3: Main characteristics of selected studies.

Study	Design Duration Long-term follow- up *n*	Intervention	Result neurobiological outcomes	Result behavioural outcomes
Healthy	The elderly			
Valenzuela et al. (2003) [18]	RCT 5 weeks No follow-up *n* = 20	Method of loci	Increased creatine and choline in hippocampus	Improvement in reproduction memory task No effect on depression or anxiety scores
Nyberg et al. (2003) [30]	Prospective cohort 1 day No follow-up *n* = 24	Method of loci	**Acquisition**: no group differences **Use phase**: adults and improved elderly increased activity in intervention related areas	8 of 16 older persons no improvement in memory task (the unimproved elderly). 8 of 16 older persons and all 8 adults improved in memory task
Small et al. (2006) [20]	RCT 14 days No follow-up *n* = 17	Multicomponent health promotion	Intervention group: decreased activity prefrontal cortex	Better verbal fluency in intervention group no significant effect on memory task and subjective memory ability
Erickson et al. (2007) [21]	RCT 2-3 weeks No follow-up *n* = 65	Attentional training	Improvement in dual task performance is correlated with increased activity in left ventral prefrontal cortex and decreased activity in the dorsolateral prefrontal cortex	Both reaction time and accuracy improved most in the dual task intervention group Young and old adults showed the same degree of performance improvement after intervention.
Brehmer et al. (2011) [22]	RCT 5 weeks No follow-up *n* = 24	Adaptive working memory training. Control group: low level fixed working memory training	All participants decreased brain activity Participants who profit the most showed the largest decreases in intervention related brain areas and largest increase in caudate	Both groups Improved in span board backward, digit span backward, PASAT, RAVLT No intervention related performance gains for in scanner task Intervention group showed training related improvement in span board backward task and PASAT compared to controls
Belleville et al. (2014) [23]	RCT 3 weeks No follow-up *n* = 46	Attentional training	Better performance in single tasking correlated with decreased activity in right inferior and middle frontal gyrus In the strategic control of attention condition, a better ability to modulate attention according to task instruction correlated with increased activity in Brodmann area 10	All intervention groups improved in reaction time and accuracy for alphanumeric task, no effect for visual detection task Both dual task conditions better performance dual tasking compared to single task intervention group Strategic control of attention condition significant effect of task instruction. They were able to modify attention according to instruction.
Mild	Cognitive	Impairment		
Clare et al. (2009) [31]	Single case study 8 weeks No follow-up *n* = 1	Goal oriented cognitive intervention	**Encoding**: increased activity in intervention related brain areas, decreased activity higher visual areas, and frontal areas **Recognition**: increased activity in intervention related brain areas, decreased activity higher visual areas, and frontal areas	Better subjective memory performance, memory satisfaction

Table 3: Continued.

Study	Design Duration Long-term follow- up *n*	Intervention	Result neurobiological outcomes	Result behavioural outcomes
Hampstead et al. (2011) [32]	Multiple single cases 2 weeks No follow-up *n* = 6	Face-name association learning	**Encoding**: increased activity in default network **Effective connectivity changes**: increased connectivity	Significant improvement in performance trained and untrained memory task
Belleville et al. (2011) [33]	Case control 6 weeks No follow-up *n* = 15	Episodic memory training	**Encoding healthy elderly**: decreased activity in brain areas related to intervention. **Encoding MCI**: increased activity in brain areas related to intervention **Retrieval healthy elderly and MCI**: increased activity new brain areas and accumulated activity in specialized areas both related to intervention.	Both groups improved on a memory test
Rosen et al. (2011) [16]	RCT 2 months No follow-up *n* = 12	Auditory processing training	Increased activity hippocampus in intervention group decreased activity hippocampus in control group	Intervention group improved in memory test and training tasks
Hampstead et al. (2012) [24]	RCT 2 weeks No follow-up *n* = 34	Mnemonic training	**Encoding MCI**: increased activity left hippocampal body **Retrieval MCI**: increased activity hippocampal body and tail bilaterally **Healthy controls**: decreased activity right hippocampal body	MCI group and healthy controls improved in encoding and retrieving trained object locations. No intervention effect for untrained object locations.
Dementia				
Heiss et al. (1994) [25]	RCT 6 months No follow-up *n* = 80	(1) Social support (2) Cognitive training (3) Cognitive training + pyritinol (4) Cognitive training + phosphatidylserine	**EEG**: increased global power gr 3 + 4 Decreased delta power gr 4 **PET**: significant correlation MMSE score and glucose metabolism tempero-parietal cortex. Gr. 4 increased activity primary visual cortex during intervention, but not at the end of the intervention	Gr 4 more responders and significant higher scores on orientation than gr 1 + 2 in week 8 + 16. At the end of the intervention (6 months) there were no differences.
Nagaya et al. (2005) [34]	Within subjects Unknown No follow-up *n* = 11	Recreational rehabilitation	**Responders**: decreased activity frontal regions **Non responders**: decreased activity all regions	Responders: improved 3 MMSE points
Tanaka et al. (2007) [35]	Single case 2 months Follow-up for 6 months *n* = 1	Reminiscence	increased activity frontal areas, postcingulate gyrus, and precuneus	Improvement in cognition, vitality, volition, and daily life activities

Table 3: Continued.

Study	Design Duration Long-term follow- up *n*	Intervention	Result neurobiological outcomes	Result behavioural outcomes
Förster et al. (2011) [27]	RCT 6 months No follow-up $n = 36$	Multipurpose	**MCI controls**: decreased activity in brain regions typically impaired in AD **MCI intervention**: no declines **AD controls**: decreased activity in brain regions typically impaired in AD **AD intervention**: decreased activity in 2 clusters; lingual gyrus, left inferior temporal gyrus	No changes
Akanuma et al. (2011) [26]	RCT 3 months No follow-up $n = 24$	Reminiscence with reality orientation	**Intervention group**: increased activity anterior cingulate bilateral, left inferior temporal cortex. Correlation between increased act anterior cingulate and improvement social and communication scales brse	**Intervention group**: improved in social and communication scales (brse)
Spironelli et al. (2013) [36]	Observational study 5 weeks No follow-up $n = 11$	Cognitive training	The amplitudes of the recognition potential (negative potential) were significantly increased on the left sides of posterior regions for high frequency words	A marginally significant improvement on the verbal reasoning score No significant treatment effect on the dementia screening tests, four out of five cognitive tasks, and the independent functioning questionnaires.
van Paasschen et al. (2013) [28]	RCT 8 weeks No follow-up $n = 19$	Tailored cognitive rehabilitation	*Intervention group* **Encoding**: no significant changes. **Recognition**: significant increased activity bilateral prefrontal areas and the bilateral insula *Control group* **Recognition**: decreased activity in bilateral prefrontal areas and the bilateral insula	Intervention group improved on satisfaction and performance of individual goals (COPM) No treatment effect on the in scanner face-name association task
Baglio et al. (2014) [29]	RCT 10 weeks Follow-up for 22 weeks $n = 60$, $n = 30$ Follow-up	Multidimensional stimulation program	**Postintervention**: increased activity bilateral superior temporal gyrus (right > left), right lentiform nucleus, and thalamus	Intervention group showed clinical relevant improvement in NPI, language, and memory scales of ADAS-cog No significant change in functional status or physical well-being **Long-term follow-up**: improvement in the language and memory scales of the ADAS-cog is preserved

Legenda:
qol: quality of life.
MMSE: minimental state examination.
ADAS cog: dementia screening test.
BRSE: scale for social and communication skills.
GDS: geriatric depression scale.

In conclusion, mostly an increase in brain activation specifically in areas typically involved in intervention related cognitive processes [16, 24, 31, 33] was seen, as well as activation of the default network [24, 32]. In several studies, the authors claimed that normalisation of the pattern of brain activation after intervention had occurred as a possible result of restoration [24, 31–33] whereas the activation of additional areas was interpreted as a compensatory mechanism [24, 32].

Most of the studies tried to relate the changes in brain activation to intervention success. Most studies formulate this intervention success as performance improvement on a cognitive task that was the target of the intervention. One single case study also studied subjective complaints of cognition, mood, and anxiety. These authors reported improvement in subjective measures of memory performance and satisfaction [31].

3.3. Patients with Dementia

3.3.1. Study Characteristics. Eight studies [25–29, 34–36] focused on patients with dementia. Four of the studies used a RCT design [25–27, 29]. Study population, intervention targets, and outcome measures differed.

The most recent RCT study [29] aimed to improve cognition, behaviour, and motor functioning with an intense, multidimensional stimulation program. The effectiveness of this program was studied in 60 persons with AD on a questionnaire for behavioural and psychiatric problems (NPI), language, and memory scales of the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog), functional status, physical well-being, and fMRI. The intervention group was compared to a waiting list. Twenty healthy controls served as a reference for the typical activation pattern while performing the in-scanner verbal fluency task. The strength of this study was a long-term follow-up measurement [29].

In another RCT study [27] the effect of a six-month cognitive intervention program designed to improve global cognitive functioning, mood, and quality of life in patients with MCI and mild AD was investigated. To study disease-related brain activation differences at baseline, PET data of the MCI and AD group were compared with PET data of a group of eleven healthy elderly. In the active control condition, participants made pencil and paper assignments focused on sustained attention (mostly intact in MCI and AD). A specific PET method was used that is known to be more sensitive in detecting disease related metabolic disturbances in mild to moderate stages of neurodegenerative diseases [27].

The RCT study of Heiss et al. [25] also used a six-month intervention for 80 participants with AD. The content of their intervention was different. The 17 participants received social support (group 1), 18 participants received cognitive training twice a week (group 2), 18 participants received a combination of the cognitive training and the drug pyritinol that is used for symptomatic treatment of AD (group 3), and finally 18 participants received cognitive training and the dietary supplement phosphatidylserine. At baseline and at several times during intervention and postintervention neuropsychological tasks, the quantitative EEG, resting state PET, and stimulation PET were administered [25].

The fourth RCT study [26] investigated 24 residents of a geriatric nursing home with a diagnosis of vascular dementia (VaD). They were randomly assigned to reminiscence with reality approach condition or were treated to the standard of care. The duration of the intervention was 3 months. Reminiscence with reality approach claimed to invoke memories with the aid of materials and generated a better awareness of the "here and now." Scores on a cognitive screening test (MMSE), a mood questionnaire (GDS), a behavioural observational questionnaire (BRSE), and PET data were all collected. A region of interest analysis (anterior cingulate left and right) was conducted with the PET data. [26].

The efficacy of tailored cognitive rehabilitation in 19 people with early stage AD or mixed AD/VaD was evaluated by van Paasschen et al. [28]. The goal of this study was to relate clinically relevant improvement and differences in brain activity. A passive control group with no treatment as well as an active control group with relaxation therapy was used. In 8 weekly sessions, personalized goals concerning memory were targeted in the cognitive rehabilitation. The main outcome measure was the Canadian Occupational Performance Measure (COPM) that rated the satisfaction and performance of participants on several goals with respect to daily living. Brain activity was studied with fMRI [28].

Whereas most studies selected fMRI to study brain activation, Spironelli et al. [36] used Event Related Potentials (ERP) to evaluate possible changes in brain functioning after cognitive training in 11 people with mild to moderate AD. Their intervention aimed to stimulate different cognitive domains based on everyday activities and exercises. The 11 matched healthy controls underwent one experimental ERP session to serve as a reference for possible altered response patterns. The intervention success was also evaluated with neuropsychological tests and questionnaires of everyday activities [36].

Two studies used PET data as the neurobiological outcome. One study was a single case design on the effect of eight weekly reminiscence sessions on activities of daily living, cognition, volition, vitality, behavioural problems, well-being, caregiver burden, and PET data. A comprehensive geriatric assessment was also administered six months after intervention [35]. The other study provided 11 VaD patients with recreational rehabilitation. They used PET to study blood flow differences after intervention. The group of 11 patients was divided into responders (improved more than 3 points on the MMSE) and nonresponders [34].

3.3.2. Findings. The eight studies that investigated cognitive intervention effects on brain functioning of people suffering from dementia differed in design, type of intervention, duration of the intervention, type of neurobiological and behavioural outcomes, and the presence of follow-up measures (Table 3). Despite those differences, all studies found neurobiological changes after intervention.

In the most recent RCT study, an increased activity in the superior temporal gyrus bilaterally, the thalamus and the

right lentiform nucleus was seen after a multidimensional stimulation program. The intervention group also showed clinical relevant improvement in neuropsychiatric symptoms, language, and memory scales of a cognitive screening. There is a significant correlation between the magnitude of increased activity in the left superior temporal gyrus, precuneus and left thalamus, and the change in cognitive screening performance. The improvement in these scales of the cognitive screening is preserved at 22 weeks afte intervention [29].

Another multidimensional intervention found evidence that participants with AD showed decreased activity in two clusters (lingual gyrus, left inferior temporal gyrus), whereas the active control group showed decreased activity in a larger network prefrontal, parieto-occipital and parieto-temporal. However, there were no significant changes in the behavioural outcomes [27].

Another RCT study showed that tailored cognitive rehabilitation induced increased activity in prefrontal areas and insula bilaterally, whereas both active and waiting list control groups showed decreased activity in those areas. The intervention group improved on satisfaction and performance of individual goals; both control groups showed no improvement [28].

A RCT study that evaluated the effect of reminiscence with reality orientation found that intervention related increased activity in the anterior cingulate correlated significantly with improvement in social and communication scales [26].

A single case study on the effect of reminiscence reported increased activity in frontal areas, precuneus and posterior cingulate gyrus after intervention. The participant also improved on measures of cognition, vitality, volition, and daily life activities [35].

In a RCT study hat evaluated the effect of four different interventions, global EEG power increased in both intervention groups that combined cognitive training with a dietary supplement or a symptomatic drug for dementia. There were no significant changes in brain metabolism after intervention in predetermined target regions. Additional regions of interest were analysed; this revealed an increase in metabolism in the visual association area during functional activation for the cognitive training and phosphatidylserine group. For this intervention group there was also an increase in resting state metabolism in temporal regions, but only for the participants in this particular intervention group that had initial metabolism values below 90% of normal in the temporal region. There were also some behavioural benefits for this intervention group. In weeks 8 and 16, the group that received cognitive training and phosphatidylserine scored significantly better on orientation than the other intervention groups. This effect was no longer present at the end of the intervention [25].

An increased amplitude of the recognition potential for high frequency words on the left sides of posterior regions after cognitive training was demonstrated in an ERP study. Most behavioural outcomes fail to show a significant intervention effect, despite a marginally significant improvement on verbal reasoning [36].

Responders of a recreational rehabilitation intervention showed decreased activity in frontal areas after intervention. The nonresponders showed activity decreases in a large network of brain areas after intervention [34].

Thus, most studies found an increase in brain activation after intervention or less decrease in activation versus the control group. One study reported that the responders in their intervention showed a significant decrease in cerebral blood flow in the frontal regions, whereas nonresponders showed a decrease in a larger network of brain areas. Their study, however, is the least quality of all the included studies [34]. According to one study [25], the changes in neuropsychological measurements and brain activity were temporary and disappeared at the end of the six-month intervention. Two studies however demonstrated a behavioural intervention success of 22 weeks and six months after intervention. Both studies did not follow up with the neurobiological changes [29, 35]. The three most recent studies [28, 29, 36] and the study of Tanaka and colleagues [35] tried to link clinical improvement to changes in brain activation by using behavioural outcomes that were not only cognitive tasks but more related to daily functioning, individual goals, subjective complaints, or social skills. Baglio and colleagues took this one step further to statistically relate the brain activation changes to the behavioural outcomes [29].

3.4. Methodological Quality. The selected 19 studies were quite heterogeneous in terms of design, sample size, population, intervention methods, and neurobiological outcome measurements. Therefore, it was decided to not statistically pool the data to perform a quantitative meta-analysis. Eight studies were comprised of patients with a diagnosis of dementia; five studies involved patients with Mild Cognitive Impairment; and six studies included healthy elderly. Of the selected studies there were 13 randomized controlled trials, 3 prospective studies, 1 study using a within-subjects design, and 2 single case studies.

The overall methodological quality of the included studies varied. For the RCTs, the overall score of the methodological quality varied from 3 to 9 (maximum 9) with a level of evidence ranging from A2 to B according to the CBO (Table 1). The overall score for the methodological quality of the observational studies varied from 3 to 9 (maximum 9). The CBO level of evidence ranged from B to C (Table 2).

Six of the 13 RCT studies lacked an intention to treat analysis. Randomization was blind in only six of the 13 RCT studies. In more than half of the studies the outcome assessor was not blind to the treatment condition. In the observational studies, almost none of the studies had blinded outcome assessors and almost every study had a selection bias.

A hierarchy of quality was composed based on the design and methodology. With regard to the studies that focused on healthy elderly, the study of Belleville et al. [23] had the highest methodological quality. For the studies that comprise patients with MCI, the studies of Belleville and Bherer [15] and Erickson et al. [21] had the highest methodological quality. The study with the highest methodological quality that involved patients with dementia was that of Baglio et al.

[29]. Akanuma et al. [26] was limited in the informative value due to a lack of detailed methods and results.

4. Discussion

In this paper, the literature was reviewed to investigate whether cognitive interventions in elderly lead to changes in brain activation suggestive of neural plasticity even in damaged neural systems. The methodological quality of the 19 studies was rated according to the guidelines of the Dutch Institute for Health Care Improvement (CBO, http://www.cbo.nl/).

The results illustrate that all studies, conducted in diverse populations from healthy elderly to patients with dementia, show changes in brain activation post intervention. The methodological quality of the studies varied with the CBO level of evidence ranging from A2 to C (Tables 1 and 2).

All four studies in healthy elderly found brain activation differences after intervention. Two studies found increases in brain activation post intervention, primarily in the occipital parietal cortex and retrosplenial cortex [30] as well as in the hippocampus [18]. Post hoc only the older participants that improved on a memory test showed these brain activity increases [30]. However, this could not be documented by more clinical outcomes due to a lack of such outcomes or a fail to link brain activation changes to clinically meaningful improvement.

On the contrary, another study found a decrease after intervention in the dorsolateral brain activity [20]. The relationship between this decreased activity dorsolateral and clinically relevant improvement was not evident. Only an improvement in verbal fluency was found, but no significant intervention effects were found on the subjective measurements of self-awareness of memory performance and other cognitive tasks [20]. Three studies successfully linked intervention-related performance gains to brain activation changes by statistical analyses. One study found performance-related brain activity decreases in the cortical regions known to be involved in cognitive functions targeted by the intervention and performance related brain activity increases in subcortical areas [22]. Another study provided evidence that training induced dual task performance improvement was related to increased activity in the left ventral prefrontal cortex and decreased activity in the dorsolateral prefrontal cortex. Compared with an adult sample, age related differences in brain activity were reduced after intervention [21]. The study of Belleville and colleagues [23] concluded that the type of intervention influenced the loci and type of brain activity. A better performance in single tasking was correlated with decreased activity in the right inferior and middle frontal gyrus. An improved ability to modulate attention according to task instruction was correlated with a greater activity in Brodmann area 10 [23].

Two studies argued that the decreases in brain activity could be explained by an increased cognitive efficiency, thus demanding less effort [20, 22]. The increase in subcortical brain activity was, according to these authors, evidence that the performance was becoming less executively demanding and more proceduralized as the training proceeded [22]. This is in line with the theory of Bartrés-Faz and Arenaza-Urquijo on cognitive efficiency [19]. In addition, the study with the highest methodological quality highlighted the importance of the type of intervention format. Intervention format has effect on the loci and type of brain activation changes after intervention. They refer to the framework of Lorden and their own theoretical framework named INTERACTIVE [21]. These models state that repeated practice would lead to decreased activity in the brain areas involved in the task, indicating increased cognitive efficiency. Interventions that aim to learn participants new strategies will lead to increased activity in alternative networks involved in learning those strategies [21].

Another study interpreted the performance related brain activity pattern of increased activity in the left ventral prefrontal cortex and decreased activity in the dorsolateral prefrontal cortex, as evidence conflicting with views of compensation related reduced brain activity asymmetry. While brain activity differences between adults and older adults were significantly reduced after training, they interpreted this as evidence that cognitive training can modulate age related patterns of brain activity [23].

All of the reviewed studies of cognitive interventions in MCI patients found neurobiological changes in brain activation after intervention despite differences in methodology. There was mostly an increase in brain activation, in areas typically involved in intervention related cognitive processes. This was seen as well as activation of the default network. In several studies, even normalisation of the pattern of brain activation after intervention was claimed. The study of Rosen et al. had the highest methodological quality in this review and showed that even brain structures known to be injured in patients with MCI such as the hippocampus retained sufficient brain plasticity to benefit from cognitive interventions [16]. This activation of the default network and hippocampus is in line with Bartres' assumption that, in pathological aging, the cognitive reserve enhances the recruitment of compensating brain networks particularly the frontal areas, hippocampus, and the precentral gyrus [19]. Cognitive behavioural interventions might increase this cognitive reserve [4, 8]. Functionally relevant clinical improvement has been given little attention in these studies. A statistical approach to the relationship between intervention success on behavioural measures and brain activation changes was only made by one study [26]. Long-term follow-up measures to determine the stability of the intervention success were not included.

Studies in dementia patients also found neurobiological changes after intervention. Most of the studies found an increase in brain activation or a diminished decrease in activation after intervention. The study of Förster et al. [27] was the only one that found a decrease in activation post intervention, but the construct of this study has poor methodology with little detailed information about the methods and results. According to one study that used a six-month intervention, the increased brain activity and improvement on neuropsychological tests were temporary in persons with

AD and then disappear over time [35]. Other studies demonstrated a preserved improvement in the clinical outcomes such as cognitive tasks, daily life activities, and vitality at 22 weeks and six months after intervention. However, they did not follow up the neurobiological outcomes [26, 32]. Thus, it remained unclear if the changes in brain functioning were temporary. The study with the highest methodological quality correlated improvement in social and communication scales with increased activity in the anterior cingulate, an area known to be involved in social behaviour [26].

One study excluded [27]; all of the authors interpreted their findings as evidence for brain plasticity. Some even stated that cognitive interventions activate compensating brain networks in pathological ageing and could possibly restore brain activation. However, the stability of this effect remains unclear.

Overall, these results suggest that cognitive interventions lead to neurobiological changes even in potentially damaged neural systems. However, the interpretation of changes in activation patterns is complicated. For instance, a decrease in brain activation can indicate increased cognitive efficiency as suggested in the cognitive reserve hypotheses of Bartrés-Faz and Arenaza-Urquijo [19] and the learning phases model of Doyon in Lustig et al. [37]. On the other hand, a decrease in brain activation might reflect exhaustion of neural resources accompanied by a decline in clinical performance as suggested by the CRUNCH model [37].

Moreover, the type of intervention would influence the loci and type of activation changes after intervention [21].

The complexity of interpreting these neurobiological data underlines the importance of including clinical measurements to gain insight into the clinical relevance of neurobiological changes. Unfortunately, in several studies, this information is lacking or neurobiological data is interpreted as evidence for plasticity/restoration of function in the absence of a demonstrated intervention success on clinical outcomes. In the more recent studies, there is increased attention for the clinical relevance of neurobiological changes with promising results. In five studies [21–23, 26, 32] performance gains were linked to brain activation. Four studies used correlations to correlate improvement on a dementia screening test [22], social and communication scales [26] and changes in performance on different attentional tasks [21, 23] to relevant changes in brain activation. A fourth study used the maximum gain score on working memory tasks as a covariate in statistical analysis [32].

These studies focus on relating performance improvement to brain activity changes. However, the transfer of these performance gains to untrained tasks and more importantly to daily life functioning is a great issue [21].

The heterogeneity in populations, outcome measures and interventions as well as the small sample sizes and relatively large amount of case studies further complicate the comparability of the findings between studies.

We recommend that future studies should include measures of clinically meaningful improvement as well as long-term follow-up data to evaluate the stability of the effects. The influence of task demands, premorbid cognitive reserve, and learning phases on brain activation should be considered to increase comparability between studies. The results thus far indicate that the elderly show changes in brain activation after cognitive interventions. However, the exact interpretation and stability of these changes remain unclear just like to what extent cognitive interventions are effective to reach the ultimate goal: to delay conversion to or prevent progression of dementia.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Clinical Study

The Association between Cerebral White Matter Lesions and Plasma Omega-3 to Omega-6 Polyunsaturated Fatty Acids Ratio to Cognitive Impairment Development

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Objective. Cerebral white matter hyperintensity (WMH) with magnetic resonance imaging (MRI) has a potential for predicting cognitive impairment. Serum polyunsaturated fatty acid (PUFA) levels are important for evaluating the extent of atherosclerosis. We investigated whether abnormal PUFA levels affected WMH grading and cognitive function in patients without significant cognitive impairment. *Methods*. Atherosclerotic risk factors, the internal carotid artery (ICA) plaque, and serum ratios of eicosapentaenoic to arachidonic acids (EPA/AA) and docosahexaenoic to arachidonic acids (DHA/AA) were assessed in 286 patients. The relationship among these risk factors, WMH, and cognitive function was evaluated using WMH grading and the Mini-Mental State Examination (MMSE). *Results*. The development of WMH was associated with aging, hypertension, ICA plaques, and a low serum EPA/AA ratio (<0.38, obtained as the median value) but was not related to dyslipidemia, diabetes, smoking, and a low serum DHA/AA ratio (<0.84, obtained as the median value). In addition, the MMSE score deteriorated slightly with the progression of WMH (29.7 ± 1.0 compared to 28.4 ± 2.1, $P < 0.0001$). *Conclusions*. The progression of WMH was associated with a low serum EPA/AA ratio and accompanied minimal deterioration in cognitive function. Sufficient omega-3 PUFA intake may be effective in preventing the development of cognitive impairment.

1. Introduction

Cerebral white matter hyperintensities (WMHs) on magnetic resonance imaging (MRI) increase in the prevalence and the degree with age [1]. However, WMHs are also associated with cerebral small vessel disease affecting the same region of the brain [2]. Thus, the progression of small vessel disease is common and more extensive in patients with cardiovascular or cerebrovascular diseases and atherosclerotic risk factors [3]. Currently, several observational studies have reported that the progression of WMH and lacunes is a better predictor for the development of cognitive impairment [3–6].

There is a lower incidence of subclinical ischemic stroke in elderly patients who consume high levels of fish in their diet, compared to that in those who do not [7, 8]. In addition, a low serum eicosapentaenoic acid (EPA) level and a low EPA to arachidonic acid (AA) ratio were associated with unstableness of coronary artery disease [9]. EPA supplementation was found to be effective for the secondary prevention of coronary artery disease and in reducing the risk of recurrent stroke [9, 10]. Therefore, polyunsaturated fatty acid (PUFA) balance might act as an important diagnostic parameter for evaluating the extent of arteriosclerosis associated with coronary artery and cerebrovascular diseases [9, 10]. Finally, some investigations reported that patients with Alzheimer's disease (AD) had low serum omega-3 (ω3) PUFA levels and that high PUFA intake may postpone cognitive decline [11–13]. Also, the influence of vascular disturbance to cognitive impairment may be lessened through the improvement of ω3 PUFA level.

Therefore, we investigated whether low $\omega 3$ PUFA levels in the blood affected the development of WMH and influenced cognitive function in middle aged or presenile persons who did not develop clinically cognitive impairment.

2. Methods

2.1. Study Design. This study was carried out from January 2010 to June 2013 on 286 outpatients (161 men and 125 women, age range, 55–84 years) who had at least one atherosclerotic risk factor and accepted to have the following various examinations. Among them, 146 patients were having regular visiting with various cardiovascular diseases and were undergoing stable treatment without heart failure. Further 140 patients were visiting for health checkups and had complete physical and blood examinations for screening.

Clinical data were obtained from all patients in the outpatient clinic. Patients underwent physical examination, blood pressure measurement, chest radiography, electrocardiography, brain MRI, duplex ultrasonography of the carotid arteries, and laboratory examination including the measurement of fasting plasma levels of fatty acids and screening test for cognitive impairment using the Mini-Mental State Examination (MMSE), with the written informed consent. Patients with myocardial infarction, cardiomyopathies, stroke, documented paroxysmal or persistent atrial fibrillation and cardiac surgery for coronary artery diseases, or valvular heart diseases were excluded by history taking and physical and various examinations.

2.2. Study Patients. This study was approved by the review committee in Hokusetsu General Hospital. A total of 291 patients provided written informed consent.

Among these 286 patients, 30 had coronary artery disease, 197 exhibited hypertension with ($n = 28$) or without coronary artery disease, 192 had dyslipidemia with ($n = 22$) or without coronary artery disease, and 43 had diabetes with ($n = 11$) or without coronary artery disease.

The presence of hypertension was established if the patient had 1 of the following, systolic blood pressure >160 mmHg or diastolic pressure >90 mmHg, or if the patient used antihypertensive medications. The presence of dyslipidemia was established if the patient had a serum low-density lipoprotein level ≥160 mg/dL or if the patient received recent medication (mainly statin) for dyslipidemia. The presence of diabetes was established if the patient had a hemoglobin A1c value of ≥6.9% (NGSP) at entry or if the patient received medication for hyperglycemia. Any patient who was a former or current smoker was characterized as a smoker. The presence of coronary artery disease was established if coronary lesions had previously been identified by angiography or if the patients had undergone previous coronary intervention.

2.3. Serum Fatty Acids. Fasting serum levels of EPA, docosahexaenoic acid (DHA), and AA were measured using gas chromatography at an external laboratory (SRL Inc., Tokyo, Japan).

2.4. Brain MRI. MRI examinations, consisting of T1 (TR 4200 ms, TE 102 ms, 90° flip angle, and 3 excitations) and T2 (TR 2000 ms, TE 10 ms, TI 750 ms, 90° flip angle, and 2 excitations) weighted and FLAIR (TR 8000 ms, TE 150 ms, TI 2100 ms, 90° flip angle, and 1 excitations) images, were performed using an MRI with a 1.5-T magnet (GE SIGNA-LX, GE electronics, USA). Brain images were obtained from 13 transverse slices (5 mm slice thickness, 2.5 mm slice interval) on the base of the anterior commissure-posterior commissure line or orbitomeatal line.

Using the WMH grading scale (Supplementary Figure in Supplementary Material available online at http://dx.doi.org/10.1155/2015/153437), MRI FLAIR-defined deep and subcortical WMH (DSWMH: 5 grades from grade 0 to 4), and periventricular WMH (PVH: 5 grades from grade 0 to IV), released from the Japanese brain dock society (http://jbds.jp/guideline.html) outlined by reports of Shinohara et al. [14] and Fukuda and Kitani [15], all images were read and assessed by the same 2 investigators (1 cardiologist and 1 radiologist) who were blind to the study. The interobserver reliability of the 2 investigators using 50 MRI scans was 0.91 in DSWMH and 0.88 in PVH as Spearman's rank correlation.

2.5. Carotid Ultrasound. Carotid ultrasonography was performed by a brain surgeon, using a standard protocol and the same ultrasound equipment with a high-resolution linear-array transducer and color Doppler (9L probe, Vivid 7 Dimension, GE Health Care, Horten, Norway). The presence of a plaque was established when at least 1 protruded and localized high echo signal of more than 2 mm as intima-media thickness in the internal carotid artery (ICA) was observed.

2.6. Evaluation of Cognitive Function. The Japanese version of the MMSE was performed on a total of 216 patients on the next hospital visit after MRI examination. This cognitive examination was performed only in patients being older than age of 60 years and had agreed to do it. They were divided into 3 groups depending on their MRI results as follows: Group A: 74 patients with no or mild ischemic lesions of either hyperintensity (DSWMH grade 0 or 1 and PVH grade 0 or I), Group B: 84 patients with at least 1 moderate ischemic lesion of either hyperintensity (DSWMH grade 2 or PVH grade II), and Group C: 58 patients with at least 1 advanced MRI ischemic lesion of either hyperintensity (DSWMH grade 3 or 4 or PVH grade III or IV). MMSE scores were compared among these 3 Groups.

2.7. Statistical Analysis. Two-tailed statistical analysis was performed with a 5% level of significance. The Wilcoxon 2-sample test was used to compare continuous variables. The chi-square (χ^2) test was used to compare categorical variables. Ordered logistic regression analysis was used to assess the association of selected dichotomized (present or not, or above or less) variables including risk factors for atherosclerosis (hypertension, dyslipidemia, diabetes, smoking, ICA plaque, and the median value of serum EPA/AA

Table 1: Factors associated with the progression of deep and subcortical white matter hyperintensity (DSWMH) grades using median values of PUFA.

Factors	DSWMH			
	Estimate	SE	Chi-square	*P* value
Age	−0.1217	0.0176	47.59	<0.0001
Female sex	−0.9703	0.2650	13.41	0.0003
Hypertension	−0.8629	0.2567	11.30	0.0008
Dyslipidemia	−0.1569	0.2447	0.41	0.5215
Diabetes	−0.3323	0.3353	0.98	0.3216
Smoking	−0.1907	0.2697	0.50	0.4795
ICA plaque	−0.9129	0.2608	12.25	0.0005
EPA/AA < 0.38	−1.4752	0.2900	25.88	<0.0001
DHA/AA < 0.84	−0.2798	0.2772	1.02	0.3128

Table 2: Factors associated with the progression of periventricular hyperintensity (PVH) grades using median values of PUFA.

Factors	PVH			
	Estimate	SE	Chi-square	*P* value
Age	−0.1534	0.0194	62.48	<0.0001
Female sex	−0.8844	0.2775	10.16	0.0014
Hypertension	−0.6569	0.2730	5.79	0.0161
Dyslipidemia	−0.1749	0.2612	0.45	0.5032
Diabetes	−0.5092	0.3536	2.07	0.1498
Smoking	−0.5132	0.2859	3.22	0.0726
ICA plaque	−0.5532	0.2748	4.05	0.0441
EPA/AA < 0.38	−1.1522	0.3072	14.06	0.0002
DHA/AA < 0.84	−0.4061	0.2994	1.84	0.1750

and DHA/AA ratios) and the 5 grades of two types of WMH. MMSE were evaluated using regression analyses among the 3 groups (A to C) of hyperintensities mentioned above. These statistical analyses were performed using JMP pro, version 9.0.2 (SAS Institute, Cary, NC, USA). Data are expressed as the mean ± standard deviation (SD).

3. Results

The raw data of 3 FUFAs and their ratios according to WMH levels in the two WMH types (DSWMH and PVH) are expressed in Supplementary Table. In the current study, logistic regression analysis using the median values of ω3 to ω6 PUFA ratios (0.38 in serum EPA/AA ratio and 0.84 in DHA/AA ratio) demonstrated that the progression in DSWMH grade was associated with aging, female sex, the presence of hypertension and ICA plaque, and a low serum EPA/AA ratio (<0.38) but was not related to dyslipidemia, diabetes, smoking, and a low serum DHA/AA ratio (<0.84) (Figure 1, Table 1). In addition, the progression in PVH grade was also associated with aging, female sex, the presence of hypertension and ICA plaque, and a low serum EPA/AA ratio but was not related to the other 4 risk factors (Figure 2, Table 2).

MMSE scores, evaluated in only 216 patients, showed minimal but statistically significant reductions with the progression of MRI ischemic lesions (Table 3).

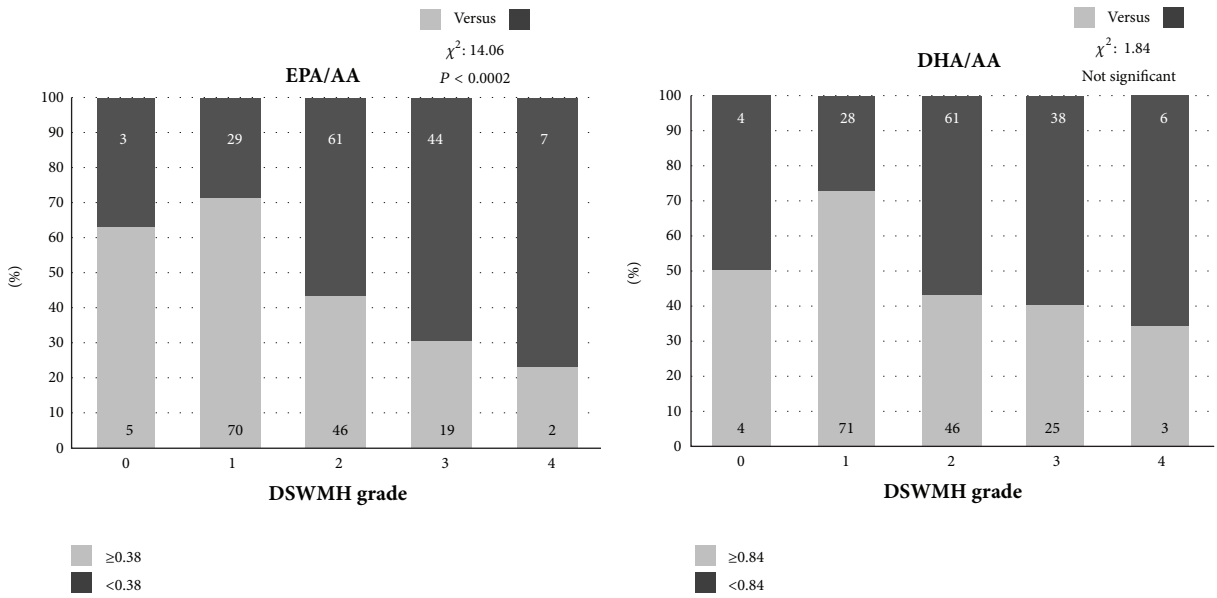
4. Discussion

The present study indicated that the progression of cerebral WMH was strongly related to low serum EPA levels as well as aging, female sex, hypertension, and the presence of ICA plaque, in presenile persons who did not develop clinically relevant cognitive impairment. Furthermore, cognitive function slightly deteriorated in these subjects with the progression of cerebral WMH.

With the development of medical technology, silent brain infarction, that is, WMH and lacunar viewed as cerebral small vessel disease, is being reported more frequently in older people [4]. The Rotterdam MRI scan study showed that newly developed silent brain infarcts were related to the presence of cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes, carotid plaques, and smoking, in addition to the age factor [3]. Several reports revealed that the increasing severity of WMH and lacunar was related to a decline in cognitive function scoring in these patients [5, 6]. Disease risks for cardiovascular disease and development of cognitive impairment are the same [16–18]. Currently, cerebrovascular disease is considered an important contributing factor to vascular cognitive impairment [19]. Furthermore, silent brain infarction provoked by small vessel disease, rather than large cortical cerebral infarction, is more important for the development of vascular cognitive impairment although various cardiovascular risk factors are related to the occurrence of both types of cerebral infarction [3, 4]. Brain tissue changes characterizing AD including amyloid β plaques and neurofibrillary pathology occur more often in patients with cerebrovascular disease than in healthy elderly people. As defined in the Nun study, a combination of Alzheimer type pathological changes and microvascular disease can worsen cognitive function in elderly persons [20]. Therefore, the development of small vessel disease has been shown to strongly influence the degree of cognitive function in patients with AD. In addition, several reports indicated that atherosclerosis in the carotid artery was associated with a prospective risk of cognitive impairment. Early intervention of carotid atherosclerosis may therefore be helpful in delaying or preventing the onset of cognitive impairment [21, 22].

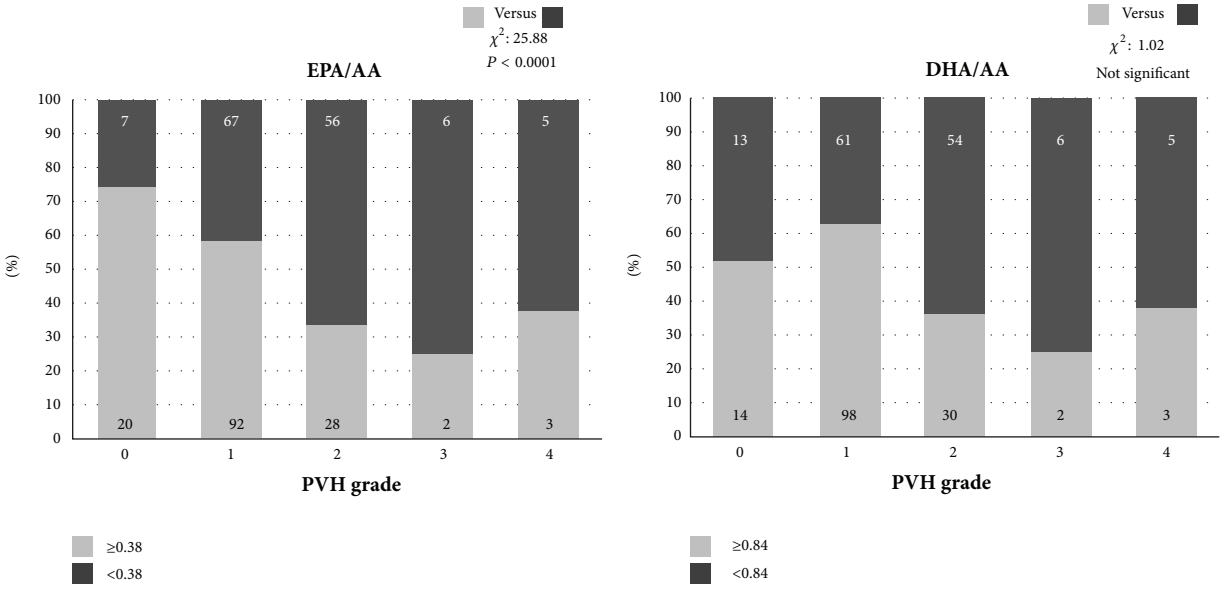
In a recent Japanese study, high intake of ω3 PUFA was shown to have antiatherogenic effects reducing the nonfatal coronary events in statin-treated patients with coronary artery diseases [9]. In addition, ω3 PUFA and low dose statin combination therapy reduced the risk of recurrent stroke in Japanese patients with hyperlipidemia [10]. These two studies and their subanalyses demonstrate that PUFA balance is an important diagnostic parameter to evaluate the disease progression in arteriosclerotic diseases associated with coronary artery and cerebrovascular diseases.

Various trials in patients with cerebrovascular diseases have indicated that ω3 PUFAs intake brings beneficial effects in primary and secondary prevention [10, 23]. In a large cohort study of older adults, high consumption of marine



(a) (b)

Figure 1: The distribution of patients with eicosapentaenoic acid to arachidonic acid (EPA/AA) ratios (a) and docosahexaenoic acid to arachidonic acid (DHA/AA) ratios (b) of more (white area in the column) and less (black area in the column) than each median value according to deep and subcortical white matter hyperintensity (DSWMH) grades 0–4. With the progression of DSWMH grade (figures in the column express patients numbers), the percentage of patients with EPA/AA ratios of less than 0.38 (black area on (a)) increased (chi-square: 43.64, $P < 0.0001$), and the percentage of those with DHA/AA ratios less than 0.84 (black area in (b)) also increased but did not reach statistical significance (chi-square: 1.02, no significance).



(a) (b)

Figure 2: The distribution of patients with eicosapentaenoic acid to arachidonic acid (EPA/AA) ratios (a) and docosahexaenoic acid to arachidonic acid (DHA/AA) ratios (b) of more (white area in the column) and less (black area in the column) than each median value according to periventricular hyperintensity (PVH) grades 0–IV. With the progression of PVH grade (figures in the column express patients numbers), the percentage of patients with EPA/AA ratios of less than 0.38 (black area on (a)) increased (chi-square: 30.20, $P < 0.0001$), and the percentage of those with DHA/AA ratios less than 0.84 (black area in (b)) also increased but did not reach statistical significance (chi-square: 1.84, no significance).

Table 3: Comparative data of Mini-Mental State Examination (MMSE) scores and background diseases between patients with advanced grade (grade ≥ 3 in DSWMH or grade ≥ III in PVH) and those with both no or mild grade in DSWMH and PVH.

Groups	A	B	C	
WMH	No or mild	Moderate	Advanced	P value
Grades	(0, I and 0, 1)	(II and 2)	(III, IV or 3, 4)	
Patients number	74	84	58	
Male/female	46/28	45/39	29/29	ns
Age	66.9 ± 5.3	67.5 ± 5.2	70.6 ± 6.3	$P < 0.0008^{**}$ $P < 0.005^{***}$
MMSE scores	29.7 ± 1.0	29.3 ± 1.3	28.4 ± 2.1	$P < 0.0001^{**}$ $P < 0.002^{***}$
EPA/AA	0.56 ± 0.20	0.36 ± 0.18	0.34 ± 0.24	$P < 0.0001^{*,**}$
DHA/AA	1.0 ± 0.24	0.79 ± 0.22	0.78 ± 0.24	$P < 0.0001^{*,**}$
Hypertension	43/31	60/24	48/10	
Dyslipidemia (+/−)	46/28	63/21	37/21	
Diabetes (+/−)	7/67	14/70	8/50	
Smoking (+/−)	22/52	30/54	23/35	
ICA plaque (+/−)	45/29	62/22	48/10	

*Between groups A and B, **between groups A and C, and ***between groups B and C.

ω3 PUFA reduced the prevalence of MRI-detected cerebral infarcts and WMH [8]. In addition, carotid intima-media thickness, reported to be a prospective risk parameter of cognitive impairment, was regressed in patients who took ω3 PUFA [24, 25]. Some investigations elucidated that patients with AD had low serum ω3 PUFA levels and this might have an etiological role in the pathogenesis of AD [26]. Some reports showed that administration of ω3 PUFA improved cognitive function in cases of mild cognitive impairment, although these studies did not include large patient cohorts [10–12]. Our investigation indicated that sufficient ω3 PUFA intake might be effective in preventing or postponing the future development of cognitive impairment in middle aged or presenile persons who do not have current cognitive decline but who do have certain atherosclerotic risk factors and serum ω3 PUFA abnormalities.

The therapeutic action of ω3 PUFA in vascular disease has been associated with antiinflammatory effects, the inhibition of platelet aggregation, the improvement of endothelial function, and plaque stabilization through the following actions [27–29]. PUFA is catalyzed through cyclooxygenases and lipoxygenases into several active eicosanoids including prostaglandins, thromboxanes, and leukotrienes and each interaction produces the physiological effects described above. EPA has 20 carbon chains in its structure and acts as an inhibitor of AA having the same 20 carbon chains [30]. From a biochemical position, EPA, having 20 carbon chains, is readily converted via both the cyclooxygenase and the 5-lipoxygenase pathways, but DHA having 22 carbon chains is not metabolized via either of these pathways. Ninomiya et al. reported that a low serum EPA/AA ratio is associated with a greater risk of cardiovascular disease in subjects with more high-sensitivity C reactive protein, but this association was not detected for the serum DHA/AA ratio [31]. In addition, in patients who underwent endarterectomy under administration of PUFA, a higher content of EPA was detected in the resected atherosclerotic plaques, but there was no difference in DHA content, compared to that in control subjects [32]. Therefore, EPA is not only a precursor of DHA, and there may be some differences in selectivity by phospholipase and metabolism in the arachidonic acid cascade between EPA and DHA, and these 2 ω3 PUFAs may show distinct therapeutic effects. In our study, only the reduction of EPA, and not DHA, was related to the progression of WMH, especially DSWMH.

The previous investigations revealed that brain had a unique PUFA composition with low level of EPA in contrast to high level of AA and DHA, and the lower level of EPA was maintained by several pathways including rapid metabolism by β-oxidation and lower recycling within brain phospholipids [33, 34]. Also, Freund Levi et al. evaluated the transfer of ω3 PUFAs (DHA-rich) to the brain by oral supplementation in patients with Alzheimer's disease (AD). So, their investigation revealed that EPA and DHA levels increased both in plasma and cerebrospinal fluid (CSF) and the increase of EPA in plasma was correlated with those in CSF levels, but there was no correlation between each DHA variation in plasma and CSF [35]. Furthermore, in this study there was an important observation that the more the DHA level increased in CSF the greater the change in AD biomarker (phosphorylated tau) in CSF. This study revealed that EPA transfer to the brain across the human blood brain barrier was much higher compared with DHA. These observations may also indicate a benefit of EPA supplement in patients with cognitive impairment.

Limitations of this study were as follows. The estimation of WMH was only semiquantitatively performed and this may potentially affect our ability to accurately estimate the true relationship between ω3 PUFA and WMH. The subjects with atherosclerotic factors, such as dyslipidemia, diabetes, or smoking, were underrepresented in the same population and these 3 risk factors were not related to the progression in WMH. This may be related to patient backgrounds, since half

of the patients in the study had received various examinations for physical checkup. In addition, only FLAIR images were used for evaluating WMH, although we had data from T1 and T2 weighted images. Therefore, other ischemic lesions may be missed.

In conclusions, this study suggested that the progression of WMH in presenile patients was associated with a low serum EPA/AA ratio, as well as aging, female sex, hypertension, and the presence of ICA plaques, and accompanied minimal, but significant, deterioration in cognitive function. Sufficient $\omega 3$ PUFA intake may be useful in preventing cognitive impairment prior to clinical development.

Conflict of Interests

The authors did not have any conflict of interests in this paper.

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Review Article

Working Memory and Executive Function Decline across Normal Aging, Mild Cognitive Impairment, and Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurodegenerative disease marked by deficits in episodic memory, working memory (WM), and executive function. Examples of executive dysfunction in AD include poor selective and divided attention, failed inhibition of interfering stimuli, and poor manipulation skills. Although episodic deficits during disease progression have been widely studied and are the benchmark of a probable AD diagnosis, more recent research has investigated WM and executive function decline during mild cognitive impairment (MCI), also referred to as the preclinical stage of AD. MCI is a critical period during which cognitive restructuring and neuroplasticity such as compensation still occur; therefore, cognitive therapies could have a beneficial effect on decreasing the likelihood of AD progression during MCI. Monitoring performance on working memory and executive function tasks to track cognitive function may signal progression from normal cognition to MCI to AD. The present review tracks WM decline through normal aging, MCI, and AD to highlight the behavioral and neurological differences that distinguish these three stages in an effort to guide future research on MCI diagnosis, cognitive therapy, and AD prevention.

1. Introduction

Alzheimer's disease (AD) is the sixth leading cause of death in the United States and the fifth leading cause of death in people over the age of 65, as determined by the Center for Disease Control [1]. The risk of developing AD increases exponentially with age [2]. Currently, verification of an AD diagnosis occurs through postmortem detection of pathology in neural tissue, specifically extracellular amyloid plaques and intracellular neurofibrillary tau tangles; however, cognitive changes are discernible early during AD pathogenesis and mild cognitive impairment (MCI). The following review examines the detection of working memory (WM) deficits through behavioral, functional, and structural changes amongst nonimpaired, MCI, and AD adults. We further investigate if tracking WM and executive function skills over time, in addition to biomarker analysis, can identify individuals during MCI as being at risk for progression towards AD.

2. Tracking Decline Pre- and Post-AD Onset

Between 10 and 20 percent of adults above the age of 65 are diagnosed with MCI [3–5], and approximately 10 percent of MCI adults progress to AD [6]. Compared to nonimpaired age-matched adults, those with MCI tend to develop AD more rapidly [7]. Neuropathologically, MCI adults exhibit amyloid plaques and neurofibrillary tau tangles in AD-vulnerable regions of the brain responsible for episodic memory, specifically in the olfactory cortex, subiculum, and parahippocampal gyrus in the medial temporal lobes [8, 9], albeit to a lesser degree compared to an AD patient's brain [10].

Behavioral research indicates that MCI adults show cognitive deficits in WM, central executive function, and attentional resources compared to nonimpaired age-matched controls [11–15]. Preclinical individuals self-report subjective cognitive decline prior to evidence of impairment on cognitive assessments [16]. While WM impairments during MCI

fall short of measurable interference with activities of daily living, they are more severe than WM deficits that result from normal aging. Although these impairments do not involve episodic memory, they can reliably predict the progression from MCI to AD [16, 17], particularly when paired with deficits in episodic memory [13, 15]. Taken together, results of neuropathology and cognitive impairment suggest that AD diagnosis can be based on a continuum that begins as MCI and develops into AD, although there may be more subtle signs prior to an MCI diagnosis.

These observations raise two unanswered questions: (1) *what differences exist between cognitively normal, MCI, and AD adults regarding neural activation and recruitment of WM resources*? and (2) *what can these differences tell us about an individual's likelihood of progressing to MCI or AD*? Research suggests there is great potential for cognitive deficit reversal and strengthening of executive function at the MCI stage [18]. MCI adults are reported to regain cognitive function by engaging in physical exercise [19], eating healthy foods (e.g., fish oils) [20], reducing LDL cholesterol intake [21], and practicing challenging cognitive tasks [22]. Therefore, clinical tools that accurately detect the progression from normal cognitive aging to MCI award preclinical adults the opportunity to actively participate in tasks that may help improve and preserve their cognitive function.

3. Working Memory: A Brief Overview

WM is a system that underpins cognitive activities ranging from attention allocation to specific stimuli (i.e., selective attention) to complex decision-making [23]. More specifically, WM promotes active short-term maintenance of information for later access and manipulation [24]. The form of the information held in WM is both auditory, as maintained by the phonological loop (e.g., to promote language comprehension), and visual, as maintained by the visuospatial sketchpad (e.g., to promote visuospatial reasoning). Behavioral methods reveal that each of these subsystems is controlled by the central executive, an attentionally limited gatekeeper that selects auditory and visual material for maintenance and manipulation [24]. Importantly, the central executive is not a memory system but an attention controller. Because attention span is limited and subject to individual differences, executive functioning varies with normal aging. For example, nonimpaired older adults exhibit impairments associated with the number of items they can selectively hold in a subsystem at any given time, suggesting WM load impairment [25, 26].

WM capacity may be assessed using behavioral tasks that result in a quantitative measure of memory span. These tasks require participants to encode lists of stimuli (such as letters, digits, words, or pictures), often involving either a selective attention task during encoding (i.e., attending to just one feature of a stimulus, such as the font color of the letters) or a divided attention task (i.e., attending to multiple features of a stimulus, such as font color and location on a computer screen) to further tax WM capacity [24]. As one example of a span task, in the "*n*-back task," participants monitor a series of presented stimuli during encoding and are asked to recall whether a specific stimulus matches one presented *n* trial previously, typically 1, 2, or 3 [27]. The behavioral measure of WM capacity is the number of correctly matched stimuli. Tasks such as the *n*-back task require divided attention and online monitoring, a process of updating the memory of presented stimuli which taxes the central executive's limited resources [27].

Region-specific neural activation in response to a memory task is analyzed through neuroimaging techniques including functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). These neuroimaging methods depict recruitment of specific brain regions during a WM task, demonstrating that activation of the prefrontal cortex (PFC), parietal regions, cingulate gyrus, and hippocampus are associated with WM processing in nonimpaired young adults [28]. To return to the *n*-back task as one measure of WM, neuroimaging during the completion of that task reveals activation of the posterior parietal cortex, premotor cortex, rostral PFC, dorsolateral PFC, and ventrolateral PFC [27]. These neuroimaging tools allow researchers to compare brain activity during WM tasks of different populations to uncover similarities and contrasts between the selected groups.

4. Working Memory in Normal Aging

One model addressing neural activation differences between nonimpaired older adults (typically 60+ years old) and nonimpaired younger adults (typically 18–30 years old) during WM tasks is the Hemispheric Asymmetry Reduction in Older Age model, or HAROLD [29]. Findings in support of the HAROLD model reveal that, during WM tasks, young adults display left PFC activation during verbal WM tasks and right PFC activation during spatial WM tasks, while older adults display bilateral activation of the PFC during both verbal and spatial WM tasks [30]. Initially, this lack of asymmetrical, specialized activation in older adults was believed to indicate poor cognitive function and inefficient communication between the two hemispheres, as older adults were not recruiting the correct resources. However, behavioral and neuroimaging data support a *compensatory view* of bilateral activation where older adults compensate for age-related decline by recruiting additional neural networks to maintain performance on the task at lower levels of complexity. These tasks involve fewer stimuli for WM maintenance and do not require as many attentional resources as more complex task levels [31]. Further, when older adults receive environmental support during complex task performance, brain region recruitment mirrors that of younger adults. For example, older adults display enhanced recruitment of the left frontal cortex, almost to the same degree as young adults, when executing semantic encoding tasks while receiving semantic elaboration prompts from an experimenter [32]. Frontal cortex recruitment suggests that the frontal cortical resources are functioning in older adults but are not recruited properly during self-initiated tasks requiring executive control.

Expounding on the compensation view of the HAROLD model, the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) [33] asserts that overactivation

of neural circuits in nonimpaired older adults, relative to nonimpaired younger adults, is necessary for completion of WM tasks and correlates with greater performance when normalized for task demand. Additionally, during specific memory tasks (e.g., incidental encoding of complex visual scenes) nonimpaired older adults display bilateral overactivation of the frontal cortex, including the PFC, to compensate for decreased activity with age of more specialized regions such as the medial temporal lobes, relative to nonimpaired younger adults [34]. Payer et al. [35] found that, during a visual WM task in older adults, underactivation of the ventral visual cortical (VVC) pathway, which includes areas of the occipital and temporal lobes, was accompanied by bilateral overactivation of the PFC.

The visual WM task involved encoding and identifying face and house stimuli that typically activate two regions of the VVC pathway: the fusiform face area and the parahippocampal place area, respectively. Twelve younger and 12 older adults were presented with three consecutive images of either faces or houses. Following image presentation, participants viewed a probe image and decided whether the image matched any one of the three preceding target images (an example of an *n*-back task). Young adults matched the probe image stimulus to target stimuli with greater accuracy than older adults, although there was no significant difference in response times between the two age groups. Interestingly, Payer et al.'s [35] imaging data failed to reliably show PFC overactivation in conjunction with VVC pathway underactivation; however, the authors note that there was a trend present. In sum, the neuroimaging data hint at bilateral overactivation as a mechanism for compensation in old age as explained by the CRUNCH model, although older adults still performed poorly compared to younger adults.

Schneider-Garces et al. [36] further assessed the impact of aging on WM by examining whether the patterns of bilateral overactivation in nonimpaired older adults predicted by the CRUNCH model would disappear when task demand was comparable across age groups. Task demand was estimated from individual performance on the Sternberg task [37], a task that requires participants to remember whether a single probe stimulus was part of a series of stimuli presented previously. Neural activation differences between nonimpaired older and younger adults during completion of the Sternberg task can be entirely attributed to WM span differences regardless of age. Further, younger adults exhibited bilateral overactivation of specific cortical areas such as the dorsolateral PFC when task demands were high (4–6 stimuli presented with the probe), suggesting that bilateral activation can be a beneficial mechanism for recruiting additional neural resources earlier in life rather than a sign of cognitive impairment.

Findings from Schneider-Garces et al. [36] further suggest that impaired WM capacity in older adults is due to reduced selective attention. Older adults struggled with Sternberg task completion when the number of stimuli presented exceeded their working memory span; they also displayed slower response times and lower accuracy rates, especially at higher WM loads (4–6 item sets). Older adults could not maintain more than four items in WM at a given time, while younger adults could maintain five or more items in WM. Neurologically, this decrease in capacity and processing speed is associated with age-related changes in the dorsolateral PFC [38].

Both groups in Schneider-Garces et al.'s [36] study exhibited neural activation of the occipital, premotor, parietal, prefrontal, and medial frontal areas during task completion. Younger adults showed mainly left hemispheric activation with some bilateral activation of frontal and parietal regions at high loads, suggesting that increasing task demand typically leads to recruitment of contralateral brain regions as posited by Reuter-Lorenz and Cappell [33] and the CRUNCH model. Older adults, on the other hand, exhibited increased neural activity (overactivation of bilateral brain regions) during low WM loads (2–4 item sets) and underactivation at high loads, suggesting that overactivation occurs only when tasks are easy enough for compensatory mechanisms to be beneficial. Underactivation occurs when the task exceeds WM capacity (4+ items for older adults). The authors speculate that older adults' brain activity peaked during low loads and declined during high loads because a smaller WM span results in decreased attentional control and greater susceptibility to interfering stimuli, a marker of failed inhibition [36]. Interestingly, the authors examined neural activation in relation to each participant's WM span and found no differences in levels of brain activity at respective peak WM capacity across age groups.

5. Working Memory in MCI

MCI is often characterized by slight but noticeable deficits in attention, learning and memory, executive function, processing speed, and semantic language [13–15]. Over the years, researchers have adjusted the definition of MCI as well as the cognitive and pathological criteria that define the various subsets of MCI [39, 40]. MCI is divided into three subtypes: amnestic-MCI (a-MCI), multiple domain a-MCI (a-MCI+), and nonamnestic-MCI (na-MCI) [13]. a-MCI adults exhibit objective episodic memory impairments, a-MCI+ adults exhibit episodic memory and other cognitive impairments (e.g., WM, executive function, processing speed, and attentional processing), and na-MCI adults exhibit cognitive impairments not related to episodic memory [13]. It was previously believed that a-MCI had the highest rate of conversion to AD given the profound episodic memory deficits in AD; however, recent findings suggest that early impairments in visual episodic memory, executive function, semantic language/memory, attention, and WM are also strong predictors of progression from MCI to AD [13, 41, 42].

As demonstrated by Schneider-Garces et al. [36], controlling for WM load differences yields a reliable measure of WM capacity that is independent of age. Kochan et al. [12] used task load to assess visuospatial WM in MCI because assessing WM decline in this preclinical population compared to nonimpaired adults may provide insight into how pre-AD pathogenesis affects WM. The researchers recruited 35 MCI individuals with various MCI subtypes and 22 age-matched nonimpaired controls to complete a visuospatial WM task with three load levels (low, medium, and high) while being

imaged in an fMRI scanner. During each trial, participants viewed a grid with abstract square shapes, the target stimuli. During the encoding phase of the task participants had to remember the position of each square on the grid, and in the retrieval phase that followed seconds later they had to identify whether there was at least one square that remained in the same encoding trial position. The researchers implemented a calibration method for the WM task to control for each participant's performance level to maintain 75–85% accuracy for the medium-load trials and 60–70% accuracy for the high-load trials.

The behavioral results from Kochan et al. [12] indicated that the percentage of MCI adults receiving lower load stimulus sets compared to higher load sets in order to achieve the calibration criteria was significantly greater than nonimpaired adults. Additionally, MCI participants exhibited slower response rates for the 2-target and 3-target trials compared to the nonimpaired controls, although this difference was only marginally significant. Upon examination of the brain imaging data, nonimpaired age-matched controls displayed increased activation of the right precuneus region of the parietal lobe and the right anterior cingulate gyrus (regions associated with WM) with increasing task load. The reverse was observed for the MCI group, where activation of these regions was greater than the nonimpaired group at low loads (overactivation) and decreased as load increased (underactivation). The MCI group as a whole, regardless of subtype classification, showed WM behavioral and neurological deficits compared to the age-matched control group.

Clément et al.'s [11] research demonstrates that compensation and neuroplasticity occur not just in normal aging but in MCI, too, as lesions and brain damage are not significant enough to hinder the recruitment of additional neural resources needed to accomplish cognitive tasks requiring executive function control (e.g., manipulation and divided attention). The authors proposed that as MCI progressed toward AD there would be a disintegration of the compensatory networks as observed by underactivation of the lateral PFC, precuneus, and posterior parietal regions, all involved in executive function, compared to nonimpaired age-matched controls. Furthermore, the authors hypothesized that MCI participants with higher cognitive functioning would display overactivation of those brain regions relative to nonimpaired controls and that this overactivation would be positively correlated with performance on the two tasks. The 14 a-MCI and a-MCI+ participants were split evenly into two groups, MCI higher-cognition and MCI lower-cognition, based on their scores on the Mattis Dementia Rating Scale (MDRS) [43] assessing global cognitive function. The manipulation task required online monitoring and manipulation of the alphabet while solving alphanumeric equations. For the divided attention task participants were required to solve more alphanumeric equations while monitoring if a color change occurred on the screen. There was a focused attention control task for both the manipulation and divided attention tasks, during which participants looked at a random string of numbers and letters and had to report whenever the font color changed from black to red.

The behavioral results showed that the MCI lower-cognition group was significantly more impaired than the MCI higher-cognition group and the nonimpaired control group on neuropsychological measures of processing speed and executive function. For the manipulation task, the two MCI groups performed significantly worse (i.e., answered fewer questions correctly) than the control group, and there was no significant difference between the two MCI groups. For the divided attention task, the MCI lower-cognition group performed worse than both the MCI higher-cognition group and the nonimpaired control group, and there was no significant difference between the MCI higher-cognition group and the nonimpaired controls.

The neuroimaging data showed that during the manipulation task MCI higher-cognition participants displayed significant overactivation in the left postcentral gyrus and the left middle and superior frontal gyri compared to the nonimpaired controls. The MCI lower-cognition group showed underactivation in the left inferior and middle frontal gyri and left occipitotemporal regions compared to the nonimpaired controls. As for the divided attention task, MCI higher-cognition participants demonstrated overactivation of the left inferior frontal gyrus, the left insula, the left caudate and putamen, the left thalamus, left cerebellum and midbrain, left fusiform gyrus, and the left and right anterior cingulate cortex. For the MCI higher-cognition group increased performance on the divided attention task was directly correlated with greater activation of the right putamen, the anterior cingulate cortex (responsible for WM), the left caudate, the left insula, and the left inferior frontal gyrus [11].

Clément et al. [11] claim that the data support their hypothesis that greater activation is indicative of neuroplasticity, which compensates for cognitive decline in the very early stages of MCI when individuals still have relatively intact cognitive abilities. This compensation is evident from the positive correlation between brain activation and performance on the divided attention task for the MCI higher-cognition group. On the other hand, performance on the manipulation task was not positively correlated with the observed overactivation in MCI higher-cognition participants. These inconsistencies could be a sign that manipulation capabilities start to deteriorate earlier than divided attention, but more research on these two attentional processes is needed using different assessment tools to clarify the existing discrepancies. Based on these findings, tracking executive function performance with divided attention and manipulation tasks in older adults can be a useful tool to assess an individual's cognitive abilities as one ages.

6. Factors Predicting Progression from MCI to AD

In order to examine when executive function and WM deficits appear, Belleville and colleagues [16] compared attentional control performance using tasks to assess divided attention, online manipulation of stimuli, and the ability to inhibit unrelated stimuli among participants in a-MCI, a-MCI+, and mild early-stage AD. Manipulation skills were assessed using an alphabetical recall task [44, 45], inhibition

of interfering stimuli was assessed with the Hayling task [46], and divided attention was assessed using the adapted Brown-Peterson procedure [45]. AD participants performed significantly worse than the nonimpaired age-matched adults on all three tasks of attentional control, whereas MCI participants performed worse than nonimpaired controls just on the Brown-Peterson procedure when there was a 30-second delayed recall.

One year following the study, a subset of the MCI participants was assessed for progression to AD. Eight people were diagnosed with AD, leading authors to revisit the data to determine if there were factors that predicted their AD prognosis. Belleville et al. [16] reported that those MCI participants who later declined to AD performed significantly worse than the control group on measures of manipulation skills and divided attention. The Brown-Peterson procedure proved to be the most sensitive of the three assessments, suggesting that deficits in divided attention may be one of the first signs of WM decline in the preclinical stages of AD. These deficits in divided attention may appear around the same time that episodic memory deficits emerge. The attentional control deficits that quickly follow as individuals with MCI progress to AD include manipulation skills and failed inhibition of irrelevant stimuli. The results indicate that individual scores on divided attention and manipulation skills seem to be predictors of progression from MCI to AD.

In light of recent research suggesting the importance of deficits in attention, WM, and episodic memory in predicting the conversion of MCI to AD, Summers and Saunders [15] designed a longitudinal study to track which MCI subtypes were more likely to progress to AD over a 20-month period; this study was an extension of a previous longitudinal study by Saunders and Summers [13]. Researchers administered a series of clinical and neuropsychological tests assessing verbal and visual episodic memory, WM, attention, executive function, and language processing at the start of the study and 20 months after study commencement. At the 20-month assessment, 10 of the 81 MCI participants (12%) were determined to have progressed to AD and 20 participants (25%) regained normal cognitive function and memory. Only participants with a baseline diagnosis of a-MCI+ were identified as having "probable AD" at 20 months by a physician who was blind to the participants' initial diagnosis. The remaining 51 participants (63%) continued to meet MCI criteria, and 25% of the 12 participants initially diagnosed with a-MCI progressed to a-MCI+. Researchers point to the need for more sensitive diagnostic criteria for MCI and for predicting which MCI individuals will progress to AD by means of longitudinally assessing cognitive function and testing for biomarkers for AD [15, 39, 40].

In agreement with Summers and Saunders [13], Klekociuk et al. [42] argue that the current MCI diagnostic tools are not sensitive enough, thus leading to great variability in the number of MCI individuals who regain normal levels of function over time and those who remain to be diagnosed with MCI. The researchers utilized a mix of cognitive and neuropsychological assessments to better predict which participants had MCI and would most likely progress to AD. The battery of neuropsychological tests used at screening was not the same as the battery of assessments used at the 9-month and at 20-month poststudies, though the same categories of function were assessed. A robust set of tests assessing nonmemory components were administered throughout the study. The results indicate that tests of sustained attention, semantic memory, WM, episodic memory, and selective attention led to correct predictions of MCI or unimpaired function with 80% accuracy. These assessments can also be used in clinical settings to monitor cognitive function and serve as a red flag for worsening performance on executive function and WM tasks over time, especially in conjunction with worsening episodic memory. The authors suggest that the a-MCI+ subtype is the only true form of MCI because declines in episodic memory and cognitive function together are distinctly associated with MCI.

The present literature has not conclusively shown whether WM, specifically executive function, predicts the progression towards AD. For example, a fairly recent study by Peters et al. [47] examined neuropsychological tests and brain imaging data to determine which factors accounted for progression from MCI to AD. Of importance is the fact that the authors did not account for different MCI subtypes. The participants in the 2014 study were diagnosed with MCI based on criteria established previously by Petersen and Morris [48]: (1) participant complaints of cognitive or memory deficits; (2) a score of 1.5 standard deviations below average (based on age and level of education) on measures assessing episodic memory, language, or attention; (3) no functional impairment with activities of daily living; and (4) a score of 26 or below on the Mini Mental Status Exam (MMSE) [49] and 130 or below on the MDRS [43] which are the two major assessments of global cognitive function. As argued by Klekociuk et al. [42], the MMSE is not sensitive in diagnosing MCI and produces a high false-positive rate. Consequently, the screening criteria used by Peters et al. [47] are too broad to distinguish between the three MCI subtypes, and as a result correlations between AD onset and specific MCI subtypes cannot be distinguished in this study.

Participants completed neuropsychological and brain imaging tests three times during a two-year period to determine which participants progressed to AD [47]. At the two-year mark 18 of the 40 total MCI participants (45%) progressed to dementia; of those, three (17%) were diagnosed with mixed dementia (i.e., met criteria for both probable AD and vascular dementia) and 15 (83%) were diagnosed with probable AD. The imaging results showed that progression from MCI to AD could be predicted by observing structural brain changes, specifically cortical thinning of the right anterior cingulate and middle frontal gyri. The neuropsychological results reported that poor performance of episodic memory and free recall, but not of executive function and WM, predicted progression to AD. However, the right anterior cingulate and middle frontal gyri are associated with WM, specifically with selection and inhibition, processes by which individuals choose relevant information to remember and irrelevant information to discard [50]. The discrepancy between the imaging and neuropsychological data in Peters et al.'s [47] study could be due to the type of WM assessment which specifically measured task switching and planning but

not inhibition. Thus the limited neuropsychological tests do not tell the full story behind the observed structural changes. Furthermore, the authors note the small sample size of 40 MCI participants.

7. Working Memory in AD

Baudic et al. [51] examined executive functioning skills in adults with AD to determine when executive function deficits emerged as the disease progressed. Participants with very mild and mild AD exhibited executive function deficits relative to nondemented control subjects as determined by their scores on a verbal fluency test, Raven's Colored Progressive Matrices [52] testing visuospatial abilities, Mental Control task (naming the months backwards) [53], Trail Making Test, Part B [54], assessing executive function, and a Modified Card Sorting Test [55] assessing perseveration. The observed deficits in visuospatial skills were explained in terms of executive functioning through poor decision-making. Although there was no significant difference between the two AD populations in performance on the Mental Control task, the mild AD patients (but not the very mild AD patients) performed worse than nonimpaired controls on the Mental Control task. Additionally, both AD groups performed significantly worse than nondemented controls on the Trail Making Test and the Modified Card Sorting Test. As a whole the results support the idea of persisting executive function deficits and perseveration in early-stage mild AD.

Castel and colleagues [56] examined two components of WM in AD by measuring WM efficiency (the number value of the words recalled) and capacity (number of words recalled). To measure WM efficiency, Castel et al. [56] assigned a value from 1 to 12 to words that participants were required to memorize from a list. Participants with early-stage AD (mild and very mild) and nonimpaired younger and older adults were instructed to memorize words with the highest point value to maximize their score. The results indicated that young adults recalled significantly more words than all other groups, thereby demonstrating greater WM capacity. The younger and older nonimpaired adults earned significantly greater value scores (a sign of WM efficiency) than both of the early AD groups. This pattern was present even when controlling for recall performance (a measure of WM capacity), thus indicating deficits in selective attention in the AD population.

8. Therapeutic Approaches and Cognitive Tasks to Activate WM

Researchers have learned much about WM decline in normal aging over the recent years. Reuter-Lorenz and Park [57] suggest that aging puts a strain on WM and that the brain must recruit additional contralateral resources even at low task demand to compensate for the decline (for a review of their Scaffolding Theory of Aging and Cognition, STAC, see [57]). Identification of the functional, structural, and behavioral hallmarks of normal aging aids in our understanding of atypical changes indicative of dementia. There is some research to suggest that this cognitive restructuring occurs in the MCI brain too, before the pathology has caused further brain damage, as in the case of AD [11]. The *underrecruitment theory* [32] suggests that the frontal brain regions may be viable but not voluntarily activated during encoding and retrieval in MCI. This calls for intervention strategies to strengthen neural pathways and preserve cognitive abilities, especially WM and executive function, in MCI. Based on the current literature reviewed, the interventions should target selective and divided attention, manipulation skills, and inhibition of interfering stimuli. These cognitive functions as part of the central executive are essential for WM efficiency and maximizing capacity; they are compromised early in AD and even during MCI. The current research on therapeutic approaches in MCI is encouraging but results are inconsistent across studies due to varying methodologies, small sample sizes, and lack of long-term follow-up.

Li et al. [58] conducted a meta-analysis of 17 studies assessing the effects of cognitive stimulation or cognitive rehabilitation on MCI participants. The results indicated that while the nonimpaired controls did not improve on measures of global cognition (MMSE scores), episodic memory, executive function/WM, visuospatial processing, or attention/processing speed, the MCI participants receiving some form of cognitive intervention made significant gains in episodic memory and executive function/WM relative to the MCI controls. Some of the interventions focused on attention, executive control, auditory processing speed and auditory WM, practical problem solving, stress reduction techniques, and occupational therapy.

A theoretical rehabilitation model for MCI proposed by Huckans et al. [59] shows how identified protective factors (Mediterranean diet and physical/mental exercise) and risk factors (smoking and heavy alcohol consumption) mediate the progression to dementia or reversal to normal cognition. The authors reviewed multiple studies of four nonpharmacological cognitive rehabilitation therapies (CRTs) used to promote reversal to normal cognitive functioning and decrease risks of progression to AD: restorative cognitive training, compensatory cognitive training, lifestyle interventions, and psychotherapeutic interventions. As a whole, the studies failed to consistently show the beneficial effects of CRTs, but some of the reviewed articles implemented a stronger experimental design and their results reflect the positive impacts of CRTs on MCI. For example, Scherder et al. [60] reported that aerobic exercise for at least 30 minutes daily (3 times a week) helped improve executive control. Additional CRT studies examining lifestyle interventions reported that resistance training twice a week for a 12-month period helped improve executive functioning, memory, and selective attention in MCI adults [61]. A study by Tsolaki et al. [62], which featured the largest sample size, implemented a multimodal CRT program in which MCI participants took part in sixty 1-hour sessions over a period of 6 months focusing on attention, memory, and executive function in addition to psychotherapeutic treatment. The MCI participants in the CRT group significantly improved on measures of global cognition, memory, attention, visuomotor ability, executive function, language, and daily functioning between pre- and postassessment. These studies, reviewed in depth in Huckans

et al. [59], demonstrate that neuroplasticity and cognitive restructuring in the MCI brain can decrease the risk of developing AD.

9. Conclusions

Recent research has illuminated compensatory mechanisms that occur in the brain as a result of aging. Older adults recruit bilateral regions of the PFC to complete WM tasks requiring executive control. Overactivation of bilateral PFC regions in older adults is an example of cognitive restructuring as individuals begin to experience difficulties with executive function tasks such as divided attention and inhibition of interfering stimuli. As a result older adults have a lower WM capacity than younger adults.

Executive dysfunction becomes more pronounced during MCI, and an increasing number of studies have reported the existence of both cognitive and memory deficits in MCI. Brain imaging data also demonstrate that MCI individuals display underactivation compared to nonimpaired adults on WM tasks of increasing load. This evidence promotes the use of WM and executive function assessments to track behavioral and functional changes to distinguish between normal aging, MCI, and AD. One suggestion is to implement a robust set of neuropsychological tests into clinical practice which detect WM and executive functioning deficits over time. Follow-up on WM and executive function skills over time can pinpoint stages of cognitive decline and prompt for cognitive intervention during the preclinical stages of AD when interventions are likely to have the greatest effect on cognitive functioning.

Importantly, very early stages of AD are marked by executive dysfunction and WM impairments in addition to episodic memory deficits. These cognitive deficits begin during MCI and appear to be a sign of progression to AD. Therefore, future studies are recommended to detect and monitor changes in WM, attention, and executive function in MCI and older nonimpaired individuals. The critical preclinical period also provides the opportunity for cognitive interventions to stop or slow the progression to AD. Such studies on therapeutic interventions should focus on tasks that emphasize executive function skills like selective or divided attention, inhibition, manipulation, and task switching. Incorporation of assessments and interventions that are targeted towards WM, attention, and executive function in research and clinical settings expands the tools available to monitor and treat patients at the early stage of disease and provide the benefit of being of low cost, noninvasive, and relatively easy to implement.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Trying to Put the Puzzle Together: Age and Performance Level Modulate the Neural Response to Increasing Task Load within Left Rostral Prefrontal Cortex

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Age-related working memory decline is associated with functional cerebral changes within prefrontal cortex (PFC). Kind and meaning of these changes are heavily discussed since they depend on performance level and task load. Hence, we investigated the effects of age, performance level, and load on spatial working memory retrieval-related brain activation in different subregions of the PFC. 19 younger (Y) and 21 older (O) adults who were further subdivided into high performers (HP) and low performers (LP) performed a modified version of the Corsi Block-Tapping test during fMRI. Brain data was analyzed by a 4 (groups: YHP, OHP, YLP, and OLP) × 3 (load levels: loads 4, 5, and 6) ANOVA. Results revealed significant group × load interaction effects within rostral dorsolateral and ventrolateral PFC. YHP showed a flexible neural upregulation with increasing load, whereas YLP reached a resource ceiling at a moderate load level. OHP showed a similar (though less intense) pattern as YHP and may have compensated age-effects at high task load. OLP showed neural inefficiency at low and no upregulation at higher load. Our findings highlight the relevance of age and performance level for load-dependent activation within rostral PFC. Results are discussed in the context of the compensation-related utilization of neural circuits hypothesis (CRUNCH) and functional PFC organization.

1. Introduction

Orientation and navigation in everyday life require a permanent adaptation of the spatial memory system. Spatial information has to be constantly integrated, maintained, updated, and recalled. The efficient control and coordination of these processes depend on effective spatial working memory operations which find their neural substrate in an anterior-posterior network of particularly prefrontal and parietal brain regions [1–3]. Damage to this network caused by stroke or neurodegeneration, for example, causes working memory deficits. With the establishment and advancement of neuroimaging techniques in the last decade, however, it could be shown that working memory performance declines across the life span even in the healthy brain [4] and that this age-related decline is associated with both structural [5–8] and functional [9–15] cerebral changes. On the functional level, age-related alterations are evident for most regions of the spatial working memory network. Nevertheless, the focus of research lies on the prefrontal cortex because it is common sense that this brain region plays the most prominent role for age-related working memory decline [16]. By contrast, the kind and meaning of activation changes within prefrontal cortex are heavily discussed. In fact, there are many studies

reporting either decreased prefrontal cortex activation in older compared to younger adults ("underactivation") as a sign of functional deficits [17, 18] or increased prefrontal activation ("overactivation") being interpreted as neural inefficiency [19, 20], a reduction of regional specificity [20–22] or compensatory neural mechanism for age-associated deficits [12, 23–25]. Specifically, neural compensation was attributed to a more bilateral activation of the prefrontal cortex as proposed by the *hemispheric asymmetry reduction in old adults* (HAROLD) model [26]. The reasons for these partly inconsistent results are manifold and can be attributed to differences in study design and methodology. In fact, one of the most important mediating factors seems to be performance quality. Prefrontal overactivation or increased bilaterality in the presence of an age-related performance decline, for example, would argue for neural inefficiency, reduced regional specificity, or failed compensation, whereas overactivation or increased bilaterality at a steady performance level may be signs of successful compensation. By contrast, reduced prefrontal activation in older adults associated with lower performance accuracy was consistently interpreted as neural dysfunction [9, 10, 27–33].

CRUNCH. A second important mediating factor next to performance accuracy is the working memory load level of the applied paradigm. In fact, the *Compensation-Related Utilization of Neural Circuits Hypothesis* (CRUNCH) by Reuter-Lorenz and Cappell [34] proposes that the kind and meaning of activation differences between older and younger adults are strongly dependent not only on performance quality, but also on the cognitive demands of the applied task: older adults, in comparison to younger adults, show comparable performances at a low demand level but more intense or bilateral prefrontal activation indicating a recruitment of additional neural resources as compensatory response to limited working memory capacity. At high task demands, by contrast, older adults show poorer working memory performances accompanied by decreased prefrontal activation, pointing toward limited neural resources and failed compensation [10, 13, 27, 28, 32, 35].

Prefrontal Cortex Organization. Finally, the impact of performance level and task load on age-related changes in prefrontal brain activation might vary across specific subregions of the prefrontal cortex. For example, age-related compensatory overactivation could manifest in dorsolateral but not ventrolateral prefrontal areas. Consequently, other approaches refer to a functional prefrontal cortex organization and specific age-related changes within its subregions. Initially, dorsolateral prefrontal parts of the prefrontal cortex were attributed to higher-level cognitive processes, whereas the ventrolateral prefrontal cortex was rather related to the relatively passive maintenance of information [36–41]. Following this dorsolateral-ventrolateral distinction, Rypma and colleagues proposed that aging affects particularly dorsolateral parts of the prefrontal cortex (control processes), whereas the ventrolateral prefrontal cortex (maintenance) is relatively spared from age-related neural change [33, 42]. Later, Rajah and D'Esposito [22] adapted these assumptions by attributing bilateral ventrolateral prefrontal activation changes to the dedifferentiation of cortical function, right dorsolateral and anterior prefrontal activation changes to functional deficits, and left dorsolateral and anterior prefrontal cortex activation changes to functional compensation.

However, more recent research rather points toward a hierarchical rostral-caudal functional distinction of the prefrontal cortex with parallel dorsal and ventral processing streams [43, 44]. According to this theory, rostral parts of both dorsolateral and ventrolateral prefrontal cortices are associated with higher-level cognitive control, whereas caudal parts are rather linked to spatial maintenance [45, 46]. Age-related changes particularly seem to affect more rostral parts along this rostral-caudal gradient leading to reduced executive control [47–49].

Noteworthy, the assumptions of the described theories are not mutually exclusive and particularly highlight the relevance of rostral parts of the dorsolateral prefrontal cortex for top-down working memory control processes. In fact, recent research of our working group revealed a load × age interaction [47] and group differences between older high and low performers [50] within rostral dorsolateral prefrontal cortex, whereas there were hardly any effects within caudal or ventrolateral areas.

Objectives. Overall, the literature on this topic suggests that the kind and meaning of age-related prefrontal activation changes varies across prefrontal subregions and is highly dependent on performance level and task load. This implies the claim for further studies analyzing the impact of all of these factors with a single approach. Many past studies did not, which also applies to our preliminary work: the first one of the referred studies did not include comparisons between high and low performers while working memory load was not manipulated in the second one. In the current experiment, we therefore analyzed the effects of performance level, working memory load, and age by comparing load-dependent brain activation in younger high performers, younger low performers, older high performers, and older low performers. Functional magnetic resonance imaging (fMRI) was used to examine brain activation of different prefrontal subregions during working memory retrieval. Based on the theoretical considerations mentioned above, age-related differences in load-dependent brain activation should particularly manifest within rostral parts of the dorsolateral prefrontal cortex. Thereby, a successful recruitment of additional neural resources should be reflected by increasing activation with higher load and performance level, whereas an unsuccessful recruitment should be reflected by unchanged or even decreasing activation with lower load and performance level. In particular, a successful recruitment should be observed in younger high performers, whereas an unsuccessful recruitment should be most obvious in older low performers. Of particular interest is the comparison between older high performers and younger low performers: in fact, older high performers, unlike younger low performers, might show a similar neural response pattern as younger high performers reflecting an at least partly successful compensation of age-related behavioral working memory deficits [10, 51].

Table 1: Sample characteristics.

	YHP	YLP	OHP	OLP
N	9	10	10	11
Gender (female/male)	4/5	7/3	5/5	6/5
Mean age/SD	27.89/5.18	27.3/5.33	59.5/5.46	61.91/5.03
Minimum age	20	21	50	56
Maximum age	35	35	68	71
School education/SD	12.67/1.0	12.4/1.08	11.0/1.63	11.09/1.92
Minimum school education	10	10	8	8
Maximum school education	13	13	13	13
MoCA score/SD	29.11/.33	27.2/2.74	27.1/2.73	26.0/2.61
MWT score/SC	32.44/2.7	30.6/3.41	32.3/3.56	31.73/3.95

Note. Age and school education are given in years. YHP = younger high performers; YLP = younger low performers; OHP = older high performers; OLP = older low performers; SD = standard deviation; MoCA = Montreal Cognitive Assessment; MWT = multiple choice vocabulary test.

2. Materials and Methods

2.1. Participants. The study included a group of 19 younger participants and a group 21 older participants with normal or corrected-to-normal vision. To analyze the impact of performance level, both age groups were further subdivided into high performers and low performers by median split (errors in the experimental paradigm). Overall, four experimental groups were analyzed (Table 1): younger high performers (YHP), younger low performers (YLP), older high performers (OHP), and older low performers (OLP).

None of the participants had a documented diagnosis of neurological or psychiatric disease in the past. Moreover, global cognitive deficits were excluded by the Montreal Cognitive Assessment (MOCA) [52]. Participants were recruited by local advertising and provided a written declaration of consent prior to study start. The study obtained ethical approval by the Institutional Review Board of the University of Giessen. All participants received an expense allowance of 8 € per hour.

YHP and YLP did not differ with respect to age, gender, school education, and MOCA score, neither did OHP and OLP. Noteworthy, YHP and OHP differed with respect to years of school education ($t(17) = 2.64$; $p = 0.017$). However, due to differences between today's general school system and former systems, the average time of received school education in years is not really comparable between younger and older participants. Consequently, the multiple choice vocabulary test (MWT) [53] was additionally applied to test for possible age-related intellectual and educational differences. The MWT is a valid German questionnaire to estimate crystallized intelligence. Its total score is a predictor for the level of education. The four experimental groups did not differ with respect to MWT scores.

2.2. Task and Experimental Procedure. To assess spatial working memory, a modified electronic version of the Corsi Block-Tapping test (CBT) [47, 54] was applied. The CBT is a multiple-item spatial working memory task requiring the storage and reproduction of spatial target sequences. It allows modulating working memory load by variation of sequence length. The modified version provides four potential target locations (instead of nine as in the original version) indicated by four horizontally arranged blocks (Figure 1). Locations are randomly presented one after another and have to be reproduced in the correct temporal order afterwards. The original [55, 56] and the modified [47] versions of the CBT were associated with nearly identical whole-brain activation patterns indicating that the same cognitive and neural processes are involved.

Participants were instructed to learn (encoding phase), maintain (maintenance phase), and reproduce (retrieval phase) sequences of randomly presented target locations. Sequence length was varied between four (load 4), five (load 5), and six (load 6) locations in a row. In the baseline condition, all four target locations were presented from left to right. The chronological order of the different experimental conditions (baseline, load 4, load 5, and load 6) was pseudo-randomized but equal for all participants. Participants were instructed to reproduce the sequence by sequential button presses after the presentation of each sequence. Therefore, a keypad with four horizontally arranged buttons was designed. Each of these four buttons represented the corresponding block on the screen. As direct feedback for the participants, each button press was confirmed by a change of the respective block's color.

Each trial of the CBT can be subdivided into an encoding phase (stimulus presentation), a maintenance phase (delay period), and a retrieval phase (stimulus reproduction). The encoding phase was preceded by a pause of 2000 ms. The encoding phase started with the onset of the first target block of every sequence and ended after the presentation of the last target block of that sequence. Duration of the target blocks was 1000 ms with a 1000 ms interstimulus interval. Due to different load levels (4, 5, and 6), the length of the encoding phase varied between 7000, 9000, and 11.000 ms. Each encoding phase was followed by a maintenance phase varying between 1500 and 2000 ms (variable jitter) [57] in which only the four horizontal blocks were shown. After the maintenance phase, the retrieval phase started indicated by the instruction "Press now" at the bottom of the screen. The retrieval phase lasted until the time of the final response.

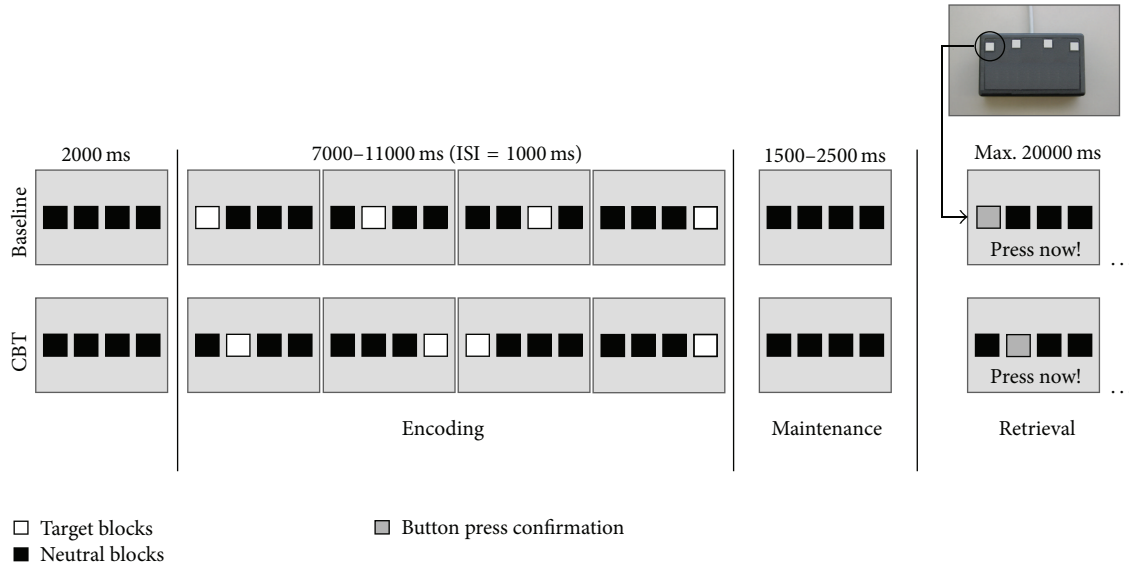

Figure 1: Exemplary illustration of the experimental design for load level 4. CBT = Corsi Block-Tapping test, ISI = interstimulus interval.

Maximum available time for making responses was set to 20.000 ms. The length of this time period was determined based on the results of preliminary studies (e.g., [47]).

Participants had to perform four trials per CBT sequence length as well as eight baseline trials. Consequently, 20 trials were randomly administered. Total duration of the experiment was about 10 minutes. Before entering the MRI examination room, participants obtained precise instructions concerning the experimental procedure. Subjects were instructed to memorize the correct locations and temporal order of the presented target blocks. For retrieval, participants were advised to reproduce the presented target sequences by successive button presses and to respond as fast and as accurate as possible. In addition, subjects had to perform a series of practice trials on a PC outside the scanner. Practice trials included two baseline trials and one load 5 trial. Duration of the practice session was about 2 minutes.

2.3. Stimulus Material. In the modified version of the CBT, four horizontally arranged black blocks (RGB 0 0 0) were displayed on gray background (RGB 163 163 163). Target blocks were displayed in red (RGB 255 0 0). In the retrieval phase, the black blocks turned to yellow (RGB 255 255 0) at button press to indicate the given response.

2.4. Data Acquisition. Functional and structural images were acquired using a 3 Tesla Siemens Magnetom Verio Scanner. Functional images were obtained using a T2*-weighted echo planar imaging (EPI) sequence. Each volume contained 30 slices covering the whole brain, measured in descending order parallel to the AC-PC line + 25° (slice thickness = 4 mm; 1 mm gap; TR = 2100 ms; TE = 30 ms; flip angle = 90°; field of view = 192 × 192 mm; matrix size = 64 × 64; voxel size = 3 × 3 × 4 mm). Visual stimuli were displayed on a screen near the tube end, which participants saw via a dual-mirror mounted to the head coil. To control for inhomogeneity of the magnetic field, field map sequences were realized before the EPI sequence. Structural image acquisition consisted of 160 T1-weighted sagittal images with 1 mm slice thickness using a magnetization prepared rapid gradient echo (MPRage) sequence. Time of acquisition in the scanner was approximately 20 minutes per individual.

2.5. Data Analysis

2.5.1. Behavioral Data Analysis. Behavioral data analysis comprised a 3 (CBT condition: load 4, load 5, and load 6) × 4 (group: YHP, YLP, OHP, and OLP) repeated measure ANOVA for the number of CBT errors. Bonferroni-tests were used for post hoc comparisons. Demographic group differences of interest (age, gender, education, and MoCA) were analyzed using two-sample t-tests and Chi-square tests, respectively. Behavioral data were analyzed using SPSS Statistics 22. All levels of significance were $\alpha = 0.05$ and two-tailed.

2.5.2. Brain Data Analysis. FMRI data were analyzed using SPM8 (Statistical Parametric Mapping Software; Wellcome Institute of Neurology at University College, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). The first three images of every EPI-recording session were discarded to account for the time needed for the magnetic field to achieve a steady state. Preprocessing of EPI-images included unwarping and realignment to the first volume (b-spline interpolation), slice time correction, normalization to the standard space of the Montreal Neurological Institute (MNI) brain, and smoothing with an isotropic three dimensional Gaussian kernel with a full-width-at-half-maximum (FWHM) of 9 mm. Data were analyzed using a general linear model (GLM) with four encoding regressors (load 4 encoding, load 5 encoding, load 6 encoding, and baseline encoding), one regressor for the maintenance phase, and four retrieval regressors (load 4 retrieval, load 5 retrieval, load 6 retrieval, and baseline

retrieval) (We included all trials instead of only correct trials into brain data analyses. Although past work has shown that results do not differ very much, this point is often heavily discussed. In fact, all aging studies are confronted with this problem since both options include pros and cons: analyzing all trials leads to higher error variance, whereas analyzing only correct trials leads to a different number of analyzed trials in the different experimental groups. Particularly in experimental designs modulating the load level, analyzing only correct trials that might lead to statistical effects: in the current work, e.g., the number of correct trials decreased with increasing load but this load-related decrease differed between the different experimental groups. Consequently, group × load interaction effects may be the statistical consequence of different trial numbers and not the consequence of activation differences. To avoid this, we decided to include all trials into brain data analyses in the current work). Compared to a model with single regressors for the maintenance phase (i.e., load 4 maintenance, load 5 maintenance, load 6 maintenance, and baseline maintenance), the present design helped to minimize correlations between the regressors of interest and the other predictors of the model. Timing of regressors followed the timing as explained in section above. In addition, six movement regressors were included into the design. Regressors were convolved using the hemodynamic response function as provided in SPM8. Design matrix was high pass filtered (128s). Since the present study focused on age-related changes during spatial working memory retrieval, only the retrieval regressors (load minus baseline) were further analyzed on the second level. A 4 × 3 factorial design matrix with the factor group (YHP, YLP, OHP, and OLP) and the factor load (load 4, load 5, and load 6) was realized using a flexible factorial model. Analyses focused on load-dependent cerebral activation (main effect of load) as well as the impact of age and performance level on this activation pattern (group × load interaction). Brain activation was analyzed at whole-brain level and by a region of interest (ROI) approach. For exploratory whole-brain analyses, a threshold of $Z \geq 3.1$ with a minimum cluster size of 10 voxels was used. Based on the theoretical considerations in the introduction section, ROI analyses comprised a priori chosen brain regions located in the prefrontal cortex: Brodmann area (BA) 10 within the anterior prefrontal cortex, BAs 9 and 46 within the dorsolateral prefrontal cortex, and BAs 44 and 45 within the ventrolateral prefrontal cortex. Data were analyzed using the corresponding ROI masks of the automated anatomical labelling atlas (AAL) [58] which is implemented in the WFU PickAtlas [59], an automated software toolbox for generating ROI masks based on the Talairach Daemon database [60–62]. All reported ROI results were tested at a local significance threshold of $p < 0.05$ (voxel level). Alpha adjustment for multiple comparisons was done for each ROI (family-wise error (FWE) correction). Bonferroni adjustments for the number of tested ROIs are optionally provided in the results section. To describe the significant group × load interaction in more detail, contrast values of the identified peak voxels were extracted for each group and load level separately (Figure 4). Using this approach, we were able to get an idea where systematic variance exceeded random variance for comparisons of special interest (t-tests uncorrected for multiple comparisons).

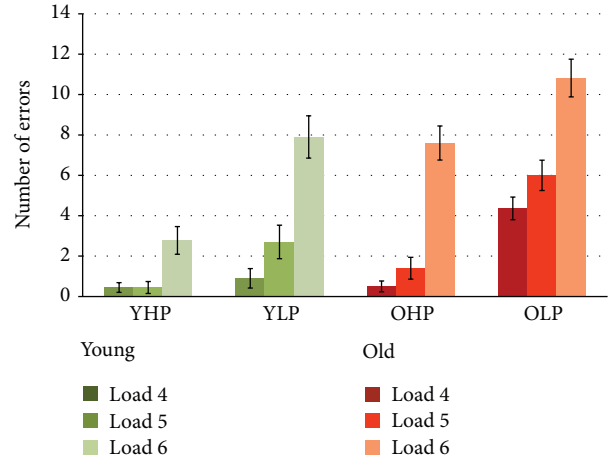

Figure 2: Number of CBT errors for each group and load level separately (displayed together with standard errors of the means). YHP = younger high performers; YLP = younger low performers; OHP = older high performers; OLP = older low performers.

3. Results

3.1. Behavioral Data. For the number of errors (Figure 2), repeated measures ANOVA revealed significant main effects of group ($F(3, 36) = 29.28$, $p < 0.001$) and load ($F(2, 72) = 89.88$, $p < 0.001$) as well as a significant group × load interaction effect ($F(6, 72) = 3.25$, $p = 0.007$). Post hoc Bonferroni-tests revealed that error rates of YLP and OHP did not differ. Besides, significant differences were found for all groups and load levels ($p < 0.05$). Results show that YHP made less errors than YLP, OHP, and OLP, with OLP showing the highest error rates. Moreover, error rates were higher at higher task load.

3.2. fMRI Data. Whole-brain analysis resulted in a significant main effect of load including different prefrontal brain regions (Figure 3, Table 2).

ROI analyses revealed increased load-dependent activation in bilateral dorsolateral (BAs 9 and 46), ventrolateral (BAs 44 and 45), and anterior prefrontal (BA 10) cortices (Table 3). Results indicate that the neural response pattern associated with task load includes various subregions of the prefrontal cortex.

For group × load interaction, whole-brain analysis revealed significant effects in the prefrontal cortex (Table 4).

ROI analyses confirmed significant interaction effects for left BAs 44 and 45 within the ventrolateral prefrontal cortex and for left BA 46 within the rostral dorsolateral prefrontal cortex (Table 5).

Signal changes in the respective peak-voxels are displayed in Figure 4 indicating comparable activation patterns in all prefrontal subregions. In particular, results show that systematic variance exceeded random variance for load 6 > load 4 in YHP within left BAs 44, 45, and 46 and in OHP

Table 2: Localization and statistics of the peak voxels for the main effect of load (whole-brain analysis).

Brain structure	Cluster size	x	y	z	F
L inferior frontal gyrus, triangular part/insula	384	−33	20	4	23.16
L superior frontal gyrus, medial part	527	−3	23	43	22.62
R insula	207	36	20	−2	21.05
L middle frontal gyrus	54	−24	5	55	12.10
L precentral gyrus	69	−39	2	34	11.21
R middle frontal gyrus	94	27	44	16	10.12
R middle frontal gyrus	32	27	5	58	9.34
L middle frontal gyrus	26	−33	53	7	9.17

Note. Threshold of $Z \geq 3.1$. All coordinates (x, y, z) are given in MNI space. L = left; R = right.

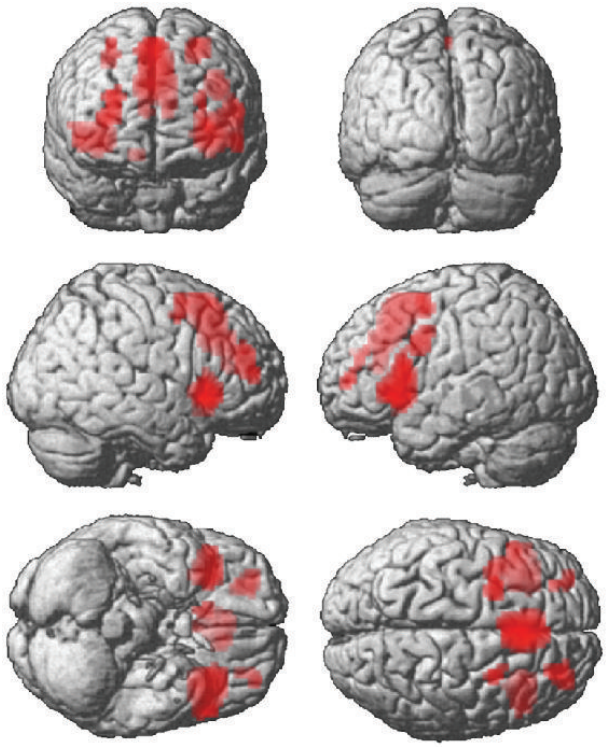

Figure 3: Main effect of load (whole-brain analysis with a threshold of $Z \geq 3.1$).

within left BAs 44 and 45. OLP showed the opposite pattern in left BA 46 with higher activation intensity at load level 4 than at load level 6. In YLP, systematic variance exceeded random variance for load 5 > load 4 in left BAs 45 and 46 but not for load 6 > load 5. Group comparisons revealed that YHP showed less activation than OLP at load level 4 within left BAs 44 and 45 (same tendency in left BA 46), but more left-hemispheric BA 45 activation than YLP at load level 6 (same tendency in BAs 44, 46). Compared with OHP, OLP showed higher activation intensity at load level 4 within left BA 45. Finally, the bar charts suggest a tendency toward higher activation in OHP than in YLP at load level 6 within BAs 44, 45, and 46.

4. Discussion

In the current study, we used fMRI to investigate the effects of age, performance level, and load on prefrontal brain activation associated with spatial working memory retrieval. The results highlight the relevance of age and performance level for load-dependent activation within left rostral dorsolateral and ventrolateral prefrontal cortices. In line with the assumptions of the CRUNCH model [34], our results suggest that younger high-performing individuals show a flexible upregulation of activation as neural response to increasing task load, whereas younger low performers seem to reach a resource ceiling at a moderate load level. Older high performers show a similar though less intense pattern than younger high performers and may compensate age-effects at high task demands. By contrast, older low performers seem to show neural inefficiency at low task demands and no upregulation of the working memory network if task demands rise.

4.1. Spatial Working Memory Performance. In line with previous research [10, 47, 56], analyses of behavioral data revealed an increasing number of errors with load across all participants. The different experimental groups showed accuracy differences across all load levels with younger high performers showing the best and older low performers showing the poorest performances. Moreover, analyses revealed a significant group × load interaction indicating that the increase of task load differentially affected the increase of errors in the different experimental subgroups. Most interestingly, younger low performers and older high performers did not only show similar error rates across all load levels but also a similar increase of errors with increasing load. Latter findings highlight that higher age is not always associated with lower performance accuracy.

4.2. Effects of Age, Load, and Performance Accuracy on Prefrontal Cortex Activation. Brain data analyses identified a load-dependent frontal network across all participants. In particular, dorsolateral (BAs 9, 46), ventrolateral (BAs 44, 45), and anterior (BA 10) prefrontal cortices showed an upregulation associated with task load. These findings are in line with previous research and point toward the relevance

Table 3: Localization and statistics of the peak voxels for the main effect of load (ROI analyses).

PFC subregion	ROI	Brain structure	x	y	z	F	p_{corr}
DLPFC	BA 9	L superior frontal medial gyrus	−6	29	37	12.35	0.003*
		R cingulum middle	3	32	34	14.18	0.001*
	BA 46	R inferior frontal, opercular part	48	17	28	8.27	0.026
VLPFC	BA 44	L inferior frontal, opercular part	−51	17	16	13.99	>0.001*
		R inferior frontal, opercular part	51	17	7	7.17	0.028
	BA 45	L insula	−36	23	4	19.42	>0.001*
		R insula	39	23	4	11.42	0.002*
aPFC	BA 10	R middle frontal gyrus	27	44	25	9.89	0.022

Note. Threshold of $p_{corr} < 0.05$ (FWE-corrected according to SPM8, small volume correction). * indicates results surviving a Bonferroni-correction for the set of ROIs ($p_{corr} < 0.005$). All coordinates (x, y, z) are given in MNI space. DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; aPFC = anterior prefrontal cortex; ROI = region of interest; BA = Brodmann area; L = left; R = right.

Table 4: Localization and statistics of the peak voxels for the load × group interaction (whole-brain analysis).

Brain structure	Cluster size	x	y	z	F
L middle frontal gyrus	149	−27	−1	52	7.90
L insula	74	−36	17	4	6.71
R superior frontal gyrus	55	27	2	61	6.10
L supplementary motor area	80	0	23	46	5.85
R insula	23	33	23	−5	5.78
L inferior frontal gyrus, triangular part	16	−48	20	22	5.04

Note. Threshold of $Z \geq 3.1$. All coordinates (x, y, z) are given in MNI space. L = left; R = right.

of prefrontal brain structures for flexible working memory processes that control the adaptation of neural resources to the demands of the applied task [2].

Moreover, the study design allowed assumptions about the impact of age and performance level on the upregulation of this load-related network. Brain data analysis revealed significant group × load interaction effects within rostral parts of different left-hemispheric dorsolateral and ventrolateral prefrontal subregions. These interaction effects indicate that the neural response to task load differed between the four experimental groups. Results suggest that younger high performers showed a sharp increase of activation intensity from the lowest to the highest load level (left BAs 44, 45, and 46). Moreover, they showed higher activation intensity than younger low performers at high task demands (left BA 45; same tendency in BAs 44 and 46) but lower activation intensity than older low performers at low task demands (left BAs 44 and 45; same tendency in 46). Together, these findings confirm the assumptions of the CRUNCH model and suggest a flexible and effective recruitment of additional resources in younger high-performing individuals to meet the demands of higher task load [34]. By contrast, this neural response seems to be qualitatively different and less effective in younger and older low performers. Following this argumentation, younger low performers showed an upregulation from low to moderate load (left BAs 45 and 46) but no further increase at high task load proposing that a resource ceiling has been reached. Older low performers appeared to show steady (left BAs 44 and 45) or even reduced (left BA 46) activation intensity with increasing load suggesting that neural resources were already exhausted at the lowest load level.

In addition, the current findings illustrate that the CRUNCH effects are modulated by the performance level of younger and older individuals. In fact, an efficient upregulation of rostral prefrontal cortex activation as neural response to higher task load could not only be observed in *younger* high-performing individuals but, to lesser degree, in *older* high performers (left BAs 45 and 46). In fact, older high performers showed a similar though less intense pattern of upregulation from the lowest to the highest load level as younger high performers which most likely indicates a qualitatively similar neural response [10, 51]. In particular, the bar charts suggest a tendency toward higher activation intensity in older high performers compared to younger low performers at high task demands (left BAs 44, 45, and 46). In the context of equivalent error rates on the behavioural level, these findings point toward compensation of age-related deficits in older high performers. By contrast, older high performers showed lower activation intensity than older low performers at low task load (left BA 45) suggesting that high activation intensity at low task load rather reflects neural inefficiency than compensation. Together, the latter findings suggest that older high-performing individuals may show compensation at high task load and less neural inefficiency than their low-performing counterparts at low task load.

Overall, our findings indicate that age and performance level modulate the cerebral response to working memory load. Younger high performers and older high performers show a qualitatively similar flexible upregulation of prefrontal activation as neural response to increasing task load, whereas younger and older low performers show a different and less effective neural response because, sooner or later, resource ceilings are reached. Noteworthy, our findings are quite in line

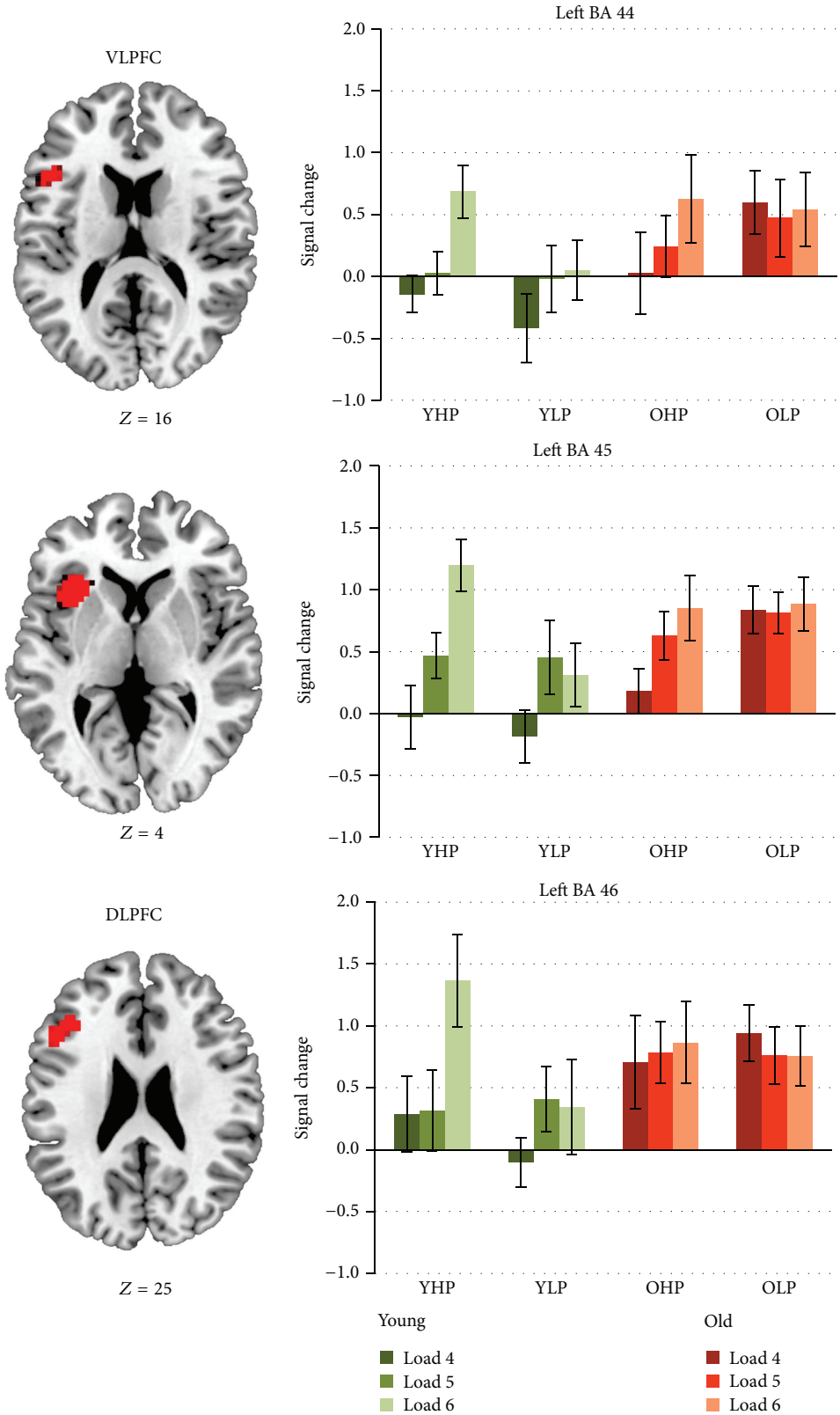

Figure 4: Contrast estimates with the respective standard errors for the identified regions associated with a group × load interaction. Signal change is plotted for younger high performers (YHP), younger low performers (YLP), older high performers (OHP), and older low performers (OLP) for the three load levels separately.

Table 5: Localization and statistics of the peak voxels for the group × load interaction (ROI analyses).

PFC subregion	ROI	Brain structure	x	y	z	F	p_{corr}
DLPFC	BA 46	L frontal inferior gyrus, triangular part	−51	23	25	4.48	0.030
VLPFC	BA 44	L frontal inferior gyrus, opercular part	−51	17	16	3.91	0.039
	BA 45	L insula	−39	20	4	5.10	0.007*

Note. Threshold of $p_{corr} < 0.05$ (FWE-corrected according to SPM8, small volume correction). * indicates results surviving a Bonferroni-correction for the set of ROIs ($p_{corr} < 0.005$). All coordinates (x, y, z) are given in MNI space. PFC = prefrontal cortex; DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; ROI = region of interest; BA = Brodmann area; L = left; R = right.

with the results of Nagel and colleagues [10]. In particular, the load-related activation patterns within left dorsolateral prefrontal cortex are amazingly similar confirming the validity of these effects. Moreover, the current results suggest that activation patterns are quite the same for different spatial working memory subprocesses since Nagel and colleagues verified these effects in a recognition task whereas our results refer to working memory retrieval. For retrieval, our results additionally suggest neural compensation in older high performers at high task load and neural inefficiency in older low performers at low task load. Finally, specific effects were not only found in dorsolateral but also in ventrolateral prefrontal subregions which provides important information about the functional organization of the prefrontal cortex.

4.3. Prefrontal Cortex Organization. As mentioned above, the prefrontal cortex can be subdivided into different functional modules. Whereas some authors propose a hierarchical dorsolateral-ventrolateral distinction with dorsolateral parts being related to higher-level working memory operations (e.g., control processes) and ventrolateral parts to passive maintenance [36–41], recent research suggests a rostral-caudal distinction with rostral parts reflecting working memory control and caudal parts being associated with maintaining information [43–46]. The results of the current work rather support the second idea, since the patterns of activation intensity at the different load levels differed between the experimental groups (interaction effect) but were, in each experimental group, quite the same for dorsolateral and ventrolateral prefrontal subregions. These findings suggest that functional differences between dorsolateral and ventrolateral prefrontal cortices may be less evident than we thought. Instead, interaction effects were located within more rostral parts of both regions (i.e., BA 46, BA 45, and anterior BA 44) indicating that particularly *rostral* parts of the prefrontal cortex are associated with age, performance level, and task load. Finally, overall activation was more intense in rostral than in caudal areas (i.e., higher activation intensity in BAs 46 and 45 than in BA 44 and no differences between BAs 46 and 45). Taken together, our findings point toward a hierarchical rostral-caudal prefrontal cortex organization and suggest that age-related alterations modulated by performance level and task load particularly manifest within different rostral regions along this axis.

4.4. Limitations and Perspectives. Noteworthy, the interpretation of regional activation intensity at the different load levels relies on descriptive results. However, the interaction effects prove that the neural response to task load differs between the four experimental groups and the post hoc comparisons verify most of the differences the bar charts suggest. Moreover, there are very similar load-related activation patterns in different prefrontal subregions (left BAs 44, 45, and 46). These patterns are fairly identical with the activation patterns identified by Nagel and colleagues which further increases the validity of the data. The strength of the current work certainly is that age, performance level, and task load are included into one analysis. Finally, the results show that, dependent on performance level and task load, overactivation may reflect either neural inefficiency or compensation. Future research should address a further distinction between these processes if possible. In addition, future studies should focus on the question how the neural response to increasing task load is affected by neurodegenerative disorders. In fact, there is evidence that increased task demands provoke a disproportionate performance decline in patients suffering from Alzheimer's disease and mild cognitive impairment [63, 64].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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