Does the brain prefer geometrical homogeneity?

A. Midorikawa\textsuperscript{a,b,*} and M. Kawamura\textsuperscript{b}
\textsuperscript{a}Department of Psychology, Chuo University Faculty of Letters, Tokyo, Japan
\textsuperscript{b}Department of Neurology, Showa University School of Medicine, Tokyo, Japan

Abstract. Some patients with frontotemporal lobar degeneration (FTLD) have shown the development of painting or musical abilities after the onset of the disease. In this report, we present another emergent ability. A female patient with FTLD showing dense atrophy of the bilateral anterior lobes and a loss of voluntary activity in aspects of daily living, presented with the characteristic behaviours when given a paper and a pair of scissors. When a shape was already drawn on the paper, she showed reasonable skills with the scissors, cutting without any hesitation. When she cut a blank piece of paper, she showed quite unique geometrical preferences. Her severely degenerated brain combined with her geometrical abilities suggests that the human brain is naturally affected by geometrical homogeneity.

Keywords: Dementia, frontotemporal lobar degeneration (FTLD), residual function, geometrical ability

1. Introduction

Dementia deprives us of various abilities, not only of memory function, but also verbal, motor, cognitive, or executive functions [2]. For a long time it had been postulated that a demented brain gradually robbed someone of his or her basic functions, leading to a person without abilities. Recently, however, several studies have shown that even after the onset of dementia some patients show a development or emergence of several different abilities, such as painting [5,7,14,15,18,21], composing music, photography, or solving a puzzle [16,17]. Some famous musical compositions were actually a product of dementia [1]. Although there are several subtypes of dementia, all of the aforementioned patients were diagnosed with, or considered to have frontotemporal lobar degeneration (FTLD), which presents as primary dementia characterized by disproportionate atrophy of the anterior frontal and temporal lobes [8]. Accordingly, a deficit of the anterior portion of the brain is considered crucial for the preservation or emergence of several abilities. However, some of these reported cases had left-sided asymmetrical atrophy, suggesting that specific latent or novel abilities are restricted to left-sided asymmetrical atrophy.

In this article, we present a case of bilateral dense atrophy of the frontotemporal lobes coinciding with newly discovered latent or novel abilities. We believe that investigation of these abilities might be a gateway to hidden human functions.

2. Case history

In December 2002, a 66-year-old female patient was admitted to Showa University Hospital in Tokyo, Japan, because of severe word-finding difficulty and a substantial change in personality. Her symptoms had begun at the end of the year 2000, and her neurological examination (conducted at another hospital) was normal then, with the exception for verbal impairment. Her spontaneous speech had decreased, but she was capable of shopping and preparing a meal by herself. Over the next two years, her condition markedly deteriorated. She was unable to perform most spontaneous activities, but was still able to follow instructions, walk, and eat, independently. In February 2003,
A. Midorikawa and M. Kawamura / Geometrical homogeneity in FTLD

Fig. 1. Magnetic resonance imaging reveals dense atrophy in the frontotemporal lobe; however, the parieto-occipital lobe remains well-preserved. The left image is of the FLAIR MRI images of coronal section of the brain; the right image is a T2-weighted horizontal section.

her Mini-Mental State Examination (MMSE) [6] score was 1/30 (only the “repetition” test was correct) and her Mental Function Impairment Scale (MENFIS) [9] score (72/78) showed severe deterioration of several functions, with the exception of topographical disorientation. At that time, neurological examination showed a strong grasping reflex in both the hands of the patient (the left hand more so than the right) and compulsive laughter. Magnetic resonance imaging (MRI) revealed dense atrophy of the bilateral frontotemporal lobe, but the parieto-occipital lobe was well-preserved (Fig. 1). Single photon emission computed tomography (SPECT) imaging also showed bilateral frontotemporal hypoperfusion (the right side more so than the left). Frontal atrophy was severe, and she progressed to a complete loss of spontaneous activity; nevertheless, some residual functions were observed. For example, she was able to navigate certain areas in her neighbourhood; not only could she take a walk without losing her way, she could also take a different route every time. She particularly preferred the narrow back streets rather than the main street. She also could take a meal independently using a pair of chopsticks skilfully, but over and over again she picked up residual tiny food particles on the bowl. She even demonstrated good skills with a pair of scissors and unusual geometrical capabilities. We examined the last point in detail in the following section.

3. Methods and results

3.1. Cutting a line-drawing

When the examiner placed a pair of scissors and a piece of paper with a simple line-drawing (e.g. a star shape) in front of the patient, she grasped them and immediately started cutting the paper without any particular instruction. Her cutting behaviour was reasonable and accurate; she started at the end of the ideal extension line originating from an actual line (Fig. 2A) and cut out the figure, leaving a narrow blank space (usually within a millimetre). When the examiner placed a complicated figure (e.g. an overlap of several figures, such as a circle, rectangle, and triangle), she cut the figure regardless of form.

These results imply that although in daily living situations she showed a severe loss of voluntary activity and grasping reflex, her spontaneous activity and hand-motor skills were still well preserved.

3.2. Cutting a blank paper I

When the examiner placed a pair of scissors and a blank A4-sized piece of paper in front of the patient, she began cutting the paper without any instruction. In this situation, not only did she cut the paper at a right angle, but also repeatedly cut the paper for twelve trials. A thorough investigation revealed that the width of each paper cut was different for every trial (Fig. 1B). In addition, not including the first trial, the ratio of remaining paper to cut paper was consistently 0.2 until the seventh trial (Fig. 1C).

3.3. Cutting a blank paper II

At a later date (August 2007), when the examiner presented her with a blank A4-sized piece of paper and a pair of scissors, she took them and cut the paper straight into a rectangle, then repeatedly sliced the
length of the rectangle. Superposing the top and bottom of the rectangle revealed that the widths of the rectangle were almost identical. When the widths of each side of the rectangle were measured using an electric slide caliper (minimum measurable width is 0.01 mm, error of measurement is 0.01 mm), the difference was less than 0.01 mm.

4. Discussion

Frontotemporal lobar degeneration (FTLD) is the term applied to patients who present with primary dementia characterized by disproportionate atrophy of the anterior frontal and temporal lobes [8]. Previous reports have shown that some patients with FTLD presented several latent or newly developed abilities after onset of the disease. Most cases involved visual art, such as painting [5,7,14,15,18,21], but composing music and solving a puzzle were also reported [16,17]. In such reported cases, crucial lesions were attributed to the unilateral left-sided frontotemporal lobes. To date, there are no reports concerning geometrical abilities associated with dementia; therefore, we think that our patient’s characteristic cutting behaviour might be a novel symptom. In addition, the bilateral lesions have never been reported to affect residual function, and thus we also think that this is the first reported case of a residual function of bilateral frontal lobe atrophy.

In this report, we described a case of FTLD and presented the following three characteristics: First, in the MR images, severe atrophy was observed in the bilateral frontal lobes and anterior portion of the temporal lobes, whereas parietal and occipital lobes were well-preserved, as well as the posterior portion of the temporal lobes. The patient’s clinical symptoms, such as the declining spontaneous activity and grasping reflexes, corresponded with the MRI results. Second, although severe frontal lobe atrophy robbed her of many spontaneous activities, she nevertheless displayed good hand-motor skills. When given a pair of scissors and shown a figure drawn on paper, she spontaneously took the scissors and carefully cut around the drawing. Third, when she cut a plain piece of paper, she showed two geometrical preferences: equal ratio and parallel shape. In addition, the patient’s parallel shape preference was unusually accurate.
Previous reports have shown that patients with a frontal lobes lesion shows several spontaneous activities when they are presented to objects without any instructions, such as putting glasses on patients’ nose or pouring water from the bottle into the glass. These spontaneous activities have been called “utilization behaviour” [12,13]. The origin of utilization behaviour have been postulated as absence of a supervisory system in the frontal lobes and automatic activation of an action schema in the parietal lobes [20]. Therefore, in the present case, the sight of a pair of scissors and paper might activate her residual functions associated with the objects, such as taking a pair of scissors, taking a paper, and cutting the paper with the scissors. In a similar way, we have considered that a large part of her ADL might be caused by utilization behaviour. For example, she took a meal using chopsticks skilfully. This is because the sight of dishes and a pair of chopsticks would activate her skilful eating behaviour. However, her eating behaviour was not normal but deviated. Even when she finished everything on her dish, over and over again, she picked up tiny food particles on the bowl with dexterity. It is believed that the onset of her performance was based on utilization behaviour but, in addition to this, her performance was modified by additional abilities, such as hypersensitivity for local information. We believed that this might be true for her cutting behaviour.

The relationship between the posterior portion and geometrical ability has been suggested during studies of the line orientation test. For example, Benton et al. [3] found that the frequency of impaired performance on the line orientation test is particularly high in patients with right posterior parietal lesions. The line orientation test is a widely used neuropsychological test to assess visuospatial processing [11], in which the subject is asked to identify the orientation of pairs of lines on a multiple-choice display. Therefore, the posterior region appears to play a crucial role in recognizing the parallelism of diagonal lines of a rectangle.

Reports that musical or painting abilities are sustained or enhanced in some FTLD patients, have been explained by an emergence of residual right hemisphere functions released from the left hemisphere function due to atrophy [16–18]. The most plausible mechanism to explain sustained or enhanced abilities after onset of the dementia was hypothesized as a reflection of the paradoxical functional facilitation (PFF) effect [16,17]. The original notion of the PFF effect was proposed by Kapur [10] and, based on this hypothesis, Miller and his colleagues subsequently postulated that degeneration of the left temporal cortex led to decreased inhibition of “the right-sided and posteriorly located visual and musical systems” [16]. We also think that the PFF hypothesis could be extrapolated to fit our patient’s symptoms; the emergence of the hidden posterior lobe function due to freedom from the frontal lobe occupation.

Concerning drawing abilities, it has been reported that some FTLD patients show excellent realistic drawing skills. Referring to the artistic abilities of autism patients [19], this kind of drawing ability has not been considered a result of a newly developed skill, but rather an expression of a hidden innate ability [4,15]. As such, we hypothesize that our patient’s hypersensitivity for geometrical homogeneity might also be a result of expression of an innate, but newly expressed ability. In other words, her geometrical preferences imply that our brains, by nature, are affected by geometrical homogeneity.

Finally, when faced with severely demented patients, clinicians or caregivers might think that they cannot coax from them any sense of capability; however, our patient’s case suggests even severe dementia patients might have several residual functions that could possibly be elicited.

Acknowledgments

AM was supported by Chuo University Grant for Special Research and AM and MK was supported by Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology (MEXT). MK was also supported in part by a Showa University Grant-in-Aid for Innovative Collaborative Research Projects and a Special Research Grant-in-Aid for Development of Characteristic Education from MEXT.

References


Does Diabetes Mellitus alter the onset and clinical course of vascular dementia?

Santosh B. Murthy\textsuperscript{a,1}, Ali Jawaid\textsuperscript{a,1,2}, Salah U. Qureshi\textsuperscript{a,c,d,f}, Yogeshwar Kalkonde\textsuperscript{a}, Andrew M. Wilson\textsuperscript{a}, Michael L. Johnson\textsuperscript{e,f}, Mark E. Kunik\textsuperscript{c,d,f} and Paul E. Schulz\textsuperscript{a,b,2,*}

\textsuperscript{a}Department of Neurology, Baylor College of Medicine, Houston, TX, USA
\textsuperscript{b}Neurology Care Line, The Michael E. DeBakey VA Medical Center, Houston, TX, USA
\textsuperscript{c}Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA
\textsuperscript{d}Center for Quality of Care and Utilization Studies, Veterans Affairs Medical Center, Houston, TX, USA
\textsuperscript{e}University of Houston, College of Pharmacy, Houston, TX, USA
\textsuperscript{f}VA South Central Mental Illness Research Education and Clinical Center, Houston, TX, USA

Abstract. Background: Vascular dementia (VaD) is the second most common dementing illness. Multiple risk factors are associated with VaD, but the individual contribution of each to disease onset and progression is unclear. We examined the relationship between diabetes mellitus type 2 (DM) and the clinical variables of VaD.

Methods: Data from 593 patients evaluated between June, 2003 and June, 2008 for cognitive impairment were prospectively entered into a database. We retrospectively reviewed the charts of 63 patients who fit the NINDS-AIREN criteria for VaD. The patients were divided into those with DM (VaD-DM, \( n = 29 \)) and those without DM (VaD, \( n = 34 \)). The groups were compared with regard to multiple variables.

Results: Patients with DM had a significantly earlier onset of VaD (71.9 ± 6.54 vs. 77.2 ± 6.03, \( p < 0.001 \)), a faster rate of decline per year on the mini mental state examination (MMSE; 3.60 ± 1.82 vs. 2.54 ± 1.60 points, \( p = 0.02 \)), and a greater prevalence of neuropsychiatric symptoms at the time of diagnosis (62% vs. 21%, \( p = 0.02 \)).

Conclusions: A history of pre-morbid DM was associated with an earlier onset and faster cognitive deterioration in VaD. Moreover, DM was associated with neuropsychiatric symptoms in patients with VaD. A larger study is needed to verify these associations. It will be important to investigate whether better glycemic control will mitigate the potential effects of DM on VaD.

1. Introduction

Vascular dementia is the second most common type of dementia in the elderly, accounting for 15–20% of all cases [1]. A number of factors are known to increase the risk of vascular dementia, including a history of hypertension, DM, hyperlipidemia, smoking and cardiac conditions [2–4]. Several studies have addressed the contribution of each risk factor to VaD and the question of which, if any, predict the rate of cognitive decline in VaD.

It has been difficult to establish the contribution of each vascular risk factor to VaD because they often occur concurrently in the elderly. DM is one risk factor for VaD and Alzheimer’s disease (AD) [5–7]. Kloppenborg et al. reviewed the incidence of both AD and VaD in relation to DM, hypertension, dyslipidemia and obesity, and concluded that DM conveys the highest risk of both dementias in the elderly, whereas hypertension has the greatest contribution in middle-aged individuals [8]. In addition to conferring a greater risk to both of these dementias, DM is also implicated in worsening the course of AD where it is associated with an earlier onset of cognitive symptoms and more rapid cognitive deterioration [9]. It has also been noted that the presence of co-morbid DM can result in a subtle alteration in the pattern of cognitive dysfunction in AD [10].
It has been difficult to establish specific factors that predict cognitive decline in VaD. Chui et al., for example, reviewed 13 studies of the natural history of VaD and concluded that no single factor predicts significantly faster cognitive decline [11]. In another study, age over 80 years was observed to be a significant predictor of faster cognitive decline in patients with VaD and it was suggested that it probably reflected a superimposed neurodegenerative condition [12]. An MRI-based analysis showed that in older individuals, cerebral small-vessel disease enhances cognitive decline, however the association is independent of the influence of selective vascular risk factors [13].

While it has been difficult to identify a specific role for DM in altering the course of VaD, DM has been associated with a worse cognitive profile for another neurodegenerative disorder, amyotrophic lateral sclerosis (ALS). We found that pre-morbid DM was associated with a 4 year later age of onset for the motor findings of ALS, but a worse cognitive profile. (Jawaid et al. Under Review)

Considering the associations between DM and dementia, we hypothesized that DM could alter the course and cognitive or behavioral profile for VaD. In order to gain insight into the effects of DM on VaD, we examined VaD in patients with and without DM. Greater insight into the contribution of individual risk factors, like DM, to VaD may have important preventive and prognostic implications.

2. Methods

2.1. Study design and participants

Five hundred and ninety-three consecutive patients were evaluated for cognitive impairment between June 2003 and June 2008 in the Cognitive Disorders Clinic at The Michael E DeBakey Veteran Affairs Medical Center (MEDVAMC), Houston, TX, USA.

The patients were labeled with a clinical diagnosis of ‘dementia’ based on the definition in Diagnostic and Statistical Manual for Mental Disorders IV (DSMIV). Patients were excluded if they gave a positive history of a major psychiatric disorder (unrelated to VaD) or substance abuse. Patients who screened positive for 'dementia' based on the definition in Diagnostic and Statistical Manual for Mental Disorders IV (DSMIV). Patients were excluded if they gave a positive history of a major psychiatric disorder (unrelated to VaD) or substance abuse. Patients who screened positive for metabolic delirium on routine clinical investigations were also excluded. The remaining patients \((n = 471)\) were entered prospectively into a database that, for the purposes of this study, was searched for patients with VaD. Patients were labeled with VaD if they fulfilled the NINDS-AIREN criteria for probable/possible VaD [14]. Patients with the diagnosis of a concomitant neurodegenerative process were excluded from the study. Patients with a history of lobar hemorrhages or space occupying lesions were also excluded.

The study was approved by the Institutional Review Board of Baylor College of Medicine and the MEDVAMC Research and Development Committee.

2.2. Baseline assessment

Dementia diagnoses were made when patients were seen in clinic by two board certified neurologists specializing in neuropsychiatry. They were unaware of the fact that patients with VaD would be part of this future investigation. For this study, the charts of patients diagnosed with VaD were abstracted by a board certified psychiatrist and a senior neurology resident, both unblinded to study design and hypotheses. The abstracted information included a neurologic and medical history (including family history and medication history), findings on neurological examination, laboratory test results, results of brief neuropsychological assessment (e.g., MMSE scores), neuroimaging findings, and multiple demographic variables.

Specifically, the electronic medical records from the first clinical visit were screened for the following past medical illnesses (yes/no): diabetes, hypertension, stroke, dyslipidemia, alcohol abuse/dependence, ischemic heart disease, valvular disease, congestive heart failure, atrial fibrillation and current smoking status (smoker/non-smoker). Electronic medical records from the first clinical visit only were assessed to ensure that the aforementioned medical illnesses were present in the patients prior to the diagnosis of dementia. If any of these medical illnesses developed after the diagnosis of dementia, the association observed between the illness and dementia variables could be spurious. Laboratory results were reviewed to calculate mean HbA1c for all patients with DM, wherever available. HbA1c values recorded at all clinical visits both prior and after the diagnosis of dementia were included. Laboratory HbA1c values were available for only 21 of the total 29 diabetic patients. For the remaining diabetics, average serum glucose values were used to estimate HbA1c using the formula: \(\text{Average Glucose (mg/dL)} = 28.7 \times \text{HbA1c} - 46.7\) [15]. Information about vascular dementia (including age of onset of cognitive symptoms, yearly rate of MMSE decline) and patient demographics (age, gender and ethnicity) were recorded for all the patients. Information about ‘age of onset’
was abstracted from the electronic record of the first clinical visit of the patient to the Neurology clinic and the values were approximated to the closest year.

Only patients with a baseline MMSE score of 10-24 with at least three follow-up evaluations were selected for further assessment. This range was chosen to be sure that patients had dementia and were within a range where cognitive changes could be accurately ascertained. 'Yearly rate of MMSE decline' was determined by calculating the difference between the MMSE score on the first and last visits to the Neurology clinic and dividing the difference by the number of years separating the first and the last clinical visit.

2.3. Assessment of neuropsychiatric symptoms

The charts of patients with possible/probable VaD were reviewed to identify neuropsychiatric symptoms recorded during their first visit to the Neurology clinic. We specifically examined charts for these symptoms: delusions, hallucinations, anxiety, aggression, euphoria, dis-inhibition, irritability, apathy, aberrant motor activity, and night-time behavioral disturbance. The documented neuropsychiatric symptoms were coded by the nearest symptom (according to the neuropsychiatric inventory, NPI [16]). For example, if the medical record suggested 'anxious behavior and panic attacks', the NPI symptom of ‘anxiety’ was coded. Patients were grouped into those without neuropsychiatric symptoms and those with one or more such symptom. This was done because the small sample size here precluded assessing the relationship between each individual neuropsychiatric symptom and DM. Thus, while we recorded each symptom, for the purposes of analysis, we defined each person as having or not having any neuropsychiatric symptoms.

2.4. Neuroimaging evaluation

Image assessment was performed by two board certified neurologists reviewing online digital CT/MRI files. The imaging modalities were used to look for evidence of vascular disease as defined by the NINDS-AIREN criteria [14].

2.5. Statistical analysis

Pearson Chi square tests were used for descriptive analysis and Student’s t tests were used to compare the continuous variables. Multivariate linear regression models were used to test for confounders. Statistical analysis was performed using SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). P values < 0.05 were considered significant. Confidence intervals (CIs) were computed based on a 95% confidence level.

For the outcome variables of age of onset and rate of MMSE decline, a minor fraction of the data was missing. Patients for whom the data on more than one outcome variable was missing were excluded from the final analysis.

3. Results

3.1. Demographics

Of 471 patients screened for pure VaD, 119 patients fulfilled the NINDS-AIREN criteria. Forty one patients were excluded because of the presence of a concomitant neurodegenerative condition (predominantly AD). Fifteen patients were excluded because the data was missing on more than one outcome variable. Sixty three patients were included in the final analysis. The majority (81%) of patients were males since this is a Veteran population.

The data was dichotomized into two groups based on the presence \( n = 29 \) or absence \( n = 34 \) of DM. The diabetics and non-diabetics did not differ with regards to age and histories of stroke, hypertension, dyslipidemia, ischemic heart disease, valvular disease, atrial fibrillation, current smoking status or alcohol abuse. A non-Caucasian ethnicity was significantly associated with DM (Table 1).

3.2. Age of onset

The univariate analysis showed that age of onset for vascular dementia was earlier for diabetics (Table 2).
In V aD patients, DM is associated with changes in the age of onset, MMSE decline per year, and neuropsychiatric symptoms. In V aD patients, DM is associated with changes in the age of onset, MMSE decline per year, and neuropsychiatric symptoms. Only a history of DM and stroke were associated with presence of one or more neuropsychiatric symptoms (Table 2).

The independent effect of individual vascular risk factors on the age of onset of vascular dementia was also studied through multiple linear regression analysis (Table 3). Only a history of DM and stroke were associated with a significantly early onset.

### 3.3. Yearly decline in MMSE

Diabetics had a faster rate of decline on MMSE per year on univariate analysis (Table 2). A multiple linear regression analysis of the data also showed that among all the vascular risk factors, only DM was associated with a significantly faster rate of MMSE decline in patients with V aD (Table 4).

### 3.4. The presence of one or more neuropsychiatric symptoms

One or more neuropsychiatric symptom was present in 18 of 29 DM patients versus 3 of 34 non-DM patients. The neuropsychiatric symptoms (anxiety, depression, hallucinations, etc.) were grouped because the sample size precluded examining the frequency of individual neuropsychiatric symptoms versus the presence or absence of DM. Grouping all the symptoms demonstrated in the univariate analysis that DM was significantly associated with presence of one or more neuropsychiatric symptoms (Table 2).

Spearman’s correlations were run between mean HbA1c, age of onset and rate of decline on MMSE. Non-statistically significant negative correlations were observed for HbA1c and age of onset (Spearman’s rho = −0.31) as well as HbA1c and rate of MMSE decline (Spearman’s rho = −0.08).

### 4. Discussion

This study suggests that the clinical course of V aD is altered by DM, which was associated with an earlier age of onset of cognitive symptoms, a faster rate of decline in MMSE, and the presence of one or more neuropsychiatric symptoms.

### 4.1. DM and cognitive decline in V aD

This study suggests that the presence of DM is associated with an earlier and faster cognitive decline in patients with V aD. The study design here (retrospective) does not allow us to conclude that there is a causal relationship between them. Applying the Bradford Hill’s criteria for causation [17] in this scenario, it can be argued that this study shows an evidence for an association between DM and altered clinical course of V aD, which is supported by a biological rationale cohesive to our current knowledge. However, the retrospective study design precludes any evidence which would have suggested a temporal relationship. Future studies will be required to establish a consistency of this evidence.

There are pathophysiologic changes in DM that may explain the earlier onset and swifter progression of V aD found in this study. For example, DM has been shown to lead to neuronal injury through a variety of metabolic pathways that may affect endothelial function, protein...
synthesis, DNA, and mitochondrial function, and may enhance free radical damage and inflammation [18]. Another study, which was autopsy based, demonstrated that elderly patients with dementia and DM had more microvascular infarcts and increased cortical IL-6 concentration [19]. Thus, in addition to producing vascular insults, DM could worsen VaD through a variety of non-vascular mechanisms of neuronal loss or dysfunction.

DM could also worsen VaD by increasing the vascular disease burden at a swifter rate than other risk factors for VaD resulting in earlier onset and faster clinical deterioration. However, this hypothesis remains to be investigated, perhaps by quantifying vascular disease burden in VaD patients with DM versus without DM.

The association between diabetes and worse clinical features of VaD could be interesting from a therapeutic point of view if there is a cause-and-effect relationship between them. A causal relationship, for example, might suggest that better glycemic control could slow the progression of VaD. Interestingly, one finding here seems to weigh against the hypothesis that tighter DM control will mitigate the effects of DM on VaD: there was no significant correlation here between HbA1c and age of onset or the rate of cognitive deterioration in VaD patients. HbA1c is an established indicator of glycemic control. We would caution, however, that this lack of correlation could be due to the small sample size of this study. Alternatively, recent HbA1c values were selected, and it is possible that past HbA1c values are more relevant. For example, it is possible that glycemic control is more important for preventing the onset of cognitive symptoms than for influencing the disease course once the cognitive deficits have begun.

Another important consideration is that the population studied was predominantly male. A recent study in Italy showed a differential effect of DM on baseline cognitive impairment in men vs. women. Women aged 65–84 years with DM had worse cognition at baseline when compared to non-diabetic women, but did not show worsening at four and eight year follow-up assessments. Men with and without DM did not differ in cognitive performance at baseline, but showed a worsening over time [20]. Interestingly, our male predominant cohort showed both an earlier onset and swifter rate of cognitive decline as assessed by MMSE.

4.2. DM and neuropsychiatric symptoms of dementia

Neuropsychiatric symptoms are common in VaD patients. They are reported to be present in up to 96.4% of patients [21]. In AD, vascular risk factors, particularly hypertension and stroke, have been associated with an increased risk of neuropsychiatric symptoms [22]. To the best of our knowledge, however, no predictors/correlates for neuropsychiatric symptoms in VaD have been identified. This study suggests that DM may be associated with an increased risk of neuropsychiatric symptoms. This suggests that diabetes with VaD be screened for neuropsychiatric symptoms, such as anxiety or depression, since many can be treated. The retrospective design of this study, however, precludes our recommending such screening at this time. A prospective study will be important to clarify this relationship.

If there are, in fact, more neuropsychiatric symptoms in VaD patients with DM, it suggests that the neuroanatomic dysfunction in DM patients differs from that associated with other etiologies for VaD. Using volumetric analyses, fronto-subcortical changes have been noted in DM that are associated with depression and cognitive changes [23]. It is possible that changes in this area, or like this, led to the increased frequency of neuropsychiatric symptoms noted in our DM patients.

An alternate possibility is that some neuropsychiatric symptoms observed in the DM group are somatopsychic manifestations of DM [24]. The relationships between DM, VaD, and neuropsychiatric symptoms warrant further investigation.

4.3. Diagnostic and therapeutic implications

The observation that DM is associated with earlier onset and faster cognitive deterioration in VaD is potentially important from a therapeutic and diagnostic point of view. In terms of therapeutics, it raises the question of whether improved glycemic control would improve the outcome for VaD. The results of the ongoing multi-centric trial, Action to Control Cardiovascular Risk in Diabetes Memory (ACCORD-MIND) [18], will be particularly important in this regard. It will assess the impact of strict glycemic, blood pressure and lipid control on the outcomes for validated cognitive measures.

With regard to diagnosis, the earlier onset for VaD in diabetics raises the question of whether they can and should be screened for cognitive changes before VaD develops. There is evidence that cognitive changes are, in fact, present in diabetics before dementia develops. For example, in comparing the cognitive performance of non-demented patients with and without diabetes, diabetic individuals over the age of 80 years perform
worse on fronto-subcortical cognitive tasks [25]. Moreover, an MRI-based study of normal elderly suggested that DM is the greatest independent risk factor for deep white matter lesions and those white matter lesions occur more frequently in individuals with DM independent of a history of hypertension [26]. Presumably the gradual accumulation of white matter lesions eventually leads to VaD. Perhaps annual cognitive screening of diabetics, then, would identify persons with early changes in whom VaD might develop subsequently [27].

Support for this suggestion comes from a study by Raji et al. They screened 100 consecutive patient aged ≥ 55 presenting to an eye clinic for routine eye check-ups for cognitive impairment. They found that cognitive deficits were greatest in diabetics [28] suggesting that this population might benefit the most from annual screening examinations. There may also be a role for MRI scans in the screening process. It remains to be demonstrated, however, whether early cognitive or MRI changes progress to VaD, and whether identifying them early is useful for altering the course of VaD.

4.4. Conclusions

DM was associated with an earlier onset, faster rate of decline, and the presence of one or more neuropsychiatric symptoms in this study. However, one should be cautious about generalizing the results of this study since it predominantly involved male Veterans, had a retrospective design, and had a modest sample size. Another important consideration is the use of MMSE to gauge cognitive deterioration in this study. Although the tool is widely used, it is known to have a limited sensitivity to cognitive symptoms of dementia subtypes other than AD [29]. Prospective studies will be necessary to corroborate the results of this study and to ascertain whether stricter glycemic control delays the onset and slows the cognitive deterioration in VaD. The association between DM and cognitive changes in other studies and a more malignant course to VaD in this study suggests that cognitive screening for diabetics may be warranted, though future studies will be necessary to determine whether this is valuable. The pathophysiology underlying the enhancement of VaD by DM observed here also remains to be explicated, but appears to have many plausible candidate mechanisms.

Disclosure

The authors report no conflicts of interest

Acknowledgements

The authors thank the Lou DeGeorge family for its continued generous support. This material is the result of work supported with resources and the use of facilities at the Michael E. DeBakey Veterans Affairs Medical Center.

References


Erratum

A Preliminary Characterisation of Cognition and Social Cognition in Spinocerebellar Ataxia types 2, 1, and 7

N. Sokolovsky, A. Cook, H. Hunt, P. Giunti and L. Cipolotti

[Behavioural Neurology 23(1,2), 2010, 17–29, DOI10.3233/BEN-2010-0270]

On page 17, in the affiliations and footnote, the second corresponding author P. Giunti was missing. The corresponding author information should be:

Corresponding authors: Prof. Lisa Cipolotti, PhD, Department of Neuropsychology, Box 37, National Hospital for Neurology and Neurosurgery, Queen Square, WC1N 3BG, London, UK. Tel.: +91 0207829 8793; Fax: +91 080 7813 2516; E-mail: l.cipolotti@ion.ucl.ac.uk; P. Giunti, MD, PhD, Department of Molecular Neuroscience, Institute of Neurology, UCL, Queen Square, London, WC1N 3BG, UK. E-mail: p.giunti@ion.ucl.ac.uk.
Decision making under risk condition in patients with Parkinson’s disease: A behavioural and fMRI study

Kirsten Labudda\textsuperscript{a,b,*}, Matthias Brand\textsuperscript{c,d}, Markus Mertens\textsuperscript{b}, Isabelle Ollech\textsuperscript{b}, Hans J. Markowitsch\textsuperscript{a,e} and Friedrich G. Woermann\textsuperscript{b}
\textsuperscript{a}Department of Physiological Psychology, University of Bielefeld, Germany
\textsuperscript{b}MRI Unit, Mara Hospital, Bethel Epilepsy Center, Bielefeld, Germany
\textsuperscript{c}General Psychology: Cognition, University of Duisburg-Essen, Germany
\textsuperscript{d}Erwin L. Hahn Institute for Magnetic Resonance Imaging, Essen
\textsuperscript{e}Institute for Advanced Study, Alfried-Krupp Wissenschaftskolleg, Greifswald, Germany

Abstract. We aimed to study whether previously described impairment in decision making under risky conditions in patients with Parkinson’s disease (PD) is affected by deficits in using information about potential incentives or by processing feedback (in terms of fictitious gains and losses following each decision). Additionally, we studied whether the neural correlates of using explicit information in decision making under risk differ between PD patients and healthy subjects. We investigated ten cognitively intact PD patients and twelve healthy subjects with the Game of Dice Task (GDT) to assess risky decision making, and with an fMRI paradigm to analyse the neural correlates of information integration in the deliberative decision phase. Behaviourally, PD patients showed selective impairment in the GDT but not on the fMRI task that did not include a feedback component. Healthy subjects exhibited lateral prefrontal, anterior cingulate and parietal activations when integrating decision-relevant information. Despite similar behavioural patterns on the fMRI task, patients exhibited reduced parietal activation. Behavioural results suggest that PD patients’ deficits in risky decision making are dominated by impaired feedback utilization not compensable by intact cognitive functions. Our fMRI results suggest similarities but also differences in neural correlates when using explicit information for the decision process, potentially indicating different strategy application even if the interfering feedback component is excluded.

Keywords: Executive functions, dopamine, prefrontal cortex, anterior cingulate cortex, parietal lobe, risk

1. Introduction

Some studies report higher prevalence of impulsive and risk-seeking behaviour in patients with PD, e.g. reflected in higher rates of pathological gambling [1], risky driving behaviour [2] or hypersexuality [3] compared to the normal population. The phenomenon of risk- and reward-seeking behaviour has been discussed as a result of dopaminergic treatment. These behavioural phenomena might be more strongly related to dopamine agonist treatment than to levodopa therapy [1,4–6]. However, Avenzi et al. [2] described two PD patients who developed pathological gambling and stopped gambling after a reduction of levodopa dosage. In accordance with these behavioural observations, recent neuropsychological studies have also objectified deficits in experimental decision making tasks that demand the processing of reward and punishment [7–10]. The most frequently used task to assess this kind of decision making — termed decision making under ambiguity or feedback-based decision making — is the Iowa Gambling Task (IGT) [11,12]. This computherized card gambling task has implicit rules for gains and losses associated with four different card decks. Initially, subjects have to figure out advantageous and disad-
vantageous options by using feedback (gains and losses) received after each card selection. The assumption that disadvantageous IGT performance in PD patients is the result of reductions in processing and utilizing emotional feedback is in line with the recent finding of reduced skin conduction responses (frequently interpreted as a marker of affective responsiveness) in this patient group during IGT performance [7,13].

In a previous study, we also observed deteriorations in decision making under risk conditions in patients with PD [14]. In this study, the Game of Dice Task (GDT, [15]) was used. GDT performance in PD patients with and without additional pathological gambling was also assessed in a recent study by Rossi et al. [16]. The authors reported that PD patients with and without gambling problems did not differ in their GDT performance but, unfortunately, the author did not provide GDT netscores. Thus, it remained unclear whether or not the patients exhibited risky decision making. In contrast to the IGT, this gambling task provides explicit information about the gains and losses and the winning probabilities. By explicitly providing information about consequences and their probabilities, subjects are enabled to plan their task performance. Previous studies revealed reductions of performance in this task in several groups of patients with neurological or psychiatric disorders, such as patients with bilateral amygdala damage, Alzheimer’s disease, Korsakoff’s disease, pathological gambling, bulimia nervosa and others [15, 17–21]. These studies also indicate that GDT performance is based on a cognitive/deliberative component, i.e. mainly executive functions that are relevant for categorizing options according to gains and losses and their probabilities, developing and maintaining a long term decision strategy and monitoring, as well as modifying performance in the task’s course. Furthermore, task performance is influenced by an affective component, i.e. processing feedback in terms of gains and losses to modify decision making (see [22,23]). Our previous study on risky decision making in PD patients has shown that the patients’ GDT performance is associated with both components: GDT performance correlated with executive functioning and the utilization of feedback following a decision. This interpretation is also in line with a recent study by Euteneuer et al. [13] who report correlations between decision making deficits on the GDT and executive functions. Furthermore, PD patients in this study also showed reduced SCRs after receiving negative feedback, indicating the impact of emotional feedback processing on the GDT performance. However, to date it remains unclear which of the two components mainly dominates risky decision making in PD patients. We therefore aimed to study decision making under risk conditions in PD patients without executive and other cognitive disturbances in the current study, to assure that potential deficits cannot be due to deteriorations of the cognitive component. Beyond the original GDT, we used an additional fMRI task that is based on the GDT but does not include the feedback component [24,25]. On a behavioural level, if cognitive (e.g. executive) functions dominate risky decision making, one would expect that our sample of high-functioning PD patients is unimpaired on both, the fMRI task without feedback and the GDT with feedback. If feedback processing dominates decision making, one would expect selective impairments on the GDT but not on the fMRI task. According to previous results on altered reward processing and decision making in PD patients (see above), we assume that the given feedback might be sufficient to impair decision making despite intact executive functions and, thus, we hypothesize selective disturbances on the GDT. Frank and co-workers demonstrated that PD patients on medication are able to learn from positive but not from negative feedback in cognitive procedural learning tasks [26,27]. We therefore aimed to analyse whether the patients are equally disturbed in processing negative and positive feedback or whether feedback processing is selectively altered in the context of decision making. The use of the fMRI task further enables us to study possible alterations of the neural correlates associated with the cognitive component of decision making under risk. We recently demonstrated that this deliberative component of the risky decision making process is associated with structures discussed as relevant for executive functions such as the dorsolateral prefrontal cortex and the parietal lobe [25]. We also found activations within the anterior cingulate gyrus that were assumed to be due to conflict detection between concurring decision options.

Neuroimaging studies using cognitive tasks in PD patients have delivered inconclusive results with regard to task relevant – e.g. prefrontal – activation in PD patients. With respect to the lateral prefrontal cortex, some findings suggest increased activity in high-level cognitive tasks – at least if patients have deficits on the behavioural level [28]. Other neuroimaging studies reported frontalhyper- as well as hypactiva-

K. Labudda et al. / Decision making under risk condition in patients with Parkinson’s disease
prefrontal activation very similar to those of healthy subjects when performing tasks assessing executive functions [34]. With respect to frontomesial activations, results from neuroimaging studies using executive tasks, such as the Wisconsin Card Sorting Test [29, 35] but also reward-based tasks [36] revealed increased activation within this prefrontal brain region compared to healthy subjects.

There is only one study on the neural correlates of decision making in PD patients. Using FDG PET, Thiel et al. demonstrated reduced frontomesial activation and thalamic deactivation in patients when performing the IGT [37]. Only the healthy subjects showed activation within the mesial prefrontal, orbitofrontal and anterior cingulate cortex. Dorsolateral prefrontal activity was comparable in PD patients and healthy subjects.

In the current study, we only investigated cognitively intact patients on dopaminergic medication (dopamine agonist and/or levodopa) and of the akinetic-rigid type. We therefore hypothesized that PD patients are unimpaired on the behavioural measures of the fMRI task and assume that their lateral prefrontal activation pattern might also be similar to those of the control subjects. However, according to the neuroimaging studies mentioned above, we assume that the patients might show reduced activity within the anterior cingulate gyrus, a region that has been shown to be crucially involved in the fMRI task used in this study in healthy subjects [25]. Beyond its general role in processing uncertainty [38], this region seems to be stronger associated with the selection of an option compared to the anticipation of feedback [39], is discussed as relevant for detecting conflicts between concurring decision options [40] and has been demonstrated to be activated when choosing risky alternatives [41].

2. Methods and subjects

2.1. Participants

We investigated 12 patients with PD recruited from a local support group and/or from a practice-based neurologist specialized on PD. One patient was excluded from the original sample due to technical problems that led to missing behavioural data during the fMRI task. Another patient was excluded due to a major depression diagnosis. Thus, ten right-handed PD patients (8 males) finally constituted the PD group. Exclusion criteria were current psychiatric comorbidity, neurological disorders other than PD, medical treatment with anticholinergic medication and/or other psychotropic substances. To assure that participants had no signs of cognitive impairment or dementia, we excluded participants with a DemTect transformed score < 13 (according to the test cut-off proposed by Kessler et al. [44]) and t-scores of < 40 on the Modified Card Sorting Test measuring executive functions (see below). All patients were treated with typical dopaminergic medication (levodopa, dopamine agonists), seven patients were additionally medicated with MAO-B inhibitors and/or NMDA agonists. According to the criteria of Hoehn and Yahr [42], most of the patients were classified as stage III (median = 3, range 2–4) and mean duration of illness was 84.75 months (SD = 44.49, range: 24–144 months). To avoid movement artifacts within the fMRI data, we only recruited patients of the akinetic-rigid type.

Additionally, a comparison group (CG) with 12 healthy control subjects (6 males, all right-handed) was investigated with the neuropsychological test battery and the decision making fMRI task. Imaging data of the healthy subjects, but not the neuropsychological results, were reported previously [25]. Patients and CG subjects did not differ according to gender distribution ($\chi^2 = 2.12$, $df = 1$, $p = 0.10$), age (PD patients: mean = 57.60, SD = 7.83; CG subjects: mean = 62.33, SD = 4.81, $t = 1.74$, df = 20, $p = 0.10$) and years of education (PD patients: mean = 10.20, SD = 2.10; CG subjects: mean = 10.92, SD = 1.78, $t = 0.87$, df = 20, $p = 0.40$). All participants gave written informed consent prior to the investigation. Neither control subjects nor patients received financial compensation for participation. The study was approved by the local ethic commission.

2.2. Neuropsychological assessment

The neuropsychological test battery comprised standardized tests. To exclude subjects with signs of general cognitive impairment, the DemTect [44], consisting of subtests for direct and delayed verbal learning, number transcoding, verbal fluency and working memory, was used. We administered the subtest ‘reasoning’ from a German intelligence test battery (Leistungsprüfsystem, [45]) to estimate subjects’ IQs. Verbal learning and memory were measured with the California Verbal Learning Test (CVLT [46]), a word list

\[\text{Although not significant, gender distribution slightly differs in the two groups. However, a number of studies did not find any impact of gender on GDT performance [43].}\]
learning task with an additional delayed recall trial. Short-term and working memory were assessed with the revised Wechsler Memory Scale subtests digit and block span forward and backward [47]. In addition, we employed three tests to measure executive functions: The Modified Card Sorting Test (MCST, [48]) for the assessment of organisation, cognitive flexibility and set-shifting, the Word Colour Interference Test [49] and the Trail Making Test for the assessment of inhibition, interference susceptibility, and cognitive flexibility. Results of the neuropsychological test battery are summarized in Table 1. For a detailed description of the neuropsychological tasks see Lezak [50] and Spreen and Strauss [51].

2.3. Game of dice task

We used the computerized Game of Dice Task (GDT, [15]) to assess decision making under risk conditions. In this task, a single die was thrown 18 times. Subjects were instructed to maximize a fictitious starting capital (1,000 €) by guessing which number would be thrown before the die is rolled. Subjects can choose between different options associated with defined gains/losses: they can select one specific number of the die (winning probability 1:6, associated gain/loss 1,000 €), a combination of two numbers (‘1, 2’ or ‘3, 4’ or ‘5, 6’; winning probability 2:6, associated gain/loss 500 €), a combination of three numbers (‘1, 2, 3’ or ‘4, 5, 6’; winning probability 3:6, associated gain/loss 200 €), or a combination of four numbers (‘1, 2, 3, 4’ or ‘2, 3, 4, 5’ or ‘3, 4, 5, 6’; winning probability 4:6, associated gain/loss 100 €). Subjects received an associated amount of money (1,000, 500, 200 or 100 €) when one of the numbers of a combination chosen was thrown with the single die. In the event that a number not contained in the selected combination was thrown, subjects lost the same amount of fictitious money. The amounts of gains and losses were linked to the winning probabilities, i.e. high potential gains/losses were associated with low winning probabilities and low gains/losses were associated with high winning probabilities (e.g. the choice of one number was linked with 1,000 € gain/loss; the choice of a combination of four dice was associated with 100 € gain/loss). After each roll of the die, a visual and acoustic signal indicated whether the subject had won or lost, and the gained or lost sum was added to or subtracted from the current balance.

In order to analyse task performance, we categorized two out of the four alternative categories as risky, or disadvantageous, (one single number and combinations of two numbers), because winning probabilities were lower than 34%. Thus, a frequent selection of these options would lead to a negative outcome in the long run. The selection of the combinations of three or four numbers was considered non-risky, or advantageous, because winning probabilities were higher than 50%. Furthermore, we analyzed the use of negative feedback in the GDT. Feedback was evaluated as used when a subject lost 500 or 1,000 € after the selection of one of the risky options and subsequently selected a non-risky option before the next die was rolled. As the number of negative feedback differs between subjects, the percentage of negative feedback use was calculated for all subjects that received negative feedback at least one time.

2.4. fMRI paradigm

3. Stimulus presentation and design

The stimuli presented in the blocked fMRI paradigm are based on the GDT, but the feedback phase was completely removed to avoid potential confounds of the neural correlates underlying the cognitive-deliberative phase and the feedback phase [24,25]. The fMRI task had one activation condition (A), one high-level control condition (B) and a low-level control condition (C). The conditions are described in detail below. A baseline condition that required the fixation of a moving cross was presented between conditions A, B and C to avoid carryover effects of activation between conditions. For stimulus presentation and response acquisition, Presentation software (Neurobehavioral Systems, Albany, CA, USA) was used on a laptop computer. The stimuli were displayed onto a translucent screen, watched through a mirror attached to the inside of the head coil.

Conditions A, B and C were separated into six blocks, each containing six items (36 items per condition), that were shown in random order to the subjects. In each block, stimuli were presented for five seconds (6 items x 5 seconds = 30 seconds per block). The baseline condition was presented for 30 seconds between each block of conditions A, B and C. Altogether, 18 activation blocks and 19 baseline blocks were performed by each subject. Prior to the fMRI proce-

---

2Using fictitious instead of real gains and losses is common in neuropsychological decision making research. This method was used in numerous studies using the GDT and other gambling tasks (see e.g. review by Dunn, Dalgleish and Lawrence [52]).
In this condition, two combinations of dice were presented on the screen. Each dice arrangement was linked to a specific gain/loss (see Fig. 1A). According to the GDT, a single die was associated with 1,000 € gain/loss, a combination of two dice with a gain/loss of 500 €, an arrangement containing three dice with 200 € gain/loss and combinations of four dice were always presented with a potential gain/loss of 100 €. Subjects were instructed to imagine that a single die was thrown. They were told that the amount of money presented above each dice arrangement would be theoretically received, if the number fictitiously thrown was included in the chosen combination. Subjects were also told that they would lose the same amount of money if the thrown number was not contained in the chosen arrangement. Participants were explicitly briefed that no die would actually be thrown and that they, therefore, would not receive feedback after a decision. They were instructed to always choose one of the two arrangements presented and to behave like being in a real gambling situation. Subjects should follow their personal preferences. Decisions were made by a button press (right thumb for choosing arrangements on the right side of the screen and left thumb for choosing arrangements on the left side) and were recorded with Presentation software.

3.2. Condition B

Analogous to condition A, two arrangement of dice, each containing different numbers of dice (1 to 4), were presented on the screen (see Fig. 1B). In contrast to condition A, no potential gains/losses were indicated. Subjects were again told to imagine that one single die would be thrown. In this condition, participants always had to indicate, by a button press, which of the two dice arrangements had a higher winning probability. Winning probability was defined as the probability of reaching congruency between a virtually thrown number and one of the numbers of the chosen dice arrangement. The arrangements presented were analogous to those of the GDT (see above). In the instruction, it was again emphasized that it was not indicated whether the subjects’ decisions were right or wrong after a decision was made.

3.3. Condition C (low-level control condition)

Again, two arrangements of dice were shown on the screen and, analogous to condition B, no incentives were announced. One of the two arrangements always contained a blank die. Subjects were instructed to indicate the side of the blank die via button pressing. This condition was added because visual input and required motor activity was comparable to the other conditions of the task used, but no information about probabilities and incentives had to be processed.

4. Data acquisition

Functional MRI scanning was performed with a 1.5 Tesla scanner (Siemens Magnetom Symphony, Erlangen, Germany) equipped with echo planar imaging (EPI) capability and a standard head coil. Scout T1-weighted images were obtained in every subject before the fMRI procedure to position the axial T2*-weighted images along the anterior commissure-posterior commissure (AC-PC) line. To exclude subjects with gross brain pathology and to provide anatomical references,
Table 1
Results of the neuropsychological assessment for the PD patients and the CG

<table>
<thead>
<tr>
<th>Domain/test</th>
<th>Value</th>
<th>PD patients</th>
<th>CG</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General cognitive abilities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtest ‘reasoning’ (LPS 4)</td>
<td></td>
<td>110.80 (14.19)</td>
<td>108.73 (10.96)</td>
<td>0.71</td>
</tr>
<tr>
<td>Estimated IQ</td>
<td></td>
<td>110.80 (14.19)</td>
<td>108.73 (10.96)</td>
<td>0.71</td>
</tr>
<tr>
<td>DemTect Transformed score max = 18</td>
<td></td>
<td>16.10 (2.13)</td>
<td>16.83 (1.64)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>California Verbal Learning Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Learning (sum of trial 1–5) per</td>
<td></td>
<td>61.80 (25.51)</td>
<td>54.92 (29.14)</td>
<td>0.57</td>
</tr>
<tr>
<td>Recall short delay (trial 7) per</td>
<td></td>
<td>39.40 (28.69)</td>
<td>37.75 (29.91)</td>
<td>0.90</td>
</tr>
<tr>
<td>Recall long delay (trial 8) per</td>
<td></td>
<td>50.40 (28.96)</td>
<td>55.33 (33.76)</td>
<td>0.72</td>
</tr>
<tr>
<td>Wechsler Memory Scale – Revised</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span forward per</td>
<td></td>
<td>59.50 (30.37)</td>
<td>61.17 (24.05)</td>
<td>0.89</td>
</tr>
<tr>
<td>Digit span backward per</td>
<td></td>
<td>55.30 (26.66)</td>
<td>56.83 (29.53)</td>
<td>0.90</td>
</tr>
<tr>
<td>Block span forward per</td>
<td></td>
<td>50.60 (27.45)</td>
<td>34.33 (28.00)</td>
<td>0.19</td>
</tr>
<tr>
<td>Block span backward per</td>
<td></td>
<td>65.20 (31.00)</td>
<td>56.50 (29.68)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Information processing and executive functions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word Colour Interference Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading words per per</td>
<td></td>
<td>69.90 (22.40)</td>
<td>85.42 (11.65)</td>
<td>0.05</td>
</tr>
<tr>
<td>Naming colours per per</td>
<td></td>
<td>70.70 (17.75)</td>
<td>81.25 (14.06)</td>
<td>0.14</td>
</tr>
<tr>
<td>Interference trial per</td>
<td></td>
<td>73.20 (19.95)</td>
<td>82.33 (8.48)</td>
<td>0.20</td>
</tr>
<tr>
<td>Modified Card Sorting Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categories t-score</td>
<td></td>
<td>49.90 (7.13)</td>
<td>52.17 (5.81)</td>
<td>0.98</td>
</tr>
<tr>
<td>Errors t-score</td>
<td></td>
<td>47.30 (3.56)</td>
<td>47.25 (4.90)</td>
<td>0.91</td>
</tr>
<tr>
<td>Perseverations t-score</td>
<td></td>
<td>53.80 (5.03)</td>
<td>53.58 (3.40)</td>
<td>0.42</td>
</tr>
<tr>
<td>Semantic verbal fluency RS</td>
<td></td>
<td>26.60 (5.42)</td>
<td>29.50 (5.58)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

S.D. = Standard deviation.
max = maximum.
per = percentiles.
sec = seconds.
LPS = Leistungsprüfsystem (German intelligence test battery; Sturm, Willmes & Horn, 1993).
RS = raw scores.

5. Image analysis

Functional MRI data were analyzed by using MATLAB and Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm) for all imaging pre-processing and voxel-based statistical analyses within the context of general linear model. The T2*-weighted images were realigned using the default SPM5 algorithm to correct for subjects’ movements. Spatial normalization, to reduce anatomical differences before group comparison, was conducted by again using default settings and the standard stereotactic space of SPM5, i.e. the Montreal Neurological Institute (MNI) brain. Spatial smoothing followed with a Gaussian kernel (10 mm full width at half maximum) to increase signal and anatomical conformity. A fixed-effect analysis on a voxel-by-voxel basis was carried out for individual subjects (threshold p < 0.001, uncorrected) and contrast images were created for the different task conditions. A second level t-test (random-effects) analysis was conducted to identify significant differences of the BOLD response within the planned linear contrast for the whole group. T-statistics were corrected for multiple comparisons at p=0.05 and the minimum size of displayed clusters was 10 voxels. The MNI coordinates of the major activations were transformed into the Talairach and Tournoux space [53] using a correction procedure [54] and subsequently fed
into the Talairach Daemon [55] to obtain anatomical projections of maximum activation.

6. Statistical analysis

All variables were tested for normal distribution with the Kolmogorov-Smirnov-Test separately for the patient and comparison group. No significant deviations from the normal distribution were revealed for all neuropsychological variables (all \( p \geq 0.07 \)), as well as for the IGT and GDT scores (all \( p \geq 0.19 \)). Thus, we used parametric methods (t-tests for independent samples) for all analyses of neuropsychological and sociodemographic data.

7. Results

7.1. Neuropsychological assessment

The results of the neuropsychological test battery are summarized in Table 1. Results indicate that the PD patients’ performance was entirely within the normal range in all domains studied and that patients did not differ significantly from the CG subjects.

7.2. GDT performance

Patients’ performance differed significantly from that of the healthy subjects: PD patients selected the risky options (one die or two dice) more frequently than the healthy subjects did (PD patients: mean = 10.30, SD = 5.27; CG subjects: mean = 5.67, SD = 4.79, \( t = 2.16, df = 20, p = 0.04 \)). PD patients used negative feedback less frequently compared to the CG subjects (i.e. the selection of a non-risky option following a loss due to the selection of a risky option).\(^3\) PD patients only changed to a non-risky option after a loss due to a risky selection in 36.45% (SD = 36.24) whereas CG subjects used 82.32% (SD = 33.22) of the negative feedback received after a risky decision and an accordant loss (\( t = 3.03, df = 19, p = 0.007 \)). PD patients and healthy subjects did not differ according to the percentage of used positive feedback following a non-risky selection (100 or 200 € gain) in order to again select a non-risky option in the next trial (PD patients: mean = 63.14%, SD = 33.05; CG: mean = 75.51%, SD = 20.85; \( t = 1.00, df = 17, p = 0.33 \)).

\(^3\)As one of the healthy subjects did never receive negative feedback after the selection of a risky option, feedback analysis is based on the data of 11 CG subjects and 10 PD patients.

7.3. Behavioural results of the fMRI task

Behavioural data of the fMRI paradigm are similar in both groups. In condition A, both groups did not differ according to the number of selections of the non-risky options (PD patients: mean = 91.57%, SD = 11.06, CG subjects: mean = 91.29%, SD = 8.26, \( t = 0.08, df = 20, p = 0.94 \)). In condition B, both groups did not differ according to the frequency of selections of those dice arrangements with a higher winning probability (PD patients: mean = 97.77%, SD = 3.42, CG subjects: mean = 97.64%, SD = 4.25, \( t = 0.07, df = 20, p = 0.95 \)). In the low level control condition C, both groups reliably identified the blank die (PD patients: mean = 97.72%, SD = 5.35, CG subjects: mean = 98.79%, SD = 2.01, \( t = 0.64, df = 20, p = 0.53 \)).

7.4. Imaging results

As a first step, we analysed activation patterns in the contrasts of interest within both groups separately. We subtracted BOLD responses in condition B (information about probabilities only) from those of condition A (information about probabilities and incentives) to objectify activations associated with the integration of information about probabilities and incentives compared to those associated with the processing of probabilities only (A > B). Furthermore, we subtracted activations associated with the low level control condition from those of condition A (A > C). Within the PD group, we did not find significant activation patterns within all contrasts analysed (A > B, A > C) and within the inverted contrasts (A < B, A < C; one sample t-tests, all \( p \) corrected > 0.49).

Results of the healthy subjects are described in detail elsewhere [25]. In short, main results of the contrast A > B (second level analysis, one sample t-test; all corrected \( p < 0.05 \)) revealed significant activations within the dorsolateral prefrontal cortex (DLPFC) bilaterally (\( x = 50, y = 32, z = 24, k = 1459, Z = 4.62; x = -34, y = 10, z = 46, k = 210, Z = 4.35 \)) within the right anterior cingulated gyrus (\( x = 2, y = 28, z = 36, k = 1526, Z = 4.90 \)), within the left parietal lobe (\( x = -48, y = -58, z = 42, k = 182, Z = 4.35 \)) and the right precuneus (\( x = 4, y = -74, z = 54, k = 180, Z = 3.80 \)), as well as within the occipital lingual gyrus (\( x = 6, y = -90, z = -14, k = 169, Z = 4.24 \)). Within the contrast of the conditions A > C, we found significant activations within the left and right DLPFC (\( x = 46, y = 34, z = 24, k = 918, Z = 4.94; x = -52, y = 18, z = 26, k = 190, Z = 3.67 \)).
the supramarginal gyrus \( (x = 42, y = -46, z = 38, k = 733, Z = 3.96) \) and the right cerebellum (declive of vermis; \( x = 2, y = -72, z = -29, k = 436, Z = 4.08 \)).

We then compared activation patterns of the CG and the PD group. The only significant group difference was found within the contrast \( A > C \). Healthy subjects showed significantly stronger activations within the right inferior parietal lobe than PD patients did \( (x = 42, y = -44, z = 40; k = 222, Z = 3.83, p \text{ corrected} = 0.001, \text{see Fig. 2}) \).

PD patients did not exhibit stronger activations in any contrast compared to the CG (all \( p \text{ corrects} > 0.80 \)). In order to test whether there was a condition \( \times \) group interaction, we calculated a two-way ANOVA with condition \( (A > C, B > C) \) and group as independent variables. We did not find a significant interaction even at a low uncorrected threshold of \( p < 0.05 \).

We additionally analysed potential differences within the PD group and between both groups in the contrasts of interest \( (A > B, B > C) \) in anatomically defined regions of interest (ROI, using the WFU Pickatlas Tool 1.03; http://fmri.wfubmc.edu/cms/software#WFU Pick Atlas, ANSIR Laboratory, Department of Radiology, Wake Forest University School of Medicine, Winston-Samell, North Carolina, USA). We did not find further within or between group BOLD differences in a lateral prefrontal ROI, in an anterior cingulate gyrus ROI, in a ventral striatum ROI and in a ROI including putamen, pallidum and caudate nucleus.

8. Discussion

Behavioural results of the present study confirm our previous findings of impaired decision making under risk in non-demented patients with PD using the GDT. In a decision making situation that provides explicit information about consequences and probabilities and fictitious monetary reward and punishment, PD patients chose the risky options, i.e. options with high luring gains but low winning probabilities, more frequently compared to healthy subjects. The additional feedback analysis reflected that PD patients’ ability to use negative feedback after a risky decision is strongly reduced. Nevertheless, as hypothesized, on the decision making fMRI task that did not include the feedback aspect of the GDT, we did not find any behavioural difference between the PD patients and healthy subjects. Therefore, we assume that PD patients are not generally impaired in the cognitive processing of the information relevant for their decisions – at least in those patients with intact cognitive and executive functions. Our results rather suggest that reductions in reward and punishment processing are sufficient to deteriorate the whole decision process in PD patients even when cognitive functions are intact. The behavioural fMRI results further exemplify that – in contrast to receiving reward and punishment – the presentation of potential incentives alone does not lead to disadvantageous decision making. In contrast to PD patients, healthy subjects benefit from receiving feedback. Brand [23] has shown that in an experimental GDT version without feedback, healthy subjects had a higher frequency of selecting risky options compared to the original version. Thus, providing feedback in healthy subjects leads to a moderate decrease of risky decisions. In PD patients, providing feedback leads to an increase of risky decisions whereas decision making without feedback is normal. This disadvantageous decision making seems to be specifically due to an impairment of using negative feedback. In accordance with the results of Frank et al. [26,27], impairments of feedback processing were selective in the present study: PD patients did not use negative feedback (in terms of losses) to modify their behaviour. In contrast, they did not differ from the healthy subjects according to the use of positive feedback (in terms of gains) to stick to the non-risky options in the next trial. Our results thus support the view that decision making deficits in PD patients might be due to impairments of the so-called limbic loop, linking the mesial orbitofrontal cortex and the anterior cingulate gyrus to the ventral striatum [56,57]. This loop has been demonstrated to be involved in feedback processing in a number of studies and was assumed to be affected already in early PD [37]. However, in the recent study by Euteneuer et al., the authors attribute a reduced GDT performance to dysfunctions of the so-called dorsolateral prefrontal cognitive loop [13]. This loop mainly comprises the dorsolateral prefrontal cortex, the lateral orbitofronatal cortex and the striatum and is associated with executive dysfunctions in PD patients [58]. In contrast to our study, the patients in the study of Euteneuer and colleagues had reductions in executive functions. However, the authors also assume deteriorations of the limbic loop to some degree, as their patients also showed altered SCRs, linked to deficient negative feedback processing. Taken together, our previous results [14] and those of Euteneuer suggest that impairments of both, the cognitive and the limbic loop may cause risky decision making impairments. Our current results extend these findings by showing that
deficits in negative feedback processing are sufficient to cause decision making problems, despite intact cognitive functioning in PD patients.

Our fMRI results further support the interpretation of an intact cognitive loop in our PD patients, as we did not find significant activation differences within the PFC between healthy subjects and PD patients while integrating information provided for the decision process. However, healthy subjects showed stronger activation within the parietal lobe when processing information about probabilities and incentives. Parietal hypometabolism has frequently been described in PD patients with dementia [59,60] but also without cognitive impairments [61–63]. Some studies also report direct associations between hypometabolism within the parietal lobe and cognitive functions in PD patients [64, 65]. Additionally, less parietal activations in an fMRI Stroop task in PD patients on dopaminergic medication, compared to healthy subjects, were described by Fera et al. [34]. Whereas PD patients showed similar activation patterns within the PFC in the interference condition of the Stroop paradigm, healthy subjects showed an additional involvement of the superior parietal lobe. Even though in healthy subjects parietal and frontal brain regions strongly interact in the context of cognitive functions – specifically executive and attention functions (e.g. [66,67]) – PD patients of the current study are not impaired on the fMRI task despite reduced parietal activity. As discussed in our previous study on neural correlates of decision making in healthy subjects [25], we assume that the parietal lobe – beyond its relevance for attention and executive functions – might be associated with approximate arithmetic operations while comparing incentives and probabilities of the two concurring alternatives presented in each trial (see e.g. [68–70]). Potentially, deliberative strategies of PD patients differ from those of the normal subjects: less activation in this region might be due to neglecting information about incentives. Subjects knew that they would not receive the incentives presented. PD patients potentially pay less attention to the incentives to minimize interference susceptibility. The assumption that PD patients paid less attention to the incentives is also supported by the group comparison within the PD group. In contrast to the healthy subjects, PD patients did not show a significant BOLD increase when additional information about incentives was presented (compared to both control conditions). Thus, it might be that subjects based their decision on the same information in each condition (e.g. the number of dice in condition A and B that delivered information about probabilities) and ignored the incentive information provided in condition A.
We hypothesized that PD patients exhibit different activation patterns within the anterior cingulate gyrus. We suggest that cingulate activations within healthy subjects can be attributed to conflict detection mechanisms that are discussed in decision making [40,71,72]. We did not find a significant activation difference between healthy subjects and patients in this region. However, the BOLD increase seen in healthy subjects when information about probabilities and incentives is given, compared to the control condition with probabilities but no incentives, was absent within the patient group. This again might be attributed to a difference in information processing. If PD patients ignored incentives provided in the activation condition, the conflict between options diminished. Ignoring incentives could be an efficient strategy in the decision process demanded in our fMRI task, as subjects could easily know that those alternatives with lower winning probabilities (alternatives including fewer dice) are the risky options. Further studies are needed to clarify whether PD patients are more willing to ignore information about incentives and, if so, why. One hypothesis to be tested is that PD patients pay less attention to incentives as a compensation strategy because, otherwise, their cognitive, deliberative decision process is prone to be affected by mere information about reward and punishment.

One limitation of our study is that we cannot determine the impact of dopaminergic treatment on the behavioural and imaging results because we did not compare patients ‘on’ and ‘off’ medication. Recent studies suggest a complex interaction of reward processing as well as cognitive functioning and dopaminergic treatment in PD patients, most likely following an inverted U-shaped function [73]. This relationship seems to be further influenced by disease severity [36]. Thus, PD patients are not necessarily reduced in reward processing and associated behaviour per se. Cools and co-workers reported that dopaminergic treatment can improve cognitive functions but concurrently boost impulsivity [74] (see also [75]). Thus, intact cognitive functions but risky decision making in terms of reward-seeking behaviour and neglecting feedback might be associated with the current dopaminergic state. The same seems to account for neuroimaging results in PD patients. The PET study by Cools and colleagues [32], in which patients with PD performed a spatial working memory task and a planning task, has shown that activation pattern in patients with normal dosage of dopamine treatment did not differ from healthy comparison subjects. However, when the same patients were off medication, they showed stronger PFC activation within the experimental condition and decreased activation within the control condition. Further studies are needed to clarify if the patterns of our fMRI results in PD patients are specific for PD patients on medication and might be different in PD patients without dopaminergic treatment. As some finding suggest that impulsive or risk seeking behaviour may be stronger related to dopamine agonist treatment compared to levodopa therapy (see Introduction), it would also be of interest to investigate the specific impact of the type of medication on decision making processes in PD patients.

Another limitation is the fact that the subjects performed the GDT outside the scanner whereas the non-feedback task is performed within the scanner. Although the patients’ performance in the non-feedback task is not impaired and not different form the healthy subjects’ performance, we cannot exclude that environmental factors such as the scanner’s noise somehow affect task performance. In future studies, performing both tasks in the same setting (e.g. within the scanner) would be a better methodology.

Acknowledgement

This work was supported by the German Research Foundation (BR 2894/1-1 and BR 2894/4-1). We thank Dr. Renate Husmann for her support in recruiting the patients for this study. We also thank all patients and healthy subjects for participating.

References

null


Is lesion of Exner’s area linked to progressive agraphia in amyotrophic lateral sclerosis with dementia? An autopsy case report

Kenji Ishihara\textsuperscript{a,}*, Hiroo Ichikawa\textsuperscript{a}, Yoshio Suzuki\textsuperscript{b}, Jun’ichi Shiota\textsuperscript{b}, Imaharu Nakano\textsuperscript{c} and Mitsuru Kawamura\textsuperscript{a}
\textsuperscript{a}Department of Neurology, Showa University School of Medicine, Tokyo, Japan
\textsuperscript{b}Department of Neurology, Ushioda General Hospital, Kanagawa, Japan
\textsuperscript{c}Department of Neurology, Jichi Medical School, Tochigi, Japan

Abstract. Agraphia, as a neuropsychological symptom of ALS, especially ALS with dementia (ALS-D), has recently attracted more attention. However, the brain lesion responsible has not been identified. Here we present an autopsy case of ALS-D of a patient with obvious agraphia, without aphasia, that also presented cerebrospinal degeneration with TDP-43-pathology compatible with ALS-D. Of the pre-motor frontal lobe cortices, degeneration and immuno-histochemical pathology were most obvious in the caudal area of the left middle frontal gyrus, or Exner’s area. Assuring this area plays a pivotal role in the kanji and kana formation used in writing the Japanese language, this case of ALS-D showed both agraphia and Exner’s area stressed pathological lesions. It may thus be the first case to indicate an intimate relationship between the neuropsychological symptoms and an associated lesion for ALS-D.

Keywords: Amyotrophic lateral sclerosis with dementia (ALS-D), fronto-temporal lobar degeneration with TDP-43 proteinopathy (FTLD-TDP), progressive agraphia, Exner’s area

1. Introduction

Amyotrophic lateral sclerosis with dementia (ALS-D) is a nosological condition presenting motor neuron disease (MND) and dementia. The clinical features of dementia in ALS-D are of the frontal lobe type, and ALS-D is located within a framework of fronto-temporal lobar degeneration (FTLD) \cite{1}. Although analysis of language function in ALS-D is considered difficult to carry out, due to severe bulbar palsy, we previously reported that writing disorder may exist in the early stage \cite{2}. Another report, in Japanese, also describes writing disorder in a patient with ALS-D \cite{3}. Here we describe an autopsied case of ALS-D, presenting progressive agraphia without aphasia, and discuss its clinicopathological relationship.

2. Case history

A 73 year-old Japanese woman, with a history of breast cancer, was admitted to our hospital with speech disorder and personality change. Her family history provided no clues as to onset of these changes. Six months before admission, she became disoriented about dates and resistant to correction, and after three months, while playing cards with her family, she began missing her turn and became argumentative about continuing. At about the same time, her speech began to be slurred and became difficult, and her activities were slow down.

On admission, she showed no abnormality except for evidence of the surgery for breast cancer. She was cooperative during the neurological examination and...
cognizant of time and place. Her answers to questions were cogent. She could name objects and repeat sentences correctly, although her speech was slurred, slow-pitched, monotonous, and difficult. The tongue showed no atrophy nor fasciculation. Her facial expressions were fairly normal. Although there was no amyotrophy in the extremities, muscle tone was spastic, especially in the lower extremities. Jaw jerk and tendon reflex were exaggerated. Pathological grasping reflex, Hoffman reflex and Trömner reflex were induced bilaterally. Planter reflex was flexor bilaterally. No cerebellar ataxia was observed. As is mentioned later, her writing errors were, however, of great interest. She was not conscious of her illness and scored 7/18 on the frontal assessment battery [4]. Hasegawa’s dementia rating scale (revised) was 23/30, suggesting mild cognitive impairment (normal range is above 21/30) [5]. Routine laboratory data were all within normal limits including those for syphilis, anti-human T cell leukemia virus I antibody, thyroid function, vitamin B$_{12}$ and folic acid. The cerebrospinal fluid examination was unremarkable. Needle electromyography performed on the tongue, diaphragm, and anterior tibial muscle revealed mild chronic denervation. Magnetic resonance images (MRI) of the head revealed atrophy of the anterior part of the temporal and frontal lobes, slightly predominant on the right. Single photon emission computed tomography (SPECT) images disclosed decreased uptake of tracer, bilaterally, in the frontal and temporal lobes. After discharge she was observed as an outpatient, but her mental condition and motor symptoms gradually deteriorated. About five months after discharge, gastrostomy was performed for severe dysphagia. At which time, she had tetraparesis and could not respond to the examiner’s instructions. She was transferred to the nursing hospital. Tracheostomy was not performed, and artificial ventilation not administered at the request of her family. The total duration of her illness was 18 months and she died of sudden respiratory failure.

3. Analysis of language function

Japanese language uses two distinct writing systems: kana characters, composed of simple phonograms with unambiguous phonetic readings, and kanji characters, a system of several thousand morphograms or ideograms.

On admission, her speech showed severe dysarthria and little intonation, and sounds and syllables were inconsistent. She occasionally had telegraphic speech and paraphasia during spontaneous speech. The results of the WAB, examined during the first two weeks of admission, revealed spontaneous speech was non-fluent due to severe dysarthria. Repetition was mildly impaired. Although she could repeat nine words (each word was composed of two to ten characters) and two short sentences (each sentence was composed of eight and nine characters) without an error, she made two errors in repeating a long sentence composed of 20 characters, i.e. “新しい甘酒を五本のひょうたんに入れないさい” (Put fresh sweat alcohol into five gourds, in English). Object naming was mildly impaired (18/20), however, she could name all objects given phonemic cues. Sentence completion and responses in conversation were slightly impaired (8/10 and 8/10, respectively). As shown in Yes/No questions (60/60) and auditory word recognition (59/60), comprehension was not impaired.

In contrast to the results described above, her writing was severely impaired. Although writing speed was slow, her formation of written characters showed no distortion. She made five errors in writing the same sentence as used in repetition: “新しい甘酒を五本のひょうたんに入れないさい” (she made two errors in repetition). She made four errors during writing six kana words (each word was composed of two kanji characters), two errors in six kana words (each word was composed of three or four kana characters), and thirteen errors in four sentences (each sentence was composed of nine or ten characters). Most of the errors were omission of kana characters and adjuncts, such as postpositional particles. For example: “山に1本立てて居ます” instead of “山の上に木が1本立てて居ます”. The sentence is written, as normal, using a mixture of kanji and kana, and an English translation is: “There is a tree on the mountain”. “の” and “に” are both particles, written in kana letters. And “木” is the subject of the sentence, composed of “木” (”tree”) and “が” (a postpositional particle). “ま” is one of the so-called “okurigana”, or kana characters added after kanji to indicate inflection. Other types of errors were substitution or addition of letters. Her ability to copy both letters and sentences was unimpaired. She could copy the sentence “新しい甘酒を五本のひょうたんに入れないさい” without an error.

After about three months, during follow up at the outpatient clinic, perseverative errors and paragraphia emerged. Moreover, morphology of her written characters became slightly distorted.

When tube feeding was necessary, she was no longer able to hold writing implements.
4. Neuropathological findings

General pathological examination revealed severe thinning of the diaphragma. The brain weighed 1060 g prior to fixation. Macroscopic examination revealed circumscribed atrophy of the anterior temporal and frontal lobes bilaterally. Both lateral ventricles were slightly dilated. The substantia nigra was significantly depigmented.

Sections of paraffin-embedded tissue were stained with hematoxylin and eosin (H & E), Klüver-Barrera, and Bodian stains. In addition, immunohistochemistry for selected areas was performed using anti-ubiquitin (Dako; Japan; 1:100), anti-tau (AT8; Innunogenetics; 1:1000), and anti-phosphorylated-TDP-43 (p403/404,
Table 1

<table>
<thead>
<tr>
<th>lesion ( gyrus )</th>
<th>neuronal loss</th>
<th>superficial spongiosis</th>
<th>macrophage invasion</th>
<th>TDP pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>superior frontal</td>
<td>mild</td>
<td>moderate</td>
<td>none</td>
<td>mild</td>
</tr>
<tr>
<td>middle frontal</td>
<td>mild</td>
<td>severe</td>
<td>severe</td>
<td>moderate</td>
</tr>
<tr>
<td>inferior frontal</td>
<td>mild</td>
<td>mild</td>
<td>none</td>
<td>mild</td>
</tr>
<tr>
<td>precentral</td>
<td>severe</td>
<td>severe</td>
<td>severe</td>
<td>moderate</td>
</tr>
</tbody>
</table>

Fig. 3. Neuronal intra-cytoplasmic inclusions in the cortical neurons. a: superior frontal gyrus, b: middle frontal gyrus, c: inferior frontal gyrus, d: precentral gyrus. Numerous inclusions can be seen in the middle frontal (b) and precentral (d) gyri. Anti-phosphorylated-TDP-43-immunostain. Scale bar = 80 µm.

Cosmo Bio; California; 1:1000) antibodies.

Superficial spongiosis, neuronal loss, gliosis and rarefaction of the neuropil were observed in the frontal and temporal lobe cortices, especially in the precentral gyrus and posterior part of the middle frontal gyrus bilaterally (Fig. 1). Superficial spongiosis was also observed in the other frontal cortex, but to a lesser degree. Plenty of macrophages were observed in the subcortical white matter of these areas (Fig. 2). There were several clusters of macrophages in the deeper cortical layer of the precentral gyrus, indicating loss of Betz cells. Moderate neuronal loss was observed in the transitional area between CA1 and subiculum. Only a few neurofibrillary tangles were observed in the parahippocampal gyrus. No pathological change was observed in the left parietal and occipital lobes.

The pyramidal tracts showed almost complete axonal loss in the bilateral cerebral peduncles and pyramids. Neurons in the hypoglossal and ambiguous nuclei were preserved in number, however a few Bunina bodies were observed in the remaining neurons. The substantia nigra showed severe neuronal loss and gliosis with no Lewy bodies. The locus ceruleus showed mild neuronal loss and two Lewy bodies. The cerebellum was unremarkable. There were no neurofibrillary tangles in the brainstem or cerebellum.

In the spinal cord, moderate to severe loss of anterior horn cells and several Bunina bodies in the remaining neurons were observed. The pyramidal tracts showed almost complete axonal loss in the lateral columns. The posterior columns were unremarkable. Neurons in Onuf’s nucleus were preserved in number.

Immuno-histochemistry showed ubiquitin and TDP-43-positive and tau-negative neuronal intracytoplasmic inclusions in the hippocampal dentate gyrus and frontal lobe cortex (Fig. 3). We detected these inclusions in the middle frontal and precentral gyri much more than in other frontal lobe cortices. Only a small number of TDP-43 positive dystrophic neurites were observed.
TDP-43 positive neuronal intranuclear inclusions and glial cells were not observed.

Summary of the pathological changes including immunohistochemistry are shown in Table 1.

5. Discussion

The presented case features a combination of progressive pseudobulbar palsy, frontal lobe type dementia, pyramidal tract signs and progressive amyotrophy. MRI revealed atrophy of the frontal and temporal lobes. Decreased blood flow in the frontal and temporal lobes was demonstrated by SPECT images. Pathological features of the case are: degeneration of both upper and lower motor neurons, degeneration of frontal and temporal lobes, Bunina bodies of the remaining lower motor neurons and TDP-43 pathology. These features are fully compatible with the diagnosis of ALS-D.

In progressive nonfluent aphasia, agraphia with effortful writing containing spelling error and agrammatism may be observed [6]. Agrammatism refers to omission or incorrect use of grammatical terms, including articles, prepositions, auxiliary verbs, inflexions, and derivations. From an initial stage, the presented patient showed progressive speech output disorder due to pseudobulbar palsy. Although telegraphic speech and occasional paraphasia were observed, frequency of such errors was quite less than that of writing errors. As shown in the WAB result, comprehension, naming and repetition were almost preserved when obvious agraphia was observed. Therefore, we believe the agraphia observed in our case did not derive from aphasia. Although perseverative errors were observed at a late stage, this can be attributed to frontal lobe dysfunction.

Omission of kana letters in Japanese and related syntactic errors in English have been reported in ALS with or without dementia [2,3,7,8]. The writing errors observed in our case concur well with previous descriptions. Although the lesion associated with pure agraphia is thought to be in the left frontal or parietal lobe [9], detailed clinicopathological analysis of ALS is unreported. A single autopsied case from the United States suggests that the left frontal or parietal lobe may be linked with the lesion responsible for syntactic errors in writing [7]. However, pathological findings related to agraphia were not described.

Our case reveals a left frontal lobe lesion with emphasis on the caudal part of the middle frontal gyrus, combined with immuno-histochemistry and other ALS-related indicators. Frontal and temporal lobe lesions including the hippocampal dentate gyrus have already been associated with dementia symptom in ALS-D [1]. A detailed description of each neuropsychological symptom and lesion remains to be elucidated, however.

The posterior part of the left middle frontal gyrus (Exner’s area) is thought to play a pivotal role in writing letters and lesions there to cause agraphia [10,11]. Only a small number of cases of pure agraphia due to circumscribed lesions in Exner’s area have been reported thus far [12–15]. Reports from Japan reveal phonological errors such as omission and paraphoria of kana letters associated with Exner’s area lesion in cerebrovascular disease [15–17]. These errors concur well with the writing disorders observed in our case.

In the case described here, lesion distribution in the left frontal lobe was concentrated in Exner’s area and no pathological change was observed in the left parietal lobe, which is another lesion associated with agraphia. We believe this is the first report that links clinicopathology in progressive agraphia without aphasia and detailed pathological examination including immunohistochemistry. Of course, further accumulation of clinicopathological examination focusing ALS-D and agraphia would be required to clarify our hypothesis.

Acknowledgements

This study was supported by a grant from the Tamagawa University Center of Excellence from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Core Research for Evolutionary Science and Technology (CREST; No. 17022035) and by a Grant-in-Aid for Scientific Research on Priority Areas–System Study on Higher-order Brain Functions from MEXT (No. 20020026). This study was also supported in part by a Showa University Grant-in-Aid for Innovative Collaborative Research Projects and a Special Research Grant-in-Aid for Development of Characteristic Education from MEXT.

References


Relationship between cognitive impairment and behavioural disturbances in Alzheimer’s disease patients

Laura Serra\textsuperscript{a,*}, Roberta Perri\textsuperscript{b}, Lucia Fadda\textsuperscript{b,c}, Alessandro Padovani\textsuperscript{d}, Sebastiano Lorusso\textsuperscript{e}, Carla Pettenati\textsuperscript{i}, Carlo Caltagirone\textsuperscript{b,c} and Giovanni A. Carlesimo\textsuperscript{b,c}

\textsuperscript{a}Neuroimaging Laboratory, Fondazione IRCCS Santa Lucia, Rome, Italy
\textsuperscript{b}Clinical and Behavioural Neurology, Fondazione IRCCS Santa Lucia, Rome, Italy
\textsuperscript{c}Department of Neuroscience, University of Rome Tor Vergata, Rome, Italy
\textsuperscript{d}Department of Medical and Surgical Sciences, Unit of Neurology University of Brescia, Spedali Civili di Brescia, Brescia, Italy
\textsuperscript{e}Infermi Hospital, Rimini, Italy
\textsuperscript{i}Centro Regionale Alzheimer, UOC Neurologia Ospedale Rho-Passirana, Rho, Italy

Abstract. Background and aims: Alzheimer’s disease (AD) is a neurodegenerative disorder in which the patients can exhibit some behavioural disturbances in addition to cognitive impairment. The aims of the present study were to investigate the relationship between severity and rate of decline of the cognitive and behavioural impairment in patient with AD.

Methods: 54 AD patients were assessed at baseline and after 12 months with the Mental Deterioration Battery (MDB), the Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-Cog) and the Neuropsychiatric Inventory (NPI-10).

Results: MDB was more accurate than ADAS-Cog in the early diagnosis of AD. Conversely, ADAS-Cog was more sensitive at revealing the progression of cognitive decline. Depression, Apathy and Anxiety are the most frequent and severe behavioural disturbances at baseline. At follow-up Delusions and Irritability increased significantly. Significant correlations were observed between severity of cognitive impairment and behavioural disorders both at baseline and in the progression rate passing from T0 to T12.

Conclusions: Severity and progression rate of behavioural and cognitive alterations in patients with AD are significantly associated.

Keywords: Cognitive functions, MDB, NPI-10, ADAS-Cog, BPSD, Alzheimer disease

1. Introduction

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive impairment of cognitive functions [39] that is usually defined by its core cognitive features. Nevertheless, there is agreement in the literature that at some point in their illness patients with AD also exhibit behavioural disturbances [32] that are particularly distressing for family members and contribute greatly to the need for caregiving services [38]. Different studies have estimated the prevalence of behavioural and psychological symptoms in dementia (BPSD) [28]; in fact, estimates range from 25% to 80% [31,34,36]. The most frequent BPSD described during the course of AD are agitation [36] apathy [34,47], depression [8,21,46], anxiety [41] and delusions [6,25]. However, disinhibition [49], hallucinations [7,25], aggression [23], wandering and disturbances in eating behaviour [9] have also been described.
Particularly debated in the literature is the relationship between BPSD and cognitive decline. Some authors have reported that specific behavioural disorders, such as psychotic symptoms and depression, are related to severity of the cognitive deficit [15, 26, 52] and can also influence rate of cognitive decline [2, 5, 11, 21, 22, 48, 51]. On the contrary, other authors did not find such a relationship and concluded that cognitive and behavioural disturbances are substantially independent in AD [17, 24, 46]. These contrasting findings could be due to differences among studies in the criteria adopted to recruit patients and in the instruments used to assess cognitive and behavioural disorders. However, they may also reflect some peculiarity in the relationship pattern between particular BPSD and specific aspects of the cognitive impairment in demented patients. In fact, studies investigating the relationship between a wide spectrum of BPSD and general indexes of cognitive impairment have generally found only a weak association [21, 36, 40]. Conversely, studies evaluating the relationship between the impairment of individual cognitive functions and particular BPSD have usually found more specific and robust associations [5, 25, 30, 47, 52].

The present study was aimed at further investigating the relationship between severity and qualitative aspects of the cognitive and behavioural impairment and between the rate of cognitive and behavioural decline over time in patients with AD. For this purpose, a group of patients with AD were submitted to a 12-month longitudinal evaluation of both behavioural disturbances and cognitive impairment. The 10-item version of the Neuropsychiatric Inventory (NPI-10) [14] was used to assess behavioural symptoms. The Mental Deterioration Battery (MDB) [10] and the Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-Cog) [43] were used to evaluate cognitive deficits. The MDB is a neuropsychological battery devised to detect early cognitive decline and to assess the qualitative characteristics of cognitive deficits. In a previous study, the MDB demonstrated good sensitivity and specificity in the diagnostic screening of patients with suspected dementia [10]. However, there are no data regarding the ability of the MDB to rate the progression of cognitive decline in demented patients. The ADAS-Cog is the most widely used scale for assessing the progression rate of cognitive decline in patients with AD [27, 50]. According to some authors, the ADAS-Cog can also be used as a screening test for dementia. However, sensitivity and specificity in differentiating patients with dementia from healthy controls have rarely been reported [19, 44, 53]. For this reason, a secondary aim of this study was to compare the two neuropsychological scales for sensitivity and specificity in the early diagnosis and assessment of the progression rate of cognitive deterioration in patients with AD.

2. Methods

2.1. Subjects

Fifty-four AD patients (36 females, 18 males; mean age 73.1 ± 5.8; mean years of education 5.9 ± 2.7) were recruited from the Alzheimer’s Disease Units of four neurological and geriatric centres in Italy from May 2000 to December 2002. Patients were diagnosed with probable AD based on the NINCDS-ADRDA criteria [35]. To include only patients affected by mild to moderate dementia, at the time of recruitment patients should be at the first diagnosis of AD and the Mini-Mental State Examination (MMSE) [20, 33] score had to be above 15 (range 15–26.7, mean 20.72 ± 3.33). Based on a clinical interview, patients with clinical history of major psychiatric disorders (e.g., major depression, psychosis, mania) were excluded from the study. None of the included patients were taking anti-cholinesterase drugs at the time of study entry. During the year of our observation, all patients were given an anti-cholinesterase drug for the treatment of AD. In particular, 11 patients were assuming donepezil at a dosage of 5 mg/die, 11 patients donepezil at a dosage of 10 mg/die, 1 patient rivastigmine at a dosage of 3 mg, 8 patients rivastigmine at a dosage of 6 mg and 2 patients galantamine at a dosage of 8 or 16 mg/die. Some of them were also assuming antidepressants and/or benzodiazepines or neuroleptics. Local ethical committee approval and written informed consent from participants were obtained before the study began.

2.2. Procedure

All patients were submitted to a baseline (T 0) and a 12-month follow-up (T 12) cognitive and behavioural evaluation. The entire assessment took two days (i.e., on the first day they received the MDB and on the second day the ADAS-Cog and NPI-10) with an interval of no more than 7 days.

2.2.1. Cognitive evaluation

AD patients received both the MDB [10] and the ADAS-Cog [18, 43]. The MDB includes 8 cognitive tests that assess long-term verbal episodic memory (Immediate and Delayed recall of a 15-word list), short-
term memory for visual abstract stimuli (Immediate Visual Memory), executive functions (Phonological Verbal Fluency), language abilities (Sentence Construction), reasoning (Raven’s Coloured Progressive Matrices) and constructional praxis (Copy of Drawings and Copy of Drawings with Landmarks). For each MDB test, normative data collected in an Italian population are available for score adjustment based on age and education and normality cut-off scores (≥ 95% of the lower tolerance limit of the normal population distribution) [10]. In the normative study, a score below the normality cut-off in two or more of the eight tests of the battery was considered as the boundary between normal and pathological performance, and 93% sensitivity and 98% specificity were reached in the correct classification of demented patients and normal controls [10]. To assess the sensitivity of the MDB in detecting the participants’ cognitive decline over the one-year period of our observation, we calculated an MDB total score by summing the z scores on the eight tests of the battery (means and standard deviations of the Italian standardisation sample were used for this purpose) [10].

ADAS-Cog [43] consists of 11 tests that assess different cognitive areas: memory (Immediate 10-word list recall, Recognition of a 12-word list, Remembering of Test Instructions), praxis (Constructional Praxis and Ideational Praxis), language (Naming Objects and Fingers, Communicative ability, Comprehension, and Word Finding difficulties in spontaneous speech) and Time and Place orientation. For each test, performance level calculated as the number of errors made by the subject. The sum of the errors, adjusted for the subject’s education level, provides a total score ranging from 0 to 70. A total score between 0 and 13 indicates the absence of dementia, between 14 and 17 questionable dementia, to be confirmed after six months, and total scores between 18 and 70 indicate progressively more severe forms of dementia.

2.2.2. Behavioural assessment

For the behavioural assessment, patients’ caregivers were asked to complete the NPI-10 [14] This scale permits separately quantifying the presence and severity of the following psychiatric symptoms: Delusions, Hallucinations, Agitation/Aggression, Dysphoria/Depression, Anxiety, Euphoria, Apathy, Disinhibition, Irritability/Lability and Aberrant Motor Behaviour. The score range for each item is 0-12 (derived from the rating of both severity and frequency of the behavioural disorder, with 0 corresponding to absence of the behavioural symptom and 12 to maximum frequency and severity of the disorder). A total score is obtained by summing the scores for each item.

3. Results

3.1. Cognitive scales: diagnostic accuracy and rate of cognitive decline

Twenty-six (48%) and 40 (74%) of the patients with AD were correctly classified as having dementia by the ADAS-Cog (total score ≥ 18) and the MDB (pathological scores on 2 or more tests), respectively. The diagnostic accuracy of the ADAS-Cog was significantly lower than that of the MDB (χ² = 7.64; df 1; p = 0.005).

A significant decrease in cognitive functioning over the year of our observation was detected in the total score on the ADAS-Cog (T0 = 17.84 ± 6.38; T12 = 21.40 ± 9.97; F = 8.19, p = 0.006) but not in the total score on the MDB (T0 = −11.42 ± 9.43; T12 = −12.05 ± 10.29; F = 0.21, p = n.s.).

These results confirm the good sensitivity of the MDB in diagnosing even mild forms of dementia and of the ADAS-Cog in indicating the progression of cognitive decline. Therefore, in the following analyses we used the MDB as a measure of severity of cognitive impairment at T0 and the change from T0 to T12 on the ADAS-Cog as a measure of the rate of cognitive decline.

3.2. Severity and progression of behavioural impairment

As shown in Fig. 1, Dysphoria/depression and Apathy, followed by Agitation/Aggression and Anxiety were the most frequent behavioural symptoms (panel a) and those with the highest average severity (panel b) in the overall sample of AD participants. As revealed by a significant difference between the mean NPI-10 total scores at T0 (mean 12.91 ± 8.61) and T12 (mean 16.83 ± 11.27), a global worsening of BPSD occurred in our AD group (F = 6.26 p = 0.015). After 12 months, frequency of occurrence and severity of Dysphoria/depression, Apathy, Agitation/Aggression and Anxiety remained substantially the same. Conversely, Delusions and Irritability/Lability increased significantly in terms of the number of patients affected (χ² = 3.97 and 5.11, df 1, p = 0.046 and 0.023, respectively) and mean severity (Z = 2.19 and 2.83, p = 0.028 and 0.004, respectively). Finally, Aberrant Motor Behaviour, Disinhibition, Euphoria and Hallucinations showed a low frequency of occurrence and severity at both T0 and T12.
Since some of AD patients included in the study were given an anticholinesterase drug during the year between initial evaluation and follow-up, in a further analysis we wished to evaluate if the drug administration affected the rate of cognitive and/or behavioural decline in our sample of patients. For this purpose, we divided the overall sample in two subgroups, the first \((n = 31)\) composed of individuals which were assuming an adequate dosage of anticholinesterase drug (i.e., 6 or 12 mg/die of rivastigmine, 16 mg/die of galantamine and 5 mg or 10 mg/die of donepezil) and the second \((n = 23)\) which included patients which were assuming no drug or a non adequate dosage (e.g., 3 mg/die of rivastigmine and 8 mg/die of galantamine). Two-way mixed ANOVAs with Group (adequate vs. no or non adequate treatment) as between factor and Time (T0 vs. T12) as within factor did not support a different rate of cognitive decline as a function of anticholinesterase treatment. Indeed, the Group x Time interaction fell short of significance for both the total score on the MDB \((F(1,52) = 1.55, p > 0.20)\) and the total score on the ADAS-Cog \((F(1,52) = 0.40, p > 0.20)\). Quite unexpectedly, instead, patients who were assuming an adequate dosage of anticholinesterase drugs displayed an increment of NPI total scores larger than that disclosed by patients who were assuming no or non adequate dosage of therapy \((F(1,52) = 4.43, p < 0.05)\).

### 3.3. Relationship between cognitive and behavioural impairment

At T0, the overall severity score on the NPI-10 correlated significantly with the overall \(z\) score on the MDB.
(r = −0.38; p < 0.001). Among the various MDB test scores, the Phonological Word Fluency test score was most consistently associated with the NPI-10 total score (r = −0.46; p < 0.001). Conversely, the severity score on the Disinhibition subscale of the NPI-10 had the most consistent relationship with the MDB total score (r = −0.53; p < 0.001). A stepwise forward multiple regression analysis with total MDB score as dependent variable and NPI-10 subscale scores as independent variables confirmed Disinhibition as the main behavioural predictor of cognitive performance at T0 in our AD population (β = −0.53; t = 4.46; p < 0.001).

Rate of cognitive decline (as measured by difference in ADAS-Cog score passing from T0 to T12) and progression rate of behavioural alterations (as measured by difference in NPI-10 total score passing from T0 to T12) were positively related (r = 0.35; p < 0.001). However, the total score on the NPI at T0 was not significantly correlated with the rate of cognitive decline measured by the ADAS-Cog (r = 0.08; p = n.s.).

4. Discussion

The first result of this study is the demonstration that the two neuropsychological scales used, that is, the MDB and the ADAS-Cog, have different sensitivity in the early diagnosis and longitudinal assessment of cognitive decline in patients with AD. Indeed, confirming the ineffectiveness of the ADAS-Cog as a screening test for dementia [16], a significantly lower percentage of AD patients performed in the pathological range on the ADAS-Cog than on the MDB scale. One reason for the low sensitivity of the ADAS-Cog in detecting cognitive impairment may be the lack of a delayed recall condition in the verbal memory subtest. Indeed, consistent with the early localization of neuropathological changes in the mesio-temporal structures, which are critical for declarative memory functioning [3], delayed recall tests are much more sensitive than immediate recall tests in detecting memory impairment in patients with AD [12,45]. Indeed, the MDB correctly classified 74% of the patients with AD. Applying the same diagnostic criterion used here (i.e., two or more pathological scores on the eight tests comprising the battery), in a normative study [10] diagnostic sensitivity was 93% (with a specificity of 95% in identifying healthy controls). One possible reason for the lower diagnostic accuracy in the present than in the normative study is that the AD patients here were affected by mild to moderate forms of dementia (MMSE scores ranged from 15 to 25), whereas the AD sample used for the MDB standardization also included individuals with more severe forms of dementia.

The findings of the present study confirm the reliability of the ADAS-Cog in rating cognitive decline over time in patients with dementia [16]. In fact, the total score decrement passing from the baseline to the 12-month follow-up was significant for the ADAS-Cog but not for the MDB. The high sensitivity of the ADAS-Cog in revealing even mild changes in cognitive efficiency is likely due to the wide range of the total score (0–70), which permits graduating step by step the evolution of cognitive symptoms [43]. Conversely, the poor sensitivity of the MDB in registering the progressive decrement of cognitive efficiency is likely due to the fact that on some tests in the battery (i.e., delayed recall of the word list) AD patients reach a floor effect of performance precociously and thus fail to evidence further worsening at the follow-ups.

A second result of the present study is the demonstration that Dysphoria/Depression, Apathy and Anxiety are the most frequent and severe BPSD in patients with AD. These results are in substantial agreement with findings of previous studies that also used NPI-10 to investigate the prevalence and the qualitative features of BPSD in the early phases of AD [21,46]. Conversely, we found a particularly low prevalence of positive psychotic symptoms (both Delusions and Hallucinations) in our AD sample. This is at variance with results of previous studies reporting a prevalence of over 40% of Delusions in samples of patients with AD [21,25,26,52]. The prevalence of hallucinations in AD has been estimated differently: Some studies have reported a prevalence of over 30–40% [29,52] and others less than 10% [25,26]. Only Spalletta et al. [46] reported a low occurrence of both Delusions and Hallucinations, similar to the findings of the present study. Discrepancies among studies regarding the prevalence and severity of reported BPSD are likely due to differences in the average severity of cognitive deterioration in the investigated samples and to sensitivity of the diagnostic protocols used to assess BPSD. In fact, the low prevalence of psychotic symptoms in our sample could be related to the particularly early phase of cognitive deterioration in our AD group (as demonstrated by an average MMSE score over 20) and to the use of a testing instrument (NPI-10) that assesses a wide range of BPSD and, therefore, could be less sensitive to the presence of psychotic symptoms than specifically devoted instruments (e.g., the ad hoc structured interviews used by Mizrahi et al. [37] and Wilson et al. [52].
In the present study, we found that at T0 the NPI-10 total score correlated significantly with performance on most of the MDB tests. A more specific relationship emerged between the severity score on the NPI-10. Disinhibition scale and performance level on most of the MDB tests and with the total MDB score. On the other side, performance scores on the Phonological Word Fluency test showed the most consistent relationship with individual NPI-10 scale scores. It is generally held that poor performance on a test of Phonological Word Fluency is the expression of frontal dysfunction [1]. On the other hand, factor analyses of severity scores on the various NPI-10 subscales have repeatedly demonstrated that Disinhibition correlates with the expression of other behavioural symptoms of frontal sufferance, e.g., Euphoria [21,46]. Taken together, these results suggest that neuropathological changes at the level of cortical frontal regions are responsible for the appearance of most behavioural symptoms in AD patients [4].

As further support of the parallelism between the temporal course of behavioural and cognitive symptoms in AD, we found that rate of cognitive decline passing from T0 to the T12 follow-up (as expressed by a change in the overall ADAS-cog score) and worsening of the behavioural symptoms during the same period (as manifested by an increase in the overall NPI-10 score) were significantly correlated. However, neither the overall NPI-10 score nor the partial scores on the specific NPI-10 subscales obtained at T0 were able to reliably predict the rate of cognitive decline. A similar failure of the BPDS to provide a prognostic index of the successive rate of cognitive deterioration has been reported by other authors. Nevertheless, Frisoni et al. [21] and Wilson et al. [52] reported that AD individuals with psychotic symptoms presented a steeper cognitive decline than individuals without psychosis. As noted above, in our AD sample prevalence and severity of psychotic symptoms (both Delusions and Hallucinations) were particularly low, possibly accounting for the lack of support to the above mentioned predictive role of these variables over the rate of cognitive decline.

In conclusion, the results of the present study highlight a substantial parallelism between cognitive and behavioural alterations in AD. Indeed, the severity of cognitive and behavioural symptoms at the time of study entry and the rate of decline during the year of our observation were significantly related. A more qualitative analysis of the pattern of correlation between MDB and NPI-10 sub-scores suggests an association between BPSD (particularly Disinhibition) and neuropsychological signs of frontal dysfunction. Finally, our results provide no indication that severity of BPSD in the early
phases of AD is predictive of the rate of subsequent cognitive decline. One strength of the present study was our decision to use cognitive scales that demonstrated different sensitivity in detecting the initial symptoms of cognitive impairment (MDB) or in following the rate of cognitive decline over time (ADAS-Cog) in patients with AD. This allowed us to detect an association between behavioural and cognitive alterations in both the cross-sectional (T0) and the longitudinal (from T0 to T12) part of our study. Conversely, a limit of the study was the relatively small AD sample size and the use of a testing instrument, the NPI-10, that covers the whole spectrum of possible behavioural alterations and likely has little sensitivity for detecting mild alterations (e.g., in the domain of psychotic symptoms). Further studies on larger patient populations and more focused on specific symptoms are needed to gain more insight into the relevance of behavioural alterations and their relationship to cognitive deficits in AD.

References


Depressive symptoms and one year mortality among elderly patients discharged from a rehabilitation ward after orthopaedic surgery of the lower limbs

Fabio Guerini\textsuperscript{a,b}, Sara Morghen\textsuperscript{a,b}, Elena Lucchi\textsuperscript{a,b}, Giuseppe Bellelli\textsuperscript{a,b}\textsuperscript{*} and Marco Trabucchi\textsuperscript{b,c}
\textsuperscript{a}Department of Rehabilitation and Aged Care “Ancelle della Carità” Hospital, Cremona, Italy
\textsuperscript{b}Geriatric Research Group Brescia, Brescia, Italy
\textsuperscript{c}University Tor Vergata, Rome and Geriatric Research Group Brescia, Brescia, Italy

Abstract. The objective of the present prospective observational study is to evaluate the effect of depressive symptoms on 1-year mortality in a population of elderly patients discharged from a rehabilitation unit after orthopaedic surgery of the lower limbs. A total of 222 elderly inpatients were included, and stratified according to 12-months survival. 14 (6.3\%) of the patients who were eligible for this study died during the 12-months period after discharge. As expected, patients who died were significantly older, lower cognitive performance, more depressive symptoms, poorer nutritional status and higher comorbidity in comparison to those who survived. Furthermore, they were generally more functionally dependent on admission to the Department, had worse functional recovery and were more disable at discharge, although a longer length of stay comparing to survived patients. In the adjusted logistic regression model, after adjustment for possible confounders and covariates, the presence of severe depressive symptoms significantly predicted a four-fold risk of death at 12 months. The only other factor associated poor 12-months survival was comorbidity, that predicted a 6-fold risk of death. In conclusion this study suggests that severe depressive symptoms on admission predicts 1-year mortality in elderly patients discharged from a post-acute care unit after orthopaedic rehabilitation.

Keywords: Depressive symptoms, mortality, orthopaedic rehabilitation, elderly

1. Introduction

Depressive symptoms are common among older medical inpatients [1]. Several studies have shown that DS are a risk factor for adverse outcomes and mortality in selected populations of patients, including those with stroke and cardiovascular diseases [2,3]. However, few studies systematically evaluated the impact of depressive symptoms in orthopaedic patients, especially after arthroplastic surgery. Nightingale et al. found that depressive symptoms increase the risk of mortality at 2 years in patients after hip fracture [4]. On the contrary Holmes and House found that the relative risks of mortality over 6 months after hip fracture was increased in dementia and delirium, but not in depressed patients [5]. More recently Herschkovitz et al. showed that only dementia and age were independent predictors of mortality during the first 2 years after discharge from a post-acute rehabilitation program, while the presence of depression was not [6].

This apparent inconsistency of results may be due to the fact that these studies did not report the severity of depressive symptoms, but only whether the patient were positive to depressive symptoms screening or not [5, 6]. Another confounding effect may be due to inadequate adjustment for other risk factors for mortality, such as comorbidity, physical disability, and cognitive impairment.
The aim of this study is to evaluate the effect of depressive symptoms severity on 1-year mortality in a population of elderly patients discharged from a rehabilitation unit after orthopaedic surgery of the lower limbs. This effect was measured taking into the account for the possible interference of socio-demographic, clinical, cognitive and functional variables.

2. Methods

2.1. Setting

The Department of Rehabilitation and Aged Care is a 80-beds ward devoted to the rehabilitation of post-acute and chronic disabilities of elderly patients. The most frequent reasons for admission are post-surgical interventions (hip fracture surgical repair, hip or knee arthroplasty, abdominal, cardiac or thoracic surgery), stroke (recent or chronic), peripheral vascular diseases, subacute and chronic heart failure, subacute and chronic obstructive pulmonary diseases, Parkinson diseases and parkinsonisms, gait and balance disorders due to a single or mixed etiology, including hypokinetic syndrome [7].

2.2. Subjects

The study sample was taken from all new and consecutive admissions to our Department from January 1st, 2004 to May 31st, 2007. Inclusion criteria were age greater or equal to 65 years and the need of rehabilitation after orthopaedic surgery (hip fracture surgical repair, elective knee or hip surgical replacement). Exclusion criteria were a length of stay in the orthopaedic ward before admission longer than 1 week, a written order not to ambulate after orthopaedic surgery, pathological or multiple fractures and/or other illnesses reducing life expectancy to less than 6 months or poor reliability of self reported depressive symptoms (score < 15/30 on Mini Mental State Examination – MMSE) [8].

Informed consent was obtained on admission by the patients or their legal representative. The study was approved by the Ethics Committee of Gerontological Sciences of the Geriatric Research Group.

2.3. Comprehensive geriatric assessment

All subjects underwent on admission a comprehensive multidimensional geriatric assessment including demographics, cognitive, clinical and functional characteristics. The global cognitive status was assessed with the Mini Mental State Examination (MMSE), and the physical health status with the Charlson Index, a well-known measure of comorbidity [9]. Depressive symptoms were evaluated on admission using the 15-items Geriatric Depression Scale (GDS), a commonly used screening tool in geriatric settings, with higher scores indicating worse affective status [10]. According to previous studies, patients were defined as having mild to moderate depressive symptoms when the GDS score ranged from 6 to 10/15, while having severe depressive symptoms when GDS score was greater or equal to 11/15 [10,11]. The functional status was assessed both on admission and at discharge using the Functional Independence Measure (FIM) [12].

2.4. Follow-up

At 12 months, deaths were investigated with a telephone follow-up interview with patients (or proxies living with patients for those with cognitive impairment or in case of death) by a psychologist trained in geriatrics and blinded to the aim of this study.

2.5. Statistical analysis

All analyses were performed using the SPSS (Statistical Package for Social Sciences) software tool, version 11.0. Significance between variables was tested with the GLM model, or chisquare analysis, when appropriate. The independent association of death at 1 year with possible predictors was tested in multiple logistic regression model (method stepwise), with covariates and confounders treated as categorical variables (age, gender, GDS, MMSE, FIM, Charlson index, orthopaedic categories). For continuous variables that entered in the model, an analysis of the quartiles has been performed in order to select the best cut-off to categorize these variables.

3. Results

In Table 1 are shown the demographic, clinical and functional characteristics of 222 patients who were eligible for this study. Of these, 14 (6.3%) died during the 12-months period after discharge. As expected, patients who died were significantly older, had lower cognitive performance and more severe depressive symptoms. From a clinical point of view they had more frequently hip fracture, poorer nutritional status (as ex-
Table 1
Demographic, clinical and functional characteristics of 222 orthopaedic elderly patients admitted to the Department of Rehabilitation and Aged Care according to 12-months survival

<table>
<thead>
<tr>
<th></th>
<th>Death (n = 14, 6.3%)</th>
<th>Alive (n = 208, 93.7%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD or n(%)</td>
<td>Mean ± SD or n(%)</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>82.2 ± 6.5c</td>
<td>77.4 ± 7.7</td>
<td>0.000</td>
</tr>
<tr>
<td>Gender female</td>
<td>11 (78.6%)</td>
<td>164 (78.8%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Orthopaedic categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hip fracture surgical repair</td>
<td>12 (85.7%)</td>
<td>122 (58.7%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Elective knee or hip replacement</td>
<td>2 (14.3%)</td>
<td>86 (41.3%)</td>
<td></td>
</tr>
<tr>
<td>Cognitive and affective status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini Mental State Examination (0–30)</td>
<td>22.3 ± 4.0</td>
<td>25.4 ± 3.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Geriatric Depression Scale (0–15)</td>
<td>7.0 ± 3.1</td>
<td>4.5 ± 3.1</td>
<td>0.005</td>
</tr>
<tr>
<td>– GDS ⩽ 5/15</td>
<td>4 (28.6%)</td>
<td>141 (67.8%)</td>
<td></td>
</tr>
<tr>
<td>– GDS from 6 to 10/15</td>
<td>7 (50.0%)</td>
<td>57 (27.4%)</td>
<td></td>
</tr>
<tr>
<td>– GDS ⩾ 11/15</td>
<td>3 (21.4%)</td>
<td>10 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Health Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson index of comorbidity (0–37)</td>
<td>4.1 ± 2.6</td>
<td>1.8 ± 1.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum albumin levels (gr/dl)</td>
<td>2.6 ± 0.4</td>
<td>2.9 ± 0.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Serum cholesterol levels (gr/dl)</td>
<td>134.1 ± 36.9</td>
<td>167.9 ± 35.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Functional Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIM* Admission (0–126)</td>
<td>56.0 ± 18.3</td>
<td>75.6 ± 21.8</td>
<td>0.001</td>
</tr>
<tr>
<td>FIM* Discharge (0–126)</td>
<td>72.0 ± 26.8</td>
<td>99.5 ± 19.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Length of Stay, days</td>
<td>30.1 ± 9.4</td>
<td>24.2 ± 7.9</td>
<td>0.008</td>
</tr>
</tbody>
</table>

P denotes significance between variables using the GLM model (or chi-square analysis where appropriate).

<table>
<thead>
<tr>
<th></th>
<th>OR (Confidence intervals, 95%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe depressive symptoms</td>
<td>4.4 (1.4 to 14.0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Moderate to severe comorbidity</td>
<td>6.0 (1.8 to 20.2)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

The adjusted regression model assessing the power of depressive symptoms and other covariates (treated as categorical variables) to predict deaths at follow-up is shown in Table 2. It could be observed that the presence of severe depressive symptoms predicted a four-fold risk of death. Interestingly, the only other factor associated with 12-months deaths was comorbidity (measured with the Charlson index), predicting a 6-fold risk of death. The other covariates in the model (age, gender, GDS, MMSE, FIM, orthopaedic categories) were not significant predictors.

4. Discussion

The study shows that severe depressive symptoms are predictors, in addition to comorbidity, of 1-year mortality in post-surgery orthopaedic rehabilitation. The association is independent from a number of potential clinical, cognitive and functional confounders.

Depressive symptoms in old patients are known to have a large clinical heterogeneity, which may exert these adverse effects throughout different mechanisms. On the one side, the lack of motivation might affect
the participation of patient with depressive symptoms in the rehabilitative project [13], which in turn might influence the functional recovery at discharge and the adherence to pharmacological treatments. This could lead to inadequate lifestyle habits and increase the susceptibility to diseases. On the other side, depressive symptoms may be viewed as a marker of frailty, indirectly revealing the lack of patient’s competence toward distressful events. In line with this observation, recent studies have shown a derangement of some biochemical circuits (serotonine and noradrenaline transmitters) [14] and an increase of atherosclerosis in depressed patients [15].

The observation that comorbidity is an independent predictor of mortality in elderly patients after orthopaedic surgical intervention is not surprising, since it has been demonstrated in several studies [16,17]. However, the finding that only severe depressive symptoms, and not mild or moderate depressive symptoms, are associated with 1-year outcomes comments. The most probable explanation is that high scores on GDS are more accurate to detect a real affective disorder or an underlying condition of frailty, which in turn may lead to increased mortality. In line with this interpretation, a study by Chiang and colleagues has recently shown that the 15-items GDS is more accurate to detect moderate or severe levels of depression than mild ones [18].

Our data are in line to previous studies showing an inverse relationship between severity of depressive symptoms and adverse clinical outcomes [19] and suggest that physicians may consider these symptoms as a key target of their routine rehabilitative practice. A limitation of this study is that our population included patients with elective and non-elective surgical interventions. However, it should be underscored that in the multiple logistic regression model we considered this confounding factor, and the orthopaedic typology (hip fracture surgical repair vs elective knee or hip surgical replacement) did not significantly predict mortality in this population. Another limitation is the population size, thus further studies are needed, with higher number of cases, in particular on patients with severe depressive symptoms, to confirm our findings.

In conclusion this study suggests that severe depressive symptoms on admission predicts 1-year mortality in elderly patients discharged from a post-acute care unit after orthopaedic rehabilitation. Because of its potential implications, depressive symptoms should be routinely screened among elderly patients in orthopaedic rehabilitative settings.

References


The contribution of the dorsolateral prefrontal cortex in full and divided encoding: A paired-pulse transcranial magnetic stimulation study

Sophie Blanchet\textsuperscript{a,b,*}, Geneviève Gagnon\textsuperscript{a,b} and Cyril Schneider\textsuperscript{c}
\textsuperscript{a}Center for Interdisciplinary Research in Rehabilitation and Social Integration, Quebec City, Canada
\textsuperscript{b}School of Psychology, Université Laval, Quebec City, QC, Canada
\textsuperscript{c}CHUQ Research Center, Department of Rehabilitation, Université Laval, Quebec City, QC, Canada

Abstract. This research investigated the contribution of the dorsolateral prefrontal cortex (DLPFC) in the attentional resources in episodic encoding for both verbal and non-verbal material. Paired-pulse transcranial magnetic stimulations (TMS) were used to interfere transiently with either the left or right DLPFC during encoding under full attention (FA) or under divided attention (DA) in a recognition paradigm using words and random shapes. Participants recognized fewer items after TMS over the left DLPFC than over the right DLPFC during FA encoding. However, TMS over the left DLPFC did not impair performance when compared to sham condition. Conversely, participants produced fewer items after TMS over the right DLPFC in DA encoding compared to sham condition, but not compared to TMS over the left DLPFC. These effects were found for both words and random shapes. These results suggest that the right DLPFC play an important role in successful encoding with a concomitant task regardless of the type of material.

Keywords: Episodic memory, attentional resources, verbal material, visuospatial material, hemispheric asymmetry, transcranial magnetic stimulation (TMS)

1. Introduction

Episodic memory allows an individual to remember the temporal and spatial context of events [29]. Successful encoding into episodic memory depends on the availability of attentional resources. Accordingly, divided attention (DA) during encoding has a detrimental effect on subsequent recall performance in healthy young individuals [2,14,22]. The decreased performance following encoding under DA compared to encoding under full attention (FA) would reflect limitations of control processes that depend on the prefrontal (PFC) areas. Left PFC is often activated in episodic encoding under FA regardless of the type of material (see [12] for a review). The dorsolateral PFC (DLPFC) subareas have been reported to be sensitive to the DA detrimental effect during encoding. Indeed, using positron emission tomography (PET), decreased left DLPFC activations have been found during encoding when semantic organizational or associative strategies were explicitly required in encoding concomitantly to a secondary task [17,22]. Only verbal material was used in the previous DA studies. Non-verbal material that is novel without any pre-existing representation, however, may solicit greater attentional processes than verbal material [6]. In addition, the previous findings rely on neuroimaging data, which use hemodynamic and metabolic indices. This may be an issue because...
the activations do not mean that the activated structures are functionally necessary to perform the targeted cognitive task [42].

By inducing a safe and transient interference with transcranial magnetic stimulations (TMS) in healthy individuals, the mandatory role of a cortical area in a given cognitive task can be investigated. Memory performance disruption by TMS demonstrates thus that the stimulated area is critical to perform the task. Impaired recall performance was also observed following repetitive TMS (rTMS) over the left DLPFC during FA encoding of a story [35], semantically unrelated word pairs [20,41] and complex indoor/outdoor pictures [36]. Recall deficits, however, have been found after TMS over the right DLPFC during encoding of word pairs with high imagery content [41]; this may be indicative of the role that this region plays in image-based processing [41]. These previous TMS studies investigated the DLPFC role in episodic memory uniquely under FA but not in DA. Whether the DLPFC is required or not for successful encoding in DA remains unclear. Indeed, patients with anterior injuries did not suffer from a large detrimental effect of DA compared to those with posterior injury [48] or healthy controls [3]. However, in these studies, patients were pooled regardless of the injured frontal subareas that are known to play different functions. In addition, it cannot be ruled out that their cognitive profiles reflect the involvement of neural and/or cognitive compensatory processes occurring after injury.

We investigated the contribution of the left and right DLPFC in encoding according to the availability of attentional resources for both verbal and non-verbal material. To this end, paired-pulse TMS was applied to interfere transiently with the left or right DLPFC during encoding under FA or DA of random shapes or words. In reference to TMS or neuroimaging studies in encoding under FA [17,20,22,35,37], we expected that TMS over left DLPFC exert a detrimental effect on memory performance compared to TMS delivered over right DLPFC. Since previous neuroimaging studies found that a secondary task decreased the left frontal activity during encoding [2,22], the interferential effect of TMS on memory performance when applied over the left DLPFC should be less pronounced for encoding under DA.

2. Methods

2.1. Participants

Sixteen healthy young participants (mean age, 22.75 ± 3.33; range, 18–30 years) with an average of 16.37 (2.89) years of formal education gave their written consent before taking part in the protocol. Participants were all right-handed. The mean of their laterality index is estimated at 83 (17.09) on the basis of Edinburgh Handedness Inventory [34]. The other inclusion criteria were normal or corrected-to-normal vision and French as the native language. The exclusion criteria were a history of psychiatric or neurological disorders (e.g., stroke, head injury) and alcoholism. None received anxiolytic or antidepressant treatments known to interfere with attention or memory. In respect of safety guidelines for the use of TMS [37,49], participants did not present any history of epilepsy, migraine, cardiovascular diseases, or metal in head or jaw. In compliance with the Declaration of Helsinki, the project was approved by the local Ethics Committees.

2.2. TMS memory paradigm

The paradigm is illustrated in Figure 1. Participants were seated at a distance of 23 inches from a computer monitor. All stimuli were displayed in white on a black screen and each one was unique. The non-verbal material consisted of complex random shapes designed to be neither figurative nor verbalizable (see [7], for more details). The verbal material consisted of unrelated nouns of four- to eight-letters [15]. All lists of words were equivalent in frequency (4.46 ± 0.79) and imageability (5.19 ± 0.89). For each condition, one list of 20 targets was presented. For both verbal and non-verbal materials, there were six TMS conditions: (1) the right DLPFC was stimulated during FA encoding; (2) the left DLPFC was stimulated during FA encoding; (3) the right DLPFC was stimulated during DA encoding; (4) the left DLPFC was stimulated during DA encoding; (5) a sham TMS encoding condition under FA; (6) a sham TMS encoding condition under DA. During the encoding phase, each stimulus appeared for 1000 ms in the center of the screen, with a 2500 ms inter-stimulus interval. The encoding phase was separated from the recognition phase by a gray screen lasting 5000 ms. In the recognition phase, probes corresponding to half of the previously displayed items mixed with the same number of novel items appeared successively in the center of the screen. Each probe was presented for 1000 ms. The elapsed time between two successive probes was 3500 ms. Participants pressed the green key with the right index finger for a previously seen item and the red key with the left index finger for an item not seen previously. The position of the targets in the recognition phase was pseudo-random to avoid serial effects.
Fig. 1. Transcranial magnetic stimulations were applied during encoding under full or divided attention either on the left or the right dorsolateral prefrontal cortex.

Each list was separated by a pause lasting about 3 min. During the FA encoding phase, participants only memorized the stimuli (i.e., without any concurrent task). During the DA encoding phase, participants were instructed to divide their attention equally between the encoding task and a secondary task. The latter consisted of an auditory digit-monitoring task. Participants listened to series of odd and even digits at a rate of 1 digit every 2000 ms. They pressed the green key for an odd preceded by an even, the red key in other case. Key order was counterbalanced between participants. For each material, participants were trained on two lists of 8 items prior to the experimental conditions. There was one session for non-verbal material and one session for verbal material, each of which was administered on different days. Each session lasted approximately 90 minutes. Memory paradigms were run on E-Prime software in interface with the TMS system.

2.3. TMS protocol

Transcranial magnetic stimulations were applied to the scalp using a custom made 70-mm (wing diameter) double-cone coil connected to 2 Magstim 200 electromagnetic stimulators coupled with a Bistim module (Magstim Company Limited, Whitland, UK). The coil was positioned over the left or the right DLPFC corresponding respectively to the F3 and F4 scalp sites according to a reference grid (10–20 EEG system; [23]). F3 and F4 sites correspond to Broadmann’s area 9 [45]. Double TMS pulses were induced at a fixed inter-stimulus interval (ISI). It is well documented that 3 to 5-ms ISIs induce an intracortical inhibition in the primary motor cortex [26] and interfere with higher cognitive functions (see [38] for a review). Therefore, we used 2 sub-threshold TMS elicited 3 ms apart to induce a transient interference in DLPFC processing. As previously applied in TMS memory studies [35,36,41], TMS intensity was set at 90% motor-threshold. Motor-threshold was determined as the minimal intensity of the stimulator output enabling us to induce a motor evoked potential in the resting first dorsal interosseus higher than 50 µV for 5 out of 10 TMS trials [39]. Motor-thresholds were estimated for right and left motor cortices (means, 25.28 ± 2.42 and 25 ± 2.39, respectively). Each paired-pulse TMS was delivered 500 ms after each stimulus onset. We chose to induce paired-pulse TMS 500 ms after stimulus onset in encoding because DLPFC-related strategy processes occurred during this time-interval (e.g. [4,8]). For the sham encoding conditions under FA or DA, the TMS coil was placed above the interhemispheric scissure (at Cz) and was rotated 90 degrees tangentially to the head. Thus the participants kept hearing the discharge TMS noise, while elicited TMS did not penetrate into the scalp. These sham encoding conditions enabled us to control for the impact of the auditory noise (still audible at the same TMS intensity between all conditions). Unfortunately we cannot control the impact of the superficial epidermal reactions over the muscles of the scalp induced in the experimental TMS condition. The muscular contractions are, however, quite minimal when TMS are delivered under the subthreshold motor level as in our study.

2.4. Data analysis

Different response indices were analyzed to assess memory performance and strategies. In reference to
the two-high threshold model [44], we analyzed hits (H), false alarms (FA) and discrimination rate (H–FA). The discrimination rate, that ensures that the participants discriminated correctly between the targets and the distractors during recognition, had to be greater than chance levels (Ø). The response time of hits was also considered. For each type of material, an ANOVA with repeated measures was conducted with Attention (DA, FA), Material (random shapes, words) and TMS Condition (right DLPFC, left DLPFC, sham) as within subject factors. Post-hoc analyses were conducted using Fisher’s LSD test.

3. Results

Performance obtained in recognition following each encoding condition is illustrated in Table 1.

3.1. Hits

A significant Attention x TMS Condition interaction was found [F(2,30) = 3.46, P = 0.04]. The interaction is illustrated in Fig. 2. Post-hoc analyses detected that participants recalled significantly fewer items after TMS over the left DLPFC than over the right DLPFC during encoding under FA (P = 0.03), but not versus the sham FA encoding condition. In contrast, participants recalled fewer items after TMS over the right DLPFC during encoding under DA as compared to the sham DA encoding condition (P = 0.05), but not versus left TMS. The main effect of Attention was significant [F(1,15) = 56.76, P < 0.001].

The Material x TMS Condition interaction did not reach the level of significance [F(1, 30) = 3.46, P = 0.14]. Finally, ANOVA failed to detect any main effect of TMS Condition or Material [F(2,30) = 1.98, P = 0.15, and F(1, 30) = 2.95, P = 0.11, respectively] and any interaction between Attention, TMS Condition and Material (F < 1).

3.2. Discrimination rates

ANOVA applied on discrimination rates detected a main effect of Attention [F(1,15) = 24.05, P < 0.001], indicating that the discrimination rate was higher after encoding under FA (63.97 % ± 18.7) than encoding under DA (50.7 % ± 20.16). A main effect of Material was also significant [F(1,15) = 30.92, P < 0.001], reflecting a higher discrimination rate for words (58.86 % ± 17.43) than for random shapes (45.81 % ± 23.05).

3.3. False alarms

The Material main effect was significant [F(1,15) = 27.11, P < 0.001], indicating that more false alarms were produced for random shapes (22.63 % ± 14.11) than for words (5.82 % ± 4.66). There was no main effect of Attention [F(1, 15) = 1.24, P = 0.28]. No other interaction or effects were significant (F < 1).

3.4. Response time of hits

The interaction Attention, Material by TMS Condition was significant [F(1,30) = 3.74, P = 0.04]. Post-hoc analyses revealed that for random shapes encoded under FA, response time was longer after TMS over the left DLPFC than in the sham condition (P = 0.04). After encoding under DA, the response time for random shapes was longer after TMS over the right DLPFC than after TMS over the left DLPFC (P < 0.005).
Table 1
Means and standard deviations obtained at the recognition paradigm according to the TMS encoding conditions

<table>
<thead>
<tr>
<th>Indices</th>
<th>Full attention</th>
<th>Divided attention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-verbal</td>
<td>Verbal</td>
</tr>
<tr>
<td></td>
<td>Left DLPFC</td>
<td>Right DLPFC</td>
</tr>
<tr>
<td>Hits (%)</td>
<td>Mean</td>
<td>75.97</td>
</tr>
<tr>
<td></td>
<td>StDev</td>
<td>19.22</td>
</tr>
<tr>
<td>DR (%)</td>
<td>Mean</td>
<td>49.65</td>
</tr>
<tr>
<td></td>
<td>StDev</td>
<td>29.74</td>
</tr>
<tr>
<td>Hits RT</td>
<td>Mean</td>
<td>908.95</td>
</tr>
<tr>
<td></td>
<td>(ms)</td>
<td>187.54</td>
</tr>
</tbody>
</table>

DLPFC: Dorsolateral Prefrontal Cortex; FA: False Alarms; DR: Discrimination Rate; RT: Response Times.

was also longer in the sham DA encoding condition than after left DLPFC TMS ($P = 0.03$). There was also a Material main effect [$F(1,15) = 7.73, P = 0.01$]. The Attention x TMS Condition interaction was not significant [$F(1,30) = 2.47, P = 0.11$], neither the Material x Condition interaction [$F(1, 30) = 2.54, P = 0.11$]. No other interactions or effects were detected ($F < 1$).

3.5. Digit monitoring task performance

An ANOVA Material (random shapes, words) by TMS Condition (left DLPFC, right DLPFC, sham) revealed only a Material main effect [$F(1,30) = 6.15, P = 0.03$], indicating fewer responses at the digit monitoring task when random shapes ($93.33% ± 8.15$) were presented as compared to words ($96.73% ± 4.55$). Neither Condition effect nor interaction was significant ($F < 1$).

4. Discussion

The present study aimed to investigate the involvement of the DLPFC in the attentional resources during encoding according to the type of material (verbal or non-verbal). For this purpose, safe focal paired-pulse TMS was applied to interfere transiently with either the left or right DLPFC during encoding under FA or DA of words or random shapes. Our results detected a dichotomy for the TMS interference of DLPFC during encoding. Indeed, under FA, TMS over the left DLPFC interfered detrimentally on memory performance whereas TMS over the right DLPFC interfered only under DA, regardless of the type of material. The discussion that follows presents the concurrent involvement of the left and right DLPFC in encoding under FA and DA, respectively.

We found that TMS over the left DLPFC during encoding under FA decreased hit percent when compared to TMS over the right DLPFC, for both random shapes and words. Hit response time was also longer after TMS over left DLPFC than in the sham condition. These findings are in agreement with previous neuroimaging data showing that the left DLPFC is preferentially activated in encoding in healthy young individuals [2,22]. Impaired recall performance has also been reported after rTMS over the left DLPFC during encoding compared to rTMS over the right DLPFC for verifiable material such as a short story [35], unrelated words [20,41] or indoor/outdoor pictures [36]. Our results extend further that the left DLPFC is not only activated during encoding under FA, but it is also necessary for successful encoding of both unrelated verbal and non-verbal material. Surprisingly, the inhibitory effects of TMS over the left DLPFC during FA encoding were detected only for the hits, but not for the discrimination rates. Previous neuroimaging studies showed that DLPFC activations in organizational or elaborative strategies during encoding are a predictive value of subsequent long-term memory performance [9, 31] (for a review, see [10]). In our study, the inhibitory TMS effect over the left DLPFC during FA encoding would thus exert a detrimental effect on strategies that contribute to successful encoding. Even if our instructions did not explicitly orient participants to adopt mnemonic strategies, our participants may have applied them. This is in agreement with impaired performance on different memory indices in patients with left posterior DLPFC lesions (BA 44, 9, 46) [1]. According to these authors, these deficits are related to difficulties in applying strategies of encoding. Findings from complementary approaches therefore demonstrated that the left DLPFC plays an important role in episodic encoding.
During encoding under DA, hit percent was lower after TMS over the right DLPFC than after TMS over the left DLPFC. Response time for non-verbal material was also longer after TMS over the right DLPFC than after TMS over the left DLPFC. Contrary to encoding under FA, we found that the inhibitory effects of TMS on memory performance when delivered over the left DLPFC are less pronounced for encoding under DA. In this way, neuroimaging studies reported that the left DLPFC activations were decreased under DA for an encoding task that required explicit semantic organizational or associative strategies of related words [17,22]. Conversely, our results brought about the evidence of the role of the right DLPFC during encoding under DA. This may be related to the involvement of control executive system in both the encoding of unrelated items that would greater solicit self-initiated elaborative strategy than related items, as well as the secondary task. This right lateralized DLPFC contribution under DA may reflect item-related processes during encoding as already evidenced by means of techniques investigating item-related activity (e.g., event-related potentials, event-related functional magnetic resonance imagery) rather than task-related activity (e.g., PET). Indeed, using event-related potentials, Mangels, Picton and Craik [28] reported greater right frontal sustained activity for recalled and remembered words when encoded concomitantly to a difficult secondary task. This experimental condition depended on efficient self-initiative strategy and involved an executive control that was necessary for the active maintenance and manipulation of information. Using event-related functional magnetic resonance imaging, Uncapher and Rugg [47] even found a trade-off on the right DLPFC activations indicated by a reduced study-item activity contrasting with an increased auditory-item activity in the difficult, relative to easy, secondary task condition. In the present study, TMS over the right DLPFC may have therefore interfered with the right DLPFC item-activity involved during both the encoding and secondary tasks, independently of the type of the material to encode.

Some methodological considerations specific to our study, such as the frequency TMS and type of TMS coil used need to be addressed. Surprisingly, in our study, subsequent recall memory performance decreased only when TMS was applied over left DLPFC during FA encoding compared to TMS over right DLPFC. In contrast, this difference did not reach the significant level when TMS was applied over left DLPFC compared to the sham condition. The HERA model postulates that the left PFC is preferentially more involved in encoding of episodic memory than the right PFC [46]. However, the Nyberg et al.’s meta-analysis of neuroimaging studies supported that the predominant activation of the left PFC for encoding was detected in comparison to reference tasks [31]. Using rTMS, in agreement with our findings, Rami et al. [35] also found this asymmetry between left and right DLPFC, but not with sham or baseline conditions. One explanation for the discrepancy between these TMS and neuroimaging studies could be the disruption of the balance of the interhemispheric activity by interferential TMS. Actually, it is known that various cortical functions depend on a balance between both hemispheres, controlled by reciprocal interhemispheric inhibition [19,27]. Monohemispheric application of low-frequency rTMS that decreases the cortical excitability (i.e., inhibition) can disrupt this balance and disinhibit the contralateral non-stimulated hemisphere via transcallosal pathways [33]. Conversely, high-frequency rTMS that increases locally the excitability disrupts the balance by exacerbating the inhibition over the contralateral non-stimulated hemisphere. In the memory field, the increase of excitability in the left DLPFC during encoding by high-frequency rTMS (e.g., 20 Hz) may have thus inhibited the right DLPFC, leading to a worsening of subsequent recall memory performance [18,20,36,37,41,43]. In contrast, low-frequency rTMS (1 Hz) of the right posterior ventrolateral PFC during encoding led to a better memory performance as compared to left TMS [24]; transcallosal disinhibition of the left PFC may be the physiological substrate of enhanced encoding, in line with the authors’ suggestion of a transient ‘disengagement’ of right PFC. In our protocol, we used inhibitory low-frequency paired-pulse TMS (0.5 Hz, 3-ms inter-stimulus interval) over either the left or the right DLPFC during encoding under FA. Right TMS (i.e., decrease of right DLPFC excitability) may have disinhibited the left DLPFC (via the decrease of transcallosal inhibition) thus leading to improved encoding compared to the sham condition. This may explain why the left TMS during encoding under FA worsened subsequent recall memory performance only when compared to the right TMS, but not to the sham condition. Therefore, it cannot be ruled out that low-frequency TMS induces weaker memory performance decrease than high-frequency TMS. Following this reasoning, Rami et al. [35] reported lower subsequent memory performance after TMS over the left DLPFC, at a rate of 1-Hz (low-frequency) as compared to 5 Hz (high-frequency). In contrast, in our study, memory performance was dropped by right
TMS during encoding under DA (thus supporting the engagement of the right DLPFC in encoding under DA) but only when compared to the sham condition and not to the left TMS. TMS over the left DLPFC (i.e., disinhibiting further the right DLPFC already engaged in encoding) may have altered performance likely by a disruption of the activity balance between both DLPFC. This may therefore support a cooperative involvement of both sides in encoding under DA.

One another methodological issue concerns the type of coil used. The TMS double cone coil we employed usually enables recruitment of deep structures [40]. In this way, our TMS protocol may have influenced areas below the target DLPFC between 3 to 4 cm in depth. This is quite different from most memory studies having used a flat figure-of-eight coil to induce inhibitory effects in specific areas [16,18,20,36]. Indeed, the electric current under the flat coil is circumscribed to superficial (cortical) brain areas and is thus vertically more focal than the double cone coil [13]. Conversely, the flat coil is less focal horizontally (i.e., recruitment of adjacent areas under the coil wings) than the double cone coil whose wings curvature enables a stronger current in the middle point of the coil [21]. However, we can argue that the subthreshold paired-pulse TMS paradigm we used to induce DLPFC inhibition produced the largest effects at the site of stimulation with fewer effects from the stimulated site to distant areas than rTMS did [30]. Indeed, when coupling both paired-pulse TMS and fMRI recordings, Bestman et al. [4] have shown that paired-pulse TMS did not activate distant areas when delivered at a subthreshold intensity. Since we used a subthreshold 3-ms paired-pulse TMS paradigm, we are confident that TMS direct effects were circumscribed to DLPFC area. Nevertheless, it can be argued that indirect influence on remote areas may have occurred at the functional connections that DLPFC shares with, for example, the cingulate cortex and thalamic nuclei [29]. In our study, because TMS effects in FA encoding varied according to the laterality of the stimulations in agreement with the HERA model, our findings show influence in favour of circumscribed inhibitory effects induced by paired-pulse TMS over DLPFC. In the future, studies combining neuroimaging techniques and paired-pulse TMS may be relevant to probe how paired-pulse TMS affects neural mechanisms of cognitive functions.

In conclusion, our interferential TMS study confirms that the left DLPFC plays an important role in FA encoding. Originally, our results provide the first new evidence of the critical concurrent involvement of the right DLPFC in successful encoding with a secondary task for both unrelated verbal and non-verbal materials. Interestingly, the right DLPFC may benefit from neural/cognitive compensatory recovery after an acquired brain injury since the memory performance of patients with anterior injuries is not impaired after encoding under DA [3,48]. However, this needs to be confirmed because in these studies patients were not classified according to the specific PFC subareas that were altered. Future studies in patients with acquired brain injury should thus focus on cerebral plasticity by coupling neuropsychological investigations with neuroimaging or event-related potential techniques.

Acknowledgments

This study was supported by a National Science and Engineering Research Council (299425-04) grant, a research scholarship from Fonds de la Recherche en Santé du Québec as well as a grant for summer students from the Quebec Rehabilitation Research Network (REPAR) to Sophie Blanchet. The authors thank Gabrielle Chabot and Caroline Gagnon for their assistance in data collection.

References


