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Neural correlates of the DemTect in Alzheimer's disease and frontotemporal lobar degeneration – A combined MRI & FDG-PET study

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ABSTRACT

Valid screening devices are critical for an early diagnosis of dementia. The DemTect is such an internationally accepted tool. We aimed to characterize the neural networks associated with performance on the DemTect's subtests in two frequent dementia syndromes: early Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). Voxel-based group comparisons of cerebral glucose utilization (as measured by F-18-fluorodeoxyglucose positron emission tomography) and gray matter atrophy (as measured by structural magnetic resonance imaging) were performed on data from 48 subjects with AD (n = 21), FTLD (n = 14) or subjective cognitive impairment (n = 13) as a control group. We performed group comparisons and correlation analyses between multimodal imaging data and performance on the DemTect's subtests. Group comparisons showed regional patterns consistent with previous findings for AD and FTLD. Interestingly, atrophy dominated in FTLD, whereas hypometabolism in AD. Across diagnostic groups performance on the "wordlist" subtest was positively correlated with glucose metabolism in the left temporal lobe. The "number transcoding" subtest was significantly associated with glucose metabolism in both a predominantly left lateralized frontotemporal network and a parietooccipital network including parts of the basal ganglia. Moreover, this subtest was associated with gray matter density in an extensive network including frontal, temporal, parietal and occipital areas. No significant correlates were observed for the "supermarket task" subtest. Scores on the "digit span reverse" subtest correlated with glucose metabolism in the left frontal cortex, the bilateral putamen, the head of caudate nucleus and the anterior insula. Disease-specific correlation analyses could partly verify or extend the correlates shown in the analyses across diagnostic groups. Correlates of gray matter density were found in FTLD for the "number transcoding" subtest and the "digit span reverse" subtest. Correlates of glucose metabolism were found in AD for the "wordlist" subtest and in FTLD for the "digit span reverse" subtest. Our study contributes to the understanding of the neural correlates of cognitive deficits in AD and FTLD and supports an external validation of the DemTect providing preliminary conclusions about disease-specific correlates.

1. Introduction

Today, dementia disorders are a major health problem — affecting about 35.6 million people worldwide in 2010 (World Health Organisation, 2012). An early diagnosis is crucial to identify dementia-related diseases and administer appropriate therapeutic interventions; valid clinical screening and treatment progression devices are necessary to investigate specifically impaired cognitive domains. One of the most important and frequently used clinical dementia screening devices is the DemTect (Kalbe et al., 2004), which has obtained international acceptance as a neuropsychological

Abbreviations: AD, Alzheimer's disease; ANOVA, Analysis of variance; BA, Brodmann area; CDR, Clinical dementia rating scale; DARTEL, Diffeomorphic anatomical registration through exponentiated lie algebra; FDG-PET, F-18-fluorodeoxyglucose positron emission tomography; FTLD, Frontotemporal lobar degeneration; MMSE, Mini-Mental State Examination; MNI, Montreal Neurological Institute; MRI, Magnetic resonance imaging; PVE, Partial volume effects; SPM, Statistical parametric mapping.

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dementia screening test in recent years (Jacova et al., 2007). The DemTect consists of five subtests: learning of a ten item wordlist in two trials ("wordlist"), transcoding numbers in numerals and vice-versa ("number transcoding"), a semantic word fluency task ("supermarket task"), a task in which the patient has to repeat sequences of numbers in backward order ("digit span reverse"), and finally the wordlist's delayed recall ("wordlist, delayed recall"). In comparison to the more established Mini-Mental State Examination (MMSE) (Folstein et al., 1975), the DemTect has been shown to be superior in several studies (Kalbe et al., 2004; Perneczky, 2003), especially concerning the detection of mild dementia, which is a well-known weakness of the MMSE (Simard, 1998). Although the neural correlates of the MMSE have been investigated in studies with magnetic resonance imaging (MRI) (Apostolova et al., 2006; Baxter et al., 2006; Ferrarini et al., 2008; Jack et al., 2002; Nickl-Jockschat et al., 2011) and F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) (Mielke et al., 1994), these studies described neural correlates of total MMSE scores only. In order to link dementia syndromes to underlying impairments in neural networks, investigation of subtests addressing specific cognitive domains is necessary.

The neural networks affected by neurodegenerative diseases, especially Alzheimer's disease (AD) (Barnes et al., 2007; Baron et al., 2001; Boxer et al., 2003; Buckner et al., 2005; Chetelat et al., 2008; Frisoni et al., 2002; Rabinovici et al., 2007; Schroeter et al., 2009; Seeley et al., 2009) and frontotemporal lobar degeneration (FTLD) (Barnes et al., 2007; Boxer et al., 2003; Chetelat et al., 2008; Desgranges et al., 2007; Ishii et al., 1998; Jeong et al., 2005; Mummery et al., 2000; Rabinovici et al., 2007; Rosen et al., 2002; Schroeter et al., 2008, 2011; Seeley et al., 2009), have been described thoroughly in recent years in several studies and meta-analyses (Schroeter et al., 2008; Schroeter et al., 2009). Underlying different etiologies and pathomechanisms (Finder, 2010; Rabinovici and Miller, 2010), AD and FTLD have been related to specific metabolic and atrophic brain changes. MRI provides information about gray matter atrophy, whereas glucose metabolism is investigated with FDG-PET. However, results of FDG-PET analyses may be biased by gray matter atrophy if they are not corrected for partial volume effects (PVE) (Rousset et al., 1998). Accordingly, the correction for partial volume effects is a state-of-the-art step in preprocessing of FDG-PET imaging data (see also Baete et al., 2004). Recently, PVE-correction has been successfully applied when comparing atrophy and hypometabolism in AD (Chetelat et al., 2008). Although one study has investigated glucose metabolism and amyloid plaque density in subjects with AD and semantic dementia (Drzezga et al., 2008), to date, no study using FDG-PET has integrated other FTLD subtypes into a PVE corrected group comparison.

Firstly, our study aimed at investigating differences in FDG metabolism and gray matter atrophy with regard to their localization, as well as their extent in subjects suffering from AD or FTLD, using data corrected for PVE. Second, we intended to contribute to the external validation of the DemTect as a diagnostic tool capable of detecting cognitive deficits and linking them to morphological and glucose metabolic changes in the brain. Although the DemTect has already been conceptually validated as a sensitive and specific screening tool for AD by the use of FDG-PET as an in-vivo reference method (Scheurich et al., 2005), and there are studies that have investigated the neural networks involved in cognitive paradigms similar to those used in the DemTect in healthy subjects and dementia patients (Andreasen et al., 1995; Awh et al., 1996; Cabeza et al., 2002; Demonet et al., 1992; Fiez et al., 1996; Grasby et al., 1993; Henson et al., 2000; Jonides et al., 1998; Peters et al., 2009; Sato et al., 1999; Schroeter et al., 2012; Smith and Jonides, 1997; Smith et al., 1996, 1998), no study has systematically examined the neural correlates of the subtests of the DemTect. Accordingly, our study aimed to investigate the DemTect in relation to two neurodegenerative diseases (AD and FTLD) using a multimodal imaging study including MRI and FDG-PET. We hypothesized that performance in the DemTect subtests is associated with temporoparietal regions in AD and frontotemporal regions in FTLD. After correlating DemTect scores with MRI and FDG-PET data in the whole cohort to isolate the neural correlates of this test *per se*, we combined results with group comparisons between AD or FTLD patients and the control cohort in a conjunction analysis, and calculated disease-specific correlation analyses to identify neural correlates of the DemTect for AD and FTLD.

2. Methods

2.1. Subjects

We included 48 right-handed subjects from age 40 to 74 (25 females, 23 males), who were admitted to the Clinic of Cognitive Neurology at the University of Leipzig (Table 1; (Dukart et al., 2011)). They had presented with complaints of cognitive and/or behavioral alterations, by their own account and/or by the account of caregivers. Upon admittance, subjects underwent a high-quality FDG-PET and structural MRI scan; a comprehensive neurological and psychiatric history and examination; neuropsychological rating of behavioral deficits (Hughes et al., 1982); and testing of memory, executive function, attention and language. Details of the test batteries involved in our assessment are described in Frisch et al. (2013) and Schroeter et al. (2011, 2012). Inclusion criteria were a diagnosis of either probable AD, according to the revised NINCDS–ADRDA criteria (McKhann et al., 1984), FTLD, in accordance to criteria proposed by Neary et al. (1998), or subjective cognitive impairment, characterized by complaints of cognitive impairment that could not be confirmed by neuropsychological testing. The last group was chosen as a control group (please see also Discussion). Patients were excluded if structural imaging revealed lesions due to stroke, traumatic head injury, brain tumor or inflammatory diseases. All data were acquired for diagnostic purposes. Within the whole group, 29 subjects from age 40 to 74 (16

Table 1
Demographic and clinical characteristics of the patient groups.

	AD	FTLD	Control	Group difference
Whole group				
N	21	14	13	–
Age	61.1 ± 6.7	60.8 ± 6.4	53.9 ± 6.0	5.8, 2, 0.006[a]
Sex (f/m)	12/9	7/7	6/7	0.4, 2, 0.809[b]
Education (years)	10.7 ± 3.1	11.6 ± 3.8	12.3 ± 3.1	1.0, 2, 0.368[a]
CDR	0.7 ± 0.3	0.8 ± 0.4	0.2 ± 0.3	13.9, 2, 0.000[a]
MMSE[c]	23.2 ± 3.9	24.4 ± 4.2	28.8 ± 1.3	4.5, 2, 0.019[a]
DemTect group				
N	14	9	6	–
Age	61.5 ± 7.6	59.3 ± 7.4	51.2 ± 7.6	3.9, 2, 0.032[a]
Sex (f/m)	9/5	5/4	2/4	1.6, 2, 0.443[b]
Education (years)	11.1 ± 3.2	10.9 ± 3.5	13.0 ± 3.3	0.9, 2, 0.427[a]
CDR	0.8 ± 0.3	0.8 ± 0.3	0.3 ± 0.3	10.3, 2, 0.001[a]
MMSE[c]	24.3 ± 3.8	23.8 ± 4.3	28.0 ± 1.0	1.4, 2, 0.263 [a]
DemTect sum score	7.9 ± 3.4	7.3 ± 5.8	15.5 ± 2.9	8.3, 2, 0.002[a]
DemTect subscores[d]				
Wordlist	1.43 ± 1.22	1.11 ± 1.05	2.67 ± 0.52	4.1, 2, 0.028[a]
Number transcoding	1.64 ± 0.93	1.67 ± 1.32	2.50 ± 0.55	1.7, 2, 0.209[a]
Supermarket task	1.71 ± 1.27	1.00 ± 1.41	4.00 ± 0.00	12.0, 2, 0.000[a]
Digit span reverse	2.21 ± 0.98	1.89 ± 0.93	2.50 ± 0.84	0.8, 2, 0.462[a]
Wordlist (delayed recall)	0.86 ± 0.77	1.67 ± 2.06	3.83 ± 1.84	8.3, 2, 0.002[a]

Note. All values given in mean ± standard deviation. AD = Alzheimer's disease, CDR = clinical dementia rating scale (Hughes et al., 1982), f = female, FTLD = frontotemporal lobar degeneration, m = male, MMSE = Mini-Mental State Examination (Folstein et al., 1975), n = total number.

[a] As tested with One-Way ANOVA: F, degrees of freedom (df), p.

[b] As tested with two-tailed chi-square test: chi-square, df, p.

[c] For twelve/four subjects MMSE was not available.

[d] Transformed scores.