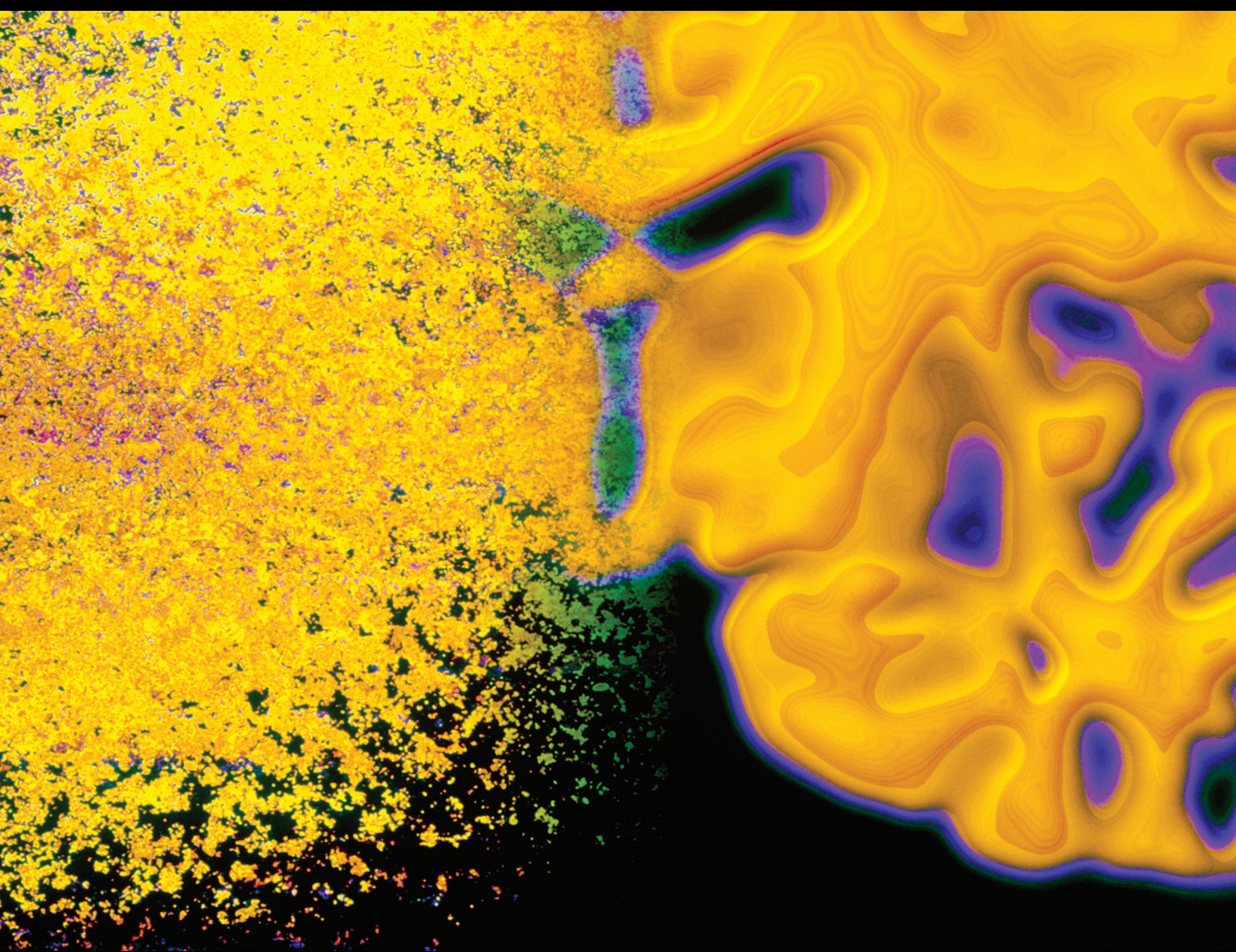
Behavioural Neurology

Behavioural and Cognitive Changes in Neurodegenerative Diseases and Brain Injury

Lead Guest Editor: Francesca Trojsi
Guest Editors: Foteini Christidi, Raffaella Migliaccio, Hernando Santamaría-García, and Gabriella Santangelo



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Editorial

Behavioural and Cognitive Changes in Neurodegenerative Diseases and Brain Injury

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Neurodegenerative diseases (NDs) are a wide range of neurological disorders affecting distinct subsets of neurons in specific anatomic systems, resulting in variable disease phenotypes [1]. Conventional clinicopathological approach allowed to identify several spectra of neurodegeneration, such as those associated to tauopathies, synucleinopathies, and Tar-DNA binding protein (TDP) 43-proteinopathies. However, it has been increasingly appreciated that many NDs overlap at multiple levels, including genetic, molecular, and neuroimaging levels [2–7], thereby overcoming classification approaches based only on clinicopathological patterns [1]. In particular, with regard to clinical phenotypes, behavioural and cognitive changes, proven to impact negatively patients' quality of life and prognosis [8, 9], have been associated to a large array of NDs, although showing peculiar profiles across the different syndromes. Alzheimer's disease (AD) is usually characterized by a progressive amnestic syndrome in elderly subjects, although younger patients may also present an atypical, focal, clinical syndrome in which a single cognitive domain, not related to memory, is predominantly affected, such as logopenic variant of primary progressive aphasia (lvPPA) and posterior cortical atrophy (PCA) [10]. Behavioural changes are the clinical core of the behavioural variant of frontotemporal dementia (bvFTD), ranging from apathy to disinhibition [11], but are also frequently reported in amyotrophic lateral sclerosis (ALS) [4] and parkinsonian plus syndromes (dementia with Lewy bodies, progressive supranuclear palsy, corticobasal syndrome, and Parkinson's disease—dementia) [12]. Specifically, impairments of primary motor and/or executive and language functions are more commonly reported in ALS and frontotemporal lobar degeneration (FTLD) [4, 11], while an increasing detection of both extrapyramidal symptoms and cognitive changes, including executive and language dysfunctions, limb apraxia, and visuoconstructive deficits, has been described within the parkinsonian plus syndromes [12]. Finally, ischemic/hemorrhagic stroke or traumatic brain injury (TBI) may be associated to behavioural and cognitive alterations similar to those described in NDs [8]. To note, molecular modifications, involving AD-related proteins (i.e., β-amyloid peptide, hyperphosphorylated tau protein, presenilins, apolipoproteins, and secretases), seem to play a pivotal role also on poststroke dementia and neuroinflammatory response to TBI [13].

On this background, this special issue addresses most recent insights into the field of neuropsychology of NDs, poststroke dementia, and TBI, from several points of view, ranging from the animal models of disease to potential and innovative therapeutic approaches on the neurodegenerative process.

With regard to animal models useful for investigating the role of physical exercise (PE) on counteracting stressors, L. Zhang et al. ("Effect of Voluntary Wheel Running on Striatal Dopamine Level and Neurocognitive Behaviors after Molar Loss in Rats") addressed the effect of voluntary wheel running on striatal dopamine levels in Sprague-Dawley rats randomly divided into 4 groups (i.e., controls, molar loss group, 1-week PE before tooth loss group, and 4-week PE before tooth loss group). By comparing striatal levels of dopamine and performances at cognitive and behavioural tasks among the four groups, the two groups performing PE before tooth loss exhibited significantly increased striatal dopamine levels and improved neurobehavioural performances. These findings interestingly supported the positive effect of PE on cognition and emotion, emphasizing the yet recognized pivotal role of striatonigral pathway on behaviour and emotion regulation.

With regard to the clinical studies published in this special issue, the prospective investigation by F.G. van Rooij et al. ("Subjective Cognitive Impairment, Depressive Symptoms, and Fatigue after a TIA or Transient Neurological Attack: A Prospective Study") explored the clinical course of 103 patients after transient ischemic attack (TIA) or nonfocal transient neurological attack (TNA), in terms of cognitive and behavioural changes, and investigated the longitudinal diffusion-weighted imaging (DWI) brain white matter alterations. Interestingly, subjective cognitive impairment and fatigue were more severe after six months only in DWI-positive patients, without showing differences between TIA and TNA, thereby confirming the concept that DWI hyperintensities are associated with permanent brain damage, cognitive decline, mood disorders, and fatigue in stroke patients.

With regard to cognitive assessment tools, C. Meyniel et al. ("COGEVIS: A New Scale to Evaluate Cognition in Patients with Visual Deficiency") introduced a new evaluation tool, named COGEVIS (COGnitive Evaluation in VISual impairment), a set of neuropsychological tests conceived to assess the cognitive functions without the use of vision. COGEVIS was used to study the cognitive status of 38 visually impaired patients referred to the low vision rehabilitation (LVR) center of Sainte-Marie Hospital in Paris (France). COGEVIS was able to identify cognitive impairment with significant diagnostic value (area under the ROC curve of 0.84) and was also proposed to assess the cognitive evolution after LVR.

The Spanish/Colombian/Canadian group of R. Iodice et al. ("Sentence Context and Word-Picture Cued-Recall Paired-Associate Learning Procedure Boosts Recall in Normal and Mild Alzheimer's Disease Patients") employed a word-picture paradigm to examine the effectiveness of combined pictorial illustrations and sentences to explore the word-recall performance in 18 healthy older adults (HOA) and 18 mild Alzheimer's disease (AD) patients. The authors revealed that, in both groups, pictures improved item recall compared to word condition such as sentences and that the HOA group performs better than mild AD group in all conditions. Moreover, word picture and sentence context were demonstrated to strengthen the encoding in the explicit memory task in both groups. These findings are consistent with the idea that older individuals, with and without dementia, are sensitive to the semantic constraints provided by a sentence context or picture. Moreover, they suggest future research lines on implementation of strategies to improve the memory of older people for verbalized instructions, in order to restore or potentiate sequential abilities in everyday life.

With regard to nonpharmacological interventions used for inducing neuroplasticity, P. Cruz Gonzalez et al. ("The Effects of Transcranial Direct Current Stimulation on the Cognitive Functions in Older Adults with Mild Cognitive Impairment: A Pilot Study") aimed to investigate the effect of a combined approach, which associated transcranial direct current stimulation (tDCS) on the left dorsolateral prefrontal cortex and cognitive rehabilitation through cognitive stimulation (CS) programme, on cognitive performances of five patients with mild cognitive impairment (MCI). The authors revealed that tDCS together with CS improved performances in multiple cognitive domains showing better results than those achieved by using CS alone. These preliminary findings could give further clues to optimize therapeutic approaches by noninvasive brain stimulation.

With regard to advanced neuroimaging evidence, the study by P. Reyes et al. ("Functional Connectivity Changes in Behavioral, Semantic, and Nonfluent Variants of Frontotemporal Dementia") investigated brain functional connectivity changes by resting state functional magnetic resonance imaging (RS-fMRI) in 76 patients exhibiting the three FTD variants (bvFTD, semantic, and nonfluent variants of primary progressive aphasia—svPPA and nfvPPA) in order to find specific connectivity alteration in each variant. The authors compared the whole brain functional connectivity and the topologic measures, such as global efficiency, degree, path length, and clustering, obtained in FTD patients with those measured in healthy controls and between the three variants. Both neuropsychological and neuroimaging results showed similarity among FTD variants. In particular, there were no differences between the PPA variants. Nevertheless, the nfvPPA variant showed loss of global efficiency compared to bvFTD, more severe than that exhibited by svPPA group compared with bvFTD. Conversely, the bvFTD group showed an extended bilateral disconnection between frontal and limbic hubs and the basal ganglia that seems to be associated with the disruption between affective and self-referential brain systems in bvFTD patients.

Finally, the review article, written by the guest editors team, on "Social Cognition Dysfunctions in Neurodegenerative Diseases: Neuroanatomical Correlates and Clinical Implications" widely addressed recent evidence regarding the impairment of brain networks related to emotion

processing, theory of mind, and empathy. Moreover, the review article addressed the most updated evidence on clinical manifestations and assessment tools for evaluating social cognitive dysfunctions in most NDs, such as FTLD, amyotrophic lateral sclerosis (ALS), and Parkinson's and Alzheimer's diseases, prospecting potential benefits on patients' well-being, quality of life, and outcome derived from pharmacological and nonpharmacological therapeutic approaches to these deficits.

In conclusion, the substantial message of this special issue is that abnormal behaviour and cognitive changes, commonly observed in clinical practice, represent an important part of the core diagnostic criteria for many clinical disorders. Cognitive and behavioural alterations are a risk factor for morbidity and mortality through not adherence to treatments and social isolation [8, 9]. Pharmacological and also nonphamacological interventions, aimed to counteract the potential consequences related to cognitive and behavioural alterations, should be implemented in order to reduce the negative effects of such disabilities on patients' and their caregivers' well-being and quality of life.

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Foteini Christidi
Raffaella Migliaccio
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References

[1] R. M. Ahmed, E. M. Devenney, M. Irish et al., "Neuronal network disintegration: common pathways linking neurodegenerative diseases," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 87, no. 11, pp. 1234–1241, 2016.

[2] C. Lomen-Hoerth, T. Anderson, and B. Miller, "The overlap of amyotrophic lateral sclerosis and frontotemporal dementia," *Neurology*, vol. 59, no. 7, pp. 1077–1079, 2002.

[3] C. Kobylecki, M. Jones, J. C. Thompson et al., "Cognitive-behavioural features of progressive supranuclear palsy syndrome overlap with frontotemporal dementia," *Journal of Neurology*, vol. 262, no. 4, pp. 916–922, 2015.

[4] M. J. Strong, S. Abrahams, L. H. Goldstein et al., "Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): revised diagnostic criteria," *Amyotrophic lateral sclerosis and frontotemporal degeneration*, vol. 18, no. 3-4, pp. 153–174, 2017.

[5] L. Heyburn and C. E. Moussa, "TDP-43 in the spectrum of MND-FTLD pathologies," *Molecular and Cellular Neurosciences*, vol. 83, pp. 46–54, 2017.

[6] L. A. A. Giannini, D. J. Irwin, C. T. McMillan et al., "Clinical marker for Alzheimer disease pathology in logopenic primary progressive aphasia," *Neurology*, vol. 88, no. 24, pp. 2276–2284, 2017.

[7] C. Peng, R. J. Gathagan, and V. M. Lee, "Distinct α-synuclein strains and implications for heterogeneity among α-synucleinopathies," *Neurobiology of disease*, vol. 109, Part B, pp. 209–218, 2018.

[8] E. Douven, P. Aalten, J. Staals et al., "Co-occurrence of depressive symptoms and executive dysfunction after stroke: associations with brain pathology and prognosis," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 89, no. 8, pp. 859–865, 2018.

[9] I. Hallikainen, K. Hongisto, T. Välimäki, T. Hänninen, J. Martikainen, and A. M. Koivisto, "The progression of neuropsychiatric symptoms in Alzheimer's disease during a five-year follow-up: Kuopio ALSOVA study," *Journal of Alzheimer's Disease*, vol. 61, no. 4, pp. 1367–1376, 2018.

[10] J. D. Warren, P. D. Fletcher, and H. L. Golden, "The paradox of syndromic diversity in Alzheimer disease," *Nature Reviews Neurology*, vol. 8, no. 8, pp. 451–464, 2012.

[11] J. R. Hodges and O. Piguet, "Progress and challenges in frontotemporal dementia research: a 20-year review," *Journal of Alzheimer's Disease*, vol. 62, no. 3, pp. 1467–1480, 2018.

[12] A. B. Deutschländer, O. A. Ross, D. W. Dickson, and Z. K. Wszolek, "Atypical parkinsonian syndromes: a general neurologist's perspective," *European Journal of Neurology*, vol. 25, no. 1, pp. 41–58, 2018.

[13] O. N. Kokiko-Cochran and J. P. Godbout, "The inflammatory continuum of traumatic brain injury and Alzheimer's disease," *Frontiers in Immunology*, vol. 9, p. 672, 2018.

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Clinical Study

COGEVIS: A New Scale to Evaluate Cognition in Patients with Visual Deficiency

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We evaluated the cognitive status of visually impaired patients referred to low vision rehabilitation (LVR) based on a standard cognitive battery and a new evaluation tool, named the COGEVIS, which can be used to assess patients with severe visual deficits. We studied patients aged 60 and above, referred to the LVR Hospital in Paris. Neurological and cognitive evaluations were performed in an expert memory center. Thirty-eight individuals, 17 women and 21 men with a mean age of 70.3 ± 1.3 years and a mean visual acuity of 0.12 ± 0.02, were recruited over a one-year period. Sixty-three percent of participants had normal cognitive status. Cognitive impairment was diagnosed in 37.5% of participants. The COGEVIS score cutoff point to screen for cognitive impairment was 24 (maximum score of 30) with a sensitivity of 66.7% and a specificity of 95%. Evaluation following 4 months of visual rehabilitation showed an improvement of Instrumental Activities of Daily Living ($p = 0.004$), National Eye Institute Visual Functioning Questionnaire ($p = 0.035$), and Montgomery–Åsberg Depression Rating Scale ($p = 0.037$). This study introduces a new short test to screen for cognitive impairment in visually impaired patients.

1. Introduction

Visual impairment, defined as visual acuity of 20/40 or less in the best-corrected better-seeing eye, affects over 280 million people worldwide. Excluding curable etiology such as cataracts or refractive disorders, the most frequent causes are age-related, such as macular degeneration, glaucoma, and diabetic retinopathy [1]. The condition of low vision is

therefore strongly age-dependent and affects more than 73% of individuals aged over 65 years [2].

Loss of visual acuity impairs many activities of daily living, including reading, cooking, or selecting clothing/dressing. Associated loss of the peripheral visual field may also cause difficulties for detecting obstacles while walking. Low vision rehabilitation (LVR) delivers multidisciplinary training including visual strategies, occupational therapy, and mobility techniques. Optic aids and nonoptic aids such as tactile marking and signature guides can be used [3]. As the effectiveness of such a multidisciplinary training is difficult to evaluate, few studies have been published on the subject. One study reported a mild improvement of quality of life after LVR [4].

Even though cognitive and visual impairments are both frequent in the elderly, the relationship between the two disorders is still a matter of debate. Several studies have reported an increased cognitive impairment in patients with age-related macular degeneration compared to age-matched subjects [5, 6]. In geriatric health services, the percentage of patients with poor visual acuity was extremely high but patients with visual impairment were found to have lower cognitive scores compared to patients with normal vision [7]. In a large cohort study, the presence of dementia at the time of diagnosis of age-related macular degeneration is not different from what is expected by chance at that age [8]. Moreover, studies assessing the association between dementia and visual impairment are limited due to the fact that many cognitive tests rely on visual skills. Patients presenting a severe loss of vision or blindness can therefore only complete part of the evaluation.

The main objective of this study was the validation of a new scale named the COGEVIS to evaluate the cognitive status of visually impaired patients and therefore detect mild cognitive impairment. The COGEVIS evaluates cognitive function without the use of vision. Our secondary objective was to determine whether LVR was effective in improving quality of life and autonomy among elderly patients with visual impairment.

2. Materials and Methods

2.1. Patients. We performed a monocentric/single-site prospective study including adults aged 60 and above, referred to the LVR of "Sainte Marie Hospital" of Paris between April 2015 and April 2016. All patients were referred by an ophthalmologist to the LVR outpatient department after diagnosis. Exclusion criteria were (1) previously established diagnosis of neurodegenerative disorder and dementia, (2) ongoing treatment for cancer or other medical illness that would preclude participation, (3) severe psychiatric disorder, and (4) visual acuity of the best eye above 20/70. The study was approved by the French National Research Ethics Committee (CPP, Comité de Protection des Personnes dans la Recherche Biomédicale).

2.2. Evaluation and Care in the Low Vision Rehabilitation Department. At the initial patient appointment, a detailed ophthalmologic examination was performed, including visual acuity, monocular manual visual field, and binocular manual visual field. Evaluation of autonomy in the daily living was assessed by a neuropsychologist using Lawton's Instrumental Activities of Daily Living (IADL) [9] The National Eye Institute Visual Functioning Questionnaire (NEI VFQ 25) was used to assess vision-related health status [10]. Depressive symptoms were evaluated with the Montgomery–Åsberg Depression Rating Scale (MADRS) [11]. Cognitive status was evaluated with the COGEVIS (COGnitive Evaluation in VISual impairment), a new scale developed to accommodate impaired vision.

After the first visit, patients followed the low vision rehabilitation program. This consisted of multidisciplinary training performed by optometrists, orthoptists, orientation and mobility instructors, occupational therapists, physiotherapists, and psychologists. Over four months, all patients attended twice-weekly rehabilitation sessions of three hours each. Two hours per week, orthoptists and optometrists worked on improving visual strategies and adjusting devices. Visual strategies were adapted to a patient's functional vision. For example, patients with a central scotoma were trained to use an eccentric fixation, while patients with a constricted visual field were taught how to perform visual scanning. The usefulness of optical devices was also tested: for example, magnifiers were adapted to the smallest readable character size and filters for glare control and lamps were proposed. One hour per week, occupational therapists trained patients to improve their autonomy in activities of daily living. The main domains were cooking, personal care, gesture recognition, self-administrated medication, shopping, and financial management. Communication instructors taught patients about computer use for one hour per week. Equipment was adjusted to each patient's vision, such as large print keyboards, magnification software, audio-screen readers, or text-to-speech converters. Orientation and mobility instructors trained patients twice a week to improve walking and mobility autonomy. This work first focused on posture, balance, and foot placement. Depending on the patient's functional vision, training for use of long canes or white canes was proposed, as well as street crossing and public transport autonomy. Psychologists interviewed patients at the beginning of the program and followed patients twice per month throughout the rehabilitation period.

At the end of rehabilitation, the evaluation battery was again carried out, including the IADL, NEI VFQ 25, MADRS, and COGEVIS scales.

2.3. COGEVIS Description. COGEVIS (COGnitive Evaluation in VISual impairment) is an assessment measure of cognitive disorders that has the particularity of not soliciting patients' visual abilities. It has been designed to be easily applied in everyday practice by various professionals working with visually impaired patients (e.g., orthoptists and medical doctors).

It is largely composed of subtests derived from global efficiency scales: the Mini Mental State Examination (MMSE) [12], the Frontal Assessment Battery (FAB) [13], and a brief evaluation battery of gestural praxis [14], which were adapted to avoid visual modality.

COGEVIS is composed of

(i) a subtest of memory (learning and (delayed) recall of 3 words from the MMSE),

(ii) an evaluation of temporospatial orientation (adapted from MMSE),

(iii) a short computation test (adapted from MMSE),

(iv) an evaluation of language:

(a) denomination based on definitions,

(b) language comprehension (3 orders of the MMSE),

(v) an evaluation of the executive functioning:

(a) letter S fluency in 1 min (from the FAB),

(b) similarities (from the FAB),

(vi) an evaluation of the ideomotor apraxia (Mahieux battery) [14],

(vii) a tactile recognition (naming) test.

COGEVIS is thus a comprehensive cognitive evaluation tool that does not rely on the visual ability to be performed. The scale has a score range of 0–30, with higher scores indicating better function.

The exact French version of COGEVIS (with the verbal instructions and quotation system) and an English translation of it are provided in Supplementary file number 1.

2.4. Cognitive Status Categorization at the Institute of Memory and Alzheimer's Disease. Between the initial appointment and the end of the first month of rehabilitation, patients were evaluated at the Institute of Memory and Alzheimer's Disease (IM2A) of the Pitié-Salpêtrière Hospital in Paris. Evaluation included a battery of neuropsychological tests and a consultation with a senior consultant neurologist specializing in cognitive disorder. The neuropsychological battery involved only tests that could be performed by individuals with a visual deficiency, that is, relying more on auditory-verbal skills than on vision. The assessment was composed of the MMSE, the FAB, the digit span forward and backward, lexical (words starting with P) and categorical (animal names) verbal fluencies, the free and cued selective memory test, analysis of praxis, and the California Verbal Learning Test [15]. At the end of the neuropsychological tests and neurological consultation, a consensual diagnosis was made to determine (1) if the participant had normal cognition, mild cognitive impairment (MCI [16]), or a major neurocognitive disorder based on the DSM-V and (2) in the case of cognitive impairment, what was the most probable underlying cause for it. Depending on test results, a MRI and/or positron emission topography (PET) was proposed to help confirm diagnosis.

2.5. Statistics. Statistical analysis was performed using the StatView System. Descriptive statistics are presented with mean and standard deviation (SD). A comparison of the participants with normal cognition (on the basis of a consensual clinic-neuropsychological evaluation at IM2A) with those with cognitive impairment (MCI + major cognitive disorder) was performed using Student's t-test for continuous variables after visually ensuring Gaussian distribution or chi-squared test for binary or categorical variables. Also, we evaluated the performance of the COGEVIS to diagnose cognitive impairment in the studied population by examining the receiver operating characteristic (ROC) curves of this test. The Wilcoxon signed-rank test was performed to compare the evolution of the COGEVIS, MADRS, IADL, and NEI VFQ 25 pre- and postrehabilitation. The level of significance in all analyses was set at $p < 0.05$.

3. Results

Thirty-eight subjects from the LVR of Sainte Marie Hospital of Paris were included in the study. Thirty-two participants completed a neurological evaluation at the IM2A, and 24 completed the follow-up evaluation after LVR. Their mean (±standard error of the mean (SEM)) age was 70.3 ± 1.3 years. The cohort included 17 (44.7%) women and 21 (55.3%) men. They had studied for 10.4 ± 0.8 years and were predominantly right handed (87%). Their visual and cognitive statuses are described in Figure 1. A detailed description of the population including a comparison of the participants with normal cognition with the cognitively impaired ones (MCI + major cognitive disorder) is provided in Table 1. Five patients assessed presented major cognitive disorders; diagnoses included one person with a mixed pathology origin (vascular + AD), 2 with typical AD, and 2 with typical Lewy body dementia (LBD). Administration of the COGEVIS by a neuropsychologist was feasible and quick (less than 10 minutes for all subjects with a mean administration time of 5 minutes in cognitively unimpaired patients). Interestingly, COGEVIS scores were significantly different between the two groups both at baseline and at follow-up evaluation. In addition, while the cognitively normal participant's COGEVIS scores slightly improved between baseline and follow-up evaluation 4 months later, scores of cognitively impaired participants slightly decreased.

Using the ROC curve method to assess the value of COGEVIS to diagnose cognitive impairment results showed an area under the ROC curve of 0.84. The cutoff point that maximized sensitivity and specificity was 24 with a sensitivity of 66.7% and a specificity of 95% (Figure 2).

Finally, among the 24 subjects who completed a follow-up evaluation after LVR, an improvement of cognition (COGEVIS), functional ability (IADL), quality of life (NEI VFQ 25), and depressive symptoms was observed after 4 months of LVR as displayed in Table 2.

4. Discussion

The present study responds to an unmet need for an appropriate diagnostic measure of cognitive impairment in patients with visual deficiency. We developed a new cognitive tool, the COGEVIS, based on the combined expertise of cognitive neurologists, neuropsychologists, and LVR specialists. This new scale is the first comprehensive scale to be validated

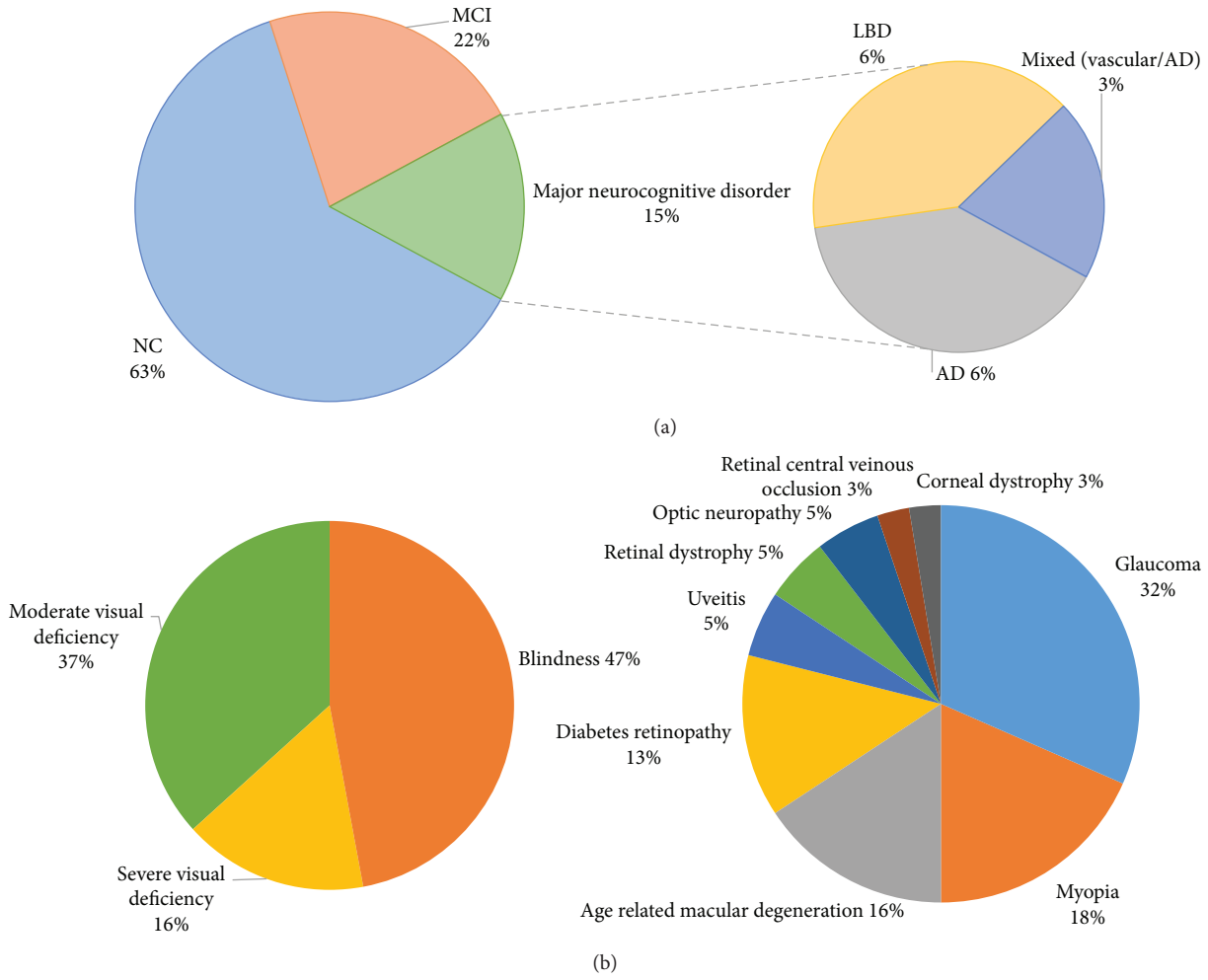

Figure 1: Distribution of the participants according to cognitive status (a) or visual status (b). AD: Alzheimer's disease; LBD: Lewy body dementia; MCI: mild cognitive impairment; NC: normal cognition.

in a cohort of elderly patients with visual deficiency in whom cognitive impairment is underdiagnosed or wrongly attributed to visual impairment [17]. In this study, COGEVIS was able to identify cognitive impairment with a good diagnostic value (area under the ROC curve of 0.84) and was also used to assess cognitive evolution after LVR. Previous studies screened visually impaired patients with only part of the test omitting items that require image processing. The Leipzig Longitudinal Study of the Aged reported results of part of the MMSE with a maximum total score of 22 instead of 30. Validity of the results was limited, restricted to individuals with very high or very low cognitive performance [18].

Although the small number of participants did not allow for statistical analysis of major neurocognitive disorder etiology, we qualitatively note that the frequency of cognitive impairment in this population was high, compared to the frequency in the general population [19]. We also found that there was a high percentage of LBD among participants presenting cognitive impairment. Importantly, LBD diagnoses in our study were made according to the latest McKeith et al. criteria [20] and not only proposed in the instance of visual hallucinations. In visual deficiency, there is a high prevalence of visual hallucination related to Charles Bonnet syndrome, a condition in which visual hallucinations develop in association with visual deprivation [21–23]. This condition does not elicit either Parkinsonism or major cognitive fluctuations, two of the three major clinical criteria for LBD. Moreover, we systematically searched for supportive features such as REM sleep behavior disorder, dysautonomia (constipation, orthostatic hypotension), or anosmia to strengthen diagnosis accuracy. However, Charles Bonnet syndrome may not be a benign disease. In Lapid et al.'s study, after an average follow-up time of 33 months, 26% of patients presenting Charles Bonnet syndrome developed dementia. The most commonly diagnosed form of the dementia was LBD [24]. Factors associated with Charles Bonnet syndrome negative outcome were fear-inducing and longer-lasting hallucination episodes associated with a reduction of daily activities [21]. LBD is a disease in which the primary visual cortex is often hypometabolic on fluorodeoxyglucose PET studies [25]. Chronic visual deficiency may induce a vulnerability of the posterior cortex, favoring the development of Lewy

Table 1: Description of the population comparing participants with normal cognition (NC) to cognitively impaired (CI) ones.

	NC ($N = 20$)	CI ($N = 12$)	p value
Age	69.1 (1.7)	75.0 (2.2)	0.04
Gender: female	9 (45)	7 (58.3)	0.5
Years of education	11.8 (1)	7.9 (1.3)	0.02
Right handedness	15 (75)	12 (100)	0.12
MMSE	26.1 (0.8)	20.1 (1)	0.0001
FAB	14.9 (0.6)	10.8 (0.7)	0.0001
Digit span forward	5.8 (0.2)	4.7 (0.3)	0.005
Digit span backward	4.2 (0.2)	3.2 (0.3)	0.03
CVLT total recall score	53.2 (2.4)	33.2 (2.1)	0.0001
Intrusions	0.8 (0.6)	3.1 (0.7)	0.02
Recognition	15.2 (0.5)	12.6 (0.7)	0.008
False recognition	0.6 (0.6)	4.3 (0.8)	0.02
Categorical (animals) fluency	29.0 (2.1)	18 (2.7)	0.004
Lexical (letter P) fluency	21.4 (1.8)	12.8 (2.4)	0.008
WAIS-IV vocabulary	10.7 (0.7)	7.0 (0.8)	0.003
Symbolic praxis	4.9 (0.1)	4.6 (0.2)	0.06
Pantomime praxis	9.8 (0.3)	8.9 (0.3)	0.04
MADRS	13.3 (2.4)	17.5 (3.3)	0.3
Baseline COGEVIS	27.5 (0.6)	22.9 (0.8)	0.0001
Follow-up COGEVIS	28.4 (0.9)	21.7 (1.1)	0.0002
Visual deficiency duration (years)	8.1 (1.9)	7.6 (2.5)	0.9
Best-seeing eye visual acuity	0.13 (0.02)	0.10 (0.03)	0.6
IADL	14.2 (1.2)	20.6 (1.5)	0.002
NEI VFQ 25	35.8 (2.9)	28.4 (3.6)	0.12

Values expressed as mean (SEM) and t-tests performed for continuous variable or N (%) and chi-squared test performed for categorical variables. CVLT: California Verbal Learning Test; FAB: Frontal Assessment Battery; IADL: Lawton's Instrumental Activities of Daily Living; MADRS: Montgomery–Åsberg Depression Rating Scale; MMSE: Mini Mental State Examination; NEI VFQ 25: National Eye Institute Visual Function Questionnaire; WAIS-IV: Wechsler Adult Intelligence Scale—Fourth Edition.

body dementia. However, this is not substantiated in our study, as neither the degree nor the duration of visual deficiency was associated with cognitive performance. Other factors, which could not be evidenced from this study, could be assessed in a larger cohort of visual deficiency patients followed longitudinally.

The evolution in scores between initial and follow-up assessments after 4 months indicates the efficacy of LVR to improve visually impaired patients' functional abilities and their quality of life. This contributes further evidence in addition to the few studies published on the improvement of quality of life [4] and ongoing utility of LVR in treating patients aged 60 and above. Interestingly, LVR improved cognition according to the significant increase in COGEVIS scores possibly related to the learning of new strategies for planning and organization. We could identify a subgroup of patients with pre-LVR cognitive impairment who did not benefit from LVR, as their post-LVR COGEVIS scores were lower than those at baseline. However, this result does not invalidate LVR in patients with cognitive impairment. Firstly, the low number of cognitively impaired participants does not allow us to draw general conclusions about this result following LVR. Secondly, a specific study, focused only on LVR efficacy in this subgroup of patients, should be conducted in a randomized, placebo-controlled, double blind trial in order to assess the true impact of this therapy. Our study emphasizes that knowing the cognitive status of visually impaired patients before LVR is critical to inform the patient and his family of possible outcomes and adjust expectations regarding LVR.

In previous studies, loss of visual acuity has been reported to be significantly associated with depression [26–28]. Interviews of visually impaired patients older than 60 pointed out the high prevalence of depression in this population (more than 30%) compared to normally sighted peers [29]. In our study, MADRS scores used to assess depressive symptoms showed above average rates of depression among visually deficient patients and higher rates when visual deficiency was associated with cognitive impairment. Depressive symptoms also decreased after LVR. Therefore, discrimination between purely depressive syndromes with cognitive complaints and cognitive impairment due to neurodegenerative diseases is important to adapt the objectives and indication of LVR. COGEVIS could be a suitable test to separate these two syndromes.

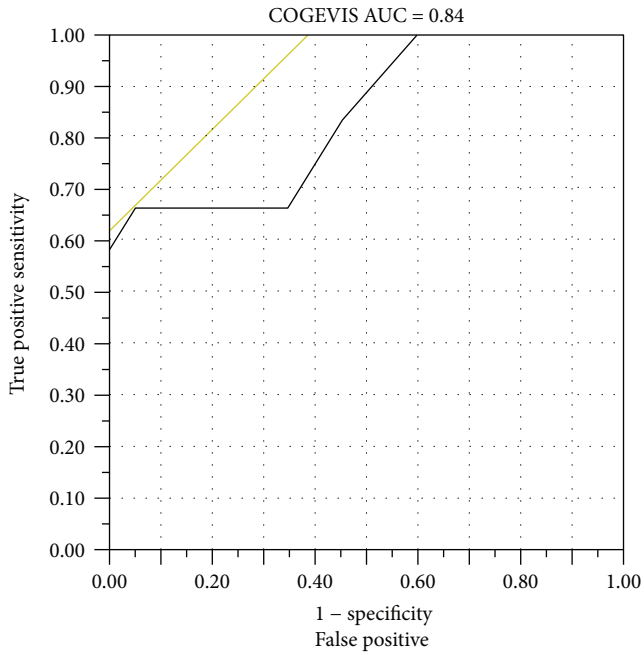

Figure 2: Receiver operating characteristic (ROC) curve of the COGEVIS to diagnose cognitive impairment. AUC: area under the curve. A yellow line is drawn at a 45-degree angle tangent to the ROC curve. This marks a good cutoff point under the assumption that false negatives and false positives have similar costs. In this case, a COGEVIS below 24 yielded a sensitivity of 66.7% and a specificity of 94.7%.

Table 2: Comparison of cognition, functional ability, quality of life, and depression before and after low vision rehabilitation (LVR).

Mean ± SD	Before LVR	After LVR	Z score	p
COGEVIS	24.70 ± 3.98	25.65 ± 4.44	−2.091	0.036*
IADL	17.97 ± 6.10	15.95 ± 6.56	−2.896	0.004**
NEI VFQ 25	34.29 ± 15.20	38.82 ± 12.74	−2.092	0.035*
MADRS	13.41 ± 9.93	9.18 ± 9.67	−2.090	0.037*

IADL: Lawton's Instrumental Activities of Daily Living; MADRS: Montgomery–Åsberg Depression Rating Scale; NEI VFQ 25: National Eye Institute Visual Function Questionnaire; *$p < 0.05$; **$p < 0.01$.

5. Conclusion

COGEVIS is a new, simple, and useful test to screen for cognitive impairment in visually impaired patients. It can also help in the assessment of therapeutic interventions (e.g., LVR) in this population.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Claire Meyniel and Stéphane Epelbaum conceived and drafted the manuscript and are the guarantors for the content. Dalila Samri, Farah Stefano, Joel Crevoisier, Florence Bonté, Raffaella Migliaccio, Laure Delaby, Anne Bertrand, Marie Odile Habert, and Bruno Dubois edited the manuscript.

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Supplementary Materials

The COGEVIS: a cognitive evaluation tool that does not rely on visual ability. The scale has a score range of 0–30 (higher scores indicating better function). *(Supplementary Materials)*

References

[1] R. R. Bourne, G. A. Stevens, R. A. White et al., "Causes of vision loss worldwide, 1990–2010: a systematic analysis," *The Lancet Global Health*, vol. 1, no. 6, pp. e339–e349, 2013.

[2] J. E. Goldstein, R. W. Massof, J. T. Deremeik et al., "Baseline traits of low vision patients served by private outpatient clinical centers in the United States," *Archives of Ophthalmology*, vol. 130, no. 8, pp. 1028–1037, 2012.

[3] G. Dagnelie, "Age-related psychophysical changes and low vision," *Investigative Ophthalmology & Visual Science*, vol. 54, no. 14, pp. ORSF88–ORSF93, 2013.

[4] J. E. Goldstein, M. L. Jackson, S. M. Fox, J. T. Deremeik, R. W. Massof, and Low Vision Research Network Study Group, "Clinically meaningful rehabilitation outcomes of low vision patients served by outpatient clinical centers," *JAMA Ophthalmology*, vol. 133, no. 7, pp. 762–769, 2015.

[5] S. J. Woo, K. H. Park, J. Ahn et al., "Cognitive impairment in age-related macular degeneration and geographic atrophy," *Ophthalmology*, vol. 119, no. 10, pp. 2094–2101, 2012.

[6] T. Q. Pham, A. Kifley, P. Mitchell, and J. J. Wang, "Relation of age-related macular degeneration and cognitive impairment in an older population," *Gerontology*, vol. 52, no. 6, pp. 353–358, 2006.

[7] H. Fukuoka, M. Nagaya, and K. Toba, "The occurrence of visual and cognitive impairment, and eye diseases in the super-elderly in Japan: a cross-sectional single-center study," *BMC Research Notes*, vol. 8, no. 1, p. 619, 2015.

[8] T. D. L. Keenan, R. Goldacre, and M. J. Goldacre, "Associations between age-related macular degeneration, Alzheimer disease, and dementia: record linkage study of hospital admissions," *JAMA Ophthalmology*, vol. 132, no. 1, pp. 63–68, 2014.

[9] M. P. Lawton and E. M. Brody, "Assessment of older people: self-maintaining and instrumental activities of daily living," *The Gerontologist*, vol. 9, 3 Part 1, pp. 179–186, 1969.

[10] C. M. Mangione, P. P. Lee, J. Pitts, P. Gutierrez, S. Berry, and R. D. Hays, "Psychometric properties of the National Eye Institute Visual Function Questionnaire (NEI-VFQ)," *Archives of Ophthalmology*, vol. 116, no. 11, pp. 1496–1504, 1998.

[11] S. A. Montgomery and M. Asberg, "A new depression scale designed to be sensitive to change," *The British Journal of Psychiatry*, vol. 134, no. 4, pp. 382–389, 1979.

[12] M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-mental state": a practical method for grading the cognitive state of

patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[13] B. Dubois, A. Slachevsky, I. Litvan, and B. Pillon, "The FAB: A frontal assessment battery at bedside," *Neurology*, vol. 55, no. 11, pp. 1621–1626, 2000.

[14] F. Mahieux-Laurent, C. Fabre, E. Galbrun, A. Dubrulle, C. Moroni, and groupe de réflexion sur les praxies du CMRR Ile-de-France Sud, "Validation of a brief screening scale evaluating praxic abilities for use in memory clinics," *Revue Neurologique*, vol. 165, no. 6-7, pp. 560–567, 2009.

[15] D. C. Delis, J. Freeland, J. H. Kramer, and E. Kaplan, "Integrating clinical assessment with cognitive neuroscience: construct validation of the California Verbal Learning Test," *Journal of Consulting and Clinical Psychology*, vol. 56, no. 1, pp. 123–130, 1988.

[16] M. S. Albert, S. T. DeKosky, D. Dickson et al., "The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's & Dementia*, vol. 7, no. 3, pp. 270–279, 2011.

[17] F. M. Reischies and B. Geiselmann, "Age-related cognitive decline and vision impairment affecting the detection of dementia syndrome in old age," *The British Journal of Psychiatry*, vol. 171, no. 5, pp. 449–451, 1997.

[18] A. Busse, A. Sonntag, J. Bischkopf, H. Matschinger, and M. C. Angermeyer, "Adaptation of dementia screening for vision-impaired older persons," *Journal of Clinical Epidemiology*, vol. 55, no. 9, pp. 909–915, 2002.

[19] B. P. Yochim, A. E. Mueller, K. D. Kane, and M. Y. Kahook, "Prevalence of cognitive impairment, depression, and anxiety symptoms among older adults with glaucoma," *Journal of Glaucoma*, vol. 21, no. 4, pp. 250–254, 2012.

[20] I. G. McKeith, D. W. Dickson, J. Lowe et al., "Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium," *Neurology*, vol. 65, no. 12, pp. 1863–1872, 2005.

[21] T. M. Cox and D. H. Ffytche, "Negative outcome Charles Bonnet syndrome," *The British Journal of Ophthalmology*, vol. 98, no. 9, pp. 1236–1239, 2014.

[22] A. P. Schadlu, R. Schadlu, and J. B. Shepherd III, "Charles Bonnet syndrome: a review," *Current Opinion in Ophthalmology*, vol. 20, no. 3, pp. 219–222, 2009.

[23] K. E. Crumbliss, M. J. Taussig, and W. M. Jay, "Vision rehabilitation and Charles Bonnet syndrome," *Seminars in Ophthalmology*, vol. 23, no. 2, pp. 121–126, 2009.

[24] M. I. Lapid, M. C. Burton, M. T. Chang et al., "Clinical phenomenology and mortality in Charles Bonnet syndrome," *Journal of Geriatric Psychiatry and Neurology*, vol. 26, no. 1, pp. 3–9, 2013.

[25] H. Fujishiro, E. Iseki, K. Kasanuki et al., "A follow up study of non-demented patients with primary visual cortical hypometabolism: prodromal dementia with Lewy bodies," *Journal of the Neurological Sciences*, vol. 334, no. 1-2, pp. 48–54, 2013.

[26] B. W. Rovner, R. J. Casten, M. T. Hegel et al., "Low vision depression prevention trial in age-related macular degeneration: a randomized clinical trial," *Ophthalmology*, vol. 121, no. 11, pp. 2204–2211, 2014.

[27] J. R. Evans, A. E. Fletcher, and R. P. L. Wormald, "Depression and anxiety in visually impaired older people," *Ophthalmology*, vol. 114, no. 2, pp. 283–288, 2007.

[28] X. Zhang, K. M. K. Bullard, M. F. Cotch et al., "Association between depression and functional vision loss in persons 20 years of age or older in the United States, NHANES 2005–2008," *JAMA Ophthalmology*, vol. 131, no. 5, pp. 573–581, 2013.

[29] H. P. A. van der Aa, H. C. Comijs, B. W. J. H. Penninx, G. H. M. B. van Rens, and R. M. A. van Nispen, "Major depressive and anxiety disorders in visually impaired older adults," *Investigative Ophthalmology & Visual Science*, vol. 56, no. 2, pp. 849–854, 2015.

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Review Article

Social Cognition Dysfunctions in Neurodegenerative Diseases: Neuroanatomical Correlates and Clinical Implications

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Social cognitive function, involved in the perception, processing, and interpretation of social information, has been shown to be crucial for successful communication and interpersonal relationships, thereby significantly impacting mental health, well-being, and quality of life. In this regard, assessment of social cognition, mainly focusing on four key domains, such as theory of mind (ToM), emotional empathy, and social perception and behavior, has been increasingly evaluated in clinical settings, given the potential implications of impairments of these skills for therapeutic decision-making. With regard to neurodegenerative diseases (NDs), most disorders, characterized by variable disease phenotypes and progression, although similar for the unfavorable prognosis, are associated to impairments of social cognitive function, with consequent negative effects on patients' management. Specifically, in some NDs these deficits may represent core diagnostic criteria, such as for behavioral variant frontotemporal dementia (bvFTD), or may emerge during the disease course as critical aspects, such as for Parkinson's and Alzheimer's diseases. On this background, we aimed to revise the most updated evidence on the neurobiological hypotheses derived from network-based approaches, clinical manifestations, and assessment tools of social cognitive dysfunctions in NDs, also prospecting potential benefits on patients' well-being, quality of life, and outcome derived from potential therapeutic perspectives of these deficits.

1. Introduction

Social cognition refers to a wide range of cognitive capacities elicited by, about, and directed towards other people [1]. In particular, these skills allow humans to both understand themselves and interact with and understand others, engaging in appropriate goal-directed behaviors [1]. Given that social cognition may play a prominent role in clinical care of most psychiatric and neurological illnesses [2], including neurodegenerative conditions, an emerging literature addresses the study of the neurobiological processes underlying social interactions and the behavioral correlates of the breakdown of these processes. In particular, growing evidence suggests that neurodegenerative diseases (NDs) are associated with some level of social cognitive impairment that has the potential to disrupt interpersonal relationships, thereby eliminating the benefits that social interactions may have for patients with other neurocognitive impairments. However, the frequency, extent, and clinical correlates of these abnormalities are not fully established.

This review aims to summarize some of the basic components of social cognition, also referring recent hypotheses derived from network-based approaches, and to discuss clinical manifestations of social cognitive dysfunctions in most NDs, addressing the pertinent literature published in the last 10 years.

1.1. Social Cognition, Social Behavior, and Social Functioning. The term "social" implies that the processing demands are related to specific classes of stimuli, such as emotional expressions on a face, in the voice, or from body posture, also including higher-order functions, such as making inferences about other people's mental states (e.g., theory of mind (ToM)), making moral decisions, regulating emotions and feelings, and experiencing and expressing empathy [1, 3, 4]. Moreover, at the outset, it is useful to clarify the significance of social behavior, cognition, and functioning, which are substantially related to one another.

"Social cognition" refers to any cognitive processing (e.g., perception, reasoning, memory, attention, motivation, and decision-making) that appears to be relatively specialized for the social domain. It causes "social behavior" that comprises the readily observable interactions between an individual and other people, while "social functioning" is broader than social behavior in that it consists in the long-term and contextualized ability of an individual to interact with others (i.e., social behavior when integrated over time and context) [5]. Finally, the "social brain" historically refers to a number of brain structures, some of which, when damaged, may be involved in the impairment of social cognition and behavior (i.e., ventromedial and dorsomedial prefrontal cortex, temporoparietal junction and superior temporal cortex, insula, and fusiform gyrus) [3], while others have been found activated in healthy brains when people perform social tasks in a magnetic resonance scanner by using functional magnetic resonance imaging (fMRI) [1, 3, 6]. Furthermore, considering that no social process can be attributed to a single structure alone, the recent network-based approach to brain function, principally related to the growing implementation of resting state fMRI (rs-fMRI) studies, allowed the identification of a distributed network supporting social function, which included regions from the original social brain [1, 6, 7].

1.2. Network-Based Approach to Social Cognition. A core social cognition network is centered on the amygdala which has been proven to play a pivotal role in emotion processing, from triggering emotional responses to detecting socially salient stimuli and performing social affiliative behaviors [4, 8, 9], and to be connected to multiple brain regions involved in emotion circuits [10, 11]. Abnormalities within this network, comprising most components of the social brain (i.e., medial prefrontal cortex, orbitofrontal cortex (OFC), anterior cingulate cortex, temporoparietal junction, inferior frontal gyrus, and superior temporal sulcus), have been revealed in patients affected by schizophrenia [12, 13], frontotemporal lobar degeneration (FTLD) [14, 15], and autism spectrum disorder [16-18]. In particular, activation in the OFC and ventromedial prefrontal cortex has been shown to be not essential for affective responses, but critical for the attribution of meaning to an affective stimulus [19], while activation in the lateral part of the prefrontal region has been found to be associated with a feeling of displeasure and inhibits behavior [20]. Therefore, alterations in these areas may lead to inappropriate social behaviors [21, 22].

A second network involved in social cognition is the so-called "mentalizing" network, which includes the right temporoparietal junction as a key region [23], found to be activated when a subject spontaneously tracks others' mental states [24, 25] and when mentalizing is required as part of another judgment, such as in the case of moral judgments [26] or even when a subject observes a scenario in which a protagonist holds a false belief [27, 28, 29]. In this regard, while ToM refers to the cognitive ability to infer and reason about our own and other people's beliefs, intentions, or emotions, empathy consists in a basic perceptual capacity of understanding others' feelings and subjective psychological states [30], motivating prosocial behaviors [31]. The empathy network, the third circuit implicated in social cognition, includes cingulo-insular structures [32] and has been shown to be impaired in several neuropsychiatric conditions [33, 34]. Finally, of interest for social interactions is also the so-called "mirror neuron system", mainly involving the inferior frontal gyrus, the inferior parietal lobule, the fusiform face area, and the superior temporal sulcus [35, 36], activated during the observation of the actions of others, including emotion recognition [37, 38], and, therefore, typically impaired in autism [39-41].

1.3. Clinical Assessment of Social Cognition. From a clinical point of view, failures of social cognition, most often characterized by impairment of one or more of the four networks cited above, have been assessed using more specific tools useful to investigate the four different domains. Evidence underlined the need for introducing validated tasks of social cognition in the assessment of patients with neurodegenerative diseases [42-44]. In particular, some neurological disorders, characterized by the neurodegeneration of frontomedian areas, such as the behavioral variant frontotemporal dementia (bvFTD), need more specific neuropsychological testing of social cognition for assessing frontomedian cortex functions, in contrast to the well-known sensitivity of executive tests mainly for the frontolateral cortex [45].

With regard to social cognitive measures designed to detect abnormal social behaviors, a range of informant-rated measures (i.e., patients' self-report data might be distorted because of the lack of emotional insight), such as those derived from the Frontal Systems Behavior Scale (FrSBe) [46] and Frontal Behavioral Inventory (FBI) [47], both exploring changes in personality and behavior that are associated with frontoexecutive dysfunction, and from Socioemotional Dysfunction Scale (SDS) [48], Social Inappropriateness Scale [49], and Social Impairment Rating Scale (SIRS) [50], focused on the detection of interpersonal phenomena and social impairment.

With regard to assessing ToM abilities, several tools allow exploring a patient's ability to infer what others are thinking and feeling, and to reason about how their thoughts and

feelings will influence their behavior. False-belief tasks [51] are extensively validated measures of ToM that assess the ability to disregard one's own knowledge about the world and consider that someone else might have a different, erroneous belief.

Measures that assess social inference, such as the ability to detect sarcasm, also provide insight into the potential difficulties related to social interaction, such as The Awareness of Social Inference Test (TASIT) [52] that allows the detection of sincerity. ToM alterations can also be assessed with the Strange Stories test [53], in which patients are asked to demonstrate their understanding of stories in which characters' behavior can be best understood by attributing to him/her a specific underlying mental state. The Faux-Pas Test [54] also involves a series of written stories, but patients are asked to detect the *faux pas* and to understand beliefs, intentions, and inappropriateness. Finally, the Reading the Mind in the Eyes Test (RMET) [55] explores the ability to make inferences on the basis of observable features, such as facial expression and eye gaze, asking participants to infer the mental state of a person on the basis of a photograph of their eyes and the surrounding area.

To provide potential insights into empathic disturbances, valuable information may be derived from self-rated and informant-rated measures of affective empathy, such as the Empathic Concern subscale of the Interpersonal Reactivity Inventory (IRI-EC) [56], which investigates the feelings of warmth, compassion, and concern for others; the Perspective-Taking subscale of the IRI (IRI-PT), which allows distinguishing between affective abnormalities that reflect a lack of caring and those that reflect a lack of understanding; and the Empathy Quotient (EQ) [57], which measures the ability of understanding and predicting other people's affective and cognitive empathy and the nature of any emotional response to other people. Finally, among emotion-relevant performance tasks, which consist in evaluating emotional response to viewing photographs or videos, the Multifaceted Empathy Test (MET) [58] allows differentiating between mental state understanding (cognitive empathy) and subjective emotional response (affective empathy).

Deficits of social perception may be manifested as a deficit in identifying others' emotions, and this dysfunction may be assessed through the presentation of static photographs of high-intensity facial expressions. In this regard, the most commonly used task is the Ekman Faces, the one for assessing emotion labelling and discrimination [59]: participants are asked to identify which emotion is shown by a picture of a face and whether two faces show the same or different emotions. Moreover, to evaluate the intensity of a facial expression, the "Facial Expressions of Emotion: Stimuli and Tests" includes images that vary in their emotional intensity, enabling clinicians to create tasks that are graded in difficulty. The breadth and specificity of difficulties in recognizing emotions can be assessed with batteries of tests, such as the Comprehensive Affect Testing System [60] and the Florida Affect Battery [61], which use not only visual stimuli, but also auditory. Both of these batteries incorporate multiple subtasks that assess the ability to process visual (facial expressions), auditory (prosody), and visual-auditory (simultaneous facial expressions and prosody) emotional information.

The evaluation of the ability to integrate social perceptual cues with contextual information that forms part of normal social encounters can also be clinically useful. One measure that can be used for such an assessment is the Emotion Evaluation Test, which forms part of TASIT Part 1 [52], evaluating the ability to recognize emotions from dynamic, multimodal stimuli that are embedded into specific social scenarios. In particular, participants are shown videos in which an actor interprets one of seven basic emotions, sometimes with ambiguous dialogue, sometimes without any dialogue and they are asked to identify the emotional expression depicted.

In summary, when social cognitive dysfunction is suspected on the basis of clinical evidence, at least one measure of each of the four social cognitive domains should be evaluated [5] and, if specific social cognitive deficits are identified, a more comprehensive assessment that focuses on the domain(s) in question should be conducted. In this regard, Table 1 summarizes the abovementioned assessment tools, reporting the neurological disorders in which impairment of social cognition domains has been explored and the respective neuroanatomical correlates of these dysfunctions. The selection of the more appropriate protocol should be guided by the clinical validity of the tests to be administered (i.e., sensitivity and specificity for the neurological disorder of interest) and by the existence of population norms [5], and potential disadvantages may be linked to the lack of population norms in the case of some measures.

2. Social Cognition Abnormalities in Neurodegenerative Disorders

2.1. Amyotrophic Lateral Sclerosis-Frontotemporal Disease Spectrum Disorders (ALS-FTSD)

2.1.1. Frontotemporal Lobar Degeneration (FTLD). Social cognition has been reported as selectively vulnerable in FTLD, a term that grouped a clinically and pathologically complex spectrum of non-Alzheimer neurodegenerative disorders featured by selective and progressive atrophy of frontal, insular, and temporal brain lobes [62]. In the late 19th century, this complex group of disorders was denominated as Pick's disease in homage to Arnold Pick who helped in the study and description of these disorders. Although FTLD is considerably uncommon compared to Alzheimer's disease, this disease spectrum is one of the most important causes of young onset dementia and entails high clinical and socioeconomic costs [63].

Three major FTLD clinical syndromes, described considering the predominant clinical manifestations, are the bvFTD, mainly featured by disturbances in social behavior and in executive functioning [64, 65]; the primary progressive aphasias (PPAs) (semantic variant (svPPA), nonfluent agrammatic variant (nfvPPA), and logopenic variant), a group of disorders mainly characterized by linguistic and behavioral alterations [66]); and the syndromes characterized by the cooccurrence of FTLD with neurological disorders

Table 1: Social cognition domains with the related assessment tools for clinical and research investigation of social cognition deficits in neurodegenerative diseases.

Social cognition domains	Assessment tools	Neurodegenerative diseases with impairment of social cognition domains	Neuroanatomic correlates of social cognition dysfunctions in neurodegenerative diseases
Theory of mind	False-belief tasks, Faux-Pas Test, RMET, Strange Stories Test, TASIT	bvFTD	Ventromedial, dorsolateral, and ventrolateral prefrontal cortex, OFC, temporoparietal junction [42, 43, 115-119]
		nfvPPA	Temporal pole, insular cortex [113]
		svPPA	Left temporal lobe, medial frontal cortex [113]
		ALS	Dorsomedial and dorsolateral prefrontal cortex, supplementary motor areas [137]
		PD	Bilateral cingulate gyri, middle and inferior frontal gyri, fusiform and superior temporal gyri, bilateral parietal and bilateral occipital lobes [212, 213]
		PSP	Right inferior frontal gyrus, anterior medial frontal cortex [188]
		CBS	Right frontal-temporal-parietal cortices [214]
		AD	Superior temporal sulcus, posterior cingulate cortex, precuneus [42]
Empathy	EPT, EQ, IRI-EC, IRI-PT, MET	bvFTD, ALS, AD/MCI	Anterior cingulate, frontoinsular cortices [139, 115-119, 234]
Social perception	Ekman Faces test, TASIT, Comprehensive Affect Testing System, Florida Affect Battery	bvFTD	Anterior cingulate, orbitofrontal and medial prefrontal cortex, insula, striatum, and amygdala (SLN) [42, 43, 109, 115-119]
		nfvPPA	Posterior fusiform gyri, bilateral insular cortex, anterior temporal lobe [112]
		svPPA	Left temporal cortex, amygdala [112]
		ALS	Right inferior longitudinal fasciculus, inferior frontooccipital fasciculus [147, 148]
		PD	Orbitofrontal cortex, right and left superior frontal gyri, bilateral posterior cingulate gyri, somatosensory cortices, amigdala [206-209]
		PSP	Right inferior frontal gyrus [188]
		CBS	Paracentral gyrus, precuneus [163]
		AD	Temporoparietal regions [222-224]
Social behavior	AES, FBI, FrSBe scale, NPI, SDS, SIRS	bvFTD, ALS, PD, AD	Ventromedial and lateral prefrontal cortex, fronto-temporo-insular areas, anterior cingulate cortex [21, 22, 118, 129, 130, 222]

AD = Alzheimer's disease; AES = apathy evaluation scale; ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant frontotemporal dementia; CBS = corticobasal syndrome; EQ = Empathy Quotient; FrSBe = Frontal Systems Behavior; FBI = Frontal Behavioral Inventory; IRI-EC = Interpersonal Reactivity Inventory-Empathic Concern; IRI-PT = Interpersonal Reactivity Inventory-Perspective-Taking; MCI = mild cognitive impairment; MET = Multifaceted Empathy Test; NPI = Neuropsychiatric Inventory; OFC = orbitofrontal cortex; PD = Parkinson's disease; PSP = progressive supranuclear palsy; RMET = Reading the Mind in the Eyes Test; SDS = Socioemotional Dysfunction Scale; SIRS = Social Impairment Rating Scale; TASIT-S = The Awareness of Social Inference Test.

mainly affecting cortical and subcortical brain areas, including amyotrophic lateral sclerosis (ALS) [67], progressive supranuclear palsy (PSP), and the corticobasal syndrome (CBS) [63], which mainly affect motor functions, but also impact social behavior.

(1) Alterations in the Four Domains of Social Cognition. Social cognition deficits are pervasive in FTLD. However, among the aforementioned syndromes, dysfunctions in social interaction processes have been mostly described in patients with bvFTD [64, 65]. In particular, six core symptoms are recognized in the revised diagnostic criteria [64]: (i) early (i.e., within the first three years of symptom onset) behavioral disinhibition, for example, socially inappropriate behavior, loss of manners or decorum, or impulsive actions; (ii) early apathy or inertia; (iii) early loss of sympathy or empathy, for example, diminished response to other people's needs and feelings and diminished social interest; (iv) early perseverative, stereotyped, or compulsive/ritualistic behavior, for example, repetitive movements and stereotypy of speech; (v) hyperorality and dietary changes, for example, altered food preferences, binge eating, and oral exploration of inedible objects; and (vi) executive dysfunction; with at least 3 of these 6 features required for a diagnosis of bvFTD.

In bvFTD patients, impairments have been described in different social cognitive processes associated with previous behaviors ranging from basic affective to more high-order and reflexive processes [65, 68-71] and, interestingly, bvFTD has been proposed as a disease model for studying interactions between emotion processing, social cognition, and interoception [72]. In particular, with regard to basic social cognitive processes, bvFTD patients can exhibit emotion-processing alterations, including abnormalities of the perception of emotional and social cues [73-76], altered empathic concern [77], and alterations in affective expression that includes the presence of apathy or, by contrast, euphoric mood states, overfamiliarity, jocularity, and silliness [78, 79]. Furthermore, the bvFTD patients may present disturbances in the more reflexive social cognitive processes including reduced theory of mind abilities [43], mentalizing deficits [80], diminished prosocial sentiments [81], and reduced long-term cooperative behaviors [70, 82, 83]. Recently, impaired performances at RMET have been revealed to better discriminate bvFTD patients from healthy subjects or Alzheimer's disease patients than altered performances in executive tests, thereby underlining the relevance of social cognition abnormalities in bvFTD diagnosis [84-89]. In particular, executive function tests, such as Stroop task and Trail Making Test, have been shown to be less disease specific than social cognition tests, such as the RMET, for the differential diagnosis across different forms of dementia [85-89]. In support of this, recent meta-analyses confirmed the central role of ToM in bvFTD diagnosis by showing significantly higher and domain-specific impairments of ToM (and emotion recognition) in bvFTD in comparison to control subjects and Alzheimer's disease [90] or other clinical conditions including multiple psychiatric, neurological, and developmental disorders [91]. However, questionnaires that also account for behavioral disorders, such as apathy evaluation scale (AES) [92] and FrSBe scale, especially in the informant-report version, have been shown to significantly differentiate bvFTD patients from healthy controls [84]. Of note, some of the most frequent behavioral symptoms in bvFTD, including apathy, impulsivity, and disinhibition, have been associated to implicit difficulties in social interaction and alterations in the processing of social cues, suggesting a tight interplay between social cognition and neuropsychiatric symptoms in this condition [68, 93]. Thus, the apathetic presentation of bvFTD includes patients who have a lack of interest in their social surroundings as they present difficulty in initiating, planning, and motivating social behavior, related to atrophy in frontal areas and basal ganglia [93-95]. Along this vein, impulsive and disinhibited bvFTD patients exhibit inappropriate social behavior including undue familiarity, disorganized behaviors, and sexual acting out related to impaired mechanisms of cognitive control as a consequence to atrophy in the OFC, frontal ventromedial, and cingulate cortices and anterior temporal areas [96].

Alterations in the social cognitive process can also transfer to moral domains in bvFTD patients, who may show altered moral judgments, displaying more utilitarian judgments in the face of moral dilemmas [97, 98], a pattern also observed in extreme criminal terrorists [99]. Moreover, these patients can display increased antisocial and criminal behavior [100, 101], as well as a relatively high incidence of legal violations [102] and a heightened expression of counter-empathy emotions such as envy and gloating for others' misfortunes [103].

With regard to the ability to make judgements about others' behavior, attitudes, and emotions (i.e., social perception and empathy domains), patients with bvFTD may experience impaired emotion recognition, empathy, and sarcasm detection [73, 77, 104, 105]. In particular, performance on the newly developed TASIT-S, regarding emotion recognition and sarcasm detection, has been revealed impaired in bvFTD and relatively intact in AD [14]. However, although most studies have focused on the verbal categorization of facial expressions [106], deficits have also been reported under different task conditions and stimulus modalities including vocal [107], bodily [108], and musical [109] expressions of emotion. Moreover, the emotion recognition of film stimuli is also impaired [75, 110], although the psychological reactivity to negative film stimuli does not appear to differ from controls [75]. In addition to these deficits in recognizing emotions in others, bvFTD patients have also shown abnormal emotion suppression, emotion generation, and experience of self-conscious emotion, as revealed for bvFTD patients viewing disgust-invoking stimuli, who have been shown to display reduced facial expressions of disgust, reduced physiological reactivity, and reduced self-reported experience of disgust, compared to controls [111]. Furthermore, a deficit in social context processing was observed in the performance of FTLD patients in the empathy for pain task (EPT) [77], a suitable instrument that evaluates empathy in the context of intentional/accidental harm. Accidental pain situations are less clear and explicit; hence, they require greater demands to ascertain the action's intentionality and integration of contextual information. When performing the EPT, the FTLD patients do not easily discriminate between accidental and intentional situations revealing difficulties in integrating social context cues and agents' intentionality [73].

With regard to linguistic variants of FTLD, namely PPAs including svPPA and nfvPPA, some evidence also revealed alterations in several social cognitive processes. Several reports showed deficits in face and emotion recognition, and in ToM processes in both svPPA and nfvPPA [109, 112-114].

(2) Neuroanatomical Bases of Social Cognition Impairment in FTLD and Network-Based Approaches. Most of the aforementioned behavioral alterations might reflect a general disturbance in different neural networks. To date, it has been reported that the functioning of three neural networks can be altered in FTLD, including the salience network, the dorsal attention network, and the default mode network. Firstly, the salience network (SLN) [115] composed of the anterior cingulate, insula, striatum, and amygdala, which is activated in healthy subjects during tasks requiring attentional selection, task switching, and self-regulation of behavior, has been reported as impaired in FTLD as a consequence of atrophy over the main hubs of SLN [115]. In particular, the insula, a key region of SLN, is highly connected with the anterior

portion connecting with the lateral OFC, while the posterior portion connects with the superior temporal cortex; in bvFTD, both the ventral (frontoinsular) and dorsal areas of the anterior insular are affected [116]. Degeneration of these connected areas has been shown to be related to the impairment of emotion recognition and processing [109, 117], social cognition [118], and interoception [119] in bvFTD.

Secondly, it has been reported that in FTLD there is an abnormal increased connectivity in other networks including the dorsal attention network and default-mode network (DMN) [120]. Alterations in connectivity patterns of those networks seem to be at the core of the decline in executive functions and attention, as well as apathy in patients with FTLD [120, 121]. Thirdly, clinical alterations in FTLD have been associated to a disorder of functional frontolimbic disconnection leading to a compensatory hyperconnectivity in prefrontal areas in response to the absence of affective feedback during the planning and execution of behavior [121].

More recently, an integrative model suggested that the functioning of a network known as the social context network (SCN), composed by fronto-temporo-insular areas, might explain the social cognitive, executive, and behavioral alterations in FTLD [68, 122-124]. Arguably, in control subjects, the SCN favors (a) to update context cues to make predictions, (b) to consolidate context-target associative learning, and (c) to coordinate internal and external milieus [68, 122].

In linguistic variants, comparative analysis of regional gray matter related to social cognition deficits have revealed a differential pattern of fronto-insulo-temporal atrophy in bvFTD, in contrast to a set of dissociable insulo-temporal areas for svPPA and for nfvPPA [112]. Thus, face and emotion recognition impairments in nfvPPA were related to the atrophy of the bilateral posterior fusiform gyrus, bilateral insular cortex, and anterior temporal lobe [112]. Conversely, emotion recognition deficits in svPPA have been associated to atrophy in left temporal structures and also to amygdala atrophy [125]. Finally, deficits in ToM in nfvPPA have been associated with temporal pole and insular cortex degeneration. In contrast, theory of mind disturbances in svPPA are consistent with the patients' atrophy in the left temporal lobe and the medial frontal cortex [113].

Taken together, the integration of the study of social cognitive factors, such as emotion processing, empathy, ToM, moral cognition, and sociobehavioral regulation, are considered as the current target to assess complex behaviors in FTLD. In fact, a deep comprehension of the neurocognitive processes that subsume the interplay between the sociomoral cognition, the executive function, and the behavior seems to be the most robust way to create new perspectives for the diagnosis and new targets of intervention in FTLD.

2.1.2. Amyotrophic Lateral Sclerosis and Its Disease Spectrum. The presence of impaired social cognition in ALS, with or without dementia, provides additional evidence in favour of the existence of an ALS-FTLD continuum and appears to have crucial implications for patients' and caregivers' training from early disease stages. ALS, the most common motor neuron disease, has been traditionally classified as a disease of the motor system. However, cognitive and behavioral dysfunctions are now recognized as an integral part of ALS-related clinical syndrome [67, 126]. In particular, about 50–60% among ALS patients may develop frontotemporal dysfunctions [67, 127], mostly characterized by executive and language impairment, variable memory dysfunctions, and/or behavioral impairment [67, 128]. Apathy is the most pronounced ALS-related behavioral change [129], while disinhibition and disorganization have been less frequently reported [130]. In addition, approximately up to 15% of ALS patients will either present with or develop FTLD, exhibiting a strong clinical and pathological overlap between ALS and FTLD [131]. Thus, the abovementioned heterogeneity results in different categorization groups across a spectrum of disease, including cognitive impairment, behavioral impairment, and ALS-FTLD [67, 131].

Impaired social cognition is now recognized as a part of the cognitive phenotype of ALS, despite the fact that there is significant heterogeneity in tasks used to study social cognition. During the last decades, an increasing body of studies focus on patients' performance in tests related to social cognition [67] and also evaluated its neuroanatomical correlates [132]. On the other hand, social cognition is included in an ALS cognitive screening testing (i.e., Edinburg Cognitive and Behavioral ALS Screen (ECAS); [133]) and in the "Axis II: Defining the neuropsychological deficits" of the recently suggested diagnostic criteria for ALS-frontotemporal spectrum disorders (ALS-FTSD) [67]. Moreover, the evaluation of social cognition in ALS-FTSD may have an utmost importance in clinical settings, given the potential effects of its impairment on patients' quality of life and ability to engage in end-of-life decisions [134-136]. However, it is still debatable whether social cognition deficits are independent of other cognitive deficits in ALS or are part of the executive deficits or not [137-143] and to what degree they are associated with other cognitive deficits, including memory function [136]. Of note, a subgroup of ALS patients without dementia has been found to present impaired social cognition without executive dysfunction [140].

(1) Alterations in the Four Domains of Social Cognition. Changes in emotion-processing ability and reduced capacity in the emotional recognition of facial expressions (i.e., mostly related to negative emotions, including fear, anger, and disgust [144, 145]) is more likely in patients with ALS-FTLD [141, 146-148]. In particular, the latter, in association with the fact that the severity of social cognition deficits is much more pronounced and widespread in FTLD patients [149, 150], corroborates the existence of a considerable clinical overlapping between ALS and FTLD.

Social behavior dysfunction in ALS mainly includes apathy [141]. Moreover, loss of empathy [141], deficits in emotion processing [147, 151-153] and emotional empathy attribution [139], and compromised ability to make social inferences [142, 146] have also been described in nondemented ALS patients.

Patients with ALS show difficulty on tests tapping onto ToM components, exhibiting impaired abilities (i) to describe the intentions and feeling of characters [139, 142, 154], (ii) to

identify and explain social faux pas [155], and (iii) to estimate preferences for objects based on the interpretation of eye gaze direction [141, 156].

Even though previous evidence revealed a more pronounced impairment in affective rather than cognitive component of ToM [157], Trojsi et al. [136] found that both cognitive and affective ToM may be impaired in the early disease stages by simultaneously comparing both ToM components [136]. Of note, cognitive ToM impairments have been mostly linked to a more general executive dysfunction [154].

Clinical variables have been directly or indirectly related to patients' ToM and other social abilities. For instance, the majority of studies with impairments include patients with an average duration of 30 months [141, 142, 155], bulbar onset [156], and/or cognitive impairment [142, 146]. With regard to the latter, it is still unclear whether social cognitive impairment is independent of other cognitive deficits (particularly executive dysfunction) or not. In particular, Watermeyer et al. [143] revealed that impaired social cognition in ALS has been mainly attributed to primary executive dysfunction, found to be the main predictor of social cognition performance above and beyond demographics, behavior, mood, and personality variables. Severe deficits in both cognitive and affective ToM have been proven to be related to apathy and impaired verbal fluency and naming [157], while early in the disease course impaired ToM has been associated to executive dysfunction [137]. On the other hand, there are several studies that failed to find an association between social cognition/ToM and executive impairment [137, 141, 155]. In this regard, Trojsi et al. [136] recently reported that both cognitive and affective ToM components are associated with nonexecutive impairment, including memory prose and visuospatial ability.

(2) Neuroanatomical Bases of Social Cognition Impairment in ALS. Some multimodal studies have directly addressed in vivo the degeneration of social brain networks in ALS, using neuroimaging techniques tailored to the study of structural changes (gray matter, white matter) [139, 148] and functional alternations (fMRI) [132]. Evidence was related to the emotion circuits, including amygdala and medial prefrontal, OFC and anterior cingulate cortices, and "mentalizing" and "empathy" networks. In particular, patterns of gray matter atrophy in anterior cingulate and right frontoinsular cortices were found significantly associated with emotional and empathy performances in nondemented ALS patients [139]. Moreover, a significant decline of emotion recognition skills (particularly affecting the identification of negative emotions) has been found related to microstructural changes (measured through fractional anisotropy) in right inferior longitudinal fasciculus and inferior frontooccipital fasciculus in nondemented ALS patients [148]. Interestingly, also in ALS patients the right hemisphere has been confirmed to play a key role in the identification of others' emotions, especially those negative, with specific damage of ventral associative tracts connecting frontal, temporal, limbic, and occipital areas [147].

Focusing on the cognitive ToM component, Carluer et al. [137] detected significant correlations between cognitive ToM deficit (i.e., false-belief task) and brain metabolic rate of glucose consumption in the bilateral dorsomedial and dorsolateral prefrontal cortex, as well as in supplementary motor areas. These findings are in line with the involvement of dorsomedial and dorsolateral prefrontal areas in cognitive ToM [158, 159], as well as the contribution of the supplementary motor area in the "mirror neuron system" [160].

2.2. Parkinson's Disease and Parkinsonisms. Parkinson's disease (PD), mainly characterized by motor symptoms (i.e., resting tremor, bradykinesia, rigidity, and postural instability), may exhibit early nonmotor symptoms, including neuropsychiatric symptoms, sleep problems, and cognitive deficits, hypothesized to be secondary to the loss of dopaminergic neurons in the substantia nigra and the consequent hypostimulation of the prefrontal cortex [161]. Among nonmotor domains, social cognition has been explored in PD, especially with regard to emotion recognition and ToM abilities. However, emerging evidence has underlined the severity of nonmotor symptoms of PSP and CBS, which may substantially impact on social interactions and contribute to alter emotion recognition [162, 163].

2.2.1. Alterations in the Four Domains of Social Cognition. As for emotion recognition in PD, several studies [164-169] revealed emotion recognition deficits in PD patients when compared to matched healthy controls. However, other studies failed to find these deficits [170-174]. A recent meta-analytic review [175], which investigated the emotion recognition from faces and voices in PD, revealed significant and modest deficits of this ability in nondemented PD patients, independently from the level of motor disability. Furthermore, several studies revealed that PD patients were more impaired in recognizing negative emotions (anger, disgust, fear, and sadness) than positive ones (happiness, surprise) [176], while other studies suggested that the recognition of negative emotions may be impaired mainly in the early stages of PD and, then, this impairment has been shown to mainly affect the positive ones [177]. In particular, Hipp et al. [178] showed that, at the early stages, PD patients might be still prone to compensate the deficient input of low contrast sensitivity that is crucial for the appreciation of negative facial emotions.

Impairments of facial emotion recognition in PD patients were found to be independent of depressive symptoms [167, 179-181], executive deficits [179, 180], and clinical aspects (i.e., disease duration and severity, [180]). Moreover, some studies revealed that emotion recognition abnormalities may occur after subthalamic nucleus stimulation [182-185], probably due to alterations of projections to cortical areas, particularly the OFC, which has been already implicated in emotion recognition [186]. However, a recent study of Albuquerque et al. [187] did not confirm these findings in advanced PD.

With regard to PSP and CBS, also belonging to the FTLD spectrum of neurodegeneration (i.e., abnormal function/levels of the microtubule associated protein tau), patients affected by PSP may exhibit impaired facial (i.e., sadness

and sadness) and voice emotion recognition [188, 189] as well as CBS patients, who may exhibit difficulties in recognizing disgust, sadness, surprise, and happiness, but not anger and fear [163]. Moreover, half of the PSP patients reported that social impairments negatively impacted their quality of life [190] and, in this regard, this self-perceived social impairment may be the result of the loss of emotion knowledge or breakdown of higher-order social inferences, known as "theory of mind," as observed in FTLD [105]. In support of this overlap of social cognition impairment between FTLD and PSP, Shany-Ur et al. [191] assessed socioemotional comprehension, including visual perspective taking, belief representation, and emotion reading in a population of neurodegenerative patients, including patients with FTLD and PSP, using the Social Inference-Enriched (SI-E) and Social Inference-Minimal (SI-M) subtests of the TASIT [52]. They revealed that both patients with bvFTD and with PSP had significantly poorer scores than healthy controls on the TASIT SI-E "think" questions across verbal cue items, indicating an impaired ability to represent others' verbalized opinions/beliefs, and on the TASIT SI-E "do" questions across all items, indicating impaired ability to comprehend others' intentions. In particular, impairment of the comprehension of insincere communication and sarcasm was observed in PSP as well as in bvFTD patients, though to a major extent in patients with bvFTD [191]. Of note, failure to comprehend complex social interactions has been demonstrated to exacerbate patients' poor social self-monitoring and aberrant social behavior, thereby severely impacting interpersonal communication and patients' management [192]. Conversely, in CBS observation of facial apraxia, which results in the inability to express facial emotional expressions [193], and flat aprosodic speech [194] may reflect a compromised ability to express emotions.

Several studies explored the two different subcomponents of ToM (i.e., affective and cognitive subcomponents) in PD patients and revealed deficits of both across the entire disease course [169, 195-198]. Importantly, Peron et al. [199] found no different performance on ToM tasks between medicated and nonmedicated PD patients at early stages, suggesting that ToM deficits could be observed in PD patients when the degenerative process has spread beyond the dopaminergic pathways, but not in the early PD patients, in whom neuronal loss is limited to the nigrostriatal and mesolimbic dopaminergic systems. However, more recent studies did not confirm these findings, but revealed the occurrence of impairment of cognitive ToM in both medicated and unmedicated PD [196, 200], whereas other studies showed impairment of affective ToM [195] or deficits of both ToM subcomponents [198, 201].

Deficits of the cognitive ToM subcomponent have been found associated predominantly with executive dysfunction [198, 200, 202-204]. Conversely, Roca et al. [196] did not find any association between cognitive ToM, depression, executive dysfunctions, and medication usage. With regard to deficits of the affective ToM subcomponent, they have been associated with apathy [198] and reduced quality of life [201] and may be predicted by poor cognitive status and the dysfunction of visuospatial abilities [205].

2.2.2. Neuroanatomical Bases of Social Cognition Impairment in PD and Parkinsonisms. With regard to structural neural bases of the deficits in facial emotion recognition, Ibarretxe-Bilbao et al. [206] revealed an association between these deficits and reduced volume in OFC, associated to the degeneration of OFC and amygdala. More recently, Baggio et al. [207] confirmed the pivotal role of abnormalities within these areas in impaired facial emotion recognition and also found that poor sadness, disgust, and anger identification were also related to dysfunction in other cortical regions, such as postcentral and right occipital fusiform gyri, ventral striatum, subgenual cortex, and anterior cingulate cortex.

Previous neuroimaging studies, focusing on functional changes associated with the impaired recognition of emotions in PD patients, revealed that the impaired emotional facial recognition network was characterized by a decreased metabolism within the bilateral posterior cingulate gyrus (BA 31), right superior frontal gyrus (BAs 10, 9, and 6), and left superior frontal gyrus (BAs 10 and 11) [208]. Furthermore, Wabnegger et al. [209] found that, when compared to healthy subjects, PD patients showed a stronger activation in somatosensory cortices, which are involved in decoding emotional states by internally generating somatosensory representations that simulate how one feels when displaying a certain facial expression and, therefore, may be substantially involved in emotion recognition (Figure 1).

With regard to parkinsonisms, impaired emotion recognition in PSP patients have been associated with gray matter atrophy in the right inferior frontal gyrus [188], while in CBS neuroimaging analyses revealed that emotion-processing deficits were associated with the atrophy of the paracentral gyrus/precuneus region, as well as of the basal ganglia [163]. PSP patients have been proven to exhibit mild but significant focal deficits in social cognition [191], which is consistent with evidence showing that they may often manifest behavioral and personality changes, hypothesized to occur as a result of a disconnection between subcortical structures and the prefrontal cortex [210, 211].

With regard to neural correlates of ToM deficits in PD, Péron et al. [212] revealed a significant association between impaired ToM abilities and decreased cerebral glucose metabolism in brain areas belonging to the "ToM network" (i.e., bilateral cingulate gyri, middle and inferior frontal gyri, fusiform and superior temporal gyri, and bilateral parietal and bilateral occipital lobes). In addition, Diez-Ciranda et al. [213] observed that reduced gray matter volume in the precentral and postcentral gyrus and in the middle and inferior frontal gyri may be involved in ToM deficits in PD. Moreover, these authors reported an association between ToM impairment and alterations of white matter in the superior longitudinal fasciculus, adjacent to the parietal lobe, and of the white matter adjacent to the frontal lobe.

In atypical parkinsonisms, ToM abilities have been poorly explored. In detail, impaired ToM abilities have been described in PSP patients [188] and found to be related to grey matter atrophy in the right inferior frontal gyrus and in the anterior medial frontal cortex, both associated to the ToM domain. Finally, Poletti and Bonuccelli [214]

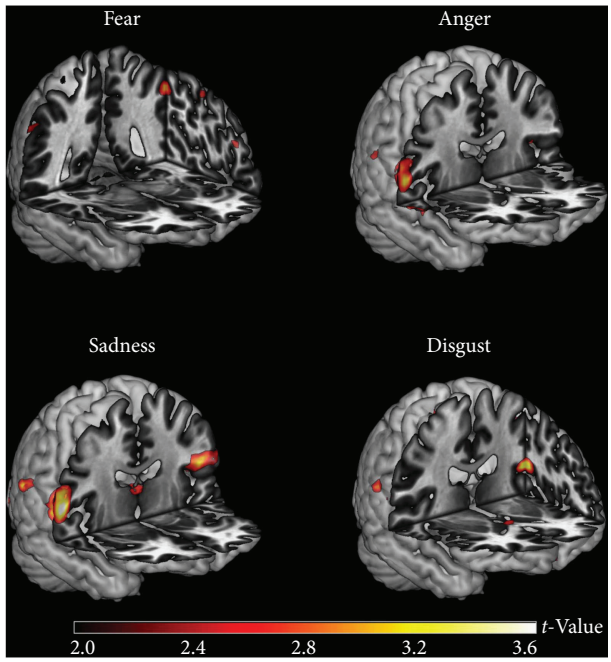

Figure 1: Regions showing increased fMRI activation in nonmedicated, nondemented PD patients ($n = 17$) compared to healthy controls ($n = 22$). PD patients may exhibit a general stronger recruitment of parietal regions when observing pictures of facial expressions depicting disgust, fear, sadness, and anger (image reproduced from Wabnegger et al. [209] under the Creative Commons license (CC-BY), no permission needed).

described a case of affective ToM impairment in a case of clinically diagnosed CBS with a bilateral 18-FDG positron emission tomography hypometabolism in the frontal-temporal-parietal cortices, more marked in the right hemisphere. However, no data have been reported about ToM abnormalities in patients affected by multisystem atrophy.

2.3. Alzheimer's Disease. Alzheimer's disease (AD), the most frequent neurodegenerative dementia and the first cause of neurocognitive disorder in the world, is typically characterized by an early and progressive episodic memory loss. From the neuropathological point of view, the progressive neurodegeneration initially affects the hippocampi, the entorhinal and posterior cingulate cortices, and, subsequently, the entire temporal, parietal, and frontal cortices [215]. Following this anatomical pathway, social cognition dysfunctions can occur during the course of the disease, particularly in the moderate-severe stages [216]. In contrast, earlier in the disease, social incongruities appear largely modulated by general cognitive decline in memory, language, and executive domains, rather than a genuine social dysfunction [217].

In particular, although considerably less common than in bvFTD, AD patients may present impaired social behavior, ToM, loss of empathy, facial emotion recognition, and inaccurate self-awareness, and, although uncommon as first symptoms, among alterations of social behavior, disinhibition, social awkwardness, and apathy have been reported, respectively, in 6.9%, 5%, and 2% of cases [218].

2.3.1. Alterations in the Four Domains of Social Cognition. With regard to apathy and disinhibition, associated with AD severity, one of the most common tools for social/behavior evaluation in dementia, the Neuropsychiatric Inventory (NPI) [219], has been used in combination with the Clinical Dementia Rating (CDR) scale [220], which is a disease severity scale, ranging from 0 (no impairment) to 2 (severe impairment). Several NPI dimensions, but in particular apathy and disinhibition, were correlated with the CDR score. Moreover, apathy was the most prevalent in all CDR groups and the only symptom with frequencies exceeding 50% in AD patients with CDR 0.5, 1, and 2 [221].

Other types of social disturbances are rarely described in AD, such as criminal behaviors, which are more recurrent in bvFTD [101]. In fact, rarely, AD patients may present an atypical, bvFTD-like clinical profile in very early stages of disease. However, this presentation is characterized by a milder and more restricted behavioral profile than in bvFTD, with high cooccurrence of memory dysfunction and dysexecutive abnormalities, and a pattern of atrophy centered on temporoparietal regions, as in typical AD [222].

Deficits in recognizing others' emotions are reported in AD [223] and in its prodromal stage, the so-called mild cognitive impairment (MCI) [224]. Most emotion recognition studies have required participants to identify emotional expressions in pictures producing mixed results, with evidence of both impaired [223, 225-227] and intact [228, 229] recognition overall. When considering specific emotions, the findings are also inconsistent. More recently, a large sample of neurodegenerative patients, including AD, was studied by using short films instead of photographs [229]. This study revealed that emotion recognition was indistinguishable by comparing the AD group to healthy controls. However, in this regard, it should be kept in mind that concomitant basic and high-level visual and visuospatial difficulties in AD may negatively impact facial recognition, which in turn translate in an impaired emotion recognition [230].

ToM deficits are reported in AD [231, 232], although ToM alterations in AD remains a controversial subject. Specifically, performances at ToM tests have been revealed to not reflect a genuine ToM deficit, rather a deficit mediated by general (and particularly executive) cognitive decline [233].

Loss of empathy has also been reported in AD, particularly as the so-called cognitive empathy (i.e., the ability to understand) in the context of a relative preservation of affective empathy (i.e., the ability to share) [234]. This pattern of spared/impaired types of empathy has been shown to be related to the vulnerability of a distributed network of regions, centered on the frontoinsular cortices, the integrity of which in AD is crucial for preserved social functioning [234].

Finally, AD patients may also present poor self-awareness of their functional limitations that may exacerbate their behavior abnormalities, as well as the reliability of the patient [235]. Self-awareness can be easily tested by asking the patient for a description of themselves, using a scale rating their competency across different domains (i.e., daily living activities and cognitive/emotional interpersonal control) (such as the Patient Competency Rating Scale) [235]. In

particular, AD patients resulted in being more prone to overestimate cognitive and emotional functioning in comparison to bvFTD patients who may overestimate their functioning in all domains [235].

3. Conclusions and Future Perspectives

Abnormal interpersonal behavior is commonly observed in clinical practice, representing part of the core diagnostic criteria for many clinical disorders. Therefore, to overcome the potential consequences related to social isolation, known to be a risk factor for morbidity and mortality [2], social cognitive intervention may be prospected to reduce the negative impact of such disabilities on mental health, improving the ability to form and consolidate interpersonal networks. Among these strategies, targeted training programs may be implemented on the basis of the recent evidence of structural plasticity in well-known socioaffective and sociocognitive brain networks after training-induced behavioral improvements in healthy adults [236] and of potential advantages from targeted training programs on emotion recognition in neurodegenerative patients [104, 237].

Recently, increasing interest has been addressed to the potential benefits of pharmacotherapy on social cognition deficits, such as the potential effects of the peripheral administration of exogenous oxytocin, shown to exert prosocial effects [238-241], probably mediated by the modulation of the serotonergic system [239].

Another emerging approach is related to the use of brain stimulation techniques, such as theta burst and high-frequency repetitive transcranial magnetic stimulation (rTMS), to modulate empathy-related brain activity. In particular, rTMS sessions, by stimulating the bilateral medial prefrontal cortex, have been revealed to be useful in improving self-reported social functioning in the case of autism spectrum disorders [242] and major depressive disorders [243].

Finally, given the critical role of caregivers' wellbeing and collaboration in any therapeutic and rehabilitation plan, treatment efforts should also be directed towards ensuring the availability of appropriate education and support for them.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding this article.

References

[1] R. Adolphs, "The social brain: neural basis of social knowledge," *Annual Review of Psychology*, vol. 60, no. 1, pp. 693–716, 2009.

[2] S. Cacioppo, J. P. Capitanio, and J. T. Cacioppo, "Toward a neurology of loneliness," *Psychological Bulletin*, vol. 140, no. 6, pp. 1464–1504, 2014.

[3] F. Adolfi, B. Couto, F. Richter et al., "Convergence of interoception, emotion, and social cognition: a two-fold fMRI meta-analysis and lesion approach," *Cortex*, vol. 88, pp. 124–142, 2017.

[4] R. Adolphs, S. Baron-Cohen, and D. Tranel, "Impaired recognition of social emotions following amygdala damage," *Journal of Cognitive Neuroscience*, vol. 14, no. 8, pp. 1264–1274, 2002.

[5] J. D. Henry, W. von Hippel, P. Molenberghs, T. Lee, and P. S. Sachdev, "Clinical assessment of social cognitive function in neurological disorders," *Nature Reviews Neurology*, vol. 12, no. 1, pp. 28–39, 2016.

[6] L. Brothers, "The social brain: a project for integrating primate behaviour and neurophysiology in a new domain," *Concepts Neuroscience*, vol. 1, pp. 27–51, 1990.

[7] J. V. Haxby, E. A. Hoffman, and M. I. Gobbini, "The distributed human neural system for face perception," *Trends in Cognitive Sciences*, vol. 4, no. 6, pp. 223–233, 2000.

[8] R. Adolphs, "What does the amygdala contribute to social cognition?," *Annals of the New York Academy of Sciences*, vol. 1191, no. 1, pp. 42–61, 2010.

[9] A. W. Young, J. P. Aggleton, D. J. Hellawell, M. Johnson, P. Broks, and J. R. Hanley, "Face processing impairments after amygdalotomy," *Brain*, vol. 118, no. 1, pp. 15–24, 1995.

[10] J. E. LeDoux, "Emotion circuits in the brain," *Annual Review of Neuroscience*, vol. 23, no. 1, pp. 155–184, 2000.

[11] L. Pessoa, "On the relationship between emotion and cognition," *Nature Reviews Neuroscience*, vol. 9, no. 2, pp. 148–158, 2008.

[12] K. H. Lee, T. F. D. Farrow, S. A. Spence, and P. W. R. Woodruff, "Social cognition, brain networks and schizophrenia," *Psychological Medicine*, vol. 34, no. 3, pp. 391–400, 2004.

[13] P. Mukherjee, H. C. Whalley, J. W. McKirdy et al., "Altered amygdala connectivity within the social brain in schizophrenia," *Schizophrenia Bulletin*, vol. 40, no. 1, pp. 152–160, 2014.

[14] F. Kumfor, C. Honan, S. McDonald, J. L. Hazelton, J. R. Hodges, and O. Piguet, "Assessing the "social brain" in dementia: applying TASIT-S," *Cortex*, vol. 93, pp. 166–177, 2017.

[15] A. Bejanin, G. Chételat, M. Laisney et al., "Distinct neural substrates of affective and cognitive theory of mind impairment in semantic dementia," *Social Neuroscience*, vol. 12, no. 3, pp. 287–302, 2017.

[16] E. A. H. von dem Hagen, R. S. Stoyanova, S. Baron-Cohen, and A. J. Calder, "Reduced functional connectivity within and between "social" resting state networks in autism spectrum conditions," *Social Cognitive and Affective Neuroscience*, vol. 8, no. 6, pp. 694–701, 2013.

[17] N. M. Kleinhans, T. Richards, L. Sterling et al., "Abnormal functional connectivity in autism spectrum disorders during face processing," *Brain*, vol. 131, no. 4, pp. 1000–1012, 2008.

[18] M. A. Patriquin, T. DeRamus, L. E. Libero, A. Laird, and R. K. Kana, "Neuroanatomical and neurofunctional markers of social cognition in autism spectrum disorder," *Human Brain Mapping*, vol. 37, no. 11, pp. 3957–3978, 2016.

[19] M. Roy, D. Shohamy, and T. D. Wager, "Ventromedial prefrontal-subcortical systems and the generation of affective meaning," *Trends in Cognitive Sciences*, vol. 16, no. 3, pp. 147–156, 2012.

[20] K. C. Berridge and M. L. Kringelbach, "Neuroscience of affect: brain mechanisms of pleasure and displeasure," *Current Opinion in Neurobiology*, vol. 23, no. 3, pp. 294–303, 2013.

[21] I. Cristofori, W. Zhong, V. Mandoske et al., "Brain regions influencing implicit violent attitudes: a lesion-mapping

study," *Journal of Neuroscience*, vol. 36, no. 9, pp. 2757–2768, 2016.

[22] J. S. Beer, O. P. John, D. Scabini, and R. T. Knight, "Orbitofrontal cortex and social behavior: integrating self-monitoring and emotion-cognition interactions," *Journal of Cognitive Neuroscience*, vol. 18, no. 6, pp. 871–879, 2006.

[23] C. A. Hill, S. Suzuki, R. Polania, M. Moisa, J. P. O'Doherty, and C. C. Ruff, "A causal account of the brain network computations underlying strategic social behavior," *Nature Neuroscience*, vol. 20, no. 8, pp. 1142–1149, 2017.

[24] D. Dodell-Feder, J. Koster-Hale, M. Bedny, and R. Saxe, "fMRI item analysis in a theory of mind task," *NeuroImage*, vol. 55, no. 2, pp. 705–712, 2011.

[25] R. Saxe, "Why and how to study Theory of Mind with fMRI," *Brain Research*, vol. 1079, no. 1, pp. 57–65, 2006.

[26] L. Young and R. Saxe, "An FMRI investigation of spontaneous mental state inference for moral judgment," *Journal of Cognitive Neuroscience*, vol. 21, no. 7, pp. 1396–1405, 2009.

[27] D. Schneider, V. P. Slaughter, S. I. Becker, and P. E. Dux, "Implicit false-belief processing in the human brain," *NeuroImage*, vol. 101, pp. 268–275, 2014.

[28] A. M. Kovacs, S. Kühn, G. Gergely, G. Csibra, and M. Brass, "Are all beliefs equal? Implicit belief attributions recruiting core brain regions of theory of mind," *PLoS One*, vol. 9, no. 9, article e106558, 2014.

[29] D. C. Hyde, M. Aparicio Betancourt, and C. E. Simon, "Human temporal-parietal junction spontaneously tracks others' beliefs: a functional near-infrared spectroscopy study," *Human Brain Mapping*, vol. 36, no. 12, pp. 4831–4846, 2015.

[30] G. Hein and T. Singer, "I feel how you feel but not always: the empathic brain and its modulation," *Current Opinion in Neurobiology*, vol. 18, no. 2, pp. 153–158, 2008.

[31] J. Decety and J. M. Cowell, "The complex relation between morality and empathy," *Trends in Cognitive Sciences*, vol. 18, no. 7, pp. 337–339, 2014.

[32] C. Lamm, J. Decety, and T. Singer, "Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain," *NeuroImage*, vol. 54, no. 3, pp. 2492–2502, 2011.

[33] C. Korponay, M. Pujara, P. Deming et al., "Impulsive antisocial psychopathic traits linked to increased volume and functional connectivity within prefrontal cortex," *Social Cognitive and Affective Neuroscience*, vol. 12, no. 7, pp. 1169–1178, 2017.

[34] S. V. Abram, K. M. Wisner, J. M. Fox et al., "Fronto-temporal connectivity predicts cognitive empathy deficits and experiential negative symptoms in schizophrenia," *Human Brain Mapping*, vol. 38, no. 3, pp. 1111–1124, 2017.

[35] M. Iacoboni, R. P. Woods, M. Brass, H. Bekkering, J. C. Mazziotta, and G. Rizzolatti, "Cortical mechanisms of human imitation," *Science*, vol. 286, no. 5449, pp. 2526–2528, 1999.

[36] J. Decety, T. Chaminade, J. Grèzes, and A. N. Meltzoff, "A PET exploration of the neural mechanisms involved in reciprocal imitation," *NeuroImage*, vol. 15, no. 1, pp. 265–272, 2002.

[37] M. C. Keuken, A. Hardie, B. T. Dorn et al., "The role of the left inferior frontal gyrus in social perception: an rTMS study," *Brain Research*, vol. 1383, pp. 196–205, 2011.

[38] P. G. Enticott, P. J. Johnston, S. E. Herring, K. E. Hoy, and P. B. Fitzgerald, "Mirror neuron activation is associated with facial emotion processing," *Neuropsychologia*, vol. 46, no. 11, pp. 2851–2854, 2008.

[39] N. Hadjikhani, R. M. Joseph, J. Snyder, and H. Tager-Flusberg, "Anatomical differences in the mirror neuron system and social cognition network in autism," *Cerebral Cortex*, vol. 16, no. 9, pp. 1276–1282, 2006.

[40] I. Fishman, C. L. Keown, A. J. Lincoln, J. A. Pineda, and R. A. Müller, "Atypical cross talk between mentalizing and mirror neuron networks in autism spectrum disorder," *Journal of the American Medical Association Psychiatry*, vol. 71, no. 7, pp. 751–760, 2014.

[41] M. Schulte-Rüther, E. Otte, K. Adigüzel et al., "Intact mirror mechanisms for automatic facial emotions in children and adolescents with autism spectrum disorder," *Autism Research*, vol. 10, no. 2, pp. 298–310, 2017.

[42] M. Poletti, I. Enrici, and M. Adenzato, "Cognitive and affective Theory of Mind in neurodegenerative diseases: neuropsychological, neuroanatomical and neurochemical levels," *Neuroscience & Biobehavioral Reviews*, vol. 36, no. 9, pp. 2147–2164, 2012.

[43] M. Adenzato, M. Cavallo, and I. Enrici, "Theory of mind ability in the behavioural variant of frontotemporal dementia: an analysis of the neural, cognitive, and social levels," *Neuropsychologia*, vol. 48, no. 1, pp. 2–12, 2010.

[44] M. L. Schroeter, "Considering the frontomedian cortex in revised criteria for behavioural variant frontotemporal dementia," *Brain*, vol. 135, no. 4, pp. e213–e212, 2012.

[45] M. L. Schroeter, B. Vogt, S. Frisch et al., "Executive deficits are related to the inferior frontal junction in early dementia," *Brain*, vol. 135, no. 1, pp. 201–215, 2012.

[46] J. Grace and P. F. Malloy, *Frontal Systems Behavior Scale Professional Manual*, Psychological Assessment Resources, Lutz, FL, USA, 2001.

[47] A. Kertesz, N. Nadkarni, W. Davidson, and A. W. Thomas, "The Frontal Behavioral Inventory in the differential diagnosis of frontotemporal dementia," *Journal of the International Neuropsychological Society*, vol. 6, no. 4, pp. 460–468, 2000.

[48] J. P. Barsuglia, N. C. Kaiser, S. S. Wilkins et al., "A scale of socioemotional dysfunction in frontotemporal dementia," *Archives of Clinical Neuropsychology*, vol. 29, no. 8, pp. 793–805, 2014.

[49] J. D. Henry, W. von Hippel, and K. Baynes, "Social inappropriateness, executive control, and aging," *Psychology and Aging*, vol. 24, no. 1, pp. 239–244, 2009.

[50] K. C. Bickart, M. Brickhouse, A. Negreira, D. Sapolsky, L. F. Barrett, and B. C. Dickerson, "Atrophy in distinct corticolimbic networks in frontotemporal dementia relates to social impairments measured using the Social Impairment Rating Scale," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 85, no. 4, pp. 438–448, 2014.

[51] H. Wimmer and J. Perner, "Beliefs about beliefs: representation and constraining function of wrong beliefs in young children's understanding of deception," *Cognition*, vol. 13, no. 1, pp. 103–128, 1983.

[52] S. McDonald, S. Flanagan, J. Rollins, and J. Kinch, "TASIT: a new clinical tool for assessing social perception after traumatic brain injury," *The Journal of Head Trauma Rehabilitation*, vol. 18, no. 3, pp. 219–238, 2003.

[53] F. G. E. Happé, "An advanced test of theory of mind: understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults," *Journal of Autism and Developmental Disorders*, vol. 24, no. 2, pp. 129–154, 1994.

[54] V. E. Stone, S. Baron-Cohen, and R. T. Knight, "Frontal lobe contributions to theory of mind," *Journal of Cognitive Neuroscience*, vol. 10, no. 5, pp. 640–656, 1998.

[55] S. Baron-Cohen, S. Wheelwright, J. Hill, Y. Raste, and I. Plumb, "The "Reading the Mind in the Eyes" test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism," *Journal of Child Psychology and Psychiatry*, vol. 42, no. 2, pp. 241–251, 2001.

[56] M. H. Davis, "Measuring individual-differences in empathy—evidence for a multidimensional approach," *Journal of Personality and Social Psychology*, vol. 44, no. 1, pp. 113–126, 1983.

[57] S. Baron-Cohen and S. Wheelwright, "The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences," *Journal of Autism and Developmental Disorders*, vol. 34, no. 2, pp. 163–175, 2004.

[58] I. Dziobek, K. Rogers, S. Fleck et al., "Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the Multifaceted Empathy Test (MET)," *Journal of Autism and Developmental Disorders*, vol. 38, no. 3, pp. 464–473, 2008.

[59] P. Ekman and W. V. Friesen, *Pictures of Facial Affect*, Consulting Psychologists Press, Palo Alto, CA, USA, 1976.

[60] K. B. Froming, M. Levy, S. G. Schaffer, and P. Ekman, *Comprehensive Affect Testing System (CATS)*, Psychology Software Inc, Gainesville, FL, USA, 2006.

[61] D. Bowers, L. X. Blonder, and K. M. Heilman, *Florida Affect Battery*, Center for Neuropsychological Studies, 1999.

[62] J. D. Warren, J. D. Rohrer, and M. N. Rossor, "Frontotemporal dementia," *BMJ*, vol. 347, article F4827, 2013.

[63] I. T. S. Coyle-Gilchrist, K. M. Dick, K. Patterson et al., "Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes," *Neurology*, vol. 86, no. 18, pp. 1736–1743, 2016.

[64] K. Rascovsky, J. R. Hodges, D. Knopman et al., "Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia," *Brain*, vol. 134, no. 9, pp. 2456–2477, 2011.

[65] O. Piguet, M. Hornberger, E. Mioshi, and J. R. Hodges, "Behavioural-variant frontotemporal dementia: diagnosis, clinical staging, and management," *Lancet Neurology*, vol. 10, no. 2, pp. 162–172, 2011.

[66] M. L. Gorno-Tempini, A. E. Hillis, S. Weintraub et al., "Classification of primary progressive aphasia and its variants," *Neurology*, vol. 76, no. 11, pp. 1006–1014, 2011.

[67] M. J. Strong, S. Abrahams, L. H. Goldstein et al., "Amyotrophic lateral sclerosis-frontotemporal spectrum disorder (ALS-FTSD): revised diagnostic criteria," *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, vol. 18, no. 3–4, pp. 153–174, 2017.

[68] A. Ibáñez and F. Manes, "Contextual social cognition and the behavioral variant of frontotemporal dementia," *Neurology*, vol. 78, no. 17, pp. 1354–1362, 2012.

[69] A. Ibáñez, R. O. Kuljis, D. Matallana, and F. Manes, "Bridging psychiatry and neurology through social neuroscience," *World Psychiatry*, vol. 13, no. 2, pp. 148-149, 2014.

[70] A. Ibáñez, P. Billeke, L. de la Fuente, P. Salamone, A. M. Garcia, and M. Melloni, "Reply: towards a neurocomputational account of social dysfunction in neurodegenerative disease," *Brain*, vol. 140, no. 3, p. e15, 2017.

[71] W. W. Seeley, J. Zhou, and E. J. Kim, "Frontotemporal dementia: what can the behavioral variant teach us about human brain organization?," *Neuroscientist*, vol. 18, no. 4, pp. 373–385, 2012.

[72] J. Van den Stock and F. Kumfor, "Behavioural variant frontotemporal dementia: at the interface of interoception, emotion and social cognition?," *Cortex*, 2017.

[73] S. Baez, J. P. Morales, A. Slachevsky et al., "Orbitofrontal and limbic signatures of empathic concern and intentional harm in the behavioral variant frontotemporal dementia," *Cortex*, vol. 75, pp. 20–32, 2016.

[74] V. E. Sturm, J. S. Yokoyama, J. A. Eckart et al., "Damage to left frontal regulatory circuits produces greater positive emotional reactivity in frontotemporal dementia," *Cortex*, vol. 64, pp. 55–67, 2015.

[75] K. H. Werner, N. A. Roberts, H. J. Rosen et al., "Emotional reactivity and emotion recognition in frontotemporal lobar degeneration," *Neurology*, vol. 69, no. 2, pp. 148–155, 2007.

[76] M. H. Cohen, A. M. Carton, C. J. Hardy et al., "Processing emotion from abstract art in frontotemporal lobar degeneration," *Neuropsychologia*, vol. 81, pp. 245–254, 2016.

[77] S. Baez, F. Manes, D. Huepe et al., "Primary empathy deficits in frontotemporal dementia," *Frontiers in Aging Neuroscience*, vol. 6, p. 262, 2014.

[78] R. W. Levenson, V. E. Sturm, and C. M. Haase, "Emotional and behavioral symptoms in neurodegenerative disease: a model for studying the neural bases of psychopathology," *Annual Review of Clinical Psychology*, vol. 10, no. 1, pp. 581–606, 2014.

[79] S. C. Lanata and B. L. Miller, "The behavioural variant frontotemporal dementia (bvFTD) syndrome in psychiatry," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 87, no. 5, pp. 501–511, 2016.

[80] S. P. Caminiti, N. Canessa, C. Cerami et al., "Affective mentalizing and brain activity at rest in the behavioral variant of frontotemporal dementia," *Neuroimage: Clinical*, vol. 9, pp. 484–497, 2015.

[81] J. Moll, R. Zahn, R. de Oliveira-Souza et al., "Impairment of prosocial sentiments is associated with frontopolar and septal damage in frontotemporal dementia," *NeuroImage*, vol. 54, no. 2, pp. 1735–1742, 2011.

[82] C. O'Callaghan, M. Bertoux, M. Irish et al., "Fair play: social norm compliance failures in behavioural variant frontotemporal dementia," *Brain*, vol. 139, no. 1, pp. 204–216, 2016.

[83] M. Melloni, P. Billeke, S. Baez et al., "Your perspective and my benefit: multiple lesion models of self-other integration strategies during social bargaining," *Brain*, vol. 139, no. 11, pp. 3022–3040, 2016.

[84] M. L. Schroeter, S. Pawelke, S. Bisenius et al., "A modified Reading the Mind in the Eyes Test predicts behavioral variant frontotemporal dementia better than executive function tests," *Frontiers in Aging Neuroscience*, vol. 10, p. 11, 2018.

[85] C. Gregory, S. Lough, V. Stone et al., "Theory of mind in patients with frontal variant frontotemporal dementia and

Alzheimer's disease: theoretical and practical implications," *Brain*, vol. 125, no. 4, pp. 752–764, 2002.

[86] T. Torralva, C. M. Kipps, J. R. Hodges et al., "The relationship between affective decision-making and theory of mind in the frontal variant of fronto-temporal dementia," *Neuropsychologia*, vol. 45, no. 2, pp. 342–349, 2007.

[87] T. Torralva, M. Roca, E. Gleichgerrcht, T. Bekinschtein, and F. Manes, "A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia," *Brain*, vol. 132, no. 5, pp. 1299–1309, 2009.

[88] E. Gleichgerrcht, T. Torralva, M. Roca, and F. Manes, "Utility of an abbreviated version of the executive and social cognition battery in the detection of executive deficits in early behavioral variant frontotemporal dementia patients," *Journal of the International Neuropsychological Society*, vol. 16, no. 4, pp. 687–694, 2010.

[89] C. Buhl, J. Stokholm, and A. Gade, "Clinical utility of short social cognitive tests in early differentiation of behavioral variant frontotemporal dementia from Alzheimer's disease," *Dementia and Geriatric Cognitive Disorders Extra*, vol. 3, no. 1, pp. 376–385, 2013.

[90] J. D. Henry, L. H. Phillips, and C. von Hippel, "A meta-analytic review of theory of mind difficulties in behavioural-variant frontotemporal dementia," *Neuropsychologia*, vol. 56, pp. 53–62, 2014.

[91] J. Cotter, K. Granger, R. Backx, M. Hobbs, C. Y. Looi, and J. H. Barnett, "Social cognitive dysfunction as a clinical marker: a systematic review of meta-analyses across 30 clinical conditions," *Neuroscience & Biobehavioral Reviews*, vol. 84, pp. 92–99, 2018.

[92] R. S. Marin, R. C. Biedrzycki, and S. Firinciogullari, "Reliability and validity of the apathy evaluation scale," *Psychiatry Research*, vol. 38, no. 2, pp. 143–162, 1991.

[93] H. Santamaria-Garcia, P. Reyes, A. Garcia et al., "First symptoms and neurocognitive correlates of behavioral variant frontotemporal dementia," *Journal of Alzheimer's Disease*, vol. 54, no. 3, pp. 957–970, 2016.

[94] G. Zamboni, E. D. Huey, F. Krueger, P. F. Nichelli, and J. Grafman, "Apathy and disinhibition in frontotemporal dementia: insights into their neural correlates," *Neurology*, vol. 71, no. 10, pp. 736–742, 2008.

[95] P. J. Eslinger, P. Moore, S. Antani, C. Anderson, and M. Grossman, "Apathy in frontotemporal dementia: behavioral and neuroimaging correlates," *Behavioural Neurology*, vol. 25, no. 2, 136 pages, 2012.

[96] M. Hornberger, J. Geng, and J. R. Hodges, "Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia," *Brain*, vol. 134, no. 9, pp. 2502–2512, 2011.

[97] S. Baez, P. Kanske, D. Matallana et al., "Integration of intention and outcome for moral judgment in frontotemporal dementia: brain structural signatures," *Neurodegenerative Diseases*, vol. 16, no. 3–4, pp. 206–217, 2016.

[98] S. Baez, B. Couto, T. Torralva et al., "Comparing moral judgments of patients with frontotemporal dementia and frontal stroke," *Journal of the American Medical Association Neurology*, vol. 71, no. 9, pp. 1172–1176, 2014.

[99] S. Baez, E. Herrera, A. M. Garcia, F. Manes, L. Young, and A. Ibáñez, "Outcome-oriented moral evaluation in terrorists," *Nature Human Behaviour*, vol. 1, no. 6, article 0118, pp. 1–8, 2017.

[100] R. de Oliveira-Souza, R. D. Hare, I. E. Bramati et al., "Psychopathy as a disorder of the moral brain: fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry," *NeuroImage*, vol. 40, no. 3, pp. 1202–1213, 2008.

[101] M. Liljegren, G. Naasan, J. Temlett et al., "Criminal behavior in frontotemporal dementia and Alzheimer disease," *Journal of the American Medical Association Neurology*, vol. 72, no. 3, pp. 295–300, 2015.

[102] M. F. Mendez, "The unique predisposition to criminal violations in frontotemporal dementia," *The Journal of the American Academy of Psychiatry and the Law*, vol. 38, no. 3, pp. 318–323, 2010.

[103] H. Santamaria-Garcia, S. Baez, P. Reyes et al., "A lesion model of envy and Schadenfreude: legal, deservingness and moral dimensions as revealed by neurodegeneration," *Brain*, vol. 140, no. 12, pp. 3357–3377, 2017.

[104] F. Kumfor, L. Miller, S. Lah et al., "Are you really angry? The effect of intensity on facial emotion recognition in frontotemporal dementia," *Social Neuroscience*, vol. 6, no. 5–6, pp. 502–514, 2011.

[105] C. M. Kipps, P. J. Nestor, J. Acosta-Cabronero, R. Arnold, and J. R. Hodges, "Understanding social dysfunction in the behavioural variant of frontotemporal dementia. The role of emotion and sarcasm processing," *Brain*, vol. 132, no. 3, pp. 592–603, 2009.

[106] F. Kumfor and O. Piguet, "Disturbance of emotion processing in frontotemporal dementia: a synthesis of cognitive and neuroimaging findings," *Neuropsychology Review*, vol. 22, no. 3, pp. 280–297, 2012.

[107] J. S. Snowden, N. A. Austin, S. Sembi, J. C. Thompson, D. Craufurd, and D. Neary, "Emotion recognition in Huntington's disease and frontotemporal dementia," *Neuropsychologia*, vol. 46, no. 11, pp. 2638–2649, 2008.

[108] J. Van den Stock, F. L. De Winter, B. de Gelder et al., "Impaired recognition of body expressions in the behavioral variant of frontotemporal dementia," *Neuropsychologia*, vol. 75, pp. 496–504, 2015.

[109] R. Omar, S. M. D. Henley, J. W. Bartlett et al., "The structural neuroanatomy of music emotion recognition: evidence from frontotemporal lobar degeneration," *NeuroImage*, vol. 56, no. 3, pp. 1814–1821, 2011.

[110] M. S. Goodkind, V. E. Sturm, E. A. Ascher et al., "Emotion recognition in frontotemporal dementia and Alzheimer's disease: a new film-based assessment," *Emotion*, vol. 15, no. 4, pp. 416–427, 2015.

[111] J. A. Eckart, V. E. Sturm, B. L. Miller, and R. W. Levenson, "Diminished disgust reactivity in behavioral variant frontotemporal dementia," *Neuropsychologia*, vol. 50, no. 5, pp. 786–790, 2012.

[112] B. Couto, F. Manes, P. Montañés et al., "Structural neuroimaging of social cognition in progressive non-fluent aphasia and behavioral variant of frontotemporal dementia," *Frontiers in Human Neuroscience*, vol. 7, p. 467, 2013.

[113] C. Duval, A. Bejanin, P. Piolino et al., "Theory of mind impairments in patients with semantic dementia," *Brain*, vol. 135, no. 1, pp. 228–241, 2012.

[114] H. J. Rosen, R. J. Perry, J. Murphy et al., "Emotion comprehension in the temporal variant of frontotemporal dementia," *Brain*, vol. 125, no. 10, pp. 2286–2295, 2002.

[115] G. S. Day, N. A. Farb, D. F. Tang-Wai et al., "Salience network resting-state activity: prediction of frontotemporal dementia progression," *Journal of the American Medical Association Neurology*, vol. 70, no. 10, pp. 1249–1253, 2013.

[116] W. W. Seeley, "Anterior insula degeneration in frontotemporal dementia," *Brain Structure and Function*, vol. 214, no. 5–6, pp. 465–475, 2010.

[117] F. Kumfor, M. Irish, J. R. Hodges, and O. Piguet, "Discrete neural correlates for the recognition of negative emotions: insights from frontotemporal dementia," *PLoS One*, vol. 8, no. 6, article e67457, 2013.

[118] S. Baez, C. Pinasco, M. Roca et al., "Brain structural correlates of executive and social cognition profiles in behavioral variant frontotemporal dementia and elderly bipolar disorder," *Neuropsychologia*, 2017.

[119] I. Garcia-Cordero, L. Sedeño, L. de la Fuente et al., "Feeling, learning from and being aware of inner states: interoceptive dimensions in neurodegeneration and stroke," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 371, no. 1708, article 20160006, 2016.

[120] R. Rytty, J. Nikkinen, L. Paavola et al., "GroupICA dual regression analysis of resting state networks in a behavioral variant of frontotemporal dementia," *Frontiers in Human Neuroscience*, vol. 7, p. 461, 2013.

[121] N. A. S. Farb, C. L. Grady, S. Strother et al., "Abnormal network connectivity in frontotemporal dementia: evidence for prefrontal isolation," *Cortex*, vol. 49, no. 7, pp. 1856–1873, 2013.

[122] S. Baez, A. M. Garcia, and A. Ibáñez, "The social context network model in psychiatric and neurological diseases," *Current Topics in Behavioral Neurosciences*, vol. 30, pp. 379–396, 2017.

[123] L. Sedeño, B. Couto, I. García-Cordero et al., "Brain network organization and social executive performance in frontotemporal dementia," *Journal of the International Neuropsychological Society*, vol. 22, no. 2, pp. 250–262, 2016.

[124] W. W. Seeley, R. Crawford, K. Rascovsky et al., "Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia," *Archives of Neurology*, vol. 65, no. 2, pp. 249–255, 2008.

[125] J. L. Whitwell, E. L. Sampson, H. C. Watt, R. J. Harvey, M. N. Rossor, and N. C. Fox, "A volumetric magnetic resonance imaging study of the amygdala in frontotemporal lobar degeneration and Alzheimer's disease," *Dementia and Geriatric Cognitive Disorders*, vol. 20, no. 4, pp. 238–244, 2005.

[126] S. Tsermentseli, P. N. Leigh, and L. H. Goldstein, "The anatomy of cognitive impairment in amyotrophic lateral sclerosis: more than frontal lobe dysfunction," *Cortex*, vol. 48, no. 2, pp. 166–182, 2012.

[127] A. Montuschi, B. Iazzolino, A. Calvo et al., "Cognitive correlates in amyotrophic lateral sclerosis: a population-based study in Italy," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 86, no. 2, pp. 168–173, 2015.

[128] E. Beeldman, J. Raaphorst, M. Klein Twennaar, M. de Visser, B. A. Schmand, and R. J. de Haan, "The cognitive profile of ALS: a systematic review and meta-analysis update," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 87, no. 6, pp. 611–619, 2016.

[129] A. B. Grossman, S. Woolley-Levine, W. G. Bradley, and R. G. Miller, "Detecting neurobehavioral changes in amyotrophic lateral sclerosis," *Amyotrophic Lateral Sclerosis*, vol. 8, no. 1, pp. 56–61, 2007.

[130] M. Witgert, A. R. Salamone, A. M. Strutt et al., "Frontal-lobe mediated behavioral dysfunction in amyotrophic lateral sclerosis," *European Journal of Neurology*, vol. 17, no. 1, pp. 103–110, 2010.

[131] J. R. Burrell, G. M. Halliday, J. J. Kril et al., "The frontotemporal dementia motor neuron disease continuum," *The Lancet*, vol. 388, no. 10047, pp. 919–931, 2016.

[132] J. Keller, S. Bohm, H. E. A. Aho-Ozhan et al., "Functional reorganization during cognitive function tasks in patients with amyotrophic lateral sclerosis," *Brain Imaging and Behavior*, 2017.

[133] S. Abrahams, J. Newton, E. Niven, J. Foley, and T. H. Bak, "Screening for cognition and behaviour changes in ALS," *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, vol. 15, no. 1–2, pp. 9–14, 2014.

[134] S. Körner, K. Kollewe, S. Abdulla, A. Zapf, R. Dengler, and S. Petri, "Interaction of physical function, quality of life and depression in amyotrophic lateral sclerosis: characterization of a large patient cohort," *BMC Neurology*, vol. 15, no. 1, p. 84, 2015.

[135] D. Lulé, B. Ehlich, D. Lang et al., "Quality of life in fatal disease: the flawed judgement of the social environment," *Journal of Neurology*, vol. 260, no. 11, pp. 2836–2843, 2013.

[136] F. Trojsi, M. Siciliano, A. Russo et al., "Theory of mind and its neuropsychological and quality of life correlates in the early stages of amyotrophic lateral sclerosis," *Frontiers in Psychology*, vol. 7, p. 1934, 2016.

[137] L. Carluer, A. Mondou, M. S. Buhour et al., "Neural substrate of cognitive theory of mind impairment in amyotrophic lateral sclerosis," *Cortex*, vol. 65, pp. 19–30, 2015.

[138] M. Cavallo, M. Adenzato, S. E. Macpherson, G. Karwig, I. Enrici, and S. Abrahams, "Evidence of social understanding impairment in patients with amyotrophic lateral sclerosis," *PLoS One*, vol. 6, no. 10, article e25948, 2011.

[139] C. Cerami, A. Dodich, N. Canessa et al., "Emotional empathy in amyotrophic lateral sclerosis: a behavioural and voxel-based morphometry study," *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, vol. 15, no. 1–2, pp. 21–29, 2014.

[140] M. Consonni, E. Catricala, E. Dalla Bella, V. C. Gessa, G. Lauria, and S. F. Cappa, "Beyond the consensus criteria: multiple cognitive profiles in amyotrophic lateral sclerosis?," *Cortex*, vol. 81, pp. 162–167, 2016.

[141] A. Girardi, S. E. Macpherson, and S. Abrahams, "Deficits in emotional and social cognition in amyotrophic lateral sclerosis," *Neuropsychology*, vol. 25, no. 1, pp. 53–65, 2011.

[142] M. Staios, F. Fisher, A. K. Lindell, B. Ong, J. Howe, and K. Reardon, "Exploring sarcasm detection in amyotrophic lateral sclerosis using ecologically valid measures," *Frontiers in Human Neuroscience*, vol. 7, p. 178, 2013.

[143] T. J. Watermeyer, R. G. Brown, K. C. L. Sidle et al., "Executive dysfunction predicts social cognition impairment in amyotrophic lateral sclerosis," *Journal of Neurology*, vol. 262, no. 7, pp. 1681–1690, 2015.

[144] H. E. A. Aho-Özhan, J. Keller, J. Heimrath et al., "Perception of emotional facial expressions in amyotrophic lateral sclerosis (ALS) at behavioural and brain metabolic level," *PLoS One*, vol. 11, no. 10, article e0164655, 2016.

[145] A. Sedda, "Disorders of emotional processing in amyotrophic lateral sclerosis," *Current Opinion in Neurology*, vol. 27, no. 6, pp. 659–665, 2014.

[146] S. A. Savage, P. Lillo, F. Kumfor, M. C. Kiernan, O. Piguet, and J. R. Hodges, "Emotion processing deficits distinguish pure amyotrophic lateral sclerosis from frontotemporal dementia," *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, vol. 15, no. 1–2, pp. 39–46, 2014.

[147] A. Palmieri, M. Naccarato, S. Abrahams et al., "Right hemisphere dysfunction and emotional processing in ALS: an fMRI study," *Journal of Neurology*, vol. 257, no. 12, pp. 1970–1978, 2010.

[148] C. Crespi, C. Cerami, A. Dodich et al., "Microstructural white matter correlates of emotion recognition impairment in amyotrophic lateral sclerosis," *Cortex*, vol. 53, pp. 1–8, 2014.

[149] E. Bora, M. Walterfang, and D. Velakoulis, "Theory of mind in behavioural-variant frontotemporal dementia and Alzheimer's disease: a meta-analysis," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 86, no. 7, pp. 714–719, 2015.

[150] E. Bora, D. Velakoulis, and M. Walterfang, "Meta-analysis of facial emotion recognition in behavioral variant frontotemporal dementia: comparison with Alzheimer disease and healthy controls," *Journal of Geriatric Psychiatry and Neurology*, vol. 29, no. 4, pp. 205–211, 2016.

[151] E. K. Zimmerman, P. J. Eslinger, Z. Simmons, and A. M. Barrett, "Emotional perception deficits in amyotrophic lateral sclerosis," *Cognitive and Behavioral Neurology*, vol. 20, no. 2, pp. 79–82, 2007.

[152] B. Papps, S. Abrahams, P. Wicks, P. N. Leigh, and L. H. Goldstein, "Changes in memory for emotional material in amyotrophic lateral sclerosis (ALS)," *Neuropsychologia*, vol. 43, no. 8, pp. 1107–1114, 2005.

[153] H. Schmolck, D. Mosnik, and P. Schulz, "Rating the approachability of faces in ALS," *Neurology*, vol. 69, no. 24, pp. 2232–2235, 2007.

[154] Z. C. Gibbons, J. S. Snowden, J. C. Thompson, F. Happé, A. Richardson, and D. Neary, "Inferring thought and action in motor neurone disease," *Neuropsychologia*, vol. 45, no. 6, pp. 1196–1207, 2007.

[155] S. L. Meier, A. J. Charleston, and L. J. Tippett, "Cognitive and behavioural deficits associated with the orbitomedial prefrontal cortex in amyotrophic lateral sclerosis," *Brain*, vol. 133, no. 11, pp. 3444–3457, 2010.

[156] T. Burke, M. Elamin, P. Bede et al., "Discordant performance on the "Reading the Mind in the Eyes" test based on disease onset in amyotrophic lateral sclerosis," *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, vol. 17, no. 7–8, pp. 467–472, 2016.

[157] E. J. van der Hulst, T. H. Bak, and S. Abrahams, "Impaired affective and cognitive theory of mind and behavioural change in amyotrophic lateral sclerosis," *Journal of Neurology, Neurosurgery & psychiatry*, vol. 86, no. 11, pp. 1208–1215, 2015.

[158] H. L. Gallagher and C. D. Frith, "Functional imaging of "theory of mind"," *Trends in Cognitive Sciences*, vol. 7, no. 2, pp. 77–83, 2003.

[159] A. Abu-Akel and S. Shamay-Tsoory, "Neuroanatomical and neurochemical bases of theory of mind," *Neuropsychologia*, vol. 49, no. 11, pp. 2971–2984, 2011.

[160] F. Filimon, J. D. Nelson, D. J. Hagler, and M. I. Sereno, "Human cortical representations for reaching: mirror neurons for execution, observation, and imagery," *Neuroimage*, vol. 37, no. 4, pp. 1315–1328, 2007.

[161] E. C. Wolters, "Non-motor extranigral signs and symptoms in Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 15, Supplement 3, pp. S6–12, 2009.

[162] F. E. Pontieri, F. Assogna, A. Stefani et al., "Sad and happy facial emotion recognition impairment in progressive supranuclear palsy in comparison with Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 18, no. 7, pp. 871–875, 2012.

[163] F. Kumfor, L. A. Sapey-Triomphe, C. E. Leyton, J. R. Burrell, J. R. Hodges, and O. Piguet, "Degradation of emotion processing ability in corticobasal syndrome and Alzheimer's disease," *Brain*, vol. 137, no. 11, pp. 3061–3072, 2014.

[164] W. W. Beatty, D. E. Goodkin, W. S. Weir, R. D. Staton, N. Monson, and P. A. Beatty, "Affective judgments by patients with Parkinson's disease or chronic progressive multiple sclerosis," *Bulletin of the Psychonomic Society*, vol. 27, no. 4, pp. 361–364, 1989.

[165] A. Ariatti, F. Benuzzi, and P. Nichelli, "Recognition of emotions from visual and prosodic cues in Parkinson's disease," *Neurological Sciences*, vol. 29, no. 4, pp. 219–227, 2008.

[166] L. X. Blonder, R. E. Gur, and R. C. Gur, "The effects of right and left hemiparkinsonism on prosody," *Brain and Language*, vol. 36, no. 2, pp. 193–207, 1989.

[167] M. De Risi, G. Di Gennaro, A. Picardi et al., "Facial emotion decoding in patients with Parkinson's disease," *The International Journal of Neuroscience*, vol. 128, no. 1, pp. 71–78, 2017.

[168] E. Herrera, F. Cuetos, and J. Rodríguez-Ferreiro, "Emotion recognition impairment in Parkinson's disease patients without dementia," *Journal of the Neurological Sciences*, vol. 310, no. 1–2, pp. 237–240, 2011.

[169] C. Xi, Y. Zhu, Y. Mu et al., "Theory of mind and decision-making processes are impaired in Parkinson's disease," *Behavioural Brain Research*, vol. 279, pp. 226–233, 2015.

[170] R. Adolphs, R. Schul, and D. Tranel, "Intact recognition of facial emotion in Parkinson's disease," *Neuropsychology*, vol. 12, no. 2, pp. 253–258, 1998.

[171] J. F. Caekebeke, A. Jennekens-Schinkel, M. E. Van der Linden, O. J. Buruma, and R. A. Roos, "The interpretation of dysprosody in patients with Parkinson's disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 54, no. 2, pp. 145–148, 1991.

[172] P. Madeley, A. W. Ellis, and R. H. S. Mindham, "Facial expressions and Parkinson's disease," *Behavioural Neurology*, vol. 8, no. 2, 119 pages, 1995.

[173] M. D. Pell and C. L. Leonard, "Facial expression decoding in early Parkinson's disease," *Cognitive Brain Research*, vol. 23, no. 2–3, pp. 327–340, 2005.

[174] R. Ille, A. Wabnegger, P. Schwingenschuh et al., "Intact emotion recognition and experience but dysfunctional emotion regulation in idiopathic Parkinson's disease," *Journal of the Neurological Sciences*, vol. 361, pp. 72–78, 2016.

[175] H. M. Gray and L. Tickle-Degnen, "A meta-analysis of performance on emotion recognition tasks in Parkinson's disease," *Neuropsychology*, vol. 24, no. 2, pp. 176–191, 2010.

[176] A. Sedda, S. Petito, M. Guarino, and A. Stracciari, "Identification and intensity of disgust: distinguishing visual, linguistic and facial expressions processing in Parkinson disease," *Behavioural Brain Research*, vol. 330, pp. 30–36, 2017.

[177] C. Y. Lin, Y. M. Tien, J. T. Huang, C. H. Tsai, and L. C. Hsu, "Degraded impairment of emotion recognition in Parkinson's disease extends from negative to positive emotions," *Behavioural Neurology*, vol. 2016, Article ID 9287092, 8 pages, 2016.

[178] G. Hipp, N. J. Diederich, V. Pieria, and M. Vaillant, "Primary vision and facial emotion recognition in early Parkinson's disease," *Journal of the Neurological Sciences*, vol. 338, no. 1–2, pp. 178–182, 2014.

[179] A. Saenz, A. Doé de Maindreville, A. Henry, S. de Labbey, S. Bakchine, and N. Ehrlé, "Recognition of facial and musical emotions in Parkinson's disease," *European Journal of Neurology*, vol. 20, no. 3, pp. 571–577, 2013.

[180] I. Enrici, M. Adenzato, R. B. Ardito et al., "Emotion processing in Parkinson's disease: a three-level study on recognition, representation, and regulation," *PLoS One*, vol. 10, no. 6, article e0131470, 2015.

[181] J. Pietschnig, L. Schröder, I. Ratheiser et al., "Facial emotion recognition and its relationship to cognition and depressive symptoms in patients with Parkinson's disease," *International Psychogeriatrics*, vol. 28, no. 7, pp. 1165–1179, 2016.

[182] I. Biseul, P. Sauleau, C. Haegelen et al., "Fear recognition is impaired by subthalamic nucleus stimulation in Parkinson's disease," *Neuropsychologia*, vol. 43, no. 7, pp. 1054–1059, 2005.

[183] D. Drapier, J. Péron, E. Leray et al., "Emotion recognition impairment and apathy after subthalamic nucleus stimulation in Parkinson's disease have separate neural substrates," *Neuropsychologia*, vol. 46, no. 11, pp. 2796–2801, 2008.

[184] J. Péron, I. Biseul, E. Leray et al., "Subthalamic nucleus stimulation affects fear and sadness recognition in Parkinson's disease," *Neuropsychology*, vol. 24, no. 1, pp. 1–8, 2010.

[185] F. Le Jeune, J. Péron, I. Biseul et al., "Subthalamic nucleus stimulation affects orbitofrontal cortex in facial emotion recognition: a PET study," *Brain*, vol. 131, no. 6, pp. 1599–1608, 2008.

[186] R. Adolphs, "Recognizing emotion from facial expressions: psychological and neurological mechanisms," *Behavioral and Cognitive Neuroscience Reviews*, vol. 1, no. 1, pp. 21–62, 2002.

[187] L. Albuquerque, M. Coelho, M. Martins et al., "STN-DBS does not change emotion recognition in advanced Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 20, no. 2, pp. 166–169, 2014.

[188] B. C. P. Ghosh, A. J. Calder, P. V. Peers et al., "Social cognitive deficits and their neural correlates in progressive supranuclear palsy," *Brain*, vol. 135, no. 7, pp. 2089–2102, 2012.

[189] B. C. P. Ghosh, J. B. Rowe, A. J. Calder, J. R. Hodges, and T. H. Bak, "Emotion recognition in progressive supranuclear palsy," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 80, no. 10, pp. 1143–1145, 2009.

[190] A. Schrag, C. Selai, J. Davis, A. J. Lees, M. Jahanshahi, and N. Quinn, "Health-related quality of life in patients with progressive supranuclear palsy," *Movement Disorders*, vol. 18, no. 12, pp. 1464–1469, 2003.

[191] T. Shany-Ur, P. Poorzand, S. N. Grossman et al., "Comprehension of insincere communication in neurodegenerative disease: lies, sarcasm, and theory of mind," *Cortex*, vol. 48, no. 10, pp. 1329–1341, 2012.

[192] E. Winner, H. Brownell, F. Happe, A. Blum, and D. Pincus, "Distinguishing lies from jokes: theory of mind deficits and discourse interpretation in right hemisphere brain-damaged patients," *Brain and Language*, vol. 62, no. 1, pp. 89–106, 1998.

[193] B. M. Kluger and K. M. Heilman, "Dysfunctional facial emotional expression and comprehension in a patient with corticobasal degeneration," *Neurocase*, vol. 13, no. 3, pp. 165–168, 2007.

[194] A. Kertesz and P. McMonagle, "Behavior and cognition in corticobasal degeneration and progressive supranuclear palsy," *Journal of the Neurological Sciences*, vol. 289, no. 1–2, pp. 138–143, 2010.

[195] M. Poletti, A. Vergallo, M. Ulivi, A. Sonnoli, and U. Bonuccelli, "Affective theory of mind in patients with Parkinson's disease," *Psychiatry and Clinical Neurosciences*, vol. 67, no. 4, pp. 273–276, 2013.

[196] M. Roca, T. Torralva, E. Gleichgerrcht et al., "Impairments in social cognition in early medicated and unmedicated Parkinson disease," *Cognitive and Behavioral Neurology*, vol. 23, no. 3, pp. 152–158, 2010.

[197] G. Santangelo, C. Vitale, D. Errico, D. Grossi, L. Trojano, and P. Barone, "Affective theory of mind in patients with Parkinson's disease: comment," *Psychiatry and Clinical Neurosciences*, vol. 68, no. 3, p. 242, 2014.

[198] G. Santangelo, C. Vitale, L. Trojano et al., "Neuropsychological correlates of theory of mind in patients with early Parkinson's disease," *Movement Disorders*, vol. 27, no. 1, pp. 98–105, 2012.

[199] J. Péron, S. Vicente, E. Leray et al., "Are dopaminergic pathways involved in theory of mind? A study in Parkinson's disease," *Neuropsychologia*, vol. 47, no. 2, pp. 406–414, 2009.

[200] R. L. Yu, R. M. Wu, M. J. Chiu, C. H. Tai, C. H. Lin, and M. S. Hua, "Advanced Theory of Mind in patients at early stage of Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 18, no. 1, pp. 21–24, 2012.

[201] M. E. Bodden, B. Mollenhauer, C. Trenkwalder et al., "Affective and cognitive Theory of Mind in patients with Parkinson's disease," *Parkinsonism & Related Disorders*, vol. 16, no. 7, pp. 466–470, 2010.

[202] E. Bora, M. Walterfang, and D. Velakoulis, "Theory of mind in Parkinson's disease: a meta-analysis," *Behavioural Brain Research*, vol. 292, no. 1, pp. 515–520, 2015.

[203] L. Nobis, K. Schindlbeck, F. Ehlen et al., "Theory of mind performance in Parkinson's disease is associated with motor and cognitive functions, but not with symptom lateralization," *Journal of Neural Transmission*, vol. 124, no. 9, pp. 1067–1072, 2017.

[204] A. Costa, A. Peppe, M. Martini et al., "Parkinsonian patients with deficits in the dysexecutive spectrum are impaired on theory of mind tasks," *Behavioural Neurology*, vol. 27, no. 4, 533 pages, 2013.

[205] A. McKinlay, M. Albicini, and P. S. Kavanagh, "The effect of cognitive status and visuospatial performance on affective theory of mind in Parkinson's disease," *Neuropsychiatric Disease and Treatment*, vol. 9, pp. 1071–1076, 2013.

[206] N. Ibarretxe-Bilbao, C. Junque, E. Tolosa et al., "Neuroanatomical correlates of impaired decision-making and facial emotion recognition in early Parkinson's disease," *European Journal of Neuroscience*, vol. 30, no. 6, pp. 1162–1171, 2009.

[207] H. C. Baggio, B. Segura, N. Ibarretxe-Bilbao et al., "Structural correlates of facial emotion recognition deficits in

Parkinson's disease patients," *Neuropsychologia*, vol. 50, no. 8, pp. 2121–2128, 2012.

[208] G. Robert, F. Le Jeune, T. Dondaine et al., "Apathy and impaired emotional facial recognition networks overlap in Parkinson's disease: a PET study with conjunction analyses," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 85, no. 10, pp. 1153–1158, 2014.

[209] A. Wabnegger, R. Ille, P. Schwingenschuh et al., "Facial emotion recognition in Parkinson's disease: an fMRI investigation," *PLoS One*, vol. 10, no. 8, article e0136110, 2015.

[210] J. Grafman, I. Litvan, C. Gomez, and T. N. Chase, "Frontal lobe function in progressive supranuclear palsy," *Archives of Neurology*, vol. 47, no. 5, pp. 553–558, 1990.

[211] L. D. Kaat, A. J. W. Boon, W. Kamphorst, R. Ravid, H. J. Duivenvoorden, and J. C. van Swieten, "Frontal presentation in progressive supranuclear palsy," *Neurology*, vol. 69, no. 8, pp. 723–729, 2007.

[212] J. Péron, F. Le Jeune, C. Haegelen et al., "Subthalamic nucleus stimulation affects theory of mind network: a PET study in Parkinson's disease," *PLoS One*, vol. 5, no. 3, article e9919, 2010.

[213] M. Díez-Cirarda, N. Ojeda, J. Peña et al., "Neuroanatomical correlates of Theory of Mind deficit in Parkinson's disease: a multimodal imaging study," *PLoS One*, vol. 10, no. 11, article e0142234, 2015.

[214] M. Poletti and U. Bonuccelli, "Impairment of affective theory of mind in corticobasal degeneration," *The Journal of Neuropsychiatry and Clinical Neurosciences*, vol. 24, no. 1, p. E7, 2012.

[215] G. B. Frisoni, N. C. Fox, C. R. Jack, P. Scheltens, and P. M. Thompson, "The clinical use of structural MRI in Alzheimer disease," *Nature Reviews Neurology*, vol. 6, no. 2, pp. 67–77, 2010.

[216] F. Kumfor, M. Irish, C. Leyton et al., "Tracking the progression of social cognition in neurodegenerative disorders," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 85, no. 10, pp. 1076–1083, 2014.

[217] A. Dodich, C. Cerami, C. Crespi et al., "Differential impairment of cognitive and affective mentalizing abilities in neurodegenerative dementias: evidence from behavioral variant of frontotemporal dementia, Alzheimer's disease, and mild cognitive impairment," *Journal of Alzheimer's Disease*, vol. 50, no. 4, pp. 1011–1022, 2016.

[218] M. Lindau, O. Almkvist, J. Kushi et al., "First symptoms—frontotemporal dementia versus Alzheimer's disease," *Dementia and Geriatric Cognitive Disorders*, vol. 11, no. 5, pp. 286–293, 2000.

[219] J. L. Cummings, M. Mega, K. Gray, S. Rosenberg-Thompson, D. A. Carusi, and J. Gornbein, "The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia," *Neurology*, vol. 44, no. 12, pp. 2308–2314, 1994.

[220] J. C. Morris, "The Clinical Dementia Rating (CDR): current version and scoring rules," *Neurology*, vol. 43, no. 11, pp. 2412–2414, 1993.

[221] H. Kazui, K. Yoshiyama, H. Kanemoto et al., "Differences of behavioral and psychological symptoms of dementia in disease severity in four major dementias," *PLoS One*, vol. 11, no. 8, article e0161092, 2016.

[222] R. Ossenkoppele, Y. A. L. Pijnenburg, D. C. Perry et al., "The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features," *Brain*, vol. 138, no. 9, pp. 2732–2749, 2015.

[223] N. L. Cadieux and K. W. Greve, "Emotion processing in Alzheimer's disease," *Journal of the International Neuropsychological Society*, vol. 3, no. 5, pp. 411–419, 1997.

[224] E. Teng, P. H. Lu, and J. L. Cummings, "Deficits in facial emotion processing in mild cognitive impairment," *Dementia and Geriatric Cognitive Disorders*, vol. 23, no. 4, pp. 271–279, 2007.

[225] M. S. Albert, C. Cohen, and E. Koff, "Perception of affect in patients with dementia of the Alzheimer type," *Archives of Neurology*, vol. 48, no. 8, pp. 791–795, 1991.

[226] J. Allender and A. W. Kaszniak, "Processing of emotional cues in patients with dementia of the Alzheimer's type," *The International Journal of Neuroscience*, vol. 46, no. 3–4, pp. 147–155, 1989.

[227] A. Shimokawa, N. Yatomi, S. Anamizu, S. Torii, H. Isono, and Y. Sugai, "Recognition of facial expressions and emotional situations in patients with dementia of the Alzheimer and vascular types," *Dementia and Geriatric Cognitive Disorders*, vol. 15, no. 3, pp. 163–168, 2003.

[228] H. Burnham and E. Hogervorst, "Recognition of facial expressions of emotion by patients with dementia of the Alzheimer type," *Dementia and Geriatric Cognitive Disorders*, vol. 18, no. 1, pp. 75–79, 2004.

[229] I. Lavenu, F. Pasquier, F. Lebert, H. Petit, and M. v. der Linden, "Perception of emotion in frontotemporal dementia and Alzheimer disease," *Alzheimer Disease & Associated Disorders*, vol. 13, no. 2, pp. 96–101, 1999.

[230] I. Spoletini, C. Marra, F. D. Iulio et al., "Facial emotion recognition deficit in amnestic mild cognitive impairment and Alzheimer disease," *The American Journal of Geriatric Psychiatry*, vol. 16, no. 5, pp. 389–398, 2008.

[231] M. Freedman, M. A. Binns, S. E. Black, C. Murphy, and D. T. Stuss, "Theory of mind and recognition of facial emotion in dementia: challenge to current concepts," *Alzheimer Disease & Associated Disorders*, vol. 27, no. 1, pp. 56–61, 2013.

[232] N. Moreau, S. Rauzy, F. Viallet, and M. Champagne-Lavau, "Theory of mind in Alzheimer disease: evidence of authentic impairment during social interaction," *Neuropsychology*, vol. 30, no. 3, pp. 312–321, 2016.

[233] S. Ramanan, L. C. de Souza, N. Moreau et al., "Determinants of theory of mind performance in Alzheimer's disease: a data-mining study," *Cortex*, vol. 88, pp. 8–18, 2017.

[234] N. Dermody, S. Wong, R. Ahmed, O. Piguet, J. R. Hodges, and M. Irish, "Uncovering the neural bases of cognitive and affective empathy deficits in Alzheimer's disease and the behavioral-variant of frontotemporal dementia," *Journal of Alzheimer's Disease*, vol. 53, no. 3, pp. 801–816, 2016.

[235] T. Shany-Ur, N. Lin, H. J. Rosen, M. Sollberger, B. L. Miller, and K. P. Rankin, "Self-awareness in neurodegenerative disease relies on neural structures mediating reward-driven attention," *Brain*, vol. 137, no. 8, pp. 2368–2381, 2014.

[236] S. L. Valk, B. C. Bernhardt, F. M. Trautwein et al., "Structural plasticity of the social brain: differential change after socio-affective and cognitive mental training," *Science Advances*, vol. 3, no. 10, article e1700489, 2017.

[237] C. L. Kempnich, D. Wong, N. Georgiou-Karistianis, and J. C. Stout, "Feasibility and efficacy of brief computerized training to improve emotion recognition in premanifest and early-symptomatic Huntington's disease," *Journal of*

the International Neuropsychological Society, vol. 23, no. 4, pp. 314–321, 2017.

[238] S. Yao, B. Becker, W. Zhao et al., "Oxytocin modulates attention switching between interoceptive signals and external social cues," *Neuropsychopharmacology*, vol. 43, no. 2, pp. 294–301, 2017.

[239] M. Fukai, T. Hirosawa, M. Kikuchi et al., "Oxytocin effects on emotional response to others' faces via serotonin system in autism: a pilot study," *Psychiatry Research*, vol. 267, pp. 45–50, 2017.

[240] M. Timmermann, H. Jeung, R. Schmitt et al., "Oxytocin improves facial emotion recognition in young adults with antisocial personality disorder," *Psychoneuroendocrinology*, vol. 85, pp. 158–164, 2017.

[241] K. J. Parker, O. Oztan, R. A. Libove et al., "Intranasal oxytocin treatment for social deficits and biomarkers of response in children with autism," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 114, no. 30, pp. 8119–8124, 2017.

[242] P. G. Enticott, H. A. Kennedy, A. Zangen, and P. B. Fitzgerald, "Deep repetitive transcranial magnetic stimulation associated with improved social functioning in a young woman with an autism spectrum disorder," *Journal of Electroconvulsive Therapy*, vol. 27, no. 1, pp. 41–43, 2011.

[243] M. T. Berlim, A. McGirr, M. M. Beaulieu, and G. Turecki, "Theory of mind in subjects with major depressive disorder: is it influenced by repetitive transcranial magnetic stimulation?," *World Journal of Biological Psychiatry*, vol. 13, no. 6, pp. 474–479, 2012.

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Research Article

Sentence Context and Word-Picture Cued-Recall Paired-Associate Learning Procedure Boosts Recall in Normal and Mild Alzheimer's Disease Patients

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Introduction. The aim of this study was to employ the word-picture paradigm to examine the effectiveness of combined pictorial illustrations and sentences as strong contextual cues. The experiment details the performance of word recall in healthy older adults (HOA) and mild Alzheimer's disease (AD). The researchers enhanced the words' recall with word-picture condition and when the pair was associated with a sentence contextualizing the two items. *Method*. The sample was composed of 18 HOA and 18 people with mild AD. Participants memorized 15 pairs of words under word-word and word-picture conditions, with and without a sentence context. In the paired-associate test, the first item of the pair was read aloud by participants and used to elicit retrieval of the associated item. *Results*. The findings suggest that both HOA and mild-AD pictures improved item recall compared to word condition such as sentences which further enabled item recall. Additionally, the HOA group performs better than the mild-AD group in all conditions. *Conclusions*. Word-picture and sentence context strengthen the encoding in the explicit memory task, both in HOA and mild AD. These results open a potential window to improve the memory for verbalized instructions and restore sequential abilities in everyday life, such as brushing one's teeth, fastening one's pants, or drying one's hands.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that includes deterioration across many cognitive domains. The most commonly reported problem in the early stages of AD is progressive memory loss, in particular episodic recent memory impairment that produces serious difficulty to encode and consolidate new information, resulting from medial temporal lobe (MTL) neural degeneration [1].

Despite the loss of episodic memory in the context of MTL degeneration, there is a relative preservation of semantic knowledge in the AD patients [2, 3] which could represent an opportunity to improve episodic memory, because there exists a relation between semantic and episodic memory. A proof of this is paired associated learning (PAL) in which the encoding of a new episodic memory is affected by the degree of association between the two words (semantic memory) [4]. Generally, the verbal PAL task has been used as an instrument for assessing explicit episodic memory performance in healthy older people, with mild cognitive impairment (MCI) and with early AD [5–8]. In this study, we used PAL task in a new way, not as an assessment instrument but like strategic memory control processes to investigate together the strategic component of episodic memory (organization and manipulation of information during encoding, storage, or retrieval) [9] and the types of mediators (pairs of words, the word followed by an image, and sentence-generation strategies) that determine individuals' encoding performance. The mediator is an aid or strategy that is used to link together the items to be remembered [10]. In these terms, the encoding operation

constitutes a control process that can promote the increased levels of recall performance [11].

One possible mediator that has shown improvements in memory performance in healthy young [12] and older adults [13] and has promoted the modality congruency effect (this refers to the congruency between the modality of presentation and the modality of recall) is the interactive imagery strategy. Decades of research (over 50 years) have found that pictures are retained in memory better than words are (picture superiority effect). There exists a wide range of cognitive psychology studies that have shown that pictures enhance recollection compared with words in healthy young and older adults [14]. Consistent empirical finding shows that when a word can evoke an image or have a semantic relation with a pictorial representation, verbal and image codes are stored in interconnected symbolic system memory [15, 16]. The effectiveness of a pictorial representation can improve memory for words, because semantic elaboration enhances the pictorial superiority effect [17, 18]. One theory that explains the picture superiority effect proposes that the pictures allow a deeper and more elaborate conceptual processing than solely words do (semantic processing account) [19, 20]. Several authors have found that individuals with amnesic mild cognitive impairment (aMCI) and mild AD can enhance memory by extracting the conceptual meaning from pictures [21] because they enhance conceptual fluency [22, 23]. Furthermore, the picture enhances perceptual fluency and improves the sense of familiarity [24], which in turn improves accuracy and reduces false recognition [25] compared with words.

Despite that, the widespread limitation found in the experimental designs in which the purpose has been to demonstrate the effectiveness of pictorial representation to improve the memory for words in aMCI or mild AD is that the majority of experimental tasks are based on recognition memory [26].

In this work, we want to propose a sentence's linguistic structure combined with pictorial representation, as a possible mediator to improve the process of encoding new items in mild-AD patients and promote explicit memory retrieval for words. We consider that the linguistic structure of a sentence can be thought as an autopoietic system that receives feedback from itself (in terms of linguistic structure) strengthening the unity between the elements (words). The phrase is inserted in a network that allows it to be activated in different ways (lexical, semantic, and visual). The diversification of activation supports the duration of the memory and therefore access to it [27–29]. There is little research that has directly examined the possibility to use sentence as a mediator in mild AD; generally, the sentence has been used to assess the problem in verbal comprehension in mild AD, as we extensively found in literature [30–33]. We consider that it not is the only form to use the linguistic property of the sentence, because it can be converted into an adequate strategy (mediator) that could improve the process of encoding new items in mild-AD patients, because the sentence favors a sufficient semantic richness which allows it to improve the retrieval of the information preview learned [34]. Sentence processing is a natural task, and it can take advantage of sentence cues when processing the meaning, especially when the sentence context primes certain aspects of a target word's meaning. Retrieval of words in the sentences is facilitated when there is a unique cue-target association that reduces the interference and reliable access to the information. Moreover, a sentential context provides a semantic structure for integration of the meaning across the words and allows the formation of a comprehensive mental image [35, 36].

According to these purposes, it is important to take into account that sentence contexts activate both semantic and lexical hierarchical networks in which stimulation of a concept's representation activates other concept nodes associated with the original concept [37, 38], priming the target words included in a phrase [39] and improving the encoding and retrieval of information [40]. Several authors attributed the advantages of sentence context to an activation of automatic processes, especially when a word is thought to prime other semantically related concepts and boost the processing of a target word [41, 42]. Furthermore, the semantic content of a sentence can provide a semantic structure for the integration of meaning across the words and thus allows the formation of a comprehensive mental image [41].

To further enhance encoding, some authors suggest combining verbal and pictorial stimuli to activate a presemantic level of information that interacts with the episodic and semantic systems. Paivio et al. [43] have shown that the ability to generate interactive visual images facilitates verbal PAL performance, independently from the effect of stimulus relatedness. That is, the interconnectivity of words and images facilitates access to a common conceptual memory storage area [18, 44]. Cherry et al. [45] carried out a study with younger and older adults, where the encoding stimuli consisted of sets of 16 sentences with pictorial illustrations (e.g., The dusty man held the rope), and the retrieval stimuli consisted of "what" question sentences (e.g., "What did the dusty man do?"). They found that the combination of verbal and visual supports allowed retrieval of the main point of the sentences and improved recall performance.

Although these strategies are based on known cognitive paradigms and have a long path of experimentation when they are combined with pictorial and verbal material, the greatest limitation found in previous research is that mild AD is able to extract only the gist from pictorial information, but they can remember the information in verbatim form. The mnemonic strategy is not easy to learn because they are often complex and have a high level of artificiality that generates difficulties using them in daily life. Furthermore, when the therapists interact with mild-AD patients, they found serious difficulties to promote the memorization of complex information such as sentences; generally, the mnemonic method is limited to a simple and short piece of information (face nouns, date, and single words) (see [46] for limitations of mnemonics in clinical applications). In this work, we propose the use of the combinations of two known strategies according to which the sentence context enriched by pictorial illustration represents a form of environmental support where the activation of a sentential semantic network more robustly connects to a visual representation [14, 15, 39, 47]. We consider it important to investigate the relationship

between semantic/conceptual (sentences) and visual perception conditions (pictures) during both encoding and retrieval in mild-AD patients, because understanding this relationship would generate new reflections and suggest new forms to use and combine mnemonic strategies that favor the codification of new information.

Taking into account that it is possible to use sentences as contextual cue combined with pictorial representation, we consider that it is also possible in mild AD, because the older adults have a greater experience with sentence processing during their lives because they reprocess the verbal information every day, and they depend more heavily on a set of rich sentential context cues for recalling the information [47]. However, this may have several implications in a clinical context: on the one hand, the linguistic structure of sentences makes mnemonic techniques more natural and familiar, allowing easy use of them in everyday life and promoting the retrieval in explicit memory task.

Despite advances in our understanding of the effects of sentence context as contextual cue, there is little research and timid attempts that have directly examined the importance of the relationship between semantic/conceptual and visual perception conditions during both encoding and retrieval of items embedded in short sentences for healthy older adults (HOA) and persons with mild AD. Understanding these mechanisms would open up new directions for cognitive interventions in older adults with cognitive impairment. Therefore, the specific aim of this work, based on the theoretical models and empirical research described above, was to assess the effectiveness of encoding sentence context as a strong contextual cue (cue-target association) and different types of stimuli in HOA and persons with mild AD. In this study, we used the word-word (WW) and word-picture (WP) conditions as target items [15], comparing the encoding and retrieval of the target item (second item of the pair) in the presence or absence of a sentence contextual cue. Our first hypothesis was that the WP condition would yield a higher recall rate of second pair items compared to the WW condition. Our second hypothesis was that sentence context would improve the recall of the second pair items, in both WW and WP conditions relative to the null sentence context condition. Our third prediction was that the first and second hypotheses would be confirmed for both HOA and mild-AD participants.

2. Method

2.1. Participants. Thirty-six elderly Spanish people were included in the study, forming two groups. The first group was made up of 18 patients at the State Reference Center for people with Alzheimer's disease of Spain (Salamanca). As inclusion criteria, participants had been previously diagnosed with AD (not mixed dementia) for the Spanish National Health System following the criteria of NINCDS-ADRDA [48] and whose diagnosis as AD was later confirmed according to GDS stages 2 and 3 by the center's medical and neurological service (very mild–mild cognitive decline) [49]. The mean age was 83.9 years (SD = 13.573; range 65–90), with a Mini Mental State Examination (MMSE) mean of 20.3, (SD = 2.20; range 18–24) [50]. The families of these patients provided informed consent for their participation in the study. In accordance with the Ethics Committee at the center, a form was sent out to the patients' immediate family or guardian for them to sign and return. The second group was made up of 18 people living in nursing homes who did not have a neurodegenerative pathology and who were classified as cognitively healthy older adults by a physician at the home. The mean age of the group was 80.1 (SD = 7.415; range 63–91) with a MMSE mean of 27.3 (SD = 2.024; range 24–30) [50]. The healthy older adults provided informed consent to participate in the study. We found significant differences between the two experimental groups in terms of their scores on the MMSE, $t\,(32) = 6.2$, $p < .001$ [5]. We confirmed that there were no significant differences between the two groups in terms of educational level, years of schooling, age, or gender distribution (see Table 1). The study excluded those participants with any depressive symptoms, measured by the Beck Depression Inventory (value > 10) [51], as well as those participants with medical backgrounds involving problems in their communication system (auditory or visual) or in their ability to read.

Table 1: Demographic data.

	Groups			
	18 Mild AD		18 healthy older adults	
	Means	SD	Means	SD
Years of education	7.1	3.10	7.0	2.80
Age	83.94	2.62	80.12	1.46
MMSE	20.30	4.10	27.30	2.10
Men	22%		17%	
Women	78%		83%	

MMSE: Mini Mental State Examination.

2.2. Materials. We employed a database of 60 pairs of Spanish words from which we randomly created 4 lists of 15 pairs (e.g., owl-woods, umbrella-winter). We selected and matched all pairs of stimuli based on the factors' "frequency of use" and "proportion" from the normative study by Fernandez et al. [52]. Each list of stimuli contained one of the following four combinations: WW and WP each embedded in a sentence context and WW and WP each not embedded in a sentence context. The pictures for the WP condition were obtained by associating the words with corresponding Snodgrass drawings [53]. The presentation order of these stimuli was counterbalanced across the Paired Associate Learning (PAL) form and, in the embedded context condition, was embedded in a short sentence (sentence context cue), favoring the encoding and retrieval of the second (right) item of the pair. All stimuli were presented using the experimental program E-Prime® V1.1, presented on a 15″ screen with a resolution of 1024 × 768, and placed at a distance of 48″ from participants. The words were displayed in black against a white background, and the images were 3 cm in size (width 45% × height 45% in E-Prime) in the form of line drawings (see Figure 1).

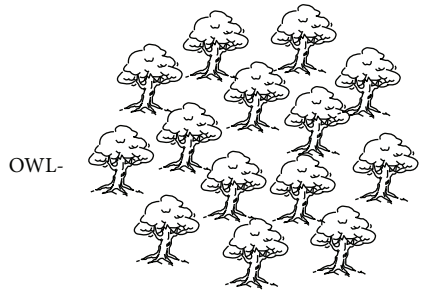

Figure 1: Word-picture pair (*owl-woods*) embedded in sentence context *"The owl lives in the woods."*

2.3. Procedure. Each participant was tested individually and completed four 30-minute sessions, each one corresponding to one of the four list types. The order of conditions was counterbalanced across participants, and sessions were held one week apart. The individual sessions were divided into two phases, a study phase and a retrieval phase. In the study phase, 15 pairs of stimuli were presented one at a time on the computer screen for ten seconds. In the null sentence context condition, the stimuli were presented in a PAL task as two words (WW) or as a word followed by picture (WP), and the participants only read the words and named the pictures aloud. In the embedded sentence context condition, the stimuli were again presented in a PAL task (WW or WP), but, in addition, the experimenter read a corresponding sentence (e.g., after presenting the "owl-woods" pair, the experimenter read the embedded sentence: "The *owl* lives in the *woods*"; see Figure 1). In between trials, a fixation point was displayed in the center of the screen for 1 second. After the study phase (approximately 150 seconds), the participants were informed, through instructions presented on the computer screen, that the learning task had been completed and that the retrieval task was to begin immediately. During the retrieval task, the first item in the pair was presented on the screen, and the participants were asked to recall the associated second items. The participant was instructed to say "I do not remember" when he/she thought he/she was not able to recover the information. In these circumstances, the omission of the information was considered as absence of an error instead of a fault; the experimenter provided a phonological cue according to the method of "errorless learning" [54], to corroborate the presence or absence of the encoding process. For example, with the pair "umbrella (word)-winter (image)," to facilitate the recovery of the second element of the pair according to the technique of errorless learning, a phonological cue constituted by the first significant syllables of the word was provided orally, in this case "win-" (for the word winter). With this cue, the participant was invited to complete the word. If the experimenter realized that there was no clarity from the participant about the type of sounds pronounced, the letters were written on a sheet, showed to the person, and pronounced aloud again. The stimulus presentation in the recall phase was not subject to a time limit [15]. The time elapsed in this phase was managed through the recovery process described previously (inviting the participant to remember the associated pair in order to provide a phonetic cue in the absence of the memory and to finalize the recovery phase if the participant had given a correct or incorrect response). The retrieval process took no more than 5 minutes. One point was assigned for each correct retrieval, 0.5 for each retrieval by means of a phonetic cue using "errorless learning" (e.g., "wo" for "woods"), and 0 for each incorrect retrieval or persistent omission of the information. The persistent omission was considered as an omission after it provided four times the phonetic cue [55].

2.3.1. Statistical Analysis. A $2 \times 2 \times 2$ repeated-measures mixed-design analysis of variance model was performed with two within-subject variables: encoding type (WW and WP) and the presence or absence of sentence context (Presence and Absence), and one between-subject variable: participant group (mild-AD and healthy older adults). The dependent variable was the recall accuracy of the second item of each learning pair. The significance level was set at $p < 0.05$. Descriptive data for recall is shown in Table 2.

3. Results

A significant effect of the group factor was also observed, $F(1, 34) = 28.645$, $p < .001$, eta = .46, indicating that, as expected, the HOA had 24% greater recall success overall (mean = 12,035) than the mild-AD group had (mean = 8389, $p < .001$). Of the two manipulated variables, we found that there was a significant main effect in the type of encoding, $F(1, 34) = 158.43$, $p < .001$, eta = .82). We confirmed the superiority rate recall of WP (mean = 11,528) compared to WW as a contextual cue (mean = 8896, $p < .001$). In this case, we found a significant interaction effect between the type of encoding and group, $F(1, 34) = 6.539$, $p < .05$, eta = .16. Pairwise comparisons of the interaction confirmed that there were significant differences between the HOA (mean = 10.87) and mild-AD groups (mean = 6.81; $p < 0.01$) in the WW condition ($p < .001$, eta = .51) and in the WP condition (mean = 13.10 for HOA and mean = 9.97 for mild AD; $p < .001$, eta = .35) (see Figure 2). We also found differences between WW and WP conditions in both HOA (mean differences = 2097; $p < 0.01$, eta = .60) and mild AD (mean differences = 3167; $p < 0.01$, eta = .77). There was also a significant main effect of sentence context ($F(1, 34) = 66.768$, $p < .001$, eta = .66), in which recall was better when the items were embedded in sentences (mean = 11,556) compared to the null sentence context condition (mean = 8868, $p < .001$). There were no interactions between the use of sentences and the groups, the use of WP and sentences, and the use of WP, sentences, and groups.

4. Discussion

The purpose of this study was to investigate the mechanisms to improve encoding of words in the explicit memory task under WW versus WP, and sentence context versus null sentence conditions, in both HOA and persons with mild AD. The WP and sentence context improved retrieval performance in both groups. The word associated with an image (WP) improves the recall rates (17.54%) with respect to

Table 2: Recall rates of the second element of the pair with and without sentence context.

Variables	Groups									
	18 mild AD				18 healthy older adults					
	Without sentence		With sentence		Without sentence		With sentence		Means	
	Means	SD	Means	SD	Means	SD	Means	SD	Means	SD
Word/word	5.50	2.56	8.11*	2.85	9.30	2.39	12.66*	1.63	8.89	2.35
Word/picture	8.94*	2.61	11.00*	3.19	11.72*	2.49	14.44*	1.09	11.52	2.34
Means	7.22	2.58	9.55	3.02	10.51	2.44	13.55	1.36		

ANOVA $2 \times 2 \times 2$ was performed; variables encoding type word-word, word-picture, and the presence or absence of sentence context. *The significance level was set at $p < .05$. A significant main effect in word-picture compared with word-word, and in sentences compared to the null sentence context condition, in both groups was found.

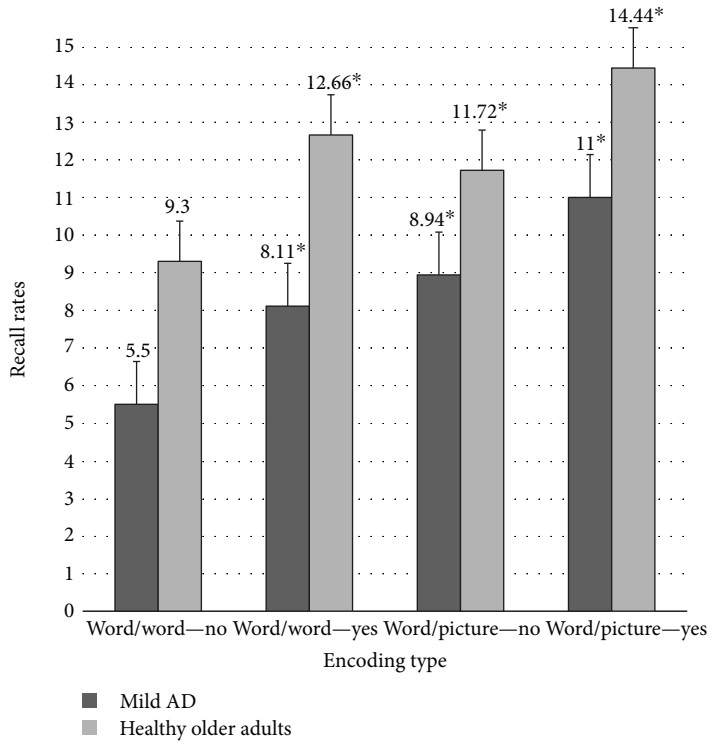

Figure 2: Recall rates of the second element of the pair with (yes) and without (no) sentence context, in healthy older adults and mild AD. ANOVA $2 \times 2 \times 2$ was performed. *The significance level was set at $p < .05$. A significant main effect in word-picture compared with word-word, and in sentences compared to the null sentence context condition, in both groups was found.

WW, with more effectiveness in people with mild AD than in HOA. Similarly, the sentence context condition improves the recall rates (17.91%) compared to the null sentence condition. We found a significant interaction effect between the type of encoding and group. This result can be in agreement with previous studies which show that the magnitude of the picture superiority effect is greater in patients than in HOA [26]. The improvement in recall rates is similar in both coding conditions. Nevertheless, the results do not show an interaction between the variables. Both types of intervention seem to act independently and therefore can be used as a way to improve memory in the elderly. There are several possible reasons for why such an interaction did not emerge. One possibility is that there was such a strong benefit of each cue by itself that any further gains by combining cues were minimal. Another reason could be related to the extra task demands associated with processing stimuli from multiple modalities (word and image) in conjunction with sentential semantic processing. Previous research has shown that processing stimuli under more complex cue conditions can actually create extra attentional demands, leading to declines in performance [56]. Despite the lack of interaction between WP and sentence context, the strong independent effects of each suggest possible intervention approaches capitalizing on the strengths of each cue type, as described below. To understand this possible application in clinical context, we

take into account that there is extensive literature which highlights the difficulty of implementing mnemonic strategies for older people, especially for people with mild AD [57, 58]. One of the main criticisms about mnemonic strategies is that they are difficult to learn because they are often complex and have a high level of artificiality that generates difficulties using them in daily life. Our results indicate that, despite the memory deficit based on MTL neural degeneration that causes deficit both in episodic and in semantic memory, the HOA and mild-AD persons are able to extract the gist from pictorial information and learn with less interference because they focus on the conceptual aspect [59, 60]. The HOA individuals process the information with more amplitude as well as depth. The mild-AD persons showed that they were able to benefit from the way material was encoded at acquisition, generating a cued assistance, and that it is related to assistance provided at retrieval, enhancing recall. The results obtained in this study, although they refer to a specific section of a much wider problem (memory problem in the AD), are consistent with cross-sectional studies, where it is reported that the episodic memory impairment of mild-AD patients is characterized by encoding deficit and low retrieval performance compared to HOA [40]. At the same time, the results also show that despite the fact that mild-AD persons were unable to encode and process all the semantic properties, all participants in the present study were able to extract the gist from pictorial information and they were able to learn with less interference because they focus on the conceptual aspect of information. The results of the present study extend past research, in which it was demonstrated that mild-AD persons receive cue benefits when they are provided with instructions to encode the "to be remembered" (TBR). While in this work the patients were able to utilize cues without instructions to encode, they simply received a particular information structure (image and sentence) that generates deep encoding and provides support at retrieval [15, 61].

The results also show that sentences not only serve to assess the problem in verbal comprehension in AD patients [30–33, 62]. The sentences can be used as contextual cue, because the syntactic properties of the sentence (subject, verb, complement (SVC)) create an organized structure where the words are stringed into chunks that improve their recall performance. Several studies have shown that mild-AD patients remained structurally rich with similar syntactic structure as the HOA controls, and mild-AD patients are not impaired to determine aspects of sentence meaning, despite working memory deficits. This means that they can perform relatively normally on some semantic tasks when they are not required to search for, or intentionally manipulate, semantic information [63, 64]. The sentences can be thought as a linguistic structure that strengthens the unity between the elements (words). The simultaneous engagement of the images and words produces an overlap of codes allowing the access to a common conceptual memory storage area [41]. According to some authors, this is because the information has been drawn to a presemantic level and has interacted with episodic and semantic systems [65]. The results from the present study therefore suggest that mnemonic training, based on the WP and sentence context processing, may enhance encoding and recall by persons with mild AD. Moreover, because the WP paradigm targets lexical level processing, it would perhaps be most useful in addressing semantic memory "access" problems in mild-AD persons, whereas the deeper encoding primed by a sentence context may help persons with mild AD encode and recall a higher level of propositional information. Future research is needed to address these possibilities and to explore how mnemonics based on WP and sentence context can be effectively implemented in real-world contexts.

This study indicates that older individuals, with and without dementia, are sensitive to the semantic constraints provided by a sentence context or picture. Thus, it appears that syntactic properties of the sentence can facilitate the abilities of HOA and those with mild AD to carry out operations such as those involved in retrieval of target information [66]. There is data which indicates that patients with mild AD retain their knowledge of semantic features, but they have difficulty voluntarily accessing it because the information is disorganized [67]. The results of the present study suggest that, first of all, these individuals' performance is improved in encoding because the sentence context and picture generate sets of feature restrictions that serve to organize and integrate the words and allow the formation of a comprehensive mental image [15]. Secondly, the sentence and visual representation of the target words creates a context in which there is an accumulation of presemantic activations. This condition enables the person to better process higher-level representations of the meaning of a sentence and a picture, including relevant attributes that are necessary for promoting a deeper encoding of information [68]. Thirdly, reading a sentence requires deeper processing of its constituent words than does reading a pair of nouns [69]. Thus, our two interventions establish a meaningful relationship among its constituent words, thereby reducing the arbitrariness of a pairwise association. The sentence context can be thought of as a mnemonic strategy, whereby the whole promotes greater depth of encoding than the sum of the parts [14].

As a consequence of the discussion and conclusion of this study, we propose a speculative question: if it is possible to increase memory for words when they are embedded in sentence context, can the same pair of target words activate a semantic network that allows to retrieve a sentence in verbatim form? It helps patients to improve memory for sentences in verbatim form, providing a potential window for nonpharmacological therapies. The sentences can be thought as an autopoietic structure. In other words, as it is possible to improve the memorization of words through a sentence by using syntactic and semantic structures which activate semantic networks, in the same way, a pair of words which would have a certain semantic relationship could activate the same networks in order to favor the integral recovery of the sentence. The phrase is inserted in a network that allows it to be activated in different ways (lexical, semantic, and visual). The diversification of activation supports the duration of the memory and therefore access to explicit memory [27–29]. This potential projection represents a premise for future research where it will be studied how to improve the

memory for verbalized instructions formulated by simple sentences and when it is needed to restore sequential abilities in everyday life, such as brushing teeth, fastening the pants waist, and drying hands [70].

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

Rosario Iodice conceived and designed the study, collected the data, and wrote the paper. Juan José Garcia Meilán conceived and designed the study, supervised the data collection, and wrote the paper. Juan Avelino Carro Ramos conducted the statistical analysis. Jeff Small supervised the design and wrote the paper.

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References

[1] E. Tsantali, D. Economidis, and M. Tsolaki, "Could language deficits really differentiate Mild Cognitive Impairment (MCI) from mild Alzheimer's disease?," *Archives of Gerontology and Geriatrics*, vol. 57, no. 3, pp. 263–270, 2013.

[2] M. Irish and O. Piguet, "The pivotal role of semantic memory in remembering the past and imagining the future," *Frontiers in Behavioral Neuroscience*, vol. 7, 2013.

[3] L. J. Tippett, S. McAuliffe, and M. J. Farah, "Preservation of categorical knowledge in Alzheimer's disease: a computational account," *Memory*, vol. 3, no. 3-4, pp. 519–533, 1995.

[4] E. Tulving, "Episodic and semantic memory," in *Organization of memory*, pp. 381–403, New York, Academic Press, 1972.

[5] G. J. Lowndes, M. M. Saling, D. Ames, E. Chiu, L. M. Gonzalez, and G. R. Savage, "Recall and recognition of verbal paired associates in early Alzheimer's disease," *Journal of the International Neuropsychological Society*, vol. 14, no. 4, pp. 591–600, 2008.

[6] J. M. Duchek, M. Cheney, F. R. Ferraro, and M. Storandt, "Paired associate learning in senile dementia of the Alzheimer type," *Archives of Neurology*, vol. 48, no. 10, pp. 1038–1040, 1991.

[7] P. E. J. Spaan, "Episodic and semantic memory impairments in (very) early Alzheimer's disease: the diagnostic accuracy of paired-associate learning formats," *Cogent Psychology*, vol. 3, no. 1, 2016.

[8] R. E. Curiel, E. Crocco, M. Rosado et al., "A brief computerized paired associate test for the detection of mild cognitive impairment in community-dwelling older adults," *Journal of Alzheimer's Disease*, vol. 54, no. 2, pp. 793–799, 2016.

[9] Y. L. Shing, M. Werkle-Bergner, S.-C. Li, and U. Lindenberger, "Associative and strategic components of episodic memory: a life-span dissociation," *Journal of Experimental Psychology: General*, vol. 137, no. 3, pp. 495–513, 2008.

[10] J. T. E. Richardson, "The availability and effectiveness of reported mediators in associative learning: a historical review and an experimental investigation," *Psychonomic Bulletin & Review*, vol. 5, no. 4, pp. 597–614, 1998.

[11] B. B. Murdock, "Context and mediators in a theory of distributed associative memory (TODAM2)," *Psychological Review*, vol. 104, no. 4, pp. 839–862, 1997.

[12] J. T. E. Richardson, *Mental Imagery and Human Memory*, Macmillan Education UK, London, 1980.

[13] P. Verhaeghen, A. Marcoen, and L. Goossens, "Facts and fiction about memory aging: a quantitative integration of research findings," *Journal of Gerontology*, vol. 48, no. 4, pp. P157–P171, 1993.

[14] T. Curran and J. Doyle, "Picture superiority doubly dissociates the ERP correlates of recollection and familiarity," *Journal of Cognitive Neuroscience*, vol. 23, no. 5, pp. 1247–1262, 2011.

[15] R. Iodice, J. J. G. Meilán, and J. Carro, "Improvement of encoding and retrieval in normal and pathological aging with word-picture paradigm," *Aging & Mental Health*, vol. 19, no. 10, pp. 940–946, 2014.

[16] A. Paivio, *Mind and Its Evolution: A Dual Coding Theoretical Approach*, Psychology Press, New York, 2014.

[17] K. E. Cherry, J. Silva Brown, E. Jackson Walker et al., "Semantic encoding enhances the pictorial superiority effect in the oldest-old," *Aging, Neuropsychology, and Cognition*, vol. 19, no. 1-2, pp. 319–337, 2012.

[18] J. A. Small and N. Sandhu, "Episodic and semantic memory influences on picture naming in Alzheimer's disease," *Brain and Language*, vol. 104, no. 1, pp. 1–9, 2008.

[19] M. S. Weldon and H. L. Roediger, "Altering retrieval demands reverses the picture superiority effect," *Memory & Cognition*, vol. 15, no. 4, pp. 269–280, 1987.

[20] M. S. Weldon, H. L. Roediger, and B. H. Challis, "The properties of retrieval cues constrain the picture superiority effect," *Memory & Cognition*, vol. 17, no. 1, pp. 95–105, 1989.

[21] R. G. Deason, E. P. Hussey, S. Flannery, and B. A. Ally, "Preserved conceptual implicit memory for pictures in patients with Alzheimer's disease," *Brain and Cognition*, vol. 99, pp. 112–117, 2015.

[22] A. P. Yonelinas, "The nature of recollection and familiarity: a review of 30 years of research," *Journal of Memory & Language*, vol. 46, no. 3, pp. 441–517, 2002.

[23] C. A. R. Martins and T. J. Lloyd-Jones, "Preserved conceptual priming in Alzheimer's disease," *Cortex*, vol. 42, no. 7, pp. 995–1004, 2006.

[24] C. E. Westerberg, K. A. Paller, S. Weintraub et al., "When memory does not fail: familiarity-based recognition in mild cognitive impairment and Alzheimer's disease," *Neuropsychology*, vol. 20, no. 2, pp. 193–205, 2006.

[25] A. E. Budson, D. A. Wolk, H. Chong, and J. D. Waring, "Episodic memory in Alzheimer's disease: separating response bias from discrimination," *Neuropsychologia*, vol. 44, no. 12, pp. 2222–2232, 2006.

[26] B. A. Ally, "Using pictures and words to understand recognition memory deterioration in amnestic mild cognitive impairment and Alzheimer's disease: a review," *Current Neurology and Neuroscience Reports*, vol. 12, no. 6, pp. 687–694, 2012.

[27] R. K. Moore, "Introducing a pictographic language for envisioning a rich variety of enactive systems with different degrees

of complexity," *International Journal of Advanced Robotic Systems*, vol. 13, no. 2, p. 74, 2017.

[28] A. Kravchenko, *Biology of cognition and linguistic analysis*, Peter Lang, Frankfurt, 2008.

[29] W. Teubert, "Writing, hermeneutics, and corpus linguistics," *Revista Signos*, vol. 40, no. 64, pp. 431–453, 2007.

[30] M. Radanovic and L. Mansur, *Language Disturbances in Adulthood: New Advances from the Neurolinguistics Perspective Language Disturbances in Adulthood*, Bentham Science Publishers Ltd., Sao Paulo, Brazil, 2012.

[31] R. López-Higes, P. Montejo, J. M. Prados, M. Montenegro, and M. Lozano, "¿Hay un déficit de comprensión gramatical multidominio en el Deterioro Cognitivo Leve?," *Universitas Psychologica*, vol. 13, no. 4, 2015.

[32] L. L. Mansur, "Language alterations in alzheimer's disease and other dementias," in *Language Disturbances in Adulthood: New Advances from the Neurolinguistics Perspective*, L. L. Mansur, Ed., pp. 59–70, Bentham Science Publishers, 2011.

[33] J. Marková, L. Horváthová, M. Králová, and Z. Cséfalvay, "Sentence comprehension in Slovak-speaking patients with Alzheimer's disease," *International Journal of Language & Communication Disorders*, vol. 52, no. 4, pp. 456–468, 2017.

[34] M. Sarazin, C. Berr, J. De Rotrou et al., "Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study," *Neurology*, vol. 69, no. 19, pp. 1859–1867, 2007.

[35] A. Prior and S. Bentin, "Incidental formation of episodic associations: the importance of sentential context," *Memory & Cognition*, vol. 31, no. 2, pp. 306–316, 2003.

[36] A. Prior and S. Bentin, "Word associations are formed incidentally during sentential semantic integration," *Acta Psychologica*, vol. 127, no. 1, pp. 57–71, 2008.

[37] E. M. Arroyo-Anlló, M. Beauchamps, P. Ingrand, J. P. Neau, and R. Gil, "Lexical priming in Alzheimer's disease and aphasia," *European Neurology*, vol. 69, no. 6, pp. 360–365, 2013.

[38] K. Segaert, G. Kempen, K. M. Petersson, and P. Hagoort, "Syntactic priming and the lexical boost effect during sentence production and sentence comprehension: an fMRI study," *Brain and Language*, vol. 124, no. 2, pp. 174–183, 2013.

[39] R. Zeelenberg, D. Pecher, R. M. Shiffrin, and J. G. W. Raaijmakers, "Semantic context effects and priming in word association," *Psychonomic Bulletin & Review*, vol. 10, no. 3, pp. 653–660, 2003.

[40] F. Clément, S. Belleville, and S. Mellah, "Functional neuroanatomy of the encoding and retrieval processes of verbal episodic memory in MCI," *Cortex*, vol. 46, no. 8, pp. 1005–1015, 2010.

[41] R. D. Nebes, D. C. Martin, and L. C. Horn, "Sparing of semantic memory in Alzheimer's disease," *Journal of Abnormal Psychology*, vol. 93, no. 3, pp. 321–330, 1984.

[42] R. D. Nebes and C. B. Brady, "The effect of contextual constraint on semantic judgments by Alzheimer patients," *Cortex*, vol. 27, no. 2, pp. 237–246, 1991.

[43] A. Paivio, M. Khan, and I. Begg, "Concreteness and relational effects on recall of adjective-noun pairs," *Canadian Journal of Experimental Psychology/Revue canadienne de psychologie expérimentale*, vol. 54, no. 3, pp. 149–160, 2000.

[44] V. A. Kazmerski and D. Friedman, "Old/new differences in direct and indirect memory tests using pictures and words in within- and cross-form conditions: event-related potential and behavioral measures," *Cognitive Brain Research*, vol. 5, no. 4, pp. 255–272, 1997.

[45] K. E. Cherry, D. K. Dokey, C. M. Reese, and S. Brigman, "Pictorial illustrations enhance memory for sentences in younger and older adults," *Experimental Aging Research*, vol. 29, no. 3, pp. 353–370, 2003.

[46] B. A. Wilson, *Memory Rehabilitation: Integrating Theory and Practice*, The Guilford Press, New York, 2009.

[47] L. E. Matzen and A. S. Benjamin, "Older and wiser: older adults' episodic word memory benefits from sentence study contexts," *Psychology and Aging*, vol. 28, no. 3, pp. 754–767, 2013.

[48] G. McKhann, D. Drachman, M. Folstein, R. Katzman, D. Price, and E. M. Stadlan, "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease," *Neurology*, vol. 34, no. 7, pp. 939–944, 1984.

[49] B. Reisberg, S. H. Ferris, M. J. de Leon, and T. Crook, "The Global Deterioration Scale for assessment of primary degenerative dementia," *American Journal of Psychiatry*, vol. 139, no. 9, pp. 1136–1139, 1982.

[50] M. F. Folstein, S. E. Folstein, and P. R. McHugh, "Mini-mental state: a practical method for grading the cognitive state of patients for the clinician," *Journal of Psychiatric Research*, vol. 12, no. 3, pp. 189–198, 1975.

[51] A. T. Beck, R. A. Steer, and G. K. Brown, "BDI-II. Beck Depression Inventory-II," The Psychological Corporation, San Antonio, TX, 1996.

[52] A. Fernandez, E. Diez, M. A. Alonso, and M. S. Beato, "Free-association norms for the Spanish names of the Snodgrass and Vanderwart pictures," *Behavior Research Methods, Instruments, & Computers*, vol. 36, no. 3, pp. 577–583, 2004.

[53] J. G. Snodgrass and M. Vanderwart, "A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity," *Journal of Experimental Psychology: Human Learning and Memory*, vol. 6, no. 2, pp. 174–215, 1980.

[54] T. Hopper, M. Bourgeois, J. Pimentel et al., "An evidence-based systematic review on cognitive interventions for individuals with dementia," *American Journal of Speech-Language Pathology*, vol. 22, no. 1, pp. 126–145, 2013.

[55] A. Baddeley and B. A. Wilson, "When implicit learning fails: amnesia and the problem of error elimination," *Neuropsychologia*, vol. 32, no. 1, pp. 53–68, 1994.

[56] C. Jacquemot, E. Dupoux, O. Decouche, and A.-C. Bachoud-Levi, "Misperception in sentences but not in words: speech perception and the phonological buffer," *Cognitive Neuropsychology*, vol. 23, no. 6, pp. 949–971, 2006.

[57] J. O. Brooks, L. Friedman, and J. A. Yesavage, "A study of the problems older adults encounter when using a mnemonic technique," *International Psychogeriatrics*, vol. 5, no. 1, pp. 57–65, 1999.

[58] A. L. Gross, J. Brandt, K. Bandeen-Roche et al., "Do older adults use the method of loci? Results from the ACTIVE study," *Experimental Aging Research*, vol. 40, no. 2, pp. 140–163, 2014.

[59] D. Bunce, "Cognitive support at encoding attenuates age differences in recollective experience among adults of lower frontal lobe function," *Neuropsychology*, vol. 17, no. 3, pp. 353–361, 2003.

[60] J. R. Quamme, A. P. Yonelinas, K. F. Widaman, N. E. A. Kroll, and M. J. Sauvé, "Recall and recognition in mild

hypoxia: using covariance structural modeling to test competing theories of explicit memory," *Neuropsychologia*, vol. 42, no. 5, pp. 672–691, 2004.

[61] F. I. M. Craik and R. S. Lockhart, "Levels of processing: a framework for memory research," *Journal of Verbal Learning and Verbal Behavior*, vol. 11, no. 6, pp. 671–684, 1972.

[62] R. López-Higes, J. M. Prados, S. Rubio, P. Montejo, and D. Del Río, "Executive functions and linguistic performance in SCD older adults and healthy controls," *Aging, Neuropsychology, and Cognition*, vol. 24, no. 6, pp. 717–734, 2016.

[63] Y.-h. Lai, H.-h. Pai, and Y.-t. Lin, "To be semantically-impaired or to be syntactically-impaired: Linguistic patterns in Chinese-speaking persons with or without dementia," *Journal of Neurolinguistics*, vol. 22, no. 5, pp. 465–475, 2009.

[64] G. Waters and D. Caplan, "Working memory and online syntactic processing in Alzheimer's disease: studies with auditory moving window presentation," *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, vol. 57, no. 4, pp. P298–P311, 2002.

[65] P. Garrard, M. Lambonralph, K. Patterson, K. Pratt, and J. Hodges, "Semantic feature knowledge and picture naming in dementia of Alzheimer's type: a new approach," *Brain and Language*, vol. 93, no. 1, pp. 79–94, 2005.

[66] E. M. Arroyo-Anlló, S. Bellouard, P. Ingrand, and R. Gil, "Effects of automatic/controlled access processes on semantic memory in Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 25, no. 3, pp. 525–533, 2011.

[67] L. R. Duarte, A. Syssau, M. Jiménez, M. Launay, and P. Terrier, "Deficit of access or storage: semantic memory processing in Alzheimer disease," *Canadian Journal on Aging*, vol. 26, no. 03, pp. 227–239, 2007.

[68] D. Caplan and G. Waters, "Memory mechanisms supporting syntactic comprehension," *Psychonomic Bulletin & Review*, vol. 20, no. 2, pp. 243–268, 2013.

[69] E. W. Wlotko and K. D. Federmeier, "Age-related changes in the impact of contextual strength on multiple aspects of sentence comprehension," *Psychophysiology*, vol. 49, no. 6, pp. 770–785, 2012.

[70] R. Iodice, *Enriquecimiento visual del aprendizaje de palabras*, M. JJG, Ed., Guía Practica de terapias estimulativas en el Alzhéimer, Madrid: Sintesis, 2015.

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Research Article

Functional Connectivity Changes in Behavioral, Semantic, and Nonfluent Variants of Frontotemporal Dementia

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Frontotemporal dementia (FTD) affects behavior, language, and personality. This study aims to explore functional connectivity changes in three FTD variants: behavioral (bvFTD), semantic (svPPA), and nonfluent variant (nfvPPA). Seventy-six patients diagnosed with FTD by international criteria and thirty-two controls were investigated. Functional connectivity from resting functional magnetic resonance imaging (fMRI) was estimated for the whole brain. Two types of analysis were done: network basic statistic and topological measures by graph theory. Several hubs in the limbic system and basal ganglia were compromised in the behavioral variant apart from frontal networks. Nonfluent variants showed a major disconnection with respect to the behavioral variant in operculum and parietal inferior. The global efficiency had lower coefficients in nonfluent variants than behavioral variants and controls. Our results support an extensive disconnection among frontal, limbic, basal ganglia, and parietal hubs.

1. Introduction

A major objective in current clinical neuroscience research is to find new and more accurate neural footprints to improve the diagnosis and follow the progression of neurodegenerative disorders [1]. Frontotemporal dementia (FTD) is a group of clinically and pathologically heterogeneous diseases [2–4]. It has variants with different kinds of manifestations in behavior, language, metacognition, and personality. This clinical heterogeneity makes it difficult to obtain an accurate diagnosis [5].

FTD has been associated with regional atrophy in the frontal and temporal lobes [6]. It usually appears in the age group 45–64 years [7] with prevalence of 0.01–4.6 per 1000 persons [8]. Moreover, the clinical and genetic features are heterogeneous and there is still no treatment available for these conditions [4]. FTD encompasses three main phenotypes characterized by specific clinical symptoms. The behavioral variant FTD (bvFTD) is characterized by changes in personality [2], alteration in social cognition [9], disinhibition, and apathy. Nonfluent/agrammatic variant primary progressive aphasia (nfvPPA) is characterized by agrammatism and fluency impairment mainly [10]. Patients with the semantic variant (svPPA) have a loss of semantic knowledge and relative preservation of grammatical aspects of language and episodic memory [5]. A clinically similar linguistic variant, differentiated by the etiology, is the logopenic variant of PPA (lvPPA); it is an atypical variant of Alzheimer's disease with anomia, hesitant speech, and alterations in episodic memory [11].

Several biomarkers have been suggested to aid the clinical diagnosis and treatment. Neuroimaging biomarkers have

Table 1: Sociodemographic characteristics.

Group	bvFTD	svPPA	nfvPPA	Controls	p value	Post hoc
Number (n)	50	14	12	32	—	—
Gender (F/M)	17/23	7/7	5/7	12/20	—	—
Age	65.85 (8.1)	60.3 (7.65)	63.63 (6.87)	61.25 (7.28)	0.02	ns
Disease duration (years)	7.27 (5.89)	5.85 (3.15)	4.28 (2.5)	—	—	—
Education (years)	12.92 (4.66)	12.3 (5.85)	11.62 (6.32)	14.4 (5.13)	0.33	ns

ns: no significant difference with Holm-Sidak.

been derived from structural magnetic resonance imaging (MRI), FDG-PET, SPECT, and functional MRI such as the resting state and functional activation imaging [12]. Structural MRI studies have consistently reported frontotemporal atrophy with a relative sparing of posterior cortical areas in bvFTD [13]. Semantic dementia involves a large area of the temporal lobe; nevertheless, there is a marked degeneration in the rostral fusiform gyrus and ventral temporal lobe bilaterally [14, 15]. In nfvPPA, imaging studies showed atrophy mainly involving the left inferior frontal lobe, insula, and premotor cortex [13, 16–18].

Another biomarker of FTD based on neuroimaging is resting-state fMRI [13, 19]. Resting-state fMRI can be used to show functionally connected brain networks by measuring synchronized time-dependent changes in blood oxygenation levels [20]. Prior research reported a reduction in limbic connectivity and the insula, putamen, anterior thalamus, and middle cingulate cortex in svPPA and bvFTD with respect to controls [21]. Another result showed an increased and diffused prefrontal hyperconnectivity, and it was significantly associated with apathy [21]. Longitudinal studies report a functional connectivity decrease over time in bvFTD between the supramarginal gyrus and the right frontoparietal network [22].

Recent studies showed that svPPA has a disrupted functional connectivity between the anterior temporal lobe [23, 24] and a broad range of regions including primary cortices (sulcus, Heschl's gyrus, precentral and postcentral gyri, and dorsal posterior insula (primary interoceptive cortex)) and auditory and visual association regions [25]. Both svPPA and bvFTD patients show a reduced functional connectivity in limbic areas of the executive network. However, svPPA patients also exhibit a reduced functional connectivity in the bilateral lateral prefrontal cortex and anterior cingulate [21]. In nfvPPA, previous studies have demonstrated compelling evidence that motor speech and grammatical deficits are associated with deficits in the left frontoinsular-striatal structures involved in speech production, a finding related to a reduced activation of a ventral portion of the left inferior cortex during attempts to understand grammatically challenging aspects of a sentence [26–29]. One study with resting-state fMRI analysis in nfvPPA showed connectivity changes in three subnetworks, namely, (a) the left inferior frontal gyrus and the left supplementary motor area, (b) inferior and superior parietal gyri between both hemispheres, and (c) striatum with the supplementary motor area in both hemispheres [30].

The functional connectivity among frontotemporal subvariants has been explored in a few studies. In the literature, usually, there are comparisons between controls and patients with bvFTD or with Alzheimer's disease [21, 31]. This study attempts to describe the alterations in functional connectivity networks among frontotemporal dementia variants to find specific connectivity alteration in each variant. First, we compared the functional connectivity of the whole brain among the variants. Second, topologic measures such as global efficiency, degree, path length, and clustering from each patient and between variants were compared.

2. Methods

2.1. Participants. Seventy-six patients with FTD were selected from Hospital Universitario San Ignacio including thirty-two healthy controls. The FTD diagnosis was initially made by a group of experts, and each case was individually reviewed at a multidisciplinary clinical meeting (neurologist, neuropsychologist, psychiatrist, and geriatrician). The sample included 50 patients with bvFTD, 14 with svPPA, and 22 with nfvPPA diagnosis. Patients were diagnosed with bvFTD based on recent guidelines [3]. These patients showed prominent changes in personality and social behavior as verified by a caregiver during their initial assessment. svPPA diagnosis were done based on international guidelines [18], and these patients included here had important semantic failures. Patients with nfvPPA have an evaluation by an expert in linguistic, and diagnosis was done based on international guidelines [11].

Control subjects were matched with bvFTD, svPPA, and nfvPPA patients (see Table 1). Matching criteria were gender, age, and years of education. An analysis of variance with Holm-Sidak's multiple comparison test did not show differences among groups to age and years of education. Subjects were recruited from a larger pool of volunteers who did not have a neurodegenerative disease diagnosis or psychiatric disorders. All the participants provided written informed consent in accordance with the institutional review board of the Hospital Universitario San Ignacio and Pontificia Universidad Javeriana.

2.2. Cognitive and Behavioral Assessment. Neuropsychological evaluation was performed in patients and controls. The test battery included screening tests, Montreal Cognitive Assessment (MoCA) [32, 33], mini-mental state examination

(MMSE), and INECO Frontal Screening (IFS) test [34]. Verbal inhibitory control was measured by Hayling test [35]. We used Wisconsin Card Sorting Test (WCST) modified to evaluate executive functions [36]. Rey-Osterrieth complex figure (ROCF) test was employed to assess visuomotor skills [37]. Frontal system behavior scale (FrSBe) [38] was used to measure behavioral changes. This test had two sections investigating premorbid or current behavior. Apathy, inhibition, and dysexecutive function subscales were estimated by FrSBe.

Verbal and design fluency tests were used to assess recall, self-monitoring and cognitive flexibility strategies, phonological (words with P and M), and semantic fluency (animals and fruits) [39]. Finally, proverbs test [40] was used to assess verbal comprehension.

2.3. Image Acquisition. Images from patients with FTD and controls were obtained using a Philips Achieva 3T scanner with a 16-channel SENSE coil. The anatomical and 3D T1-weighted images had the following parameters: TR = 7.9 ms, TE = 3.8 ms, acquisition matrix = 220×220, voxel size = $0.5 \times 0.5 \times 0.5$ mm, and 310 slices, and these images were resliced to $1 \times 1 \times 1$ mm. The blood oxygenation-dependent sequences of the entire brain were acquired in 25 axial slices by using an echoplanar imaging sequence TR = 2000, TE = 30 ms, and voxel size = 2.3. The fMRI lasted 6 minutes and the instruction to the patient was to keep their open eyes.

2.4. Data Analysis

2.4.1. Behavioral Analysis. Demographic information and scores from clinical tests were compared among groups with ANOVA tests and post hoc test for multiple comparisons and correction of p values by Sidak.

2.4.2. Processing and Analysis. Preprocessing was performed with a combination of the Statistical Parametric Mapping [39] software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) (Wellcome Department of Cognitive Neurology, University College London, UK), the Resting-State fMRI Data Analysis Toolkit (REST) version 1.8 (http://www.restfmri.net) [40], and Data Processing Assistant for Resting-State fMRI (DPABI) version 2.1 (http://rfmri.org/DPABI).

2.4.3. Resting-State Preprocessing. The main preprocessing procedure was done with DPABI [41], and the pipeline was (1) removal of the first 10 time points, (2) slice timing, (3) head motion correction, (4) nonlinear registration of the high-resolution T1 structural images to the Montreal Neurological Institute (MNI) template, in which T1 structural images were segmented as white matter, gray matter, and cerebrospinal fluid using a new segment algorithm with DARTEL (diffeomorphic anatomical registration through exponentiated lie algebra), (5) smoothing with a 6 mm full-width-half-maximum Gaussian kernel, (6) removal of the linear trend of the time series, (7) temporal band-pass filtering (0.01–0.08 Hz) to decrease the effects of low-frequency drifts and high-frequency noise, and (8) linear detrending and nuisance signal removal, white matter, cerebrospinal fluid, global signal, 6-head motion parameters, 6-head motion parameters at one time point earlier, and the 12 corresponding squared items (Friston 24-parameter model as covariates) via multiple regression. The general pipeline was reported in another research [19].

2.4.4. Seed-Based Analysis. The functional connectivity was estimated with a seed-based analysis. Regions of interest (ROIs) or seeds were selected according to automated anatomical labeling (AAL) atlas [42]. The diameter of the sphere ROI was 10 mm (approximately 27 cubic voxels). The seed analysis only included the brain. Pearson correlation coefficients were calculated between the mean time course of the ROI and the time courses for all other brain voxels. Fisher's z transform analysis was applied to the Pearson correlation coefficients to obtain an approximate normal distribution to enable the subsequent statistical analysis.

2.4.5. Network-Based Analysis. Global differences in interconnected network components between patients and controls were examined with an F-test by network-based statistics (NBS) [43] based on 10,000 permutations. The p value threshold was set at 0.01 and it was corrected by family-wise error (FWE). Contrasts between groups were bvFTD versus controls, nfvPPA + svPPA versus controls, and bvFTD versus nfvPPA + svPPA.

2.4.6. Graph Theory Analysis. In a secondary analysis, the connectivity metrics such as path length, degree, cluster, and global efficiency were estimated by the Brain Connectivity Toolbox [44]. The correlation between ROIs was graphically represented by a collection of nodes and edges (nodes represent anatomical elements like brain regions and the edges represent the connectivity between those regions). In these graphs, the degree represents the number of edges connected to a node. A cluster is an extension of local interconnectivity. The path length is the number of edges that connect a node with another node, and global efficiency measures the ability of a network to transmit information at a global level. Network centrality (NC) measures the numbers of the shortest paths that go through a node and link the other node pairs across the network [45]. It indicates the importance of a node for efficient communication and integration across a network [45]. Several studies have already used NC (also called "betweenness centrality") to identify changed connections in disconnection syndromes [31, 46, 47]. Finally, an analysis of variance between groups with connectivity metrics was used to evaluate differences among groups.

3. Results

An analysis of variance (ANOVA) on MOCA, MMSE, ROFC, semantic and phonological and fluency, and proverb scores yielded significant variation among groups ($p < 0.05$ in all cases) (see Table 2). There were no differences among variants (bvFTD, svPPA, and nfvPPA) on FrSBe before or currently ($p > 0.05$ in all cases). A post hoc test with Sidak

Table 2: Clinical findings in patients and healthy controls.

	Controls	nfvPPA	svPPA	bvFTD	p value	Post hoc
MOCA	26.32 (2.57)	8.73 (7.26)	8.8 (6.58)	15.61 (7.53)	<0.001	1, 2, 3
MMSE	28.86 (1.27)	16.9 (6.92)	16.67 (7.66)	22.47 (6.5)	<0.001	1, 2, 3
IFS	22.3 (3.37)	6.20 (6.06)	10.8 (6.94)	10.7 (6.76)	<0.001	1, 2
Hayling	—	22.1 (11.09)	18 (13.52)	24.19 (12.66)	0.607	—
Errors WSCT	10.64 (8.14)	28 (7.77)	29.63 (8.88)	21.5 (10.18)	<0.001	1
ROFC	32.66 (5.05)	17.2 (11.86)	27.89 (9.35)	20.79 (12.26)	<0.001	1
FrSBe before	—	77.13 (18.63)	74.91 (29.39)	71.67 (18.79)	0.136	—
FrSBe currently	—	121.47 (32.22)	130.73 (42.66)	129.15 (31.65)	0.449	—
FrSBe apathy before	—	21.69 (4.92)	21 (10.28)	21.14 (7.57)	0.969	—
FrSBe apathy currently	—	46.46 (11.44)	46.55 (16.9)	44 (12.46)	0.76	—
FrSBe inhibition before	—	23.15 (5.68)	22.55 (9.17)	20.65 (5.36)	0.391	—
FrSBe inhibition currently	—	28.54 (7.66)	31.18 (10.05)	32.46 (11.46)	0.516	—
FrSBe DE before	—	32.08 (11.95)	31.27 (13.14)	29.38 (9.62)	0.702	—
FrSBe DE currently	—	50.92 (16.09)	52.55 (17.31)	53.95 (15.28)	0.833	—
Semantic fluency	16.68 (3.58)	5.91 (2.86)	4.20 (3.47)	10.45 (5.26)	<0.001	1, 2, 3
Phonological fluency	14.93 (5.05)	4.69 (3.31)	3.83 (2.79)	9.75 (5.47)	<0.001	1, 2, 3
Proverbs	8.54 (2.05)	2.53 (3.06)	1.4 (2.37)	4.09 (3.49)	<0.001	1

Mean and standard deviation were reported. p value from ANOVA. FrSBe DE: FrSBe dysfunction executive; nfvPPA: primary nonfluent aphasia; svPPA: semantic dementia; BV: behavioral variant; post hoc with Holm-Sidak (<0.05); 1: controls ≠ (bvFTD or svPPA or nfvPPA); 2: bvFTD ≠ nfvPPA; 3: bvFTD ≠ svPPA; 4: svPPA ≠ nfvPPA.

correction showed higher scores in bvFTD than nfvPPA and svPPA on MOCA, semantic, and phonological fluency ($p < 0.05$ in all cases). Besides, the scores on MMSE and IFS were significantly higher in bvFTD with respect to nfvPPA ($p < 0.05$ in all cases). There were no differences among variants on Hayling, FrSBe, errors in WSCT, ROFC, and proverbs.

The results with network-based statistics showed significant differences between the control group and bvFTD, svPPA, nfvPPA, and svPPA + nfvPPA groups. The first comparison between control and bvFTD (Figure 1(a)) showed significant differences in networks with nodes mainly in the left hemisphere in the frontal and temporal lobes (Table S1). Almost 15 nodes located in the left hemisphere in different regions (anterior and posterior) had a higher disconnection than controls. Moreover, in the right hemisphere, the nodes disconnected were anterior cingulate cortex, inferior temporal gyrus, superior occipital gyrus, middle temporal gyrus, putamen, amygdala, inferior frontal triangular gyrus, and fusiform gyrus.

With respect to results with linguistic variants, there were more differences in nfvPPA than svPPA. The comparison between control and svPPA groups showed only connectivity differences between the right operculum and the left putamen (Figure 1(b) and Table S2). The analysis between control and nfvPPA showed differences mainly in the left hemisphere (Figure 1(c) and Table S3). The nodes with disconnection were the inferior temporal gyrus, fusiform gyrus, amygdala, operculum, temporo-parieto-occipital junction, caudate nuclei, inferior parietal gyrus, putamen, and insula. Also, in the right hemisphere, there were nodes disconnected such as the anterior cingulate and the putamen.

The analysis between FTD variants showed differences between bvFTD and nfvPPA into the left hemisphere to the connection between operculum with parietal and cuneus left with occipital superior gyrus (Figure 2(a)). There were no differences between controls and svPPA patients. The comparison between bvFTD and all patients with linguistic alterations showed a disconnection of the left superior occipital, left middle occipital, and right middle temporal gyri (Figure 2(b)). Finally, the comparison between controls and all linguistic variants (Figure 2(c)) showed a major disconnection in Heschl's left gyrus, left amygdala, left fusiform, left inferior temporal gyrus, right middle temporal gyrus, and left temporal pole (Table S4).

An analysis of variance based on topological metrics showed differences in global efficiency ($F(3, 65) = 11.48$, $p < 0.001$) and path length ($F(3, 65) = 3.27$, $p = 0.026$) (Figure 3). In the post hoc test, the global efficiency in bvFTD was significantly higher than nfvPPA; in addition, this measure was higher in controls than nfvPPA patients ($p < 0.05$ in both cases). Finally, we computed Pearson correlations, with correction for multiple correlational analysis [48], between topological metrics and clinical scores in all patients (Figure 4). We found significant associations of topological measures with FrSBe scores related to current behavior. The path length had significant and negative correlations with total FrSBe ($r = -0.27$), apathy ($r = -0.3$), and inhibition ($r = -0.34$). The clustering had significant and positive correlations with total FrSBe ($r = 0.33$), apathy ($r = 0.3$), and inhibition ($r = 0.41$). Also, the degree had similar correlations with total FrSBe ($r = 0.32$), apathy ($r = 0.31$), and inhibition ($r = 0.4$). Finally, the global efficiency had positive correlations with total FrSBe ($r = 0.33$), apathy ($r = 0.31$), and inhibition ($r = 0.42$).

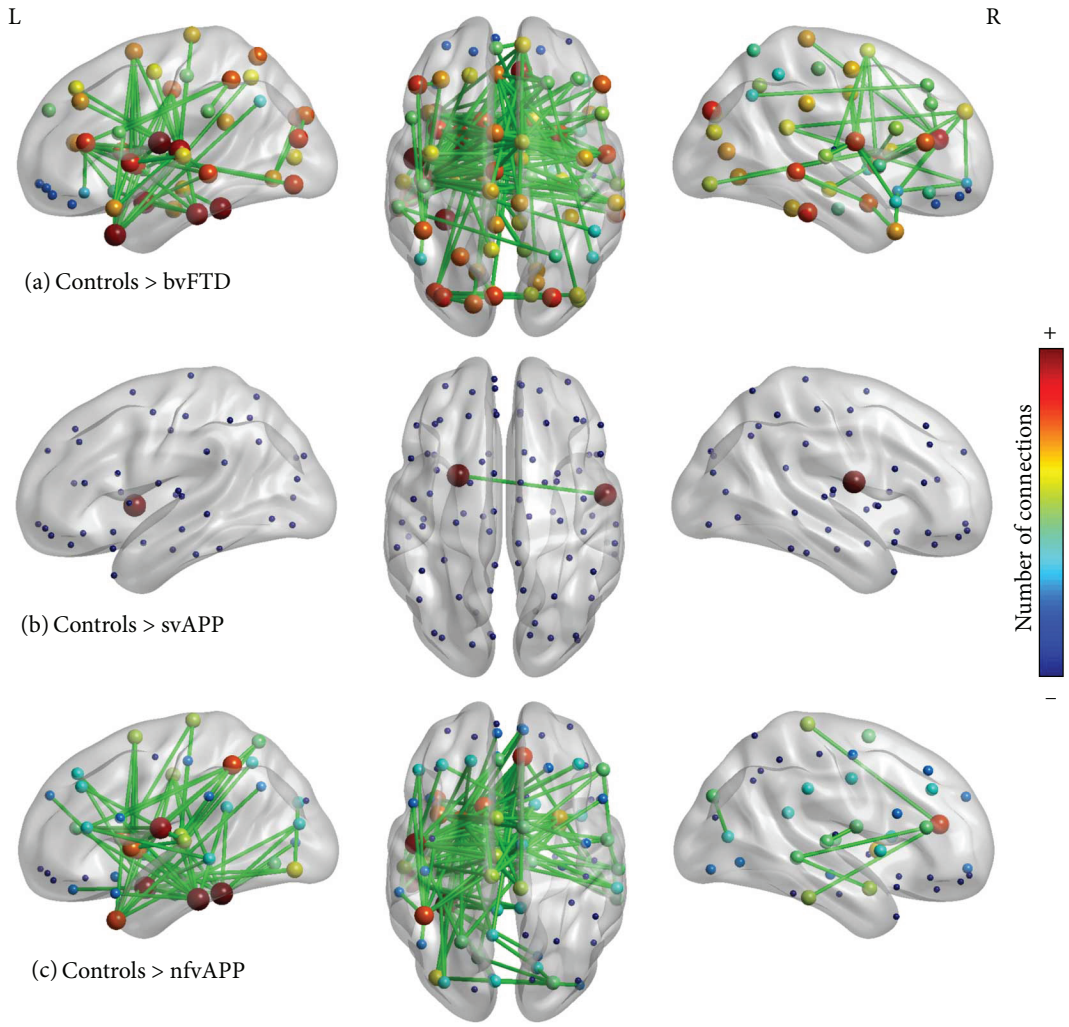

Figure 1: NBS results between controls and FTD variants. The edges are the result of *F*-test between groups. To nodes, the color corresponds to disconnection number.

3.1. Discussion. The study on connectivity based on resting-state functional MRI has the potential to identify differences among variants of FTD. The present study offers some contributions to understand the alterations in connectivity based on changes in networks and topological metrics. The approach based on network analysis showed more accuracy to detect differences than topological metrics of the whole brain with weighted matrices.

In this study, the bvFTD has a bilateral disconnection with a major tendency to nodes into the left hemisphere. Asymmetric results were reported in other studies, for example, a decrease in connectivity in the left frontoparietal network in bvFTD has been reported in comparison with controls [22]. Also, a decrease in connectivity between the right superior temporal gyrus and cuneal cortex was showed in bvFTD with respect to Alzheimer's disease [49]. Our results showed an extended bilateral disconnection between the frontal and limbic areas and the basal ganglia. A decrease between the frontal and limbic hubs was reported in another study [21]; this alteration could be associated with the disruption between affective and self-referential brain systems [21]. Also, the present results show alterations in the cingulum and insula network bilaterally. The cingulum has been associated with motivation and behavior control [50]. The anterior insula is a network hub to human emotional awareness and behavioral guidance networks [51]. Finally, in this report, the analysis supports alteration in posterior nodes in bvFTD, namely, there were disconnections in the middle occipital, inferior, and middle temporal gyri. Alterations in posterior regions in FTD are not frequent but have been reported previously [52].

The results support a connectivity decrease in linguistic variants in comparison with controls. The number of disconnected nodes was higher in nfvPPA than svPPA. In svPPA, the disconnection in the network between putamen and operculum has not been reported previously. However, one study reported atrophy in the putamen in svPPA [53], and the operculum has been associated with phonological processes that support reading [54]. In nfvPPA, a disconnection was found in networks involving hubs such as prerolandic

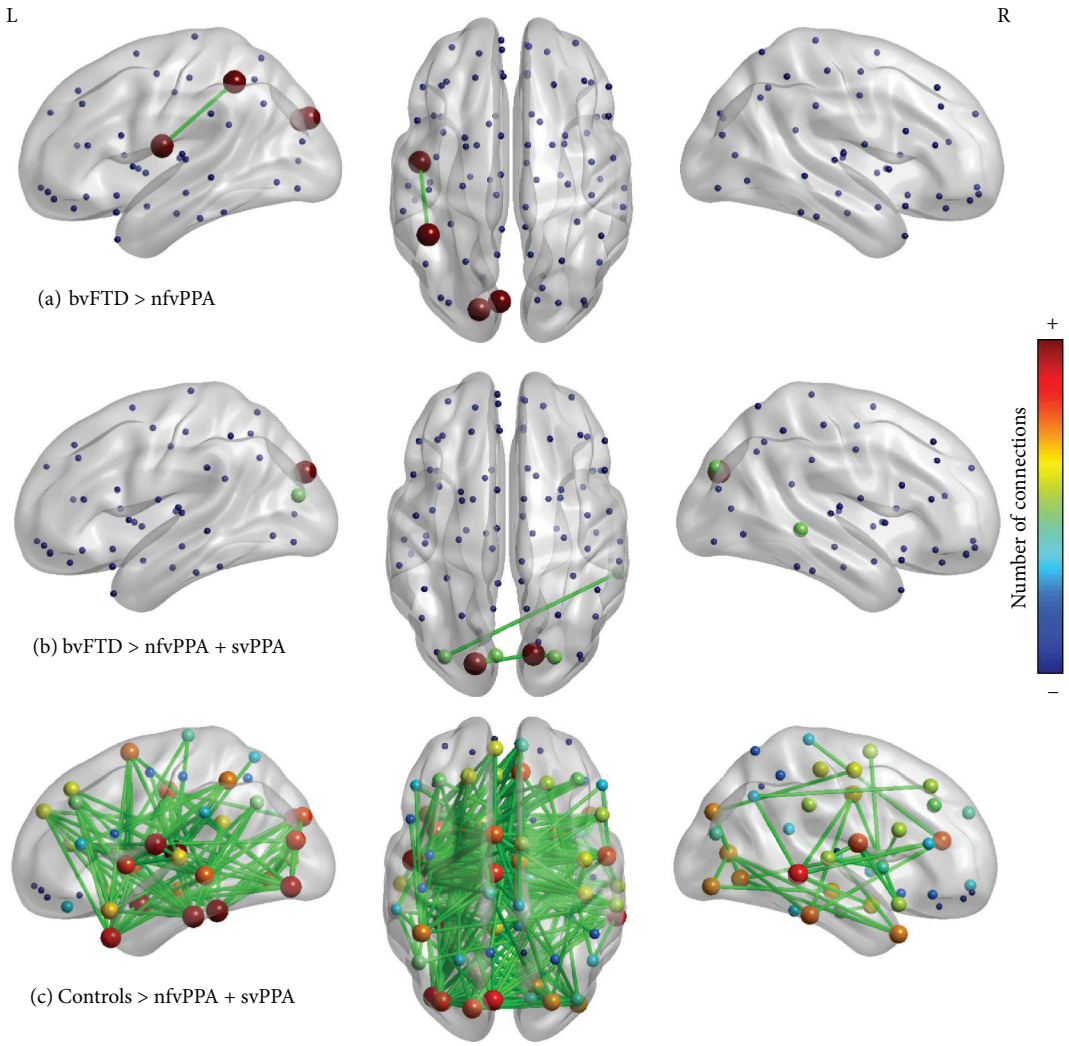

Figure 2: NBS results between FTD variants and controls.

areas and basal ganglia, regions related with speech production and syntactic process [55–57]. The topological metrics, global efficiency, and path length were useful to discriminate linguistic variants since global efficiency allows a differentiation between nfvPPA and bvFTD while path length differentiates svPPA and controls. Similar results were reported in a recent study; the path length in svPPA was higher in comparison with controls and similar to Alzheimer's disease patients, and it was correlated with the disease progression [58].

There was similarity among FTD variants in both clinical and neuroimaging analyses. Also, in this study, there were no differences between the linguistic variants (svPPA and nfvPPA). Nevertheless, nfvPPA was the variant with more differences than svPPA, both as the network analysis as topological metrics with respect to bvFTD. nfvPPA showed a worse measure in global efficiency and tends to have more degree and clustering than svPPA and bvFTD.

The behavioral changes measured by FrSBe did not show differences among variants. This result could indicate the presence of behavioral disturbances between linguistic variants and can support the presence of frontal alterations in nfvPPA and bvFTD. All patients had important behavioral changes in FrSBe scores related to premorbid and current behavior. However, only the current scores in apathy and inhibition (FrSBE subscales) were associated with topological measures. Therefore, global changes in functional connectivity could be associated with the presence of disturbances in behavior at least in these variants. The behavioral disturbances have been more reported in svPPA than nfvPPA [59–61]. Only one study reported behavioral changes in nfvPPA, and these behavioral changes were similar to Alzheimer's disease [62].

The limitations of this study are related to sample size, use of topological metrics from weighted matrices, and AAL atlas to create the seeds. The reduced sample size of nfvPPA was due to requirement of a second evaluation by an expert in order to exclude lvPPA. According to several reports, lvPPA is associated with the Alzheimer's variant [63–65]. With respect to topological metrics, these correspond to general

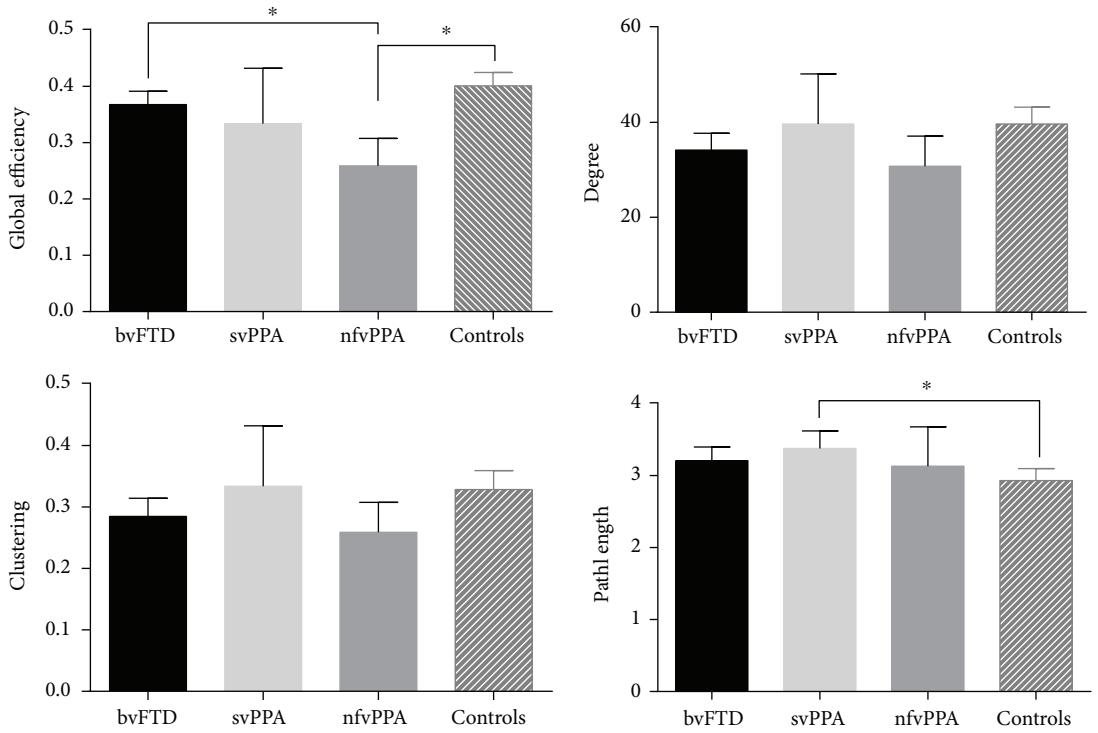

Figure 3: Mean bar of metrics from graph theory analysis by each group (global efficiency, degree, clustering, and path length). The bar represents the mean and error bars are a 95% confidence interval. *Significantly different with $p < 0.05$.

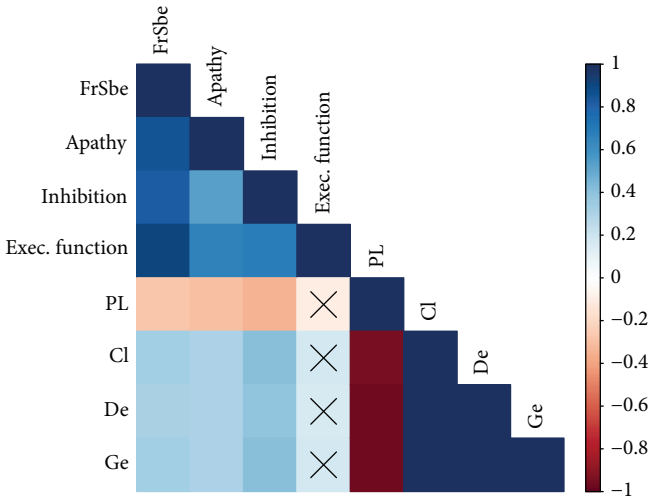

Figure 4: Matrix correlation among topological measures and clinical scores. The bar color indicates the Pearson value coefficient. Symbol X indicates p values > 0.05 with BH correction; FrSBE: total FrSBE currently; apathy: FrSBE apathy currently; inhibition: FrSBE inhibition currently; Exec. function: FrSBE dysexecutive functions currently; PL: path length; Cl: clustering; De: degree; Ge: global efficiency.

measures from graph theory [44]. Both acquisition and image preprocessing could affect the analysis and measures. However, there is no gold standard method and applied protocols similar to those used in previous studies [66]. Finally, some studies show a scale effect in graph analysis related to the number of nodes [67–69], but we used AAL standard atlas to make our results comparable with those from other studies.

In conclusion, our result supports the use of global metrics from graph theory and network analysis to explore differences among some FTD variants. The nfvPPA showed more alterations in networks and global metrics than other variants, and also, alterations in bvFTD involve hubs in frontal lobes, limbic lobes, and basal ganglia. However, there are no differences between svPPA and nfvPPA in either NBS or topological measures. This preliminary study among variants

in FTD allows us to identify several hubs and networks, and these can be used in the future to build biomarkers based on fMRI. Finally, the functional connectivity was associated with disturbances in behavior. New studies should explore the association among different biomarkers from multimodal neuroimaging, such as structural and functional connectivity, in order to obtain increased accuracy about networks with changes or alterations due to early onset dementia.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

Supplementary 1. Table S1: networks with changes in bvFTD in comparison with controls.

Supplementary 2. Table S2: networks with changes in svPPA in comparison with controls.

Supplementary 3. Table S3: networks with changes in nfvPPA in comparison with controls.

Supplementary 4. Table S4: networks with changes in nfvPPA + svPPA in comparison with controls.

References

[1] A. Horn, D. Ostwald, M. Reisert, and F. Blankenburg, "The structural–functional connectome and the default mode network of the human brain," *NeuroImage*, vol. 102, Part 1, pp. 142–151, 2014.

[2] D. Neary, J. S. Snowden, L. Gustafson et al., "Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria," *Neurology*, vol. 51, no. 6, pp. 1546–1554, 1998.

[3] K. Rascovsky, J. R. Hodges, C. M. Kipps et al., "Diagnostic criteria for the behavioral variant of frontotemporal dementia (bvFTD): current limitations and future directions," *Alzheimer Disease & Associated Disorders*, vol. 21, no. 4, pp. S14–S18, 2007.

[4] S. Gazzina, M. A. Manes, A. Padovani, and B. Borroni, "Clinical and biological phenotypes of frontotemporal dementia: perspectives for disease modifying therapies," *European Journal of Pharmacology*, vol. 817, pp. 76–85, 2017.

[5] J. S. Snowden, D. Bathgate, A. Varma, A. Blackshaw, Z. C. Gibbons, and D. Neary, "Distinct behavioural profiles in frontotemporal dementia and semantic dementia," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 70, no. 3, pp. 323–332, 2001.

[6] M. Boccardi, M. P. Laakso, L. Bresciani et al., "The MRI pattern of frontal and temporal brain atrophy in fronto-temporal dementia," *Neurobiology of Aging*, vol. 24, no. 1, pp. 95–103, 2003.

[7] C. U. Onyike and J. Diehl-Schmid, "The epidemiology of frontotemporal dementia," *International Review of Psychiatry*, vol. 25, no. 2, pp. 130–137, 2013.

[8] D. B. Hogan, N. Jetté, K. M. Fiest et al., "The prevalence and incidence of frontotemporal dementia: a systematic review," *The Canadian Journal of Neurological Sciences*, vol. 43, Supplement 1, pp. S96–S109, 2016.

[9] H. Santamaría García, P. Reyes, J. Santacruz, S. Baez, A. Ibañez, and D. Matallana, "Clinical, neuropsychological and neural correlates underlying the first symptoms in behavioral variant of fronto temporal dementia (bvFTD)," *Journal of the Neurological Sciences*, vol. 357, Supplement 1, pp. e12–e13, 2015.

[10] M. L. Gorno-Tempini and S. M. Brambati, "The logopenic/phonologic variant of primary progressive aphasia," *AAN Enterprise*, vol. 2008, pp. 1227–1234, 2016.

[11] F. M. Elahi and B. L. Miller, "A clinicopathological approach to the diagnosis of dementia," *Nature Reviews Neurology*, vol. 13, no. 8, pp. 457–476, 2017.

[12] N. Sheikh-Bahaei, S. A. Sajjadi, and A. L. Pierce, "Current role for biomarkers in clinical diagnosis of Alzheimer disease and frontotemporal dementia," *Current Treatment Options in Neurology*, vol. 19, no. 12, p. 46, 2017.

[13] J. D. Rohrer and H. J. Rosen, "Neuroimaging in frontotemporal dementia," *International Review of Psychiatry*, vol. 25, no. 2, pp. 221–229, 2013.

[14] H. Botha, J. R. Duffy, J. L. Whitwell et al., "Classification and clinicoradiologic features of primary progressive aphasia (PPA) and apraxia of speech," *Cortex*, vol. 69, pp. 220–236, 2015.

[15] C. J. Mummery, K. Patterson, C. J. Price, J. Ashburner, R. S. J. Frackowiak, and J. R. Hodges, "A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory," *Annals of Neurology*, vol. 47, no. 1, pp. 36–45, 2000.

[16] K. A. Josephs, J. R. Hodges, J. S. Snowden et al., "Neuropathological background of phenotypical variability in frontotemporal dementia," *Acta Neuropathologica*, vol. 122, no. 2, pp. 137–153, 2011.

[17] M. Catani, M. M. Mesulam, E. Jakobsen et al., "A novel frontal pathway underlies verbal fluency in primary progressive aphasia," *Brain*, vol. 136, no. 8, pp. 2619–2628, 2013.

[18] M. L. Gorno-Tempini, A. E. Hillis, S. Weintraub et al., "Classification of primary progressive aphasia and its variants," *Neurology*, vol. 76, no. 11, pp. 1006–1014, 2011.

[19] L. Sedeño, O. Piguet, S. Abrevaya et al., "Tackling variability: a multicenter study to provide a gold-standard network approach for frontotemporal dementia," *Human Brain Mapping*, vol. 38, no. 8, pp. 3804–3822, 2017.

[20] E. Gordon, J. D. Rohrer, and N. C. Fox, "Advances in neuroimaging in frontotemporal dementia," *Journal of Neurochemistry*, vol. 138, pp. 193–210, 2016.

[21] N. A. S. Farb, C. L. Grady, S. Strother et al., "Abnormal network connectivity in frontotemporal dementia: evidence for prefrontal isolation," *Cortex*, vol. 49, no. 7, pp. 1856–1873, 2013.

[22] A. Hafkemeijer, C. Möller, E. G. P. Dopper et al., "A longitudinal study on resting state functional connectivity in behavioral variant frontotemporal dementia and Alzheimer's disease,"

Journal of Alzheimer's Disease, vol. 55, no. 2, pp. 521–537, 2017.

[23] R. Landin-Romero, R. Tan, J. R. Hodges, and F. Kumfor, "An update on semantic dementia: genetics, imaging, and pathology," *Alzheimer's Research & Therapy*, vol. 8, no. 1, p. 52, 2016.

[24] Q. Yang, Q. H. Guo, and Y. C. Bi, "The brain connectivity basis of semantic dementia: a selective review," *CNS Neuroscience & Therapeutics*, vol. 21, no. 10, pp. 784–792, 2015.

[25] C. C. Guo, M. L. Gorno-Tempini, B. Gesierich et al., "Anterior temporal lobe degeneration produces widespread network-driven dysfunction," *Brain*, vol. 136, no. 10, pp. 2979–2991, 2013.

[26] J. E. Peelle, A. Cooke, P. Moore, L. Vesely, and M. Grossman, "Syntactic and thematic components of sentence processing in progressive nonfluent aphasia and nonaphasic frontotemporal dementia," *Journal of Neurolinguistics*, vol. 20, no. 6, pp. 482–494, 2007.

[27] A. Cooke, C. DeVita, J. Gee et al., "Neural basis for sentence comprehension deficits in frontotemporal dementia," *Brain and Language*, vol. 85, no. 2, pp. 211–221, 2003.

[28] K. G. Ranasinghe, L. B. Hinkley, A. J. Beagle et al., "Distinct spatiotemporal patterns of neuronal functional connectivity in primary progressive aphasia variants," *Brain*, vol. 140, no. 10, pp. 2737–2751, 2017.

[29] M. L. Mandelli, E. Caverzasi, R. J. Binney et al., "Frontal white matter tracts sustaining speech production in primary progressive aphasia," *The Journal of Neuroscience*, vol. 34, no. 29, pp. 9754–9767, 2014.

[30] M. L. Mandelli, E. Vilaplana, J. A. Brown et al., "Healthy brain connectivity predicts atrophy progression in non-fluent variant of primary progressive aphasia," *Brain*, vol. 139, no. 10, pp. 2778–2791, 2016.

[31] M. Filippi, F. Agosta, E. Scola et al., "Functional network connectivity in the behavioral variant of frontotemporal dementia," *Cortex*, vol. 49, no. 9, pp. 2389–2401, 2013.

[32] L. Gil, C. Ruiz De Sánchez, F. Gil, S. J. Romero, and F. Pretelt Burgos, "Validation of the Montreal Cognitive Assessment (MoCA) in Spanish as a screening tool for mild cognitive impairment and mild dementia in patients over 65 years old in Bogotá, Colombia," *International Journal of Geriatric Psychiatry*, vol. 30, no. 6, pp. 655–662, 2015.

[33] Z. S. Nasreddine, N. A. Phillips, V. Bédirian et al., "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," *Journal of the American Geriatrics Society*, vol. 53, no. 4, pp. 695–699, 2005.

[34] T. Torralva, M. Roca, E. Gleichgerrcht, P. López, and F. Manes, "INECO frontal screening (IFS): a brief, sensitive, and specific tool to assess executive functions in dementia," *Journal of the International Neuropsychological Society*, vol. 15, no. 5, p. 777, 2009.

[35] P. W. Burgess and T. Shallice, "Response suppression, initiation and strategy use following frontal lobe lesions," *Neuropsychologia*, vol. 34, no. 4, pp. 263–272, 1996.

[36] H. E. Nelson, "A modified card sorting test sensitive to frontal lobe defects," *Cortex*, vol. 12, no. 4, pp. 313–324, 1976.

[37] P.-A. Osterrieth, "Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire [Test of copying a complex figure; contribution to the study of perception and memory]," *Archives de Psychologie*, vol. 30, pp. 206–356, 1944.

[38] J. P. Niemeier, P. B. Perrin, M. G. Holcomb, K. S. Nersessova, and C. D. Rolston, "Factor structure, reliability, and validity of the frontal systems behavior scale (FrSBe) in an acute traumatic brain injury population," *Rehabilitation Psychology*, vol. 58, no. 1, pp. 51–63, 2013.

[39] M. M. Benito-Cuadrado, S. Esteba-Castillo, P. Böhm, J. Cejudo-Bolívar, and J. Peña-Casanova, "Semantic verbal fluency of animals: a normative and predictive study in a Spanish population," *Journal of Clinical and Experimental Neuropsychology*, vol. 24, no. 8, pp. 1117–1122, 2002.

[40] S. J. Báez, L. Mendoza, P. Reyes, D. Matallana, and P. Montañés, "Interpretación de refranes y enfermedad de Alzheimer," *Revista de Neurologia*, vol. 49, no. 11, pp. 566–572, 2009.

[41] C. G. Yan, X.-D. Wang, X. N. Zuo, and Y. F. Zang, "DPABI: data processing & analysis for (resting-state) brain imaging," *Neuroinformatics*, vol. 14, no. 3, pp. 339–351, 2016.

[42] N. Tzourio-Mazoyer, B. Landeau, D. Papathanassiou et al., "Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain," *NeuroImage*, vol. 15, no. 1, pp. 273–289, 2002.

[43] A. Zalesky, A. Fornito, and E. T. Bullmore, "Network-based statistic: identifying differences in brain networks," *NeuroImage*, vol. 53, no. 4, pp. 1197–1207, 2010.

[44] M. Rubinov and O. Sporns, "Complex network measures of brain connectivity: uses and interpretations," *NeuroImage*, vol. 52, no. 3, pp. 1059–1069, 2010.

[45] L. C. Freeman, "A set of measures of centrality based on betweenness," *Sociometry*, vol. 40, no. 1, p. 35, 1977.

[46] R. L. Buckner, J. Sepulcre, T. Talukdar et al., "Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease," *The Journal of Neuroscience*, vol. 29, no. 6, pp. 1860–1873, 2009.

[47] C. J. Goch, B. Stieltjes, R. Henze et al., "Quantification of changes in language-related brain areas in autism spectrum disorders using large-scale network analysis," *International Journal of Computer Assisted Radiology and Surgery*, vol. 9, no. 3, pp. 357–365, 2014.

[48] Y. Benjamini and Y. Hochberg, "Controlling the false discovery rate: a practical and powerful approach to multiple testing," *Journal of the Royal Statistical Society Series B (Methodological)*, vol. 57, pp. 289–300, 1995.

[49] A. Hafkemeijer, C. Möller, E. G. P. Dopper et al., "Resting state functional connectivity differences between behavioral variant frontotemporal dementia and Alzheimer's disease," *Frontiers in Human Neuroscience*, vol. 9, p. 474, 2015.

[50] M. Hoffmann, "The human frontal lobes and frontal network systems: an evolutionary, clinical, and treatment perspective," *ISRN Neurology*, vol. 2013, Article ID 892459, 34 pages, 2013.

[51] W. W. Seeley, "Anterior insula degeneration in frontotemporal dementia," *Brain Structure and Function*, vol. 214, no. 5-6, pp. 465–475, 2010.

[52] J. D. Rohrer, J. D. Warren, M. Modat et al., "Patterns of cortical thinning in the language variants of frontotemporal lobar degeneration," *Neurology*, vol. 72, no. 18, pp. 1562–1569, 2009.

[53] R. R. Davies, G. M. Halliday, J. H. Xuereb, J. J. Kril, and J. R. Hodges, "The neural basis of semantic memory: evidence from semantic dementia," *Neurobiology of Aging*, vol. 30, no. 12, pp. 2043–2052, 2009.

[54] J. A. Fiez, D. Tranel, D. Seager-Frerichs, and H. Damasio, "Specific reading and phonological processing deficits are associated with damage to the left frontal operculum," *Cortex*, vol. 42, no. 4, pp. 624–643, 2006.

[55] K. A. Josephs, J. R. Duffy, T. R. Fossett et al., "Fluorodeoxyglucose F18 positron emission tomography in progressive apraxia of speech and primary progressive aphasia variants," *Archives of Neurology*, vol. 67, no. 5, pp. 596–605, 2010.

[56] J. R. Booth, L. Wood, D. Lu, J. C. Houk, and T. Bitan, "The role of the basal ganglia and cerebellum in language processing," *Brain Research*, vol. 1133, no. 1, pp. 136–144, 2007.

[57] S. A. Kotz, S. Frisch, D. Y. von Cramon, and A. D. Friederici, "Syntactic language processing: ERP lesion data on the role of the basal ganglia," *Journal of the International Neuropsychological Society*, vol. 9, no. 7, pp. 1053–1060, 2003.

[58] J. Andreotti, T. Dierks, L. O. Wahlund, and M. Grieder, "Diverging progression of network disruption and atrophy in Alzheimer's disease and semantic dementia," *Journal of Alzheimer's Disease*, vol. 55, no. 3, pp. 981–993, 2017.

[59] Y.-H. Jeon, J. Sansoni, L.-F. Low et al., "Recommended measures for the assessment of behavioral disturbances associated with dementia," *The American Journal of Geriatric Psychiatry*, vol. 19, no. 5, pp. 403–415, 2011.

[60] J. Diehl-Schmid, C. Pohl, R. Perneczky, H. Förstl, and A. Kurz, "Behavioral disturbances in the course of frontotemporal dementia," *Dementia and Geriatric Cognitive Disorders*, vol. 22, no. 4, pp. 352–357, 2006.

[61] J. J. Hsiao, N. Kaiser, S. S. Fong, and M. F. Mendez, "Suicidal behavior and loss of the future self in semantic dementia," *Cognitive and Behavioral Neurology*, vol. 26, no. 2, pp. 85–92, 2013.

[62] H. J. Rosen, S. C. Allison, J. M. Ogar et al., "Behavioral features in semantic dementia vs other forms of progressive aphasias," *Neurology*, vol. 67, no. 10, pp. 1752–1756, 2006.

[63] S. Ahmed, C. A. de Jager, A.-M. F. Haigh, and P. Garrard, "Logopenic aphasia in Alzheimer's disease: clinical variant or clinical feature?," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 83, no. 11, pp. 1056–1062, 2012.

[64] C. E. Leyton, O. Piguet, S. Savage, J. Burrell, and J. R. Hodges, "The neural basis of logopenic progressive aphasia," *Journal of Alzheimer's Disease*, vol. 32, no. 4, pp. 1051–1059, 2012.

[65] M. F. Bonner, S. Ash, and M. Grossman, "The new classification of primary progressive aphasia into semantic, logopenic, or nonfluent/agrammatic variants," *Current Neurology and Neuroscience Reports*, vol. 10, no. 6, pp. 484–490, 2010.

[66] M. Dottori, L. Sedenõ, M. Martorell Caro et al., "Towards affordable biomarkers of frontotemporal dementia: a classification study via network's information sharing," *Scientific Reports*, vol. 7, no. 1, p. 3822, 2017.

[67] A. Zalesky, A. Fornito, I. H. Harding et al., "Whole-brain anatomical networks: does the choice of nodes matter?," *NeuroImage*, vol. 50, no. 3, pp. 970–983, 2010.

[68] A. Fornito, A. Zalesky, and E. T. Bullmore, "Network scaling effects in graph analytic studies of human resting-state fMRI data," *Frontiers in Systems Neuroscience*, vol. 4, p. 22, 2010.

[69] B. C. M. van Wijk, C. J. Stam, and A. Daffertshofer, "Comparing brain networks of different size and connectivity density using graph theory," *PLoS One*, vol. 5, no. 10, article e13701, 2010.

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Research Article

The Effects of Transcranial Direct Current Stimulation on the Cognitive Functions in Older Adults with Mild Cognitive Impairment: A Pilot Study

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Objective. The aim of this pilot study was to investigate whether the use of anodal transcranial direct current stimulation (tDCS) on the left dorsolateral prefrontal cortex could boost the effects of a cognitive stimulation (CS) programme using a tablet on five older adults with mild cognitive impairment (MCI). *Method.* A single-subject study of A-B-C-A design was used. After the baseline with the administration of CS (phase A), a sham treatment with CS was applied (B). Following the withdrawal of sham treatment, tDCS was introduced in combination with CS (C). Finally, phase A was replicated a second time. *Results.* tDCS had a significant effect on processing speed, selective attention, and planning ability tasks in terms of performance and completion time. *Conclusion.* tDCS appears to have a positive impact on some cognitive components in CS in persons with MCI. Further study on its long-term effects and generalization of power to daily activities is warranted.

1. Introduction

Mild cognitive impairment (MCI) is a syndrome of cognitive decline below the typically expected age norm in an individual. It is commonly referred to as an intermediate phase between the expected cognitive decline of normal aging and the pathological cognitive decline linked to dementia and usually does not interfere with daily activities [1]. There is a difference between MCI and a formal diagnosis of dementia: the latter represents a more severe cognitive decline and has a substantial negative impact on daily functioning [2]. In some cases, MCI will revert to normal cognition or remain stable. Only an insignificant proportion of people presenting with known MCI, 12–15% per year, will gradually worsen and develop dementia, compared to 1-2% of the general population; approximately, 40–65% of patients with MCI will eventually progress to Alzheimer's disease (AD) [1].

Regarding possible interventions to tackle MCI, there is a lack of evidence for pharmacological interventions that can prevent cognitive decline or conversion to dementia. To date, drugs have proved to have no positive impact in MCI trials [3].

As a form of nonpharmacological intervention, cognitive rehabilitation is defined as "the therapeutic process of increasing or improving an individual's capacity to process and use incoming information so as to allow increased functioning in everyday life. This includes methods to train and restore cognitive function and compensatory techniques" [4].

One type of cognitive rehabilitation is cognitive stimulation (CS) which has been used as a potential intervention to slow down the deterioration of cognitive functions in people presenting with known MCI. According to the largest randomized controlled trial of cognitive intervention carried out with older adults to date, the experimental treatment approaches used in this study support the improvement of targeted cognitive areas in different groups in comparison to the control group, which did not receive any kind of intervention [5]. Contrary to conventional cognitive tasks that are performed with paper-and-pencil with a lack of simultaneous feedback, computerized cognitive stimulation

is designed to be more enjoyable and engaging based on human-computer interaction [6, 7]. These cognitive stimulation strategies have also been shown to improve performance after repetition of computerized CT tasks in older adults presenting with known MCI [8].

A systematic review found evidence of memory and executive function enhancement while analyzing the effects of nonpharmacological interventions on cognitive functions in older people presenting with known MCI [9]. However, the appropriate protocol and optimal frequency for inducing benefits in the cognitive functioning of this population remain unknown.

Transcranial direct current stimulation (tDCS) is another type of nonpharmacological intervention that uses direct electrical currents to stimulate specific parts of the brain. It involves delivering a noninvasive weak direct current (1-2 mA) through at least two electrodes, at least one of which is placed on the scalp for a period of a few seconds to 20–30 minutes, which modulates neuronal activity. There are two types of stimulation: anodal stimulation acts to excite neuronal activity and cathodal stimulation has hyperpolarizing effects, inhibiting neuronal activity [10, 11]. As soon as tDCS is administered, the current travels in an anode-cathode circuit which is likely to cause neurons to fire in stimulated areas [10].

Priming is the change in repetitive behavior due to implicit learning based on previous stimuli [12], and it has recently been used for inducing neuroplasticity and enhancing the effects of conventional rehabilitation as combined approaches [13]. The excitability modulation induced by tDCS is considered a potential intervention to modulate the learning processes [14]. tDCS boosts subthreshold neuronal action potentials beyond their unaugmented state, thus, may achieve stronger firing patterns than would occur in the absence of tDCS. Although, repeated practice with cognitive stimuli in CS may elicit unintentional learning, mechanisms that circumvent cognitive impairments, targeting a neural circuit with tDCS whereas it is simultaneously engaged by a cognitive stimulation task, may produce better therapeutic effects than stimulating the same cortical area in the absence of cognitive stimuli [15, 16]. tDCS may augment the strength of transmission across synaptic circuits in pathways that are stimulated by cognitive practice, and thus it may also strengthen the circuits that are formed through unintentional, practice-related learning and maximize the possibility of enduring behavior change through such implicit learning. Given that CS and tDCS can enhance plastic changes, the combination of both techniques could cause a better synergistic positive effect on behavior [15, 17]. Indeed, it has been shown that anodal stimulation of the left dorsolateral prefrontal cortex (DLPFC) increases the performance of a sequential-letter working memory task in healthy young adults [18]. Recent research also indicates that healthy older adults can benefit from tDCS, enhancing retention skills of object-location learning a week after completion of the object-location task compared to participants who took part in a tDCS sham condition [19]. There is growing evidence that tDCS coupled with CS improves cognitive performance. After ten sessions of a working memory CS in combination with tDCS, healthy adults experience an enhanced effect and perform CS tasks more accurately than those who received sham tDCS [20].

The impact of tDCS has also been explored for AD, frontotemporal dementia, and mild vascular dementia. Positive effects were found in visual recognition memory tasks in persons with AD when applying anodal tDCS to the left temporal cortex [21]. Results after five consecutive sessions over five days in which anodal tDCS was applied over both hemispheres of the temporal cortex and an extracephalic cathodal tDCS (for a 30-minute period using 2 mA) showed significant improvement in the performance of a visual recognition memory test [22]. In a more recent study that involved participants presenting with mild vascular dementia, four consecutive day sessions of anodal tDCS (for a 20-minute period using 2 mA) on the left DLPFC generated positive additional effects on visual short-term memory, verbal working memory, and executive control [23].

The beneficial effects of tDCS on cognition in people presenting with known MCI have been demonstrated [24]; however, the literature on using tDCS on people presenting with known MCI is still very limited. The frequency and targeted areas are not the only significant issues that remain unknown. To optimize the positive and therapeutic benefits of noninvasive brain stimulation (NIBS), it is also worth investigating the uncertainty of combining tDCS with conventional behavioral treatments such as a CS that might also yield more information and understanding about the impact of tDCS effects for people at risk of MCI.

Based on the above background information, we considered the use of anodal tDCS on the left DLPFC (30 minutes 2 mA) with an extracephalic return electrode to be a promising and safe intervention approach to optimize the impact of CS on tablet PCs for older adults at risk of MCI. The current study aimed to compare the impact of anodal and sham tDCS applied to the left DLPFC on the cognitive performance of people at risk of MCI engaging in CS interventions on tablet PCs. We hypothesized that there would be a significant improvement in cognitive task performance after the use of tDCS, which would subsequently generalize to other cognitive domains—short-term memory, planning ability, working memory, attention, and processing speed skills. We also aim to determine the optimal frequency of tDCS application with the same dosage to improve the cognitive skills of older adults with MCI.

2. Materials and Methods

2.1. Participants. Five older adults with MCI were recruited by convenience sampling from community center groups in Hong Kong. The inclusion criteria followed the modified Petersen's criteria [25] (given by the MCI Working Group of the European Consortium on Alzheimer's Disease, Brescia Meeting, Italy, June 2005). Participants had to (a) be aged between 60 and 85; (b) obtain a score between 19 and 26 on the Montreal Cognitive Assessment Test (MoCA) [26]; (c) achieve a score of 0.5 or below on the clinical dementia rating (CDR) [27]; (d) self-report cognitive decline; (e) be

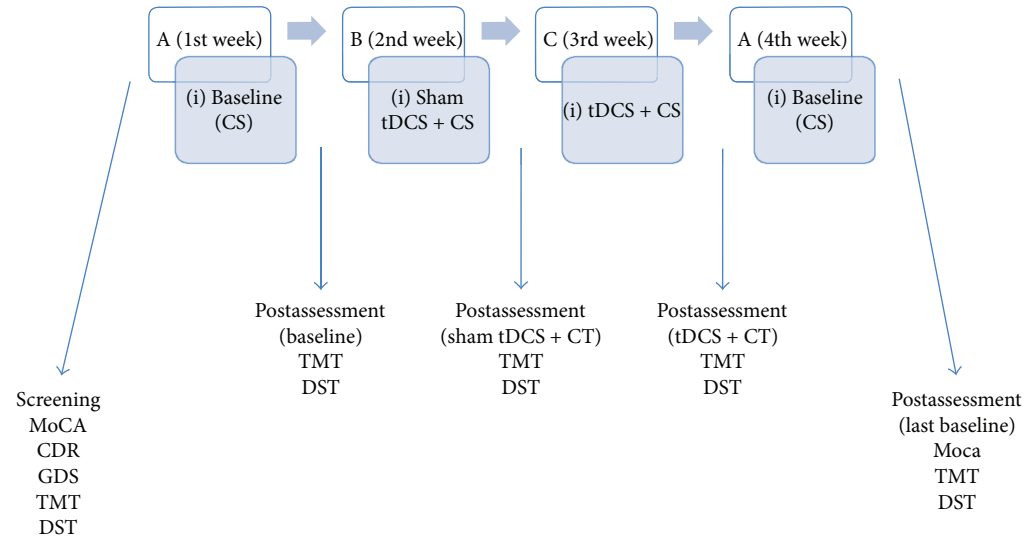

Figure 1: Intervention sequence. A-B-C-A design; MoCA: Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; GDS: Geriatric Depression Scale; TMT: Trail Making Test; DST: digit span test. Phases. CS: cognitive stimulation; tDCS: transcranial direct current stimulation.

independent in daily living activities; and (f) have completed three or more years of primary education.

Regarding exclusion criteria, the following were excluded: (a) individuals presenting with a diagnosis of dementia or any other neurological disease and mental disorders; (b) individuals with depression, determined by a score of 5 or above on the Geriatric Depression Scale (GDS) [28]; and (c) individuals who had metallic fixtures around the cephalon.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the human subject ethics committee of The Hong Kong Polytechnic University (ref. number: HSEARS20160415002). All participants gave informed written consent before the intervention began.

2.2. Design. This study utilized a prospective, single-subject design (SSD) with multiple nonconcurrent treatments—anodal tDCS + CS, sham tDCS + CS, and CS only. A four-phase A-B-C-A SSD was employed. After the baseline with the administration of CS (phase A), a sham tDCS with CS was applied (B). Following the withdrawal of this sham treatment, a tDCS treatment was introduced in combination with CS (C). Finally, phase A was replicated to provide the control needed to document the differences between the sham and tDCS phases (Figure 1).

In this design, it is assumed that both treatments—B and C—have differential and independent effects. Differences in the target responses are expected across the four phases of the study. The sham phase (B) was the first treatment intervention to be used to avoid possible carryover effects due to the tDCS stimulation treatment (i.e., phase C), thereby eliminating this potential treatment effect, which can be analyzed during the last baseline (A).

2.3. Cognitive Stimulation. "Neuron Up" was the CS administered to participants. It is a web platform (https://www.neuronup.com/) designed to serve as a fundamental support for professionals involved in cognitive rehabilitation and cognitive stimulation [29]. The display format was full screen in a 9.7-inch screen iPad situated on a desk approximately 35 centimeters in front of the participant.

Participants' individualized level was identified through two training sessions that were conducted for all the participants prior to the implementation. Five cognitive activities associated with different cognitive domains were selected:

(i) Sorting bugs: This task is associated with planning ability and divided attention. Participants are asked to move a bar located in the middle of the screen either to block the movement of bugs which are moving in different directions or to let them pass from one side to the other. The final goal is to keep the green bugs on the green side and the red bugs on the red side. Participants are allowed seven minutes to complete the task, and the completion time is measured. This task also trains sustained and selective attention.

(ii) The last light on: This task is associated with processing speed and selective attention. Participants are asked to pay attention to the windows in a building that light up. They have to touch the window which is the last to light up. This task is repeated five times per session, and the number of correct answers and completion time are measured.

(iii) Illuminated windows: This activity is associated with short-term memory. Participants are asked to remember which windows are illuminated in a building in an open memorization period. Then, all the lights are turned off and participants must identify the windows that had been lit. This activity is repeated five times. The number of correct answers, number of errors, memorization time, and completion time are measured.

(iv) Addition and subtraction questions. Both tasks are associated with calculation and working memory. Participants are given three addition operations involving four numbers of six digits each and six subtraction operations with two numbers of six digits each to solve. The number of errors and the completion time are measured.

These five cognitive activities were presented as a cognitive stimulation practice with one-to-one supervision from an occupational therapist in which all participants were exposed to repetitive testing via the computer system across sessions.

2.4. tDCS. The Soterix Medical 1×1 low-intensity tDCS stimulator was the device used to provide the stimulation. The two rubber electrodes employed for tDCS in this study were introduced in saline-soaked synthetic sponges (7×5 cm, $35\,\text{cm}^2$).

Anodal tDCS was delivered to the left DLPFC, and the cathode electrode was placed over the contralateral deltoid muscle as extracephalic cathode. The scalp electrode was positioned over F3 according to the 10–20 EEG international system. The left DLPFC was targeted as the stimulation site because of its role in high-order cognitive processes [30] and due to the existence of functional disconnection of the DLPFC in persons with MCI [31]. A constant current of 2 mA was applied for 30 minutes. For sham tDCS, the 2 mA intensity was only given for 30 seconds at the beginning and the end of the stimulation.

2.5. Experimental Protocol and Procedures. Each interval (A, B, C, and A) was staggered by a week at a time. During the baseline phases, three sessions of CS were implemented for all the participants. Both interventions, sham tDCS and anodal tDCS, were combined with the same CS that was performed for the baseline phases. However, the treatment phases varied from one to five sessions. The sessions per phase were distributed over five days. Participants were randomly assigned to combinations of intervention each of which had a different time span to compare the treatment frequency effect (Table 1).

The experimental sessions were 30 minutes in length. In this way, tDCS was administered for 30 minutes and the CS was begun five minutes after the tDCS began, thus running for 25 minutes. For the sham phase, the administration of the sham tDCS lasted 30 minutes too, with the difference that a ramping current of 2 mA was applied during the first and last 30 seconds. The participants remained blinded for both stimulation conditions.

2.6. Cognitive Measures. CS data were recorded for each task of each cognitive activity during the sessions. Data such as completion time and performance in terms of correct answers or number of errors were collected.

The standardized cognitive assessments used in this study for screening were the CDR (Hong Kong Version), and the scale was found to have good reliability with internal consistency ranging from 0.7 to 0.9 [32], the GDS-15 item (Hong Kong version) which has a satisfactory reliability with Cronbach alpha = 0.82 [33], and the MoCA (Hong Kong Version) with a sensitivity of 90% to detect MCI [26, 34].

The standardized cognitive measures to assess the study phases included the MoCA (Hong Kong version) [34], the digit span test (DST) [35], and the Trail Making Test ((TMT) Chinese version) which normative data has provided evidence that the part B (Chinese version) may be equivalent to the standard part B [36].

The participants were assessed in five phases: screening (pre-A), after baseline (post-A), after first intervention (post-B), after second intervention (post-C), and after final baseline (post-A).

To summarize, DST and TMT were conducted before the initial baseline and after each interval. However, the MoCA was only administered before the first baseline and after the last for a general comparison of the whole sequence and to avoid learning effect due to repeated testing (Figure 1).

2.7. Data Analysis. To study the effects of tDCS on the "Neuron Up" CS program across the design phases, visual analysis and two standard deviation procedures were used as analytical methods.

Visual analysis was based on observing the visual patterns presented in the graphs where the target parameter changed once the treatment was introduced or withdrawn. Difference in means among phases was also compared.

In the two standard deviation procedure, the levels of the baseline are compared to those of the intervention data points. The procedure assumes that if we are to extend the baseline, then ultimately 95 percent of our observations would be less than two standard deviations away from the baseline mean. The two standard deviations were calculated manually following the guidelines set out by Rubin and Babbie [37]. Data analyses of the cognitive assessments administered before the commencement of the baseline and after every single interval were compared.

3. Results

Although all five participants did well in the tDCS intervention, redness in the area was observed after removing the electrodes in one participant, and he also complained of having a mild headache a few hours after receiving the therapy. The remaining participants reported a tingling sensation in the DLPFC region during the stimulation phase which faded away after a few minutes of the onset of the stimulation. They completed all sessions as scheduled, with the exception of one participant who was not available to complete the last session of the last baseline.

3.1. Cognitive Stimulation Outcomes. The results are presented in graphs in the sequence in which the CS tasks were performed and following the order from fewer to more treatment sessions received. The x-axis corresponds to the observation points (the number of tasks) per day. The y-axis represents either the performance or the time taken to complete the task. The blue line is the measurement of the targeted problem across observation points. There were four intervals for each condition: (A) baseline, (B) sham tDCS

Table 1: Demographics, inclusion criteria scores, and number of sessions conducted in every interval by week.

Participant	Demographics			Inclusion assessment scores					Number of sessions conducted in every interval by week			
	Age	Gender	Medical history	MoCA preintervention	MoCA postintervention	MoCA gain (%)	CDR	GDS	1st week (A) CS alone	2nd week (B) sham tDCS + CS	3rd week (C) anodal tDCS + CS	4th week (A) CS alone
1	79	Female	Heart disease	24	26	6.66	0.5	3	3	1	1	3
2	68	Female	NA	24	25	3.33	0.5	1	3	2	2	3
3	67	Male	NA	24	29	16.6	0.5	1	3	3	3	3
4	69	Male	Diabetes	25	26	3.3	0.5	1	3	4	4	2
5	81	Male	Diabetes	26	27	3.3	0.5	2	3	5	5	3

MoCA: Montreal Cognitive Assessment; CDR: Clinical Dementia Rating; GDS: Geriatric Depression Scale; NA: not applicable; CS: cognitive stimulation; sham tDCS + CS: transcranial direct current stimulation + CS during the A, B, C, and A phases.

intervention, (C) tDCS intervention, and (A) baseline. Every single black line which crosses every interval is the mean of the performance, and the two standard deviations are marked by a black dotted line starting at the corresponding interval.

(i) Sorting bugs (Figure 2): All participants demonstrated fluctuating times of completion during the first baseline phase. There are positive effects for those subjects who received three or more tDCS sessions (participants 3, 4, and 5) with a general slight increase in time required to complete the task after withdrawal of the tDCS intervention, and a difference by more than two standard deviations was observed at the last baseline phase of participant 3.

(ii) The last light on (Figure 3): Figure 3 shows that there were differences by more than two standard deviations in participants 1, 3, and 5. With respect to the baselines and sham phases, all participants exhibited decreasing accuracy in the cognitive task in comparison with the experimental interval, except for participant 4, but no significant difference was found.

(iii) Illuminated windows (Figure 4): Despite all participants exhibiting similar outcomes in all phases, there is a slight general improvement in task performance across conditions, but no significant difference was found.

(iv) Additional question (Figure 5): Participants 1, 2, 3, and 4 demonstrated a clear intervention effect of tDCS administration, but no significant difference was found. Participants made fewer errors in operations when the tDCS was applied. However, participant 5 performed differently, reducing the number of errors after the sham tDCS intervention and especially achieved the best performance during the last baseline phase.

(v) Subtraction question (Figure 6): The outcomes of these operations were similar to the additional questions, but the change in level was not very pronounced. Participants 2, 3, and 5 were more accurate, solving the operations during the tDCS treatment, and the tendency during the baseline and sham phases was associated with a larger number of errors, but no significant difference was found. For participants 1 and 4, the results were almost identical across conditions.

3.2. Behavioral Assessment Outcomes

3.2.1. MoCA Test. All participants showed an improvement in MoCA scores. Participant 3 showed the largest improvement (Table 1).

3.2.2. Trail Making Test. Participants 1 and 4 demonstrated the greatest impact of the tDCS as revealed by the shortest completion time (parts A and B) right after the last session of the tDCS intervention. The negative ratio shown in Table 2 indicates a shorter time taken to complete the task after tDCS relative to sham tDCS. Participant 3 also improved during phase B and participant 5 during phase A (Table 2).

3.2.3. Digit Span Test. All participants improved in their digit span test scores when comparing the baseline to the last assessment. The trend shows that improvement follows a general and steady progressive pattern without obvious significant changes (Table 3).

4. Discussion

This pilot study combined anodal tDCS with CS to investigate their impact on the cognitive performance of older adults with MCI. The result shows that application of anodal tDCS to the left DLPFC and cathodal tDCS to the right deltoid muscle helps to enhance cognitive performance in processing speed, selective attention, and working memory activities, as well as the completion time in planning ability and divided attention tasks. One of the objectives of this study was to compare anodal tDCS and sham tDCS. Although the data generated with CS fluctuated and were variable, the participants did not show significantly better outcomes in the sham intervention than the baseline CS alone.

This was the first study of its kind to show mild benefits in multiple domains of cognition in older adults with MCI as other studies have focused on the possible benefits of tDCS in a single cognitive domain, usually working memory [13, 18, 38].

Placement of an anodal tDCS on the left DLPFC and a cathodal tDCS on the right deltoid muscle did not increase participants' performance in the short-term memory CS task. This agrees with previous studies that applied the same montage as the current study in combination with memory training in persons suffering from AD and which also observed no significant additional effect of tDCS on memory performance beyond that of sham tDCS with the same memory training [39].

Our study adopted extracephalic cathodal tDCS, which eliminated the confounding effect of a monocephalic cathode electrode placed on the scalp. Our findings are also in line with the study conducted by Boggio and colleagues [22] in which the return electrode was extracephalic and placed over the right deltoid muscle in people presenting with AD. The use of a monocephalic cathode setup has been controversial because "current flow direction/electrical field orientation relative to neuronal orientation might determine the effects of tDCS and it might be that the effects of an extracephalic electrode differs relevantly from that of a bipolar electrode arrangement" [40]. Monocephalic cathodes are also common in studies, but that does not mean that the return electrode is physiologically inert, since its positioning does have a critical impact on the electrical field orientation [13]. Notwithstanding, we are confident that the electrical current passes through the stimulated brain area—the left DLPFC—when

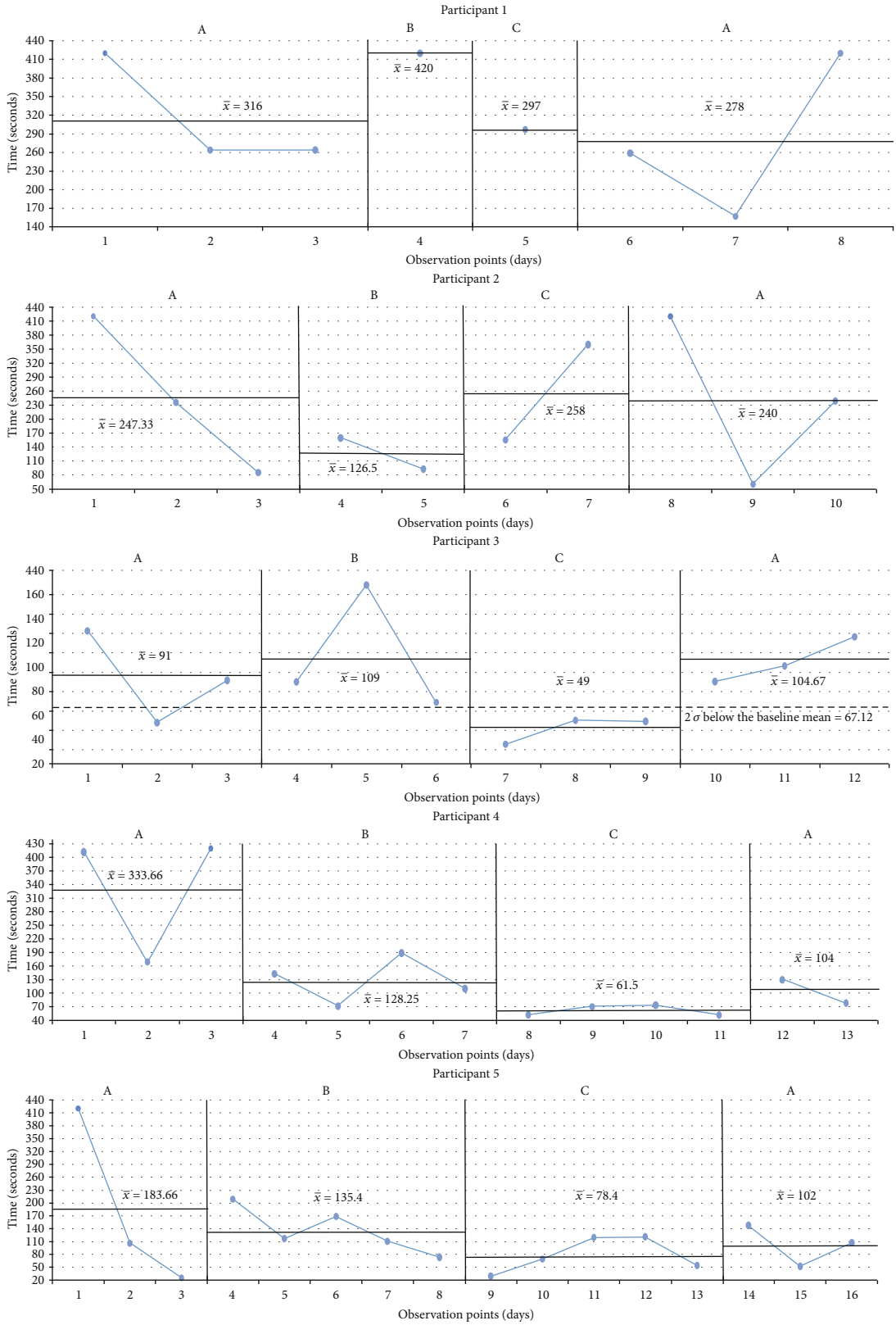

FIGURE 2: Sorting bugs. A: baseline; B: sham tDCS; C: tDCS; x-axis: observation points in days; y-axis: completion time in seconds. Scores are shown, along with black lines marking the average of each phase and with a black dotted line starting at the corresponding baseline marking 2-standard deviation (2 σ) when there is statistically significant difference (participant 3).

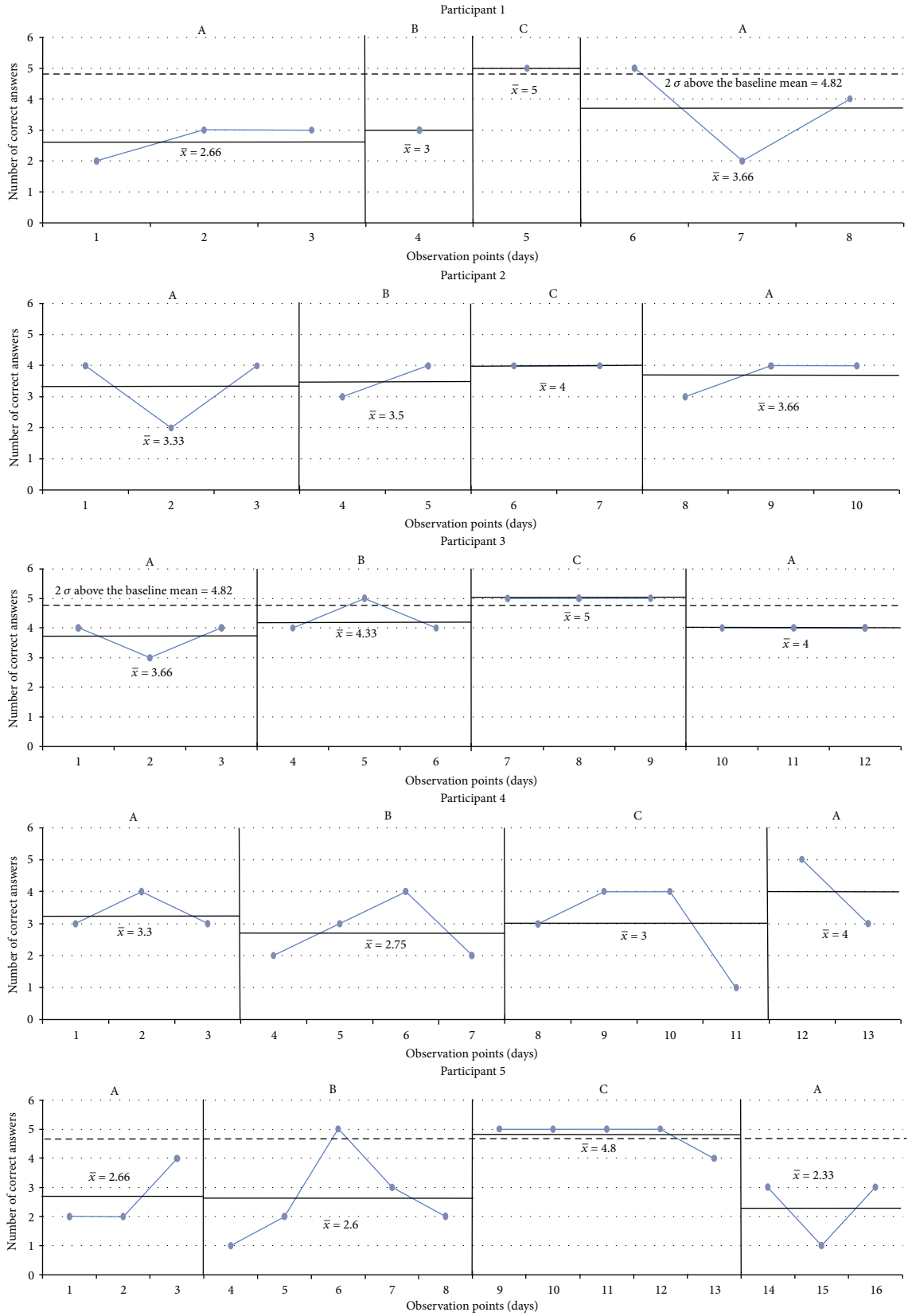

Figure 3: The last light on. A: baseline; B: sham tDCS; C: tDCS; x-axis: observation points in days; y-axis: number of correct answers. Scores are shown, along with black lines marking the average of each phase and with a black dotted line starting at the corresponding baseline marking 2-standard deviation (2 σ) when there is statistically significant difference (participants 1, 3, and 5).

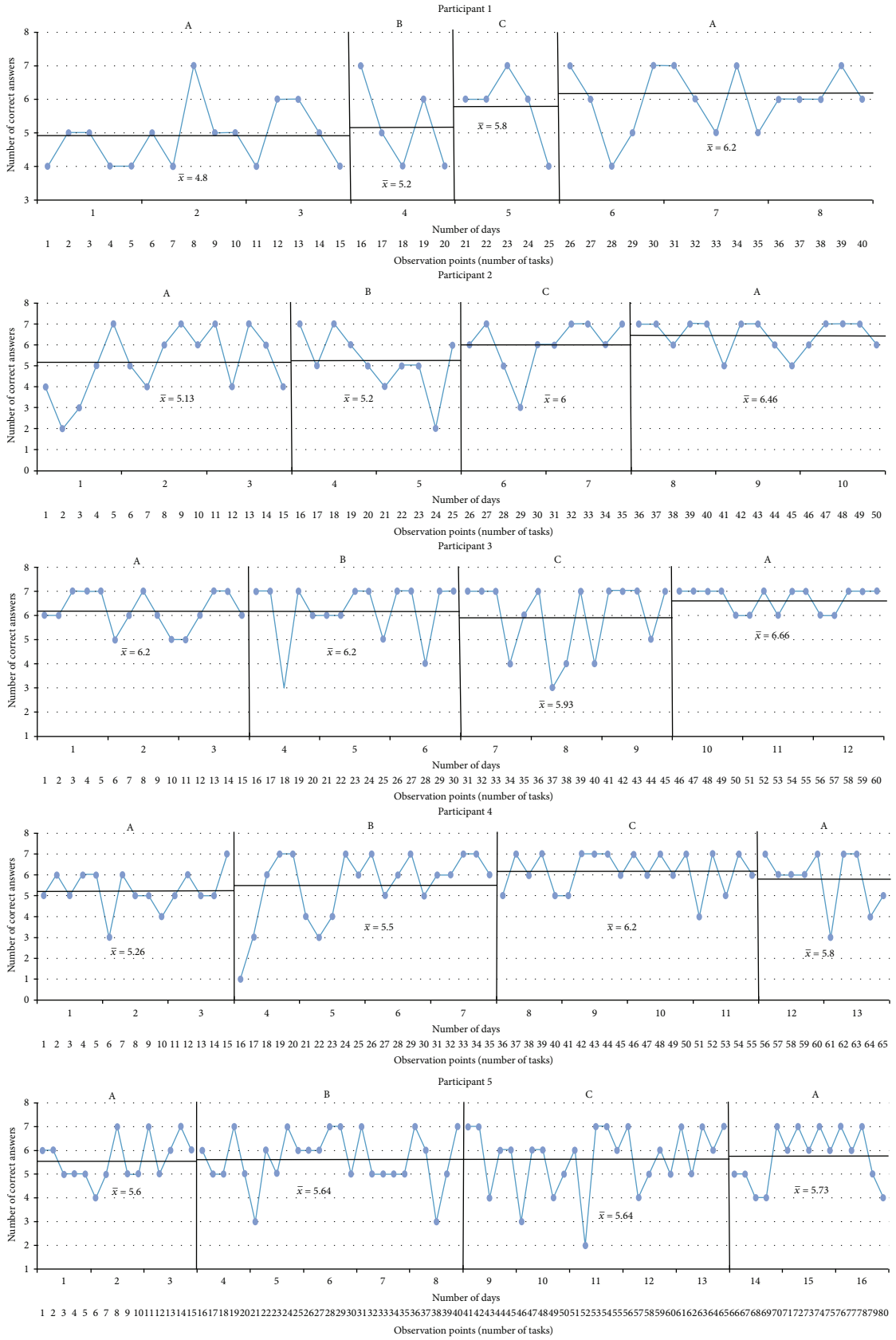

FIGURE 4: Illuminated windows. A: baseline; B: sham tDCS; C: tDCS; *x*-axis: observation points in number of tasks performed within days; *y*-axis: number of correct answers. Scores are shown, along with black lines marking the average of each phase.

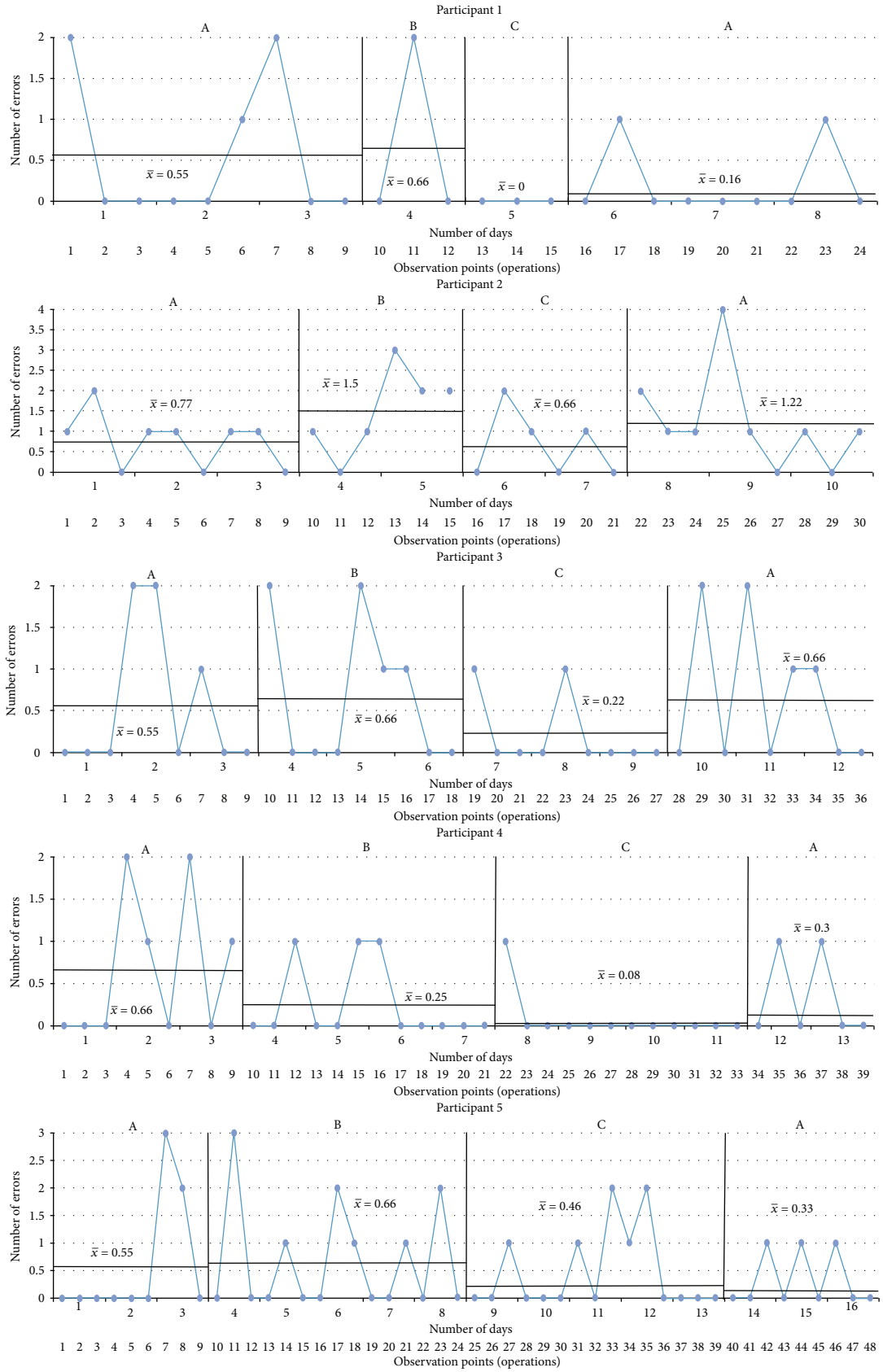

Figure 5: Additional question. A: baseline; B: sham tDCS; C: tDCS; *x*-axis: observation points in number of tasks performed within days; *y*-axis: number of errors. Scores are shown, along with black lines marking the average of each phase.

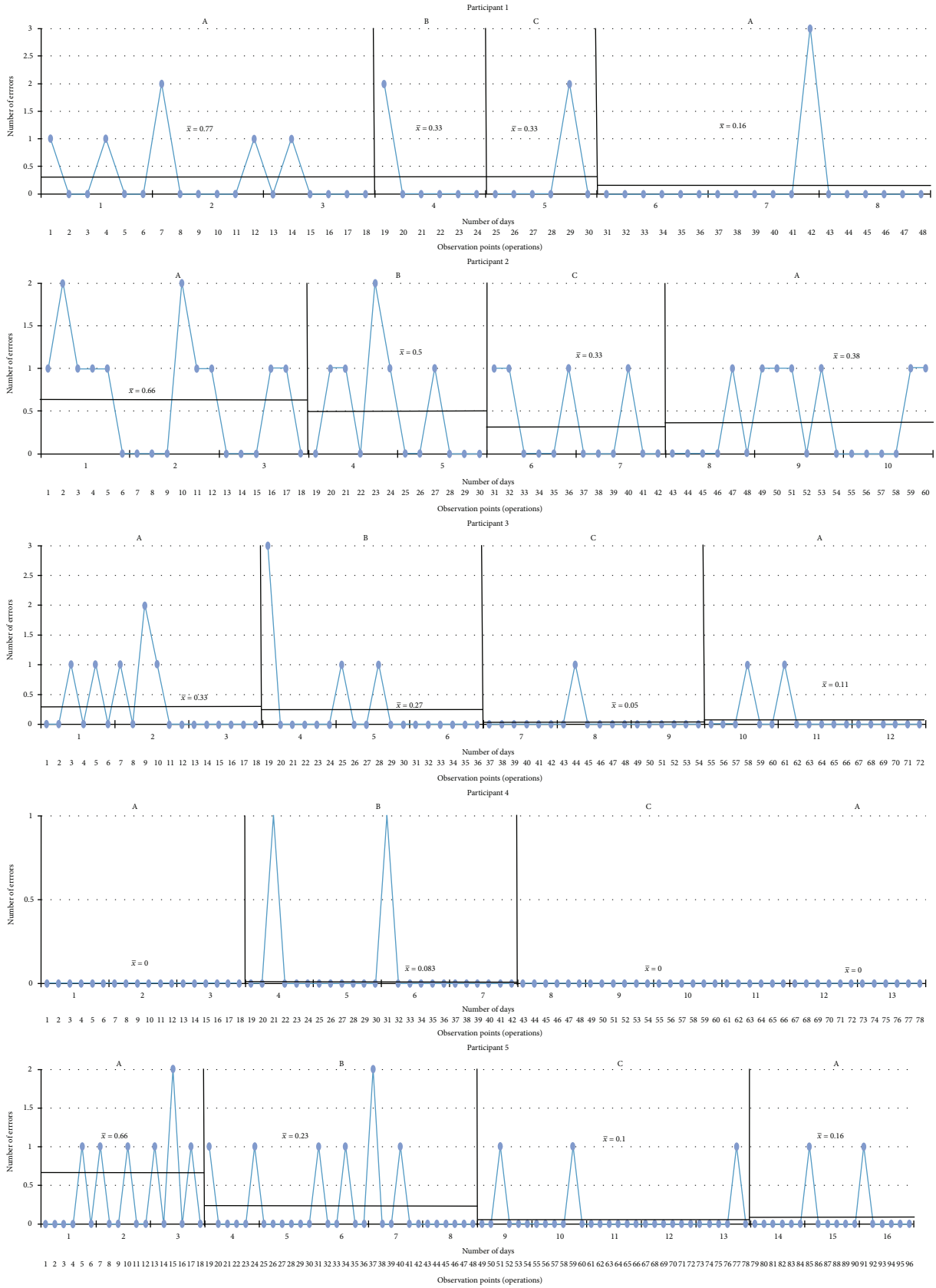

FIGURE 6: Subtraction question. A: baseline; B: sham tDCS; C: tDCS; *x*-axis: observation points in number of tasks performed within days; *y*-axis: number of errors. Scores are shown, along with black lines marking the average of each phase.

Table 2: Trail Making Test score.

Participant	Trail Making Test	Baseline	After first baseline (A1)	After sham tDCS (B)	After tDCS (C)	After last baseline (A2)	Immediate effect (seconds) (C versus baseline)	After-effect (seconds) (A2 versus C)	tDCS versus sham tDCS (seconds) (C versus B)
1	Part A	58.82	58.45	51.53	44.48	55.69	−14.34	10.81	−6.82
	Part B	109.74	87.22	67.7	60.52	67.45	−49.22	6.93	−7.18
2	Part A	38.46	38.4	32.92	41.34	28.03	2.88	−13.31	8.42
	Part B	55.45	83.04	75.73	56.55	64.77	1.1	8.22	−7.31
3	Part A	26.35	22.68	22.91	20.86	15.53	−5.49	−5.53	−2.05
	Part B	42	44.92	29.68	26.73	27.13	−15.87	0.4	−3.25
4	Part A	32.48	40.16	56.12	28.08	51.93	−4.4	23.85	−28.04
	Part B	51.6	56.23	51.5	42.35	56.74	−9.25	14.39	−9.15
5	Part A	37.58	50.4	43.76	38.48	46.55	−0.9	8.07	−5.28
	Part B	57.42	40.55	71.42	52.65	50.15	−4.77	−2.5	−18.77

Immediate effect (C versus baseline) is the gain in seconds after the application of tDCS compared with the baseline; after-effect (A2 versus C) is the maintenance or gain in seconds after tDCS withdrawal in phase C; tDCS versus sham tDCS (C versus B) is the comparison between tDCS and sham tDCS. A positive ratio implies decrement, a neutral ratio implies maintenance, and a negative ratio implies improvement in terms of time of completion.

Table 3: Digit span test score.

Participant	Digit span test	Baseline	After first baseline (A1)	After sham tDCS (B)	After tDCS (C)	After last baseline (A2)	Immediate effect (%) (C versus baseline)	After-effect (%) (A2 versus C)	tDCS versus sham tDCS (C versus B)
1	Forward score	15	16	16	15	16	0	3.33	−3.33
	Backward score	6	8	10	8	9	6.66	3.33	−6.66
	Total score	21	24	26	23	25	6.66	6.66	−9.99
2	Forward score	14	15	14	15	16	3.33	3.33	3.33
	Backward score	5	5	7	6	8	3.33	6.66	−3.33
	Total score	19	19	21	21	24	6.66	9.99	0
3	Forward score	14	16	16	16	16	6.66	0	0
	Backward score	9	9	9	9	13	0	13.32	0
	Total score	23	25	25	25	29	6.66	13.32	0
4	Forward score	16	16	16	16	16	0	0	0
	Backward score	7	8	5	8	8	3.33	0	9.99
	Total score	23	24	21	24	24	3.33	0	9.99
5	Forward score	13	16	16	16	16	9.99	0	0
	Backward score	4	4	5	7	5	9.99	−6.66	6.66
	Total score	17	20	21	23	22	19.98	−3.33	6.66

Immediate effect (C versus baseline) is the gain (%) after the application of tDCS compared with the baseline; after-effect (A2 versus C) is the maintenance or gain (%) after tDCS withdrawal in phase C; tDCS versus sham tDCS (C versus B) is the comparison in terms of gain (%) between tDCS and sham tDCS. A positive ratio implies improvement, a neutral ratio implies maintenance, and a negative ratio implies decrement in terms of accuracy.

applying tDCS. With the same cathode montage, both our study and that of Boggio and colleagues [22] indicate a significant improvement in visual recognition after the administration of multisession tDCS.

It is disappointing that all these positive CT findings are somewhat inconsistent with the results of standardized cognitive assessments, except for the TMT, in which most of the participants showed their best score of the tDCS intervention in all phases. Interestingly, TMT could be an indicator of processing speed [41] and visual selective attention domains [42], which might also correspond to the CS task improvement associated with these domains.

Despite our aim to determine the optimal frequency of tDCS application with the same dosage by modifying the number of sham tDCS and tDCS sessions among participants, the findings appear to be inconclusive. In some occasions, just one session of tDCS was sufficient to produce positive changes in performance while other participants who had up to five sessions of tDCS showed no evidence of benefiting from exposure to the tDCS intervention. Comparison of participants' individual performance of all the CS tasks indicates that the most beneficial dose of tDCS seems to be three sessions per week. However, conclusions cannot be gleaned from the session's variability due to the small

sample of this study. This should be addressed in the future as it remains unclear.

Although this study has produced encouraging results, it also has several limitations. First, an A-B-C-A SSD was used without randomization among experimental conditions. The same order was used for all the participants because if tDCS was administered in phase B right after the baseline, then it could have affected the outcomes under the sham tDCS phase due to possible carryover effects of tDCS stimulation; therefore, it could have also disguised the sham effect we originally aimed to compare with real tDCS. This could have given rise to a second limitation during the last baseline A, either due to a training effect of the CS or a carryover effect of the tDCS administration in phase C, which cannot be separated for interpretation. This is a disadvantage of using an SSD in cognitive studies. We intended to monitor daily response in behavioral terms to different treatments, but the frequency of the application of CS in some of the participants in such a short period made it problematic to decouple what participants might have achieved by continued testing from what was changed by tDCS.

For the same reason, our original intention was to observe whether the CS outcomes could match the cognitive assessment score in every condition. To check this possibility, we administered a battery of assessments five times over a four-week interval, which might provide a learning effect and reduce overinterpreting the CS task outcomes by making a linkage with the standardized cognitive evaluations, and alternative forms of cognitive assessments to measure changes over time should be used.

Despite the limitations of this pilot study, it is essential to conduct pilot studies with NIBS techniques before the implementation of larger trials. The strength of this study allow us to monitor the daily cognitive response of single or coupling therapies gathering valuable data that can shape a future robust intervention. The ultimate purpose of using NIBS is to prove if it can be used as a feasible nonpharmacological therapy in couple with conventional treatment, in this case computer CS, for older adults with MCI. The emerging application of tDCS as a therapeutic intervention gives us the obligation of conducting studies to develop treatment programmes which can support evidence base and determine the future use of these innovative techniques in the field of cognitive rehabilitation.

5. Conclusion

The current study investigated the effects of anodal tDCS on CS in older adults with MCI and found mild beneficial effects on processing speed, selective attention, planning ability, and working memory which were better than those achieved by CS alone or by sham tDCS. The optimal frequency of tDCS administration remains unclear.

Further research is required to improve understanding of the neuromechanism and to determine the behavioral effects of tDCS on CS in a larger multicentered, randomized controlled study to determine the possibility of transferability to everyday cognition.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] R. C. Petersen, G. E. Smith, S. C. Waring, R. J. Ivnik, E. G. Tangalos, and E. Kokmen, "Mild cognitive impairment," *Archives of Neurology*, vol. 56, no. 3, pp. 303–308, 1999.

[2] S. Gauthier, B. Reisberg, M. Zaudig et al., "Mild cognitive impairment," *The Lancet*, vol. 367, no. 9518, pp. 1262–1270, 2006.

[3] K. M. Langa and D. A. Levine, "The diagnosis and management of mild cognitive impairment," *JAMA*, vol. 312, no. 23, pp. 2551–2561, 2014.

[4] M. M. Sohlberg and C. A. Mateer, "Training use of compensatory memory books: a three stage behavioral approach," *Journal of Clinical and Experimental Neuropsychology*, vol. 11, no. 6, pp. 871–891, 1989.

[5] K. Ball, D. B. Berch, K. F. Helmers et al., "Effects of cognitive training interventions with older adults," *JAMA*, vol. 288, no. 18, pp. 2271–2281, 2002.

[6] N. T. M. Hill, L. Mowszowski, S. L. Naismith, V. L. Chadwick, M. Valenzuela, and A. Lampit, "Computerized cognitive training in older adults with mild cognitive impairment or dementia: a systematic review and meta-analysis," *The American Journal of Psychiatry*, vol. 174, no. 4, pp. 329–340, 2017.

[7] A. L. Faria, A. Andrade, L. Soares, and S. B. i Badia, "Benefits of virtual reality based cognitive rehabilitation through simulated activities of daily living: a randomized controlled trial with stroke patients," *Journal of NeuroEngineering and Rehabilitation*, vol. 13, no. 1, p. 96, 2016.

[8] M. Finn and S. McDonald, "Computerised cognitive training for older persons with mild cognitive impairment: a pilot study using a randomised controlled trial design," *Brain Impairment*, vol. 12, no. 3, pp. 187–199, 2011.

[9] J. Olazarán, B. Reisberg, L. Clare et al., "Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy," *Dementia and Geriatric Cognitive Disorders*, vol. 30, no. 2, pp. 161–178, 2010.

[10] M. A. Nitsche, L. G. Cohen, E. M. Wassermann et al., "Transcranial direct current stimulation: state of the art 2008," *Brain Stimulation*, vol. 1, no. 3, pp. 206–223, 2008.

[11] P. Nasseri, M. A. Nitsche, and H. Ekhtiari, "A framework for categorizing electrode montages in transcranial direct current stimulation," *Frontiers in Human Neuroscience*, vol. 9, p. 54, 2015.

[12] B. Hauptmann and A. Karni, "From primed to learn: the saturation of repetition priming and the induction of long-term memory," *Cognitive Brain Research*, vol. 13, no. 3, pp. 313–322, 2002.

[13] M. E. Stoykov and S. Madhavan, "Motor priming in neurorehabilitation," *Journal of Neurologic Physical Therapy*, vol. 39, no. 1, pp. 33–42, 2015.

[14] M. A. Nitsche, A. Antal, D. Liebetanz, N. Lang, F. Tergau, and W. Paulus, "Induction and modulation of neuroplasticity by

transcranial direct current stimulation," in *Transcranial Brain Stimulation for Treatment of Psychiatric Disorders*, M. A. Marcolin and F. Padberg, Eds., vol. 23, Karger, Basel, 2007.

[15] A. Birba, A. Ibáñez, L. Sedeño, J. Ferrari, A. M. García, and M. Zimerman, "Non-invasive brain stimulation: a new strategy in mild cognitive impairment?," *Frontiers in Aging Neuroscience*, vol. 9, p. 16, 2017.

[16] C. Miniussi, J. A. Harris, and M. Ruzzoli, "Modelling non-invasive brain stimulation in cognitive neuroscience," *Neuroscience & Biobehavioral Reviews*, vol. 37, no. 8, pp. 1702–1712, 2013.

[17] T. Ditye, L. Jacobson, V. Walsh, and M. Lavidor, "Modulating behavioral inhibition by tDCS combined with cognitive training," *Experimental Brain Research*, vol. 219, no. 3, pp. 363–368, 2012.

[18] F. Fregni, P. S. Boggio, M. Nitsche et al., "Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory," *Experimental Brain Research*, vol. 166, no. 1, pp. 23–30, 2005.

[19] A. Flöel, W. Suttorp, O. Kohl et al., "Non-invasive brain stimulation improves object-location learning in the elderly," *Neurobiology of Aging*, vol. 33, no. 8, pp. 1682–1689, 2012.

[20] D. M. Martin, R. Liu, A. Alonzo et al., "Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants," *International Journal of Neuropsychopharmacology*, vol. 16, no. 9, pp. 1927–1936, 2013.

[21] P. S. Boggio, L. P. Khoury, D. C. S. Martins, O. E. M. S. Martins, E. C. de Macedo, and F. Fregni, "Temporal cortex direct current stimulation enhances performance on a visual recognition memory task in Alzheimer disease," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 80, no. 4, pp. 444–447, 2009.

[22] P. S. Boggio, R. Ferrucci, F. Mameli et al., "Prolonged visual memory enhancement after direct current stimulation in Alzheimer's disease," *Brain Stimulation*, vol. 5, no. 3, pp. 223–230, 2012.

[23] S. André, S. Heinrich, F. Kayser et al., "At-home tDCS of the left dorsolateral prefrontal cortex improves visual short-term memory in mild vascular dementia," *Journal of the Neurological Sciences*, vol. 369, pp. 185–190, 2016.

[24] M. Meinzer, R. Lindenberg, M. T. Phan, L. Ulm, C. Volk, and A. Flöel, "Transcranial direct current stimulation in mild cognitive impairment: behavioral effects and neural mechanisms," *Alzheimer's & Dementia*, vol. 11, no. 9, pp. 1032–1040, 2015.

[25] F. Portet, P. Ousset, P. Visser, G. Frisoni, and the MCI Working Group of the European Consortium on Alzheimer's Disease (EADC), "Mild cognitive impairment (MCI) in medical practice: a critical review of the concept and new diagnostic procedure. Report of the MCI Working Group of the European Consortium on Alzheimer's Disease," *Journal of Neurology, Neurosurgery, and Psychiatry*, vol. 77, no. 6, pp. 714–718, 2006.

[26] Z. S. Nasreddine, N. A. Phillips, V. Bédirian et al., "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," *Journal of the American Geriatrics Society*, vol. 53, no. 4, pp. 695–699, 2005.

[27] J. Morris, "The Clinical Dementia Rating (CDR): current version and scoring rules," *Neurology*, vol. 43, no. 11, pp. 2412–2414, 1993.

[28] P. P. J. Lim, L. L. Ng, P. C. Chiam, P. S. Ong, F. T.-S. Ngui, and S. Sahadevan, "Validation and comparison of three brief depression scales in an elderly Chinese population," *International Journal of Geriatric Psychiatry*, vol. 15, no. 9, pp. 824–830, 2000.

[29] I. F. de Piérola, "Neuronup's next step: structured and clinically validated programs," *II International Workshop on Gamification in Health*, 2015, gHealth, http://ceur-ws.org/Vol-1547/paper5.pdf.

[30] S. Tremblay, J.-F. Lepage, A. Latulipe-Loiselle, F. Fregni, A. Pascual-Leone, and H. Théoret, "The uncertain outcome of prefrontal tDCS," *Brain Stimulation*, vol. 7, no. 6, pp. 773–783, 2014.

[31] P. Liang, Z. Wang, Y. Yang, X. Jia, and K. Li, "Functional disconnection and compensation in mild cognitive impairment: evidence from DLPFC connectivity using resting-state fMRI," *PLoS One*, vol. 6, no. 7, article e22153, 2011.

[32] A. S. Chan, A. Choi, H. Chiu, and L. Lam, "Clinical validity of the Chinese version of Mattis dementia rating scale in differentiating dementia of Alzheimer's type in Hong Kong," *Journal of the International Neuropsychological Society*, vol. 9, no. 1, pp. 45–55, 2003.

[33] A. Lam, C. W. Lam, and K. W. Boey, "The psychological well-being of elderly persons living in old urban areas of Hong Kong: a social perspective," *Citation Aging & Mental Health*, vol. 9, no. 2, pp. 162–166, 2005.

[34] A. Wong, Y. Y. Xiong, P. W. L. Kwan et al., "The validity, reliability and clinical utility of the Hong Kong Montreal cognitive assessment (HK-MoCA) in patients with cerebral small vessel disease," *Dementia and Geriatric Cognitive Disorders*, vol. 28, no. 1, pp. 81–87, 2009.

[35] D. Wechsler and M. De Lemos, *Wechsler Adult Intelligence Scale-Revised*, Australian Council for Educational Research Limited, Australia, 1981.

[36] L. Lu and E. D. Bigler, "Normative data on trail making test for neurologically normal, Chinese-speaking adults," *Applied Neuropsychology*, vol. 9, no. 4, pp. 219–225, 2002.

[37] A. Rubin and E. R. Babbie, *Research Methods for Social Work*, Brooks Cole Publishing Co., Pacific Grove, CA, USA, 2nd edition, 1993.

[38] S. H. Ohn, C.-I. Park, W.-K. Yoo et al., "Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory," *NeuroReport*, vol. 19, no. 1, pp. 43–47, 2008.

[39] M. Cotelli, R. Manenti, M. Brambilla et al., "Anodal tDCS during face-name associations memory training in Alzheimer's patients," *Frontiers in Aging Neuroscience*, vol. 6, p. 38, 2014.

[40] A. R. Brunoni, M. A. Nitsche, N. Bolognini et al., "Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions," *Brain Stimulation*, vol. 5, no. 3, pp. 175–195, 2012.

[41] T. A. Salthouse, "What cognitive abilities are involved in trail-making performance?," *Intelligence*, vol. 39, no. 4, pp. 222–232, 2011.

[42] J. M. Spikman, H. A. L. Kiers, B. G. Deelman, and A. H. van Zomeren, "Construct validity of concepts of attention in healthy controls and patients with CHI," *Brain and Cognition*, vol. 47, no. 3, pp. 446–460, 2001.

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Research Article

Effect of Voluntary Wheel Running on Striatal Dopamine Level and Neurocognitive Behaviors after Molar Loss in Rats

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The aim of the present study is to evaluate the effect of voluntary wheel running on striatal dopamine level and behavior of cognition and emotion in molar loss rats. Twenty-four Sprague-Dawley rats were enrolled in this study and randomly divided into following 4 groups: control group (C group), molar loss group (ML group), 1-week physical exercise before molar loss group (1W-ML group), and 4-week physical exercise before molar loss group (4W-ML group). The rats both in 4W-ML and 1W-ML groups were placed in the voluntary running wheel in order to exercise for 4 weeks and 1 week, respectively. Then, the rats in 4W-ML, 1W-M, and ML groups received bilateral molar loss operation. After 10 days, striatal dopamine level was detected by in vivo microdialysis coupled with high-performance liquid chromatography (HPLC) and electrochemical detection. All the rats received behavior test after microdialysis detection. The behavior tests including passive avoidance test were used to assess cognition and elevated plus maze test for emotion. The results indicated that voluntary wheel running promoted striatal dopamine level in rats of molar loss. Behavioral data indicated that voluntary wheel running promoted cognition and emotion recovery after molar loss. Therefore, we concluded physical exercise significantly improved the neurocognitive behaviors and increased the striatal dopamine level after molar loss in rats.

1. Introduction

It is well established that tooth loss is a known risk factor of Alzheimer's disease (AD) [1]. As a common disorder in senior population, loss of teeth could adversely affect human cognition and emotion [2, 3]. Clinical medicine has established that tooth loss in patients can induce neuronal cell loss and memory impairment [4, 5]. Animal research also demonstrated that molar loss can cause the functional deterioration of cognition [6]. Previous studies have demonstrated that the rat with molar loss broke the balance of the cholinergic neuronal system and caused the impairment of cognition [7]. In addition, a preliminary quantitative study revealed that wide range of emotional effects was caused by tooth loss, such as loss of self-confidence and anxiety [8]. Further studies have shown that physical exercise, aerobic fitness exercise in particularly, had a positive effect on multiple aspects of brain function [9–11]. Neurochemistry studies indicated that physical exercise increased the antioxidant ability and glucose level to enhance cognition and emotion [12–14]. Neurobiology research also confirmed that aerobic exercise predominately employed the action of BDNF and the new growth of synaptic plasticity [15–17]. In addition, dopamine acts as a classic neurotransmitter in the brain, which plays an important role in cognitive and emotive aspects [18–20]. Numerous studies have shown that dopamine degeneration caused significant alteration in cognitive and emotive function by medicating striatal dopamine pathways [21-22]. Striatum is one of the four major dopamine pathways in the brain, partially involved in reward and in the reinforcement of memory consolidation. Degeneration of dopamine-producing neurons in striatum complex leads to diminished

concentrations of dopamine in the nigrostriatal pathway, leading to reduce function and the characteristic symptoms, such as motor ability and cognitive impairment [23–25]. Therefore, this study was designed to explore the effect of voluntary wheel running on striatal dopamine level and neurocognitive behaviors after molar loss in rats. These findings may provide a theoretical basis for the clinical prevention of Alzheimer's disease.

2. Materials and Methods

2.1. Animals. Adult male Sprague-Dawley rats (3 months of age, weighting 300 ± 50 g at the time of surgery) were obtained from Experimental Animal Center of Peking University. Rats ($n = 24$) were enrolled in this study and randomly divided into following 4 groups: control group (C group, $n = 6$), molar loss group (ML group, $n = 6$), 1-week physical exercise before molar loss group (1W-ML group, $n = 6$), and 4-week physical exercise before molar loss group (4W-ML group, $n = 6$). The rats in both 4W-ML and 1W-ML groups were placed in the voluntary running wheel in order to exercise for 4 weeks or 1 week. Then, the rats in 4W-ML, 1W-ML, and ML groups received bilateral molar loss operation. In the C group, bilateral maxillary molar teeth remained intact. All rats were housed under 12 h light/dark cycle and had a sufficient amount of food and water.

2.2. Voluntary Wheel Running. The rats in both 4W-ML and 1W-ML groups received voluntary wheel running. Two rat groups were given free access to running wheels (wheel circumference, 100 cm; Harvard Apparatus) in their cages for 4 weeks or 1 week. A magnetic counter was installed to the running wheel in order to record wheel revolutions [26]. The distance was obtained by wheel revolutions multiplied by the circumference of the wheel. Those rats that cannot adapt new circumstances will be removed.

2.3. Molar Loss Surgery. Bilateral maxillary molar teeth were extracted from rats in the 4W-ML, 1W-ML, and ML groups after being anesthetized with chloral hydrate (350 mg/kg, i.p.). The rats in the C group were anesthetized, but no teeth were extracted. To provide a suitable recovery time after teeth extraction, experimental dentures were fitted to rats. Experimental dentures were produced from an impression made of silicone impression material and a resin tray. Occlusal adjustments were made until maxillomandibular incisor contacts were obtained [27].

2.4. In Vivo Microdialysis and High-Performance Liquid Chromatography. In vivo microdialysis was performed by implanting microdialysis probe into the striatum through the guide cannula by continuously perfusing with artificial cerebrospinal fluid (126 mM NaCl, 2.4 mM KCl, 1.1 mM $CaCl_2$, 0.85 mM $MgCl_2$, 27.5 mM $NaHCO_3$, 0.5 mM Na_2SO_4, and 0.5 mM KH_2PO_4, pH = 7.0) at a flow rate of 2 μL/min driven by a microinjection pump (CMA/100, CMA Microdialysis AB, Stockholm, Sweden). After 90 min, microdialysate in the striatum were collected for 60 minutes; each sample was collected in a 250 μL tubes for 10 min for a total of 6 tubes. Each tube was placed in an ice box containing 15 L of 10 mmol HCL. Then, dopamine level in the samples was measured using HPLC with electrochemical detection. The flow rate of the mobile phase (50 mM NaH_2PO_3, 2 mM decanesulfonic acid, 0.7 mM ethylenediaminetetraacetic acid, 11% *v*/*v* acetonitrile, and 11% *v*/*v* methanol, pH = 6.0) was 1 μL/min.

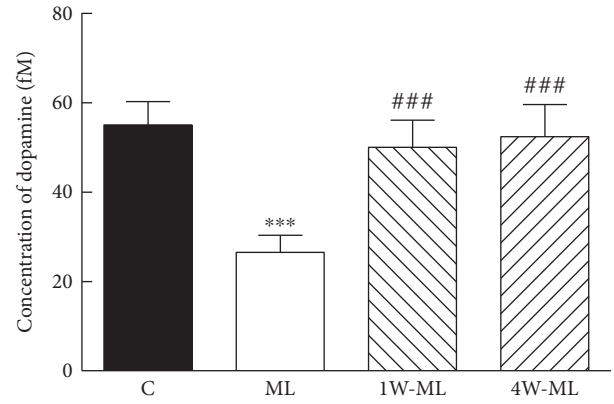

Figure 1: Dynamic changes of striatal dopamine level in each group. $^{***}P < 0.01$ compared with C group. $^{\#\#\#}P < 0.01$ compared with ML group.

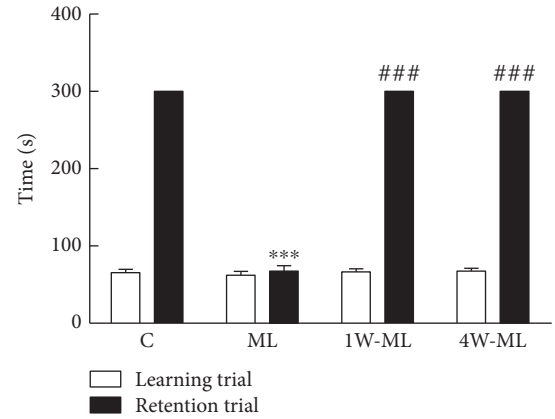

Figure 2: The latency time of rats in learning trial and retention trial. $^{***}P < 0.001$ compared with C group. $^{\#\#\#}P < 0.01$ compared with ML group.

2.5. Passive Avoidance Test. Cognitive function was assessed by passive avoidance test [28]. After the learning trail, the retention test was measured 24 h after the learning trial. Each animal was put in an illuminated compartment, and the door opened after 2 minutes. Latency to enter the dark compartment was recorded to a maximum of 300 s. Animals that did not enter the dark chamber during the retention test were allotted a latency of 300 s [29].

2.6. Elevated Plus Maze Test. Emotion was assessed by elevated plus maze test [30]. The elevated plus maze was made of plastic and consisted of two white open arms (25×8 cm), two black enclosed arms ($25 \times 8 \times 20$ cm), and a central platform ($8 \times 8 \times 8$ cm) in the form of a cross. The maze was placed 50 cm above the floor. Rats were individually placed in the center with their heads directed toward one of the closed arms. The total time spent in each arm or in the

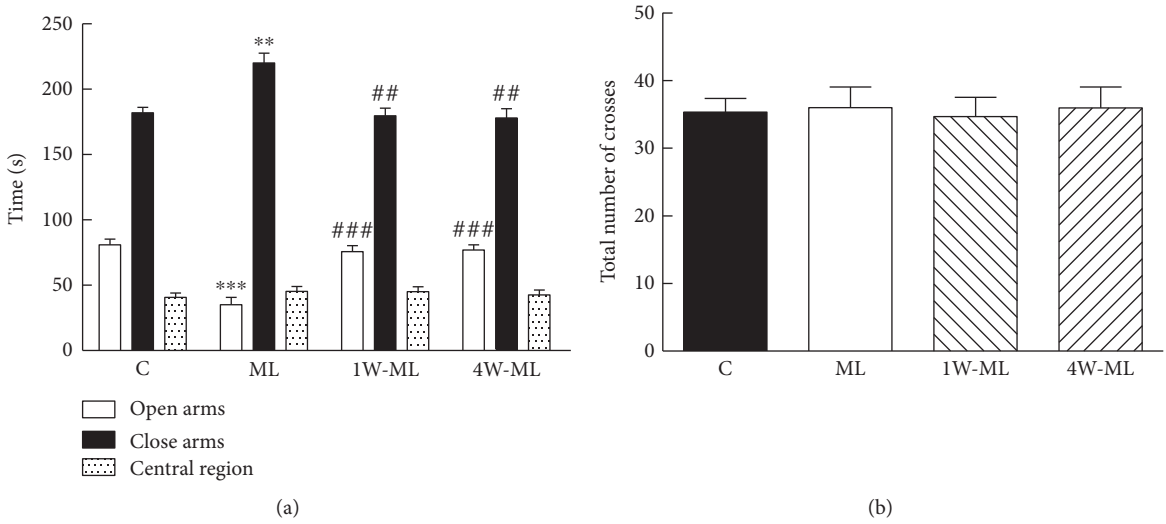

Figure 3: (a) Time spent of four rat groups in each arm. $^{***}P < 0.001$ and $^{**}P < 0.01$ compared with C group. $^{###}P < 0.001$ and $^{##}P < 0.01$ compared with ML group. (b) Total number of crosses in each group.

center and the total number of entries into each arm were analyzed by video monitoring for 5 min. After 5 min, rats were removed from the maze and returned to their home cage. The maze was then cleaned with a solution of 70% ethyl alcohol and permitted to dry between tests [31].

2.7. Statistical Analysis. Data were analyzed by GraphPad Prism 5. A two-way analysis of variance (ANOVA) was used to analyze the data. The comparison of cognition and emotion was made with two-tailed Student's *t* test.

3. Results

3.1. Dynamic Changes of Striatal Dopamine Level in Each Group. Figure 1 shows dynamic changes of striatal dopamine level in each group. The dopamine level in C, ML, 1W-ML, and 4W-ML groups was 55.02 ± 9.05 fmol, 26.48 ± 6.67 fmol, 50.01 ± 10.52 fmol, 52.34 ± 12.54 fmol, respectively. Compared with C group, the extracellular dopamine level of ML group significantly decreased ($P < 0.001$). Compared with ML group, the extracellular dopamine level of 1W-ML and 4W-ML group significantly increased ($P < 0.001$). However, the extracellular dopamine level has no significant difference between 1W-ML and 4W-ML groups ($P > 0.05$). The results indicated that 1-week or 4-week volunteer wheel running increased striatum dopamine level after molar loss.

3.2. Passive Avoidance Test. Figure 2 shows that the latency time of passive avoidance test in each group. In learning trial, the time in C, ML, 1W-ML, and 4W-ML group was 65.5 ± 11.89 s, 62 ± 13.41 s, 66.5 ± 8.56 s, and 67.5 ± 10.27 s and 300 s, 67.5 ± 16.69 s, 300 s, and 300 s in retention trial. There was no significant difference in the learning trial for each group ($P > 0.05$). Compared with C group, the retention time of ML group was significantly shorter ($P < 0.001$). Compared with ML group, the retention time of 1W-ML and 4W-ML groups was significantly longer ($P < 0.001$). However, the retention time has no significant difference between 1W-ML and 4W-ML groups ($P > 0.05$). The results indicated that 1-week and 4-week volunteer wheel running can promote cognition after molar loss.

3.3. Elevated Plus Maze Test. Figure 3(a) shows that the time spent of each rat groups in each arm. Compared with C group, the time spent of open arms in the ML group was significantly shorter ($P < 0.001$), adversely close arms ($P < 0.01$). Compared with ML group, the time spent of open arms in the 1W-ML and 4W-ML groups was significantly longer ($P < 0.001$), adversely close arms ($P < 0.01$). However, the time spent in each arm has no difference between 1W-ML and 4W-ML groups ($P > 0.05$). Meanwhile, there was no significant difference in the central region time for each group ($P > 0.05$). Figure 3(b) shows that total number of crosses in three groups. But there was no significant difference in the total number of crosses for each group ($P > 0.05$). The results indicated that 1-week or 4-week volunteer wheel running can promote emotion after molar loss.

4. Discussion

Alzheimer's disease (AD) can be considered as the most common cause of cognitive dysfunction among the aged, and tooth loss might be a risk factor for Alzheimer-type dementia [32–34]. New advances have shown that tooth loss caused the decline of cognition [35–37]. Previous research used passive avoid test to evaluate cognition, which shows that molar loss may cause accumulation of the amyloid cascade in the brain that leads to cognitive impairment [38]. Thus, we chose passive avoidance test to assess cognition in rats. We also choose elevated plus maze test to evaluate emotion. The results show that the cognition and emotion were worse after molar loss. Therefore, we successfully established the rat model of cognitive and emotive dysfunction after

molar loss in this experiment. Previous study has shown that molar loss-induced cognitive and emotive impairments are related to neural cell loss [38-39]. In this study, we also demonstrated that molar loss-induced cognitive and emotive impairments are associated with the decrease of striatal dopamine level. Clinical studies have demonstrated that cognitive impairment had pathophysiology of dopamine system by the loss of midbrain neurons that synthesize the neurotransmitter dopamine [40-41]. Animal study also demonstrated that depression and anxiety might be associated with a specific loss of dopamine innervation in the limbic system [42]. Thus, it is reasonable to suggest that the decrease of striatal dopamine level can be one of the important reason of cognitive and emotive impairment after molar loss.

However, therapeutic strategies for the cognitive and emotive impairment after molar loss have not been well established so far. Molecular chemistry and biology highlight the promoted effect of physical exercise on cognition and emotion [43–45]. Some research has shown that exercise increased synaptic plasticity and the level of BGF and promoted cognition [46-47]. Other research also have shown that exercise can enhance cell proliferation, thereby alleviating anxiety-like behavior and improve emotion [48-49]. Especially, studies also indicated that physical exercise, voluntary wheel running in particularly, can be one of the best ways to promote cognition and emotion [50-51]. So, the present study chose voluntary wheel running as intervention approach. Our behavioral data indicated that voluntary wheel running promoted cognitive and emotive recovery after molar loss. As reported previously, physical exercise promoted the new growth of synaptic plasticity and the level of brain glucose and improve cognition and emotion thereafter [52–54]. In our research, we demonstrate that 4-week and 1-week voluntary wheel running promoted cognitive and emotive recovery after molar loss is associated with the increase of striatal dopamine level. Previous studies have demonstrated that physical exercise increased antioxidant defense and dopamine levels [55–57]. The increased dopamine level is related to recovery of cognitive and emotive impairments. Thus, we suggest that the increased of striatal dopamine level can be one of the reasons to induce that voluntary wheel running promotes cognition and emotion after molar loss in rats.

It is worth to mention that there was no difference between 4 weeks and 1 week of physical exercise-promoted cognition and emotion after molar loss in dopamine concentration aspect. Since previous research have found that small amount of physical exercise could be beneficial to cognitive function, it is reasonable that 1 week of physical exercise is enough to promote cognition and emotion after molar loss in dopamine concentration aspect. Although we did not find difference of dopamine level in striatum after 1 week and 4 weeks of physical exercise in our experiment condition, it is still possible that dopamine dynamic change in different brain regions could be induced by different physical exercise processes. In addition, whether there is difference in other aspects, such as other cognitive behavioral models or cellular levels, needs to be studied further.

5. Conclusions

Physical exercise significantly promoted the cognition and emotion in rats of molar loss by increasing the striatal dopamine level. However, it is necessary to further study other neurochemicals related to dopaminergic system to elucidate more underlying mechanisms of physical exercise-promoted cognition and emotion after molar loss.

Conflicts of Interest

The authors declare that there is no conflict of interests.

Acknowledgments

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References

[1] Q. Pang, X. Hu, X. Li, J. Zhang, and Q. Jiang, "Behavioral impairments and changes of nitric oxide and inducible nitric oxide synthase in the brains of molarless KM mice," *Behavioural Brain Research*, vol. 278, pp. 411–416, 2015.

[2] K. J. Joshipura, C. W. Douglass, and W. C. Willett, "Possible explanations for the tooth loss and cardiovascular disease relationship," *Annals of Periodontology*, vol. 3, no. 1, pp. 175–183, 1998.

[3] J. Luo, B. Wu, Q. Zhao et al., "Association between tooth loss and cognitive function among 3063 Chinese older adults: a community-based study," *PLoS One*, vol. 10, no. 3, article e0120986, 2015.

[4] H. Nilsson, J. Berglund, and S. Renvert, "Tooth loss and cognitive functions among older adults," *Acta Odontologica Scandinavica*, vol. 72, no. 8, pp. 639–644, 2014.

[5] D. Lexomboon, M. Trulsson, I. Wårdh, and M. G. Parker, "Chewing ability and tooth loss: association with cognitive impairment in an elderly population study," *Journal of the American Geriatrics Society*, vol. 60, no. 10, pp. 1951–1956, 2012.

[6] K. Yamazaki, N. Wakabayashi, T. Kobayashi, and T. Suzuki, "Effect of tooth loss on spatial memory and TrkB-mRNA levels in rats," *Hippocampus*, vol. 18, no. 6, pp. 542–547, 2008.

[7] T. Kato, T. Usami, Y. Noda, M. Hasegawa, M. Ueda, and T. Nabeshima, "The effect of the loss of molar teeth on spatial memory and acetylcholine release from the parietal cortex in aged rats," *Behavioural Brain Research*, vol. 83, no. 1-2, pp. 239–242, 1997.

[8] D. Davis, J. Fiske, B. Scott, and D. R. Radford, "The emotional effects of tooth loss: a preliminary quantitative study," *British Dental Journal*, vol. 188, no. 09, pp. 503–506, 2000.

[9] C. H. Hillman, K. I. Erickson, and A. F. Kramer, "Be smart, exercise your heart: exercise effects on brain and cognition," *Nature Reviews Neuroscience*, vol. 9, no. 1, pp. 58–65, 2008.

[10] B. K. Tivadar, "Physical activity improves cognition: possible explanations," *Biogerontology*, vol. 18, no. 4, pp. 477–483, 2017.

[11] Z. Radak, S. Kumagai, A. W. Taylor, H. Naito, and S. Goto, "Effects of exercise on brain function: role of free radicals," *Applied Physiology, Nutrition, and Metabolism*, vol. 32, no. 5, pp. 942–946, 2007.

[12] N. Okudan and M. Belviranli, "Effects of exercise training on hepatic oxidative stress and antioxidant status in aged rats," *Archives of Physiology and Biochemistry*, vol. 122, no. 4, pp. 180–185, 2016.

[13] M. A. Moro, A. Almeida, J. P. Bolaños, and I. Lizasoain, "Mitochondrial respiratory chain and free radical generation in stroke," *Free Radical Biology & Medicine*, vol. 39, no. 10, pp. 1291–1304, 2005.

[14] F. T. A. Pijlman, G. Wolterink, and J. M. Van Ree, "Physical and emotional stress have differential effects on preference for saccharine and open field behaviour in rats," *Behavioural Brain Research*, vol. 139, no. 1-2, pp. 131–138, 2003.

[15] S. Vaynman, Z. Ying, and F. Gomez-Pinilla, "Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition," *European Journal of Neuroscience*, vol. 20, no. 10, pp. 2580–2590, 2004.

[16] C. H. Chae, H. C. Lee, S. L. Jung et al., "Swimming exercise increases the level of nerve growth factor and stimulates neurogenesis in adult rat hippocampus," *Neuroscience*, vol. 212, pp. 30–37, 2012.

[17] R. Šumec, P. Filip, K. Sheardová, and M. Bareš, "Psychological benefits of nonpharmacological methods aimed for improving balance in Parkinson's disease: a systematic review," *Behavioural Neurology*, vol. 2015, Article ID 620674, 16 pages, 2015.

[18] S. K. Mittal and C. Eddy, "The role of dopamine and glutamate modulation in Huntington disease," *Behavioural Neurology*, vol. 26, no. 4, pp. 255–263, 2013.

[19] A. Costa, A. Peppe, I. Mazzù, M. Longarzo, C. Caltagirone, and G. A. Carlesimo, "Dopamine treatment and cognitive functioning in individuals with Parkinson's disease: the "cognitive flexibility" hypothesis seems to work," *Behavioural Neurology*, vol. 2014, Article ID 260896, 11 pages, 2014.

[20] A. Venkatraman, B. L. Edlow, and M. H. Immordino-Yang, "The brainstem in emotion: a review," *Frontiers in Neuroanatomy*, vol. 11, p. 15, 2017.

[21] A. Nieoullon, "Dopamine and the regulation of cognition and attention," *Progress in Neurobiology*, vol. 67, no. 1, pp. 53–83, 2002.

[22] A. Nieoullon and A. Coquerel, "Dopamine: a key regulator to adapt action, emotion, motivation and cognition," *Current Opinion in Neurology*, vol. 16, Supplement 2, pp. S3–S9, 2003.

[23] R. A. Wise, "Roles for nigrostriatal—not just mesocorticolimbic—dopamine in reward and addiction," *Trends in Neurosciences*, vol. 32, no. 10, pp. 517–524, 2009.

[24] A. Gröger, R. Kolb, R. Schäfer, and U. Klose, "Dopamine reduction in the substantia nigra of Parkinson's disease patients confirmed by in vivo magnetic resonance spectroscopic imaging," *PLoS One*, vol. 9, no. 1, article e84081, 2014.

[25] D. Wang, X. Liu, and D. Qiao, "Modulatory effect of subthalamic nucleus on the development of fatigue during exhausting exercise: an in vivo electrophysiological and microdialysis study in rats," *Journal of Sports Science & Medicine*, vol. 11, no. 2, pp. 286–293, 2012.

[26] S. Fediuc, J. E. Campbell, and M. C. Riddell, "Effect of voluntary wheel running on circadian corticosterone release and on HPA axis responsiveness to restraint stress in Sprague-Dawley rats," *Journal of Applied Physiology*, vol. 100, no. 6, pp. 1867–1875, 2006.

[27] S. Iida, T. Hara, D. Araki et al., "Memory-related gene expression profile of the male rat hippocampus induced by teeth extraction and occlusal support recovery," *Archives of Oral Biology*, vol. 59, no. 2, pp. 133–141, 2014.

[28] O. Y. Calhan and V. Seyrantepe, "Mice with catalytically inactive cathepsin a display neurobehavioral alterations," *Behavioural Neurology*, vol. 2017, Article ID 4261873, 11 pages, 2017.

[29] M. Tahamtan, M. Allahtavakoli, M. Abbasnejad et al., "Exercise preconditioning improves behavioral functions following transient cerebral ischemia induced by 4-vessel occlusion (4-VO) in rats," *Archives of Iranian Medicine*, vol. 16, no. 12, pp. 697–704, 2013.

[30] L. L. Furlanetti, M. D. Döbrössy, I. A. Aranda, and V. A. Coenen, "Feasibility and safety of continuous and chronic bilateral deep brain stimulation of the medial forebrain bundle in the naïve Sprague-Dawley rat," *Behavioural Neurology*, vol. 2015, Article ID 256196, 13 pages, 2015.

[31] D. B. Pahaye, E. N. Bum, G. S. Taïwé et al., "Neuroprotective and antiamnesic effects of Mitragyna inermis willd (Rubiaceae) on scopolamine-induced memory impairment in mice," *Behavioural Neurology*, vol. 2017, Article ID 5952897, 11 pages, 2017.

[32] C. Jenner, G. Reali, M. Puopolo, and M. C. Silveri, "Can cognitive and behavioural disorders differentiate frontal variant-frontotemporal dementia from Alzheimer's disease at early stages?," *Behavioural Neurology*, vol. 17, no. 2, pp. 89–95, 2006.

[33] S. Sil and T. Ghosh, "Cox-2 plays a vital role in the impaired anxiety like behavior in colchicine induced rat model of Alzheimer disease," *Behavioural Neurology*, vol. 2016, Article ID 1501527, 8 pages, 2016.

[34] B. C. Dickerson and R. A. Sperling, "Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging," *Behavioural Neurology*, vol. 21, no. 1-2, pp. 63–75, 2009.

[35] X. Xu, B. Cao, J. Wang, T. Yu, and Y. Li, "Decision-making deficits associated with disrupted synchronization between basolateral amygdala and anterior cingulate cortex in rats after tooth loss," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 60, pp. 26–35, 2015.

[36] E. J. Yang, U. Mahmood, H. Kim et al., "Alterations in protein phosphorylation in the amygdala of the 5XFamilial Alzheimer's disease animal model," *Journal of Pharmacological Sciences*, vol. 133, no. 4, pp. 261–267, 2017.

[37] M. Onozuka, K. Watanabe, S. Nagasaki et al., "Impairment of spatial memory and changes in astroglial responsiveness following loss of molar teeth in aged SAMP8 mice," *Behavioural Brain Research*, vol. 108, no. 2, pp. 145–155, 2000.

[38] H. Oue, Y. Miyamoto, S. Okada et al., "Tooth loss induces memory impairment and neuronal cell loss in APP transgenic mice," *Behavioural Brain Research*, vol. 252, pp. 318–325, 2013.

[39] S. Sakamoto, T. Hara, A. Kurozumi et al., "Effect of occlusal rehabilitation on spatial memory and hippocampal neurons after long-term loss of molars in rats," *Journal of Oral Rehabilitation*, vol. 41, no. 10, pp. 715–722, 2014.

[40] L. Bäckman, L. Nyberg, U. Lindenberger, S. C. Li, and L. Farde, "The correlative triad among aging, dopamine, and cognition:

current status and future prospects," *Neuroscience & Biobehavioral Reviews*, vol. 30, no. 6, pp. 791–807, 2006.

[41] J. H. Kim, J. M. Auerbach, J. A. Rodríguez-Gómez et al., "Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease," *Nature*, vol. 418, no. 6893, pp. 50–56, 2002.

[42] P. Remy, M. Doder, A. Lees, N. Turjanski, and D. Brooks, "Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system," *Brain*, vol. 128, no. 6, pp. 1314–1322, 2005.

[43] J. J. Annesi, "Effects of minimal exercise and cognitive behavior modification on adherence, emotion change, self-image, and physical change in obese women," *Perceptual and Motor Skills*, vol. 91, no. 1, pp. 322–336, 2000.

[44] F. Nozariyan, P. Shafiniya, V. Shahvali, and M. A. Makiyani, "Emotion changes during exercise in males' physical education student," vol. 9, 2016.

[45] T. Nozawa, Y. Taki, A. Kanno et al., "Effects of different types of cognitive training on cognitive function, brain structure, and driving safety in senior daily drivers: a pilot study," *Behavioural Neurology*, vol. 2015, Article ID 525901, 18 pages, 2015.

[46] A. S. Aguiar Jr., A. A. Castro, E. L. Moreira et al., "Short bouts of mild-intensity physical exercise improve spatial learning and memory in aging rats: involvement of hippocampal plasticity via AKT, CREB and BDNF signaling," *Mechanisms of Ageing and Development*, vol. 132, no. 11-12, pp. 560–567, 2011.

[47] T. Kobila, Q. R. Liu, K. Gandhi, M. Mughal, Y. Shaham, and H. van Praag, "Running is the neurogenic and neurotrophic stimulus in environmental enrichment," *Learning & Memory*, vol. 18, pp. 605–609, 2011.

[48] S. J. Lee, T. W. Kim, H. K. Park et al., "Postnatal treadmill exercise alleviates prenatal stress-induced anxiety in offspring rats by enhancing cell proliferation through 5-Hydroxytryptamine 1A receptor activation," *International Neurourology Journal*, vol. 20, Supplement 1, pp. S57–S64, 2016.

[49] E. E. Bernstein and R. J. McNally, "Acute aerobic exercise hastens emotional recovery from a subsequent stressor," *Health Psychology*, vol. 36, no. 6, pp. 560–567, 2017.

[50] X. Zhao, J. Aronowski, S. J. Liu et al., "Wheel-running modestly promotes functional recovery after a unilateral cortical lesion in rats," *Behavioural Neurology*, vol. 16, no. 1, pp. 41–49, 2005.

[51] Y. Lin, X. Lu, J. Dong et al., "Involuntary, forced and voluntary exercises equally attenuate neurocognitive deficits in vascular dementia by the BDNF–pCREB mediated pathway," *Neurochemical Research*, vol. 40, no. 9, pp. 1839–1848, 2015.

[52] M. C. Lee, M. Okamoto, Y. F. Liu et al., "Voluntary resistance running with short distance enhances spatial memory related to hippocampal BDNF signaling," *Journal of Applied Physiology*, vol. 113, no. 8, pp. 1260–1266, 2012.

[53] A. C. McKee, D. H. Daneshvar, V. E. Alvarez, and T. D. Stein, "The neuropathology of sport," *Acta Neuropathologica*, vol. 127, no. 1, pp. 29–51, 2014.

[54] X. Xiao, Q. Lin, W. L. Lo et al., "Cerebral reorganization in subacute stroke survivors after virtual reality-based training: a preliminary study," *Behavioural Neurology*, vol. 2017, Article ID 6261479, 8 pages, 2017.

[55] M. Harvey, K. Muir, I. Reeves et al., "Long term improvements in activities of daily living in patients with hemispatial neglect," *Behavioural Neurology*, vol. 23, no. 4, pp. 237–239, 2010.

[56] M. Asghar, L. George, and M. F. Lokhandwala, "Exercise decreases oxidative stress and inflammation and restores renal dopamine D1 receptor function in old rats," *American Journal of Physiology-Renal Physiology*, vol. 293, no. 3, pp. F914–F919, 2007.

[57] L. Pruimboom, C. L. Raison, and F. A. J. Muskiet, "Physical activity protects the human brain against metabolic stress induced by a postprandial and chronic inflammation," *Behavioural Neurology*, vol. 2015, Article ID 569869, 11 pages, 2015.

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Research Article

Subjective Cognitive Impairment, Depressive Symptoms, and Fatigue after a TIA or Transient Neurological Attack: A Prospective Study

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Introduction. Subjective cognitive impairment (SCI), depressive symptoms, and fatigue are common after stroke and are associated with reduced quality of life. We prospectively investigated their prevalence and course after a transient ischemic attack (TIA) or nonfocal transient neurological attack (TNA) and the association with diffusion-weighted imaging (DWI) lesions. *Methods*. The Cognitive Failures Questionnaire, Hospital Anxiety and Depression Scale, and Subjective Fatigue subscale from the Checklist Individual Strength were used to assess subjective complaints shortly after TIA or TNA and six months later. With repeated measure analysis, the associations between DWI lesion presence or clinical diagnosis (TIA or TNA) and subjective complaints over time were determined. *Results*. We included 103 patients (28 DWI positive). At baseline, SCI and fatigue were less severe in DWI positive than in DWI negative patients, whereas at follow-up, there were no differences. SCI ($p = 0.02$) and fatigue ($p = 0.01$) increased in severity only in DWI positive patients. There were no differences between TIA and TNA. *Conclusions*. Subjective complaints are highly prevalent in TIA and TNA patients. The short-term prognosis is not different between DWI-positive and DWI negative patients, but SCI and fatigue increase in severity within six months after the event when an initial DWI lesion is present.

1. Introduction

Subjective cognitive impairment (SCI), depressive symptoms, and fatigue are highly prevalent after stroke and are related to stroke severity [1–4]. Although by definition the symptoms of a transient ischemic attack (TIA) subside completely within 24 hours [5], subjective cognitive complaints, depressive symptoms, and fatigue often persist in these patients as well [6–8].

Diagnosing TIA is notoriously difficult [9]. Patients often report attacks of atypical or nonfocal neurological symptoms. In the absence of an alternative diagnosis, these episodes are

referred to as transient neurological attack (TNA) [10]. In one-third of TIA patients, diffusion-weighted imaging (DWI) shows signs of acute ischemia beyond the point of symptom resolution, ascertaining a cerebrovascular etiology of the attack [11]. Acute DWI lesions are however also present in more than 20% of clinically diagnosed TNA patients [12].

Previous studies on subjective complaints after short-lasting attacks of neurological symptoms have focused solely on TIA, did not take DWI findings into account, and were cross-sectional in nature [6–8]. Since subjective complaints are associated with a reduced quality of life and are possible harbingers of forthcoming cognitive decline, it is important to understand their prevalence and determinants [13, 14].

We prospectively investigated the prevalence, severity, and course of SCI, depressive symptoms, anxiety, and fatigue in a cohort of TIA and TNA patients and determined the relation with event type and DWI results. We hypothesized that patients with acute DWI lesions would report an increase in severity of complaints in the months after the initial event. Since TIA and TNA have a comparable prevalence of DWI positivity, we expected to find no differences between these patient categories [12].

2. Methods

2.1. Study Design and Patients. This study was part of the prospective Cohort study ON Neuroimaging, Etiology, and Cognitive consequences of Transient neurological attacks (CONNECT), the details of which have been previously reported [15]. Consecutive stroke-free patients aged ≥ 45 years referred to a specialized outpatient TIA clinic within 7 days after an event of acute onset neurological symptoms lasting < 24 hours were included. Baseline measurements took place within seven days after the qualifying event, and follow-up was performed six months later. All baseline assessments were performed before the final diagnosis was discussed with the patient. The Medical Review Ethics Committee region Arnhem-Nijmegen approved the study, and written informed consent was obtained from all participants.

2.2. Classification of Qualifying Event. Based on a detailed description of the signs and symptoms of the event including a structured assessment of the presence or absence of eighteen specific predefined symptoms (Table 1), three specialized stroke neurologists adjudicated each event as TIA, TNA, or a specified other diagnosis, using previously determined definitions of TIA and TNA [5, 10]. Events with both focal and nonfocal symptoms were classified as TIA. Qualifying neurologists were blinded to results from MRI, and in case of disagreement, a consensus meeting was held.

2.3. Brain Imaging. Brain MRI was performed within seven days after the qualifying event on a 1.5 Tesla Magnetom Scanner (Siemens, Erlangen, Germany) and included DWI, FLAIR, T1-, T2-, and T2*-weighted sequences. Two experienced raters individually evaluated the severity of white matter hyperintensities, the presence of (silent) territorial infarcts, lacunes, and microbleeds [16, 17]. DWI was visually assessed for signs of acute infarction. Raters were unaware of clinical information, and a consensus meeting was held in case of disagreement.

Table 1: Predefined focal and nonfocal neurological symptoms.

Focal	Nonfocal
Hemiparesis	Decreased consciousness or unconsciousness
Hemihypesthesia	Confusion
Dysphasia	Amnesia
Dysarthria	Unsteadiness
Hemianopia	Nonrotatory dizziness
Transient monocular blindness	Positive visual phenomena
Hemiataxia	Paresthesias
Diplopia	Bilateral weakness of arms or legs
Vertigo	Unwell feelings*

Symptoms should have sudden onset, rapid clearance, and duration of <24 hours. *Referable to the nervous system if the referring physician considered TIA but patients were unable to specify further.

2.4. Subjective Cognitive Impairment. At baseline and follow-up, the presence and severity of SCI in the previous month was assessed with a 15-item semistructured interview based on the Cognitive Failures Questionnaire (CFQ) [18]. Items concerning remembering, word finding, planning, concentration, and slowness of thought were given a wider score range (0–3) than other items (0-1). SCI was considered present if ≥1 moderate problem (score ≥ 2) on an item with a score range of 0 to 3 or a score of 1 on a dichotomous item was reported [19]. Trained examiners, unaware of clinical diagnosis and DWI status, administered all semistructured interviews.

2.5. Other Measurements. At both baseline and follow-up, the Hospital Anxiety and Depression Scale (HADS) was administered to measure the severity of symptoms of depression and anxiety [20]. Relevant symptoms of depression or anxiety were defined as a value of >7 on the subscales [21]. Fatigue was assessed with the subscale Subjective Fatigue of the Checklist Individual Strength (CIS20R-fatigue) with a score > 35 considered indicative for severe fatigue [22]. Level of education was classified using seven categories (1 = less than primary school; 7 = academic degree) [23]. Vascular risk factors were assessed at baseline. Incident vascular events (stroke, TIA, and myocardial infarction) between baseline and follow-up were assessed with a standardized, structured questionnaire. All questionnaires were handed out at the baseline or follow-up visit. In case of limited time, these were filled in at home and returned within one week.

2.6. Statistical Analysis. Only patients who completed follow-up were included. Baseline characteristics were compared between patients with complete and incomplete follow-up, between TIA and TNA between patients, and patients with and without DWI lesion, using Student's t-test, χ^2 test, or Mann–Whitney U test as appropriate.

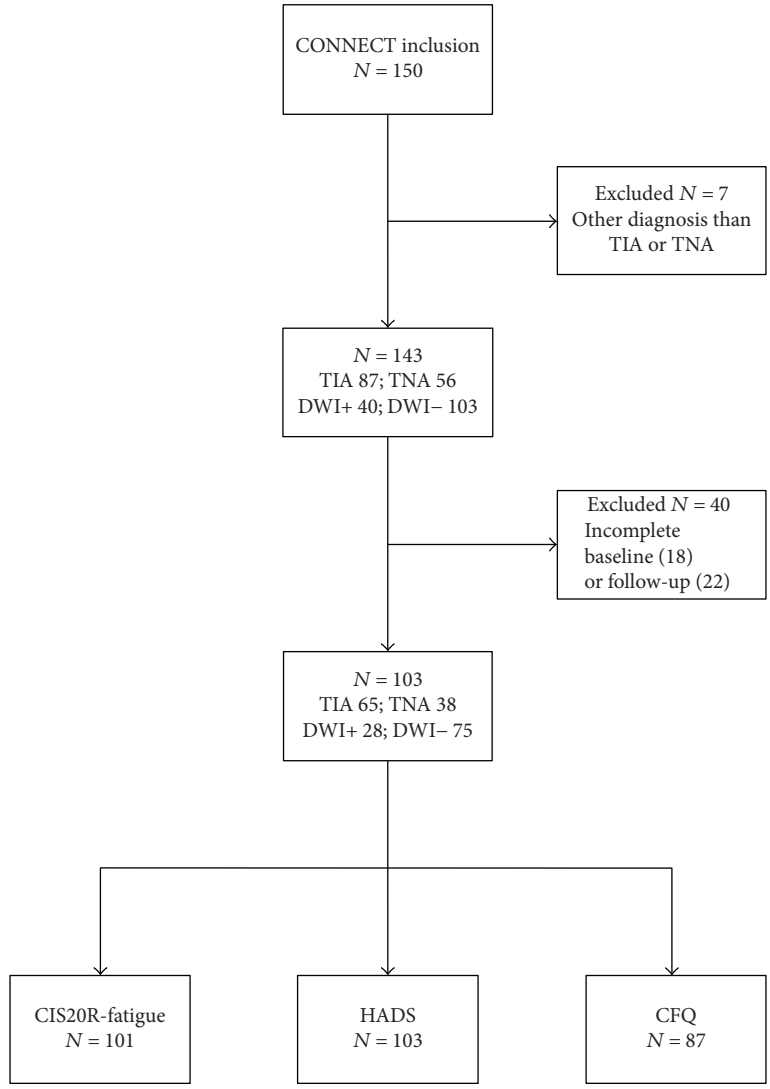

Figure 1: Study population. CFQ: Cognitive Failures Questionnaire; CIS20R-fatigue: Checklist Individual Strength, fatigue subscale; DWI: diffusion-weighted imaging; HADS: Hospital Anxiety and Depression Scale; TIA: transient ischemic attack; TNA: transient neurological attack.

Differences in prevalence of SCI, symptoms of depression or anxiety, and severe fatigue between groups (clinical diagnosis and DWI status) and time points were analyzed with McNemar's test. Subsequently, the effect of DWI lesion and clinical diagnosis on change in subjective outcomes over time was determined with repeated measures analyses of variance. Associations between SCI, fatigue, and depressive and anxiety symptoms were assessed with multivariate regression analysis.

Age, sex, and level of education were regarded as potential confounders and adjusted for in all repeated measures analyses. Alpha was set at 0.05 and statistical analyses were performed with IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY).

3. Results

CONNECT included 150 patients, 87 of whom were diagnosed as TIA, 56 as TNA, and 7 with a specific diagnosis. Patients in the last category were excluded from further analyses, as were those with incomplete baseline or follow-up assessments, leading to 103 included patients (Figure 1). Reasons for incomplete assessment were failure to return questionnaires (>95%) and refusal (<5%). Patients with incomplete HADS or CIS20R-fatigue were slightly younger (mean 61.8 [SD 10.7] years versus 65.8 [SD 9.1] years, $p = 0.04$) than those with complete evaluations. There were no differences concerning clinical diagnosis, DWI lesion presence, level of education, or presence of vascular risk factors between patients with complete and incomplete assessments. Baseline characteristics of participants with complete assessments are presented by DWI results in Table 2. DWI lesions were more often present in clinically defined TIA patients, although 13% of included TNA patients also had a DWI lesion. Most DWI lesions were small cortical or subcortical lesions. There were no incident strokes or myocardial infarctions between baseline and follow-up, and five patients had an incident TIA. Excluding patients with incident TIA from the analyses did not change the results.

Table 2: Baseline patient characteristics stratified by DWI result ($n = 103$).

	DWI+ ($n = 28$)	DWI− ($n = 75$)	p^*
Women	8 (29)	29 (39)	0.34
Age, mean (SD)	66.7 (8.5)	65.6 (9.3)	0.60
Level of education, median (IQR)	5 (3)	5 (2)	0.10
TIA	23 (82)	42 (56)	0.01
Hypertension	25 (89)	60 (80)	0.27
Dyslipidemia	18 (64)	53 (71)	0.53
Diabetes mellitus	2 (7)	7 (9)	0.73
Atrial fibrillation	3 (11)	10 (13)	0.72
Smoking	13 (46)	17 (23)	0.02
Diffusion-weighted imaging lesions, total *n*	45	N/A	N/A
Lesion type			
Small cortical	26 (58)		
Small subcortical	14 (31)		
Territorial	5 (11)		
Fazekas score, median (IQR)	1 (1)	1 (1)	0.30
Lacunes	5 (18)	12 (16)	0.82
Territorial infarcts	2 (7)	8 (11)	0.59
Microbleeds (available for 72 patients)	1 (6)	6 (11)	0.49

Values are *n* (%) unless stated otherwise. *For difference using Student's *t*-test, χ^2 test, or Mann–Whitney *U* test as appropriate. DWI: diffusion-weighted imaging; IQR: interquartile range; TIA: transient ischemic attack; N/A: not applicable.

3.1. Subjective Cognitive Impairment ($n = 87$). The overall prevalence of SCI in TIA and TNA patients was 82% at baseline and 77% at follow-up and was not significantly different between time points, DWI status, or clinical diagnosis. At baseline, the mean number of subjective cognitive failures was lower in patients with a DWI lesion than in those without (mean (SD) 1.83 (1.75) versus 3.77 (3.27), $p = 0.01$), while at follow-up, this increased to 3.00 (2.70) in the first group and decreased slightly to 3.14 (3.17) in the latter ($p = 0.73$) (Figure 2(a)). Repeated measures analysis (adjusted for age, sex, and level of education) showed that change over time in the number of subjective cognitive failures was significantly different between DWI positive and DWI negative patients ($p = 0.01$). There was no difference in SCI between TIA and TNA patients.

3.2. Depressive Symptoms and Anxiety ($n = 103$). Relevant depressive symptoms (HADS-depression subscore > 7) were present in 8% of all patients at baseline and 9% at follow-up. The prevalence of relevant anxiety symptoms (HADS-anxiety subscore > 7) was 15% at baseline and 11% at follow-up. Depressive and anxiety symptoms did not differ between DWI negative and DWI positive patients or between TIA and TNA patient groups (Figures 2(b) and 2(c)).

3.3. Fatigue ($n = 101$). Severe fatigue (CIS20R-fatigue score > 35) was present in 23% of patients at baseline and in 19% six months later. Prevalence of severe fatigue did not differ between DWI positive and DWI negative patients or between TIA and TNA patients.

Mean (SD) CIS20R-fatigue score was 25.0 (12.7) at baseline and 24.8 (11.5) at follow-up. Baseline scores were lower in DWI positive patients (21.0 (12.7) compared to 26.6 (12.4) for those without; $p = 0.07$) but equal at follow-up (24.9 (11.6) in the DWI positive group versus 24.7 (11.6) in the DWI negative group; $p = 0.86$). Patients with and without DWI lesions differed with respect to change in CIS20R-fatigue scores ($p = 0.01$) (Figure 2(d)). The clinical diagnosis was unrelated to severity or change over time of fatigue.

At both baseline and follow-up, SCI was associated with higher CIS20R-fatigue scores ($p = 0.001$), but not with symptoms of depression or anxiety.

4. Discussion

Subjective complaints, especially SCI and fatigue, are highly prevalent in TIA and TNA patients both directly before the event and after six months. The initial qualifying diagnosis was unrelated to the presence, severity, and course of subjective complaints. Patients with signs of acute ischemia on DWI reported less severe SCI and fatigue in the month before the TIA or TNA than those without such a lesion. In this group of patients, severity subsequently increased in the six months after the event to a level equal to that of DWI negative patients.

Some methodological issues need to be considered when interpreting these results. First, given the loss to follow-up, selection bias might have occurred. Patients with missing follow-up HADS and CIS20R-fatigue assessments were on average slightly younger than participants. Since especially fatigue is more often reported in older patients, this might have resulted in an overestimation of its prevalence [24]. Alternatively, patients with incomplete assessments might have dropped out because of complaints, resulting in an underestimation. Other demographic variables however did not differ between patients with and without complete assessments, and we adjusted for age in our analyses. Therefore, we feel that selection bias has not largely influenced our results. The relatively small patient numbers in our study however limit statistical power, and our results need to be replicated in a larger cohort. Secondly, we used questionnaires to obtain information on the presence of SCI, depression, anxiety, and fatigue. These screening instruments, although validated, indicate whether patients experience dysfunction when actively asked about it. This differs from spontaneously reported complaints and may explain the high frequency of SCI observed in our cohort. The CFQ handles a strict cutoff for SCI, making it a sensitive but perhaps not very specific screening instrument. Thirdly, our study did not include a control group, limiting the interpretation of an added effect of TIA or TNA on subjective complaints.

The prevalence of SCI in our study is comparable to that in both stroke patients and those with evidence of small vessel disease on neuroimaging, using the same screening instrument [2, 19, 25]. Patients in those studies were on average older, had more often suffered stroke instead of TIA, and were tested several years after the initial event. Also, vascular

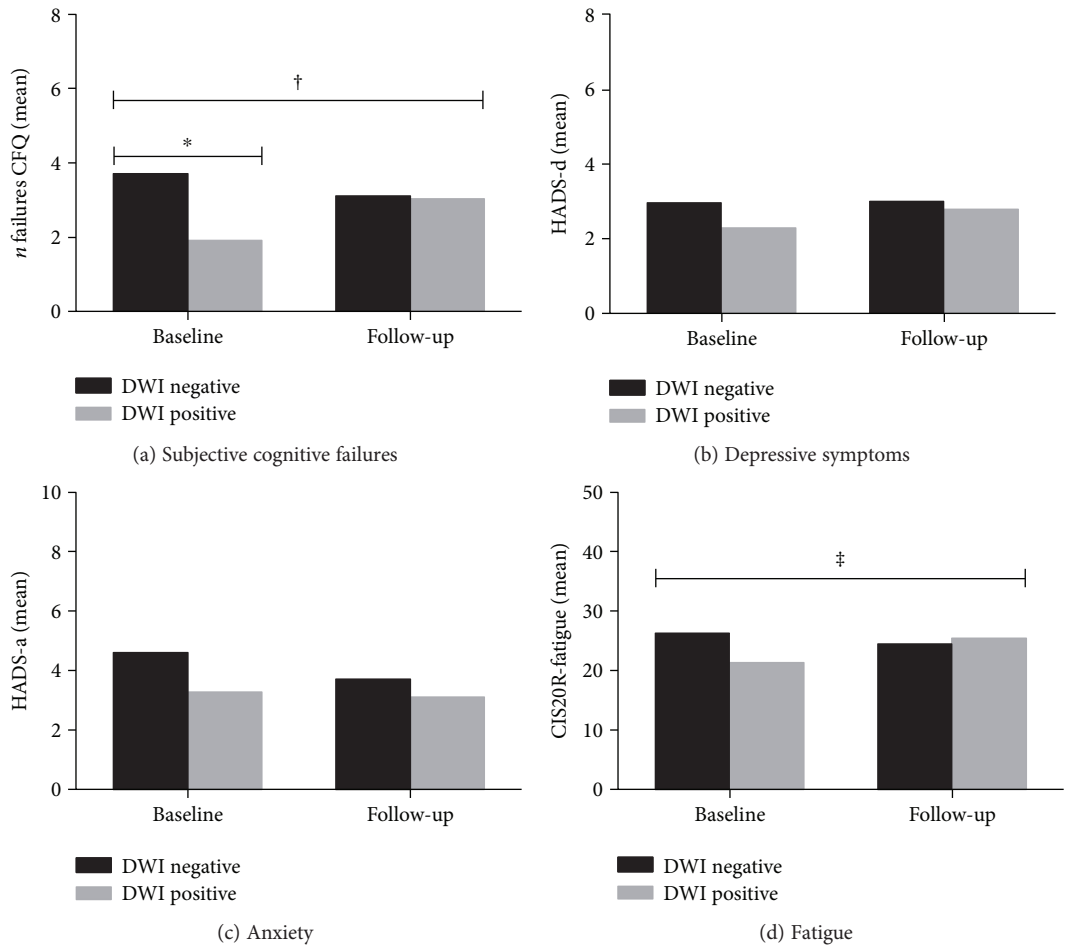

Figure 2: Subjective cognitive impairment, depressive symptoms, anxiety symptoms, and fatigue at baseline and follow-up in transient neurological attack patients with and without diffusion-weighted imaging lesions. CFQ: Cognitive Failures Questionnaire; CIS20R-fatigue: Checklist Individual Strength, fatigue subscale; DWI: diffusion-weighted imaging; HADS-a: Hospital Anxiety and Depression Scale, anxiety; HADS-d: Hospital Anxiety and Depression Scale, depression. $^{*}p = 0.02$, analysis of covariance, adjusted for age, sex, and level of education. $^{\dagger}p = 0.02$, $^{\ddagger}p = 0.01$, repeated measures analysis for the difference in change over time between DWI negative and DWI positive patients, adjusted for age, sex, and level of education.

lesions on neuroimaging were relatively sparse in our cohort, as compared to these studies [19, 25]. The high prevalence of SCI in TIA and TNA patients is therefore remarkable. Severe fatigue was less prevalent in our patients than in other stroke cohorts, as were depressive symptoms [4, 26, 27].

Interestingly, DWI positive patients reported less subjective cognitive failures and fatigue in the month before the event than those without a lesion. The DWI positive group by definition consisted of patients with a recent cerebrovascular event, independent of the clinical diagnosis. The DWI negative group possibly included some patients whose transient complaints have noncerebrovascular causes such as somatization, depression, or anxiety. Although this may explain the higher prevalence of premorbid SCI and fatigue, the lack of observed higher frequencies of depressive or anxiety symptoms does not support this hypothesis. Furthermore, we found no changes in subjective complaints in the DWI negative group, although one could expect these to increase after a disturbing event such as a TIA or TNA.

Within six months after TIA or TNA, severity of SCI and fatigue increased significantly in DWI positive patients. This can be explained in several ways. First, DWI hyperintensities are associated with permanent brain damage, which in turn is associated with cognitive decline, SCI, mood disorders, and fatigue in stroke patients [1, 3, 4, 28, 29]. Although the exact etiology remains to be established, a relationship between minor cognitive decline and recent lacunar infarct has been suggested [30]. Since the DWI lesions in our cohort were predominantly small cortical and subcortical lesions, a similar relationship may exist between these lesions and increasing subjective complaints over time. Second, the knowledge of having a DWI lesion could have influenced the perception of cognitive performance and have led to more subjective cognitive complaints. Third, secondary preventive medications including statins will more often have been started in the DWI positive patient group. Statins have been associated with cognitive complaints and fatigue. However, there are no consistent negative effects of statins on these outcome measures [31]. Finally, the increase in severity of SCI and fatigue

observed in the DWI positive patient group could be merely a correction of an unexplained baseline difference, that is, regression towards the mean. However, no changes in prevalence or severity of these complaints were found in the DWI negative group, countering this explanation.

Fatigue was associated with subjective cognitive dysfunction. Possibly, both fatigue and SCI, as measured in our study, are expressions of the same underlying sense of unwell-being. We found no association between depressive symptoms and subjective cognitive dysfunction, suggesting that the increased severity of SCI observed in DWI positive patients was not influenced by mood changes.

5. Conclusions

Subjective complaints are highly prevalent in TIA and TNA patients. Larger sampled studies with longer follow-up need to determine whether subjective complaints last beyond six months after TIA or TNA and assess the course over time with respect to DWI lesion presence and the association with cognitive performance. Furthermore, the etiology of subjective cognitive impairment and fatigue after short-lasting cerebral ischemia and the association with radiological markers of cerebrovascular damage such as lacunes and cerebral atrophy should be subject to further research. Our results nevertheless add to the growing notion that TIA and TNA are more than just transient attacks but are associated with ongoing deficits and problems. This can be used to inform patients on the potential long-term prognosis of their TIA or TNA.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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References

[1] F. Lamb, J. Anderson, M. Saling, and H. Dewey, "Predictors of subjective cognitive complaint in postacute older adult stroke patients," *Archives of Physical Medicine and Rehabilitation*, vol. 94, no. 9, pp. 1747–1752, 2013.

[2] N. A. Maaijwee, P. Schaapsmeerders, L. C. Rutten-Jacobs et al., "Subjective cognitive failures after stroke in young adults: prevalent but not related to cognitive impairment," *Journal of Neurology*, vol. 261, no. 7, pp. 1300–1308, 2014.

[3] N. El Husseini, L. B. Goldstein, E. D. Peterson et al., "Depression and antidepressant use after stroke and transient ischemic attack," *Stroke*, vol. 43, no. 6, pp. 1609–1616, 2012.

[4] A. Lerdal, L. N. Bakken, S. E. Kouwenhoven et al., "Poststroke fatigue—a review," *Journal of Pain and Symptom Management*, vol. 38, no. 6, pp. 928–949, 2009.

[5] National Institute of Neurological Disorders and Stroke Committee, "Special report from the National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III," *Stroke*, vol. 21, no. 4, pp. 637–676, 1990.

[6] M. Fens, C. M. van Heugten, G. H. Beusmans et al., "Not as transient: patients with transient ischaemic attack or minor stroke experience cognitive and communication problems; an exploratory study," *The European Journal of General Practice*, vol. 19, no. 1, pp. 11–16, 2013.

[7] H. J. Luijendijk, B. H. Stricker, R. G. Wieberdink et al., "Transient ischemic attack and incident depression," *Stroke*, vol. 42, no. 7, pp. 1857–1861, 2011.

[8] C. Winward, C. Sackley, Z. Metha, and P. M. Rothwell, "A population-based study of the prevalence of fatigue after transient ischemic attack and minor stroke," *Stroke*, vol. 40, no. 3, pp. 757–761, 2009.

[9] J. Castle, M. Mlynash, K. Lee et al., "Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists," *Stroke*, vol. 41, no. 7, pp. 1367–1370, 2010.

[10] M. J. Bos, M. J. van Rijn, J. C. Witteman, A. Hofman, P. J. Koudstaal, and M. M. Breteler, "Incidence and prognosis of transient neurological attacks," *JAMA*, vol. 298, no. 24, pp. 2877–2885, 2007.

[11] M. Brazzelli, F. M. Chappell, H. Miranda et al., "Diffusion-weighted imaging and diagnosis of transient ischemic attack," *Annals of Neurology*, vol. 75, no. 1, pp. 67–76, 2014.

[12] F. G. van Rooij, S. E. Vermeer, B. M. Goraj et al., "Diffusion-weighted imaging in transient neurological attacks," *Annals of Neurology*, vol. 78, no. 6, pp. 1005–1010, 2015.

[13] P. Montejo, M. Montenegro, M. A. Fernandez, and F. Maestu, "Memory complaints in the elderly: quality of life and daily living activities. A population based study," *Archives of Gerontology and Geriatrics*, vol. 54, no. 2, pp. 298–304, 2012.

[14] R. J. Kryscio, E. L. Abner, G. E. Cooper et al., "Self-reported memory complaints: implications from a longitudinal cohort with autopsies," *Neurology*, vol. 83, no. 15, pp. 1359–1365, 2014.

[15] F. G. van Rooij, A. M. Tuladhar, R. P. Kessels et al., "Cohort study ON Neuroimaging, Etiology and Cognitive consequences of Transient neurological attacks (CONNECT): study rationale and protocol," *BMC Neurology*, vol. 15, no. 1, p. 36, 2015.

[16] F. Fazekas, J. B. Chawluk, A. Alavi, H. I. Hurtig, and R. A. Zimmerman, "MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging," *American Journal of Roentgenology*, vol. 149, no. 2, pp. 351–356, 1987.

[17] J. M. Wardlaw, E. E. Smith, G. J. Biessels et al., "Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration," *Lancet Neurology*, vol. 12, no. 8, pp. 822–838, 2013.

[18] D. E. Broadbent, P. F. Cooper, P. FitzGerald, and K. R. Parkes, "The Cognitive Failures Questionnaire (CFQ) and its correlates," *The British Journal of Clinical Psychology*, vol. 21, no. 1, pp. 1–16, 1982.

[19] J. C. de Groot, F. E. de Leeuw, M. Oudkerk, A. Hofman, J. Jolles, and M. M. Breteler, "Cerebral white matter lesions and subjective cognitive dysfunction: the Rotterdam Scan Study," *Neurology*, vol. 56, no. 11, pp. 1539–1545, 2001.

[20] A. S. Zigmond and R. P. Snaith, "The Hospital Anxiety and Depression Scale," *Acta Psychiatrica Scandinavica*, vol. 67, no. 6, pp. 361–370, 1983.

[21] I. Bjelland, A. A. Dahl, T. T. Haug, and D. Neckelmann, "The validity of the Hospital Anxiety and Depression Scale. An updated literature review," *Journal of Psychosomatic Research*, vol. 52, no. 2, pp. 69–77, 2002.

[22] J. H. Vercoulen, C. M. Swanink, J. F. Fennis, J. M. Galama, J. W. van der Meer, and G. Bleijenberg, "Dimensional assessment of chronic fatigue syndrome," *Journal of Psychosomatic Research*, vol. 38, no. 5, pp. 383–392, 1994.

[23] J. Hochstenbach, T. Mulder, J. van Limbeek, R. Donders, and H. Schoonderwaldt, "Cognitive decline following stroke: a comprehensive study of cognitive decline following stroke*," *Journal of Clinical and Experimental Neuropsychology*, vol. 20, no. 4, pp. 503–517, 1998.

[24] J. H. Loge, O. Ekeberg, and S. Kaasa, "Fatigue in the general Norwegian population: normative data and associations," *Journal of Psychosomatic Research*, vol. 45, no. 1, pp. 53–65, 1998.

[25] A. G. van Norden, W. F. Fick, K. F. de Laat et al., "Subjective cognitive failures and hippocampal volume in elderly with white matter lesions," *Neurology*, vol. 71, no. 15, pp. 1152–1159, 2008.

[26] N. A. Maaijwee, R. M. Arntz, L. C. Rutten-Jacobs et al., "Post-stroke fatigue and its association with poor functional outcome after stroke in young adults," *Journal of Neurology, Neurosurgery & Psychiatry*, vol. 86, no. 10, pp. 1120–1126, 2015.

[27] L. Snaphaan, S. van der Werf, K. Kanselaar, and F. E. de Leeuw, "Post-stroke depressive symptoms are associated with post-stroke characteristics," *Cerebrovascular Diseases*, vol. 28, no. 6, pp. 551–557, 2009.

[28] C. Oppenheim, C. Lamy, E. Touze et al., "Do transient ischemic attacks with diffusion-weighted imaging abnormalities correspond to brain infarctions?," *American Journal of Neuroradiology*, vol. 27, no. 8, pp. 1782–1787, 2006.

[29] S. T. Pendlebury and P. M. Rothwell, "Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis," *Lancet Neurology*, vol. 8, no. 11, pp. 1006–1018, 2009.

[30] L. Blanco-Rojas, A. Arboix, D. Canovas, M. Grau-Olivares, J. C. Oliva Morera, and O. Parra, "Cognitive profile in patients with a first-ever lacunar infarct with and without silent lacunes: a comparative study," *BMC Neurology*, vol. 13, p. 203, 2013.

[31] C. S. Desai, S. S. Martin, and R. S. Blumenthal, "Non-cardiovascular effects associated with statins," *BMJ*, vol. 349, article g3743, 2014.