Differential diagnosis in the memory clinic: Exploring the value of improved neuropsychological examination
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CHAPTER 5

Cerebral correlates of cognitive performance in a naturalistic sample of memory clinic patients – A voxel-based morphometry study

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Under revision
ABSTRACT
Background: Studies investigating relations between cognitive performance and brain atrophy in patients with mild cognitive impairment (MCI) have been conducted in highly selected samples. This methodological strictness does however not reflect clinical practice, and limits the generalizability of these studies to the MCI population at large.
Objective: To identify the cerebral morphometric correlates of cognitive deficits in a large, unselective sample of elderly patients referred to memory clinics.
Methods: Participants (N=126) underwent structural, high-resolution Magnetic Resonance Imaging (MRI) and a comprehensive neuropsychological examination evaluating several cognitive domains. Whole-brain voxel-based morphometry was performed to examine relationships of cognitive functioning with regional grey matter (GM) volume.
Results: Significant correlations were found between cognitive functioning, irrespective of cognitive domain, and regional GM volume in the temporal lobes, in particular the bilateral middle temporal gyri. Cognitive function in non-memory domains was correlated with regional brain morphology outside the temporal lobes only when studied in isolation. The primary memory impairment, characteristic for MCI patients, remained specifically related to lower volume of the left hippocampus, even when variance in other cognitive domains was accounted for.
Conclusion: Our results suggest that correlations of volumetric data and cognitive data in memory clinic patients reflect the primary neurodegenerative pathology, i.e. temporal lobe atrophy. The relation between impaired memory and temporal lobe atrophy is much stronger in these patients than other brain-cognition relationships.
1. INTRODUCTION

The patient mix of memory clinics consists mostly of dementia patients and large minorities of people with mild cognitive impairment (MCI) or subjective, but unsubstantiated cognitive complaints (Hejl, Hogh, & Waldemar, 2002; Pusswald et al. 2013; Wang, Guo, Chen, Zhao, Zhou, & Hong, 2011). Subjective cognitive complaints most often concern memory (Cooper et al., 2011), and brain abnormalities have been found in elderly people with subjective memory complaints (Bartley et al., 2012; Haßmeijer et al., 2013; Kearney-Schwartz et al., 2009; Palm et al., 2013). These complaints deserve attention because they may announce dementia (Jonker, Geerlings, & Schmand, 2000; Stewart, 2012).

MCI subjects have an overall increased risk of developing dementia, but the association is far from unidirectional. Some MCI patients show full or partial recovery after initially presenting with cognitive impairments (Maioli et al., 2007; Mitchell & Shiri-Feshki, 2009; Diniz, Nunes, Yassuda, & Forlenza, 2009). Therefore, careful neuropsychological and radiological characterization of MCI patients is necessary to improve the prognostic accuracy of the MCI diagnosis (Albert et al., 2011; Schmand, Eikelenboom, & van Gool, 2011). Assessing altered brain morphology associated with the cognitive deficits of MCI patients is essential to properly analyze the pathological processes underlying cognitive dysfunction. Voxel-based morphometry (VBM) is a brain morphometric analysis technique that enables whole-brain exploration of relations between cognitive performance and regional grey matter (GM) volumes obtained using structural Magnetic Resonance Imaging (MRI). VBM allows the assessment of whole brain morphology without prior hypothesis about possible changes. Furthermore, VBM can provide a sensitive estimate of intact and damaged tissue by assigning a continuous signal intensity value to each voxel and makes it possible to correlate it with behavioral data.

The first symptomatic change in MCI patients is usually memory impairment, although deficits may also occur in other cognitive domains (for example, executive function and visuospatial skills). Studies employing VBM have demonstrated that in MCI patients, memory performance is closely associated with medial temporal lobe (MTL) measures of GM volume (Barbeau et al., 2008; Chételat et al., 2003; Chételat et al., 2011; Dos Santos et al., 2011; Hämaäinen et al., 2007; Leube et al., 2008; Schmidt-Wilcke, Poljansky, Hiermeier, Hausner, & Ibach, B., 2009), although associations with other temporal (Barbeau et al., 2008; Chételat et al., 2003; Dos Santos et al., 2011), parietal (Barbeau et al. 2008) and frontal lobe (Barbeau et al., 2008; Dos Santos et al., 2011) regions as well as subcortical sites (Dos Santos et al., 2011) have also been observed. Previous studies investigating correlations between executive
function deficits and brain atrophy in MCI reported associations particularly in the frontal and parietal lobes (Pa et al., 2009; Pa et al., 2010; Rabin et al., 2009). Deficits on language-related tasks like verbal fluency and word finding were found to correspond with density of the left frontotemporal, parietal, and left temporal areas (including the hippocampus) (Apostolova et al., 2008; Dos Santos et al., 2011). Finally, deficits in constructional praxis correlated with volume of the left thalamus and the temporal lobe, predominantly the left (Dos Santos et al., 2011; Thomann, Toro, Dos Santos, Essig, & Schröder, 2008).

These studies have been performed in highly selected samples of MCI patients with isolated cognitive impairments, or in patients who fulfilled strict MCI criteria highly predictive for the development of dementia. This methodological strictness is appropriate from a scientific point of view, but it does not reflect clinical practice, and thus limits the generalizability of these findings to the larger population visiting memory clinics. The border between MCI and dementia may be a conceptually sharp line, but in clinical reality it is a rather fluid transition zone, largely depending on clinical judgment of functional status (Forlenza et al., 2013; Morris, 2012). Similarly, there is no clearly defined border between normal aging and MCI either. Thus, the research practice to split off a strictly defined MCI category from the spectrum of cognitive impairments in memory clinic populations is somewhat artificial. Furthermore, the studies mentioned above focused on particular cognitive functions; none of the studies analyzed a battery of neuropsychological tests tapping multiple cognitive domains in the same participants.

Therefore, the first aim of our study was to identify the cerebral morphometric correlates of the spectrum of neuropsychological impairments in a large, unselective sample of elderly patients referred to memory clinics. We used a comprehensive battery of neuropsychological tests, high-resolution Magnetic Resonance Imaging (MRI), and a whole-brain VBM analysis approach. Based on the studies mentioned above, we not only expected to find associations between memory performance and atrophy in the MTL, but we also expected that executive function would be associated with regional atrophy in the frontal and parietal lobes. Furthermore, we anticipated that deficits in language tasks would be related to frontotemporal and parietal brain regions, and that deficits in constructional praxis would be correlated with abnormalities in the left thalamus and regions in the left temporal lobe. Second, we aimed to test for the domain specificity of volumetric abnormalities associated with neuropsychological test performance. This was done in multivariate regression models, where the associations found for each cognitive domain were controlled for variations in the other domains.
2. METHODS
2.1. PARTICIPANTS
The patients included in this study participated in the longitudinal project ‘Improving the early Diagnosis of Alzheimer’s Disease and Other dementias’ (IDADO). Between February 2007 and October 2009, 170 patients were recruited from neurological and geriatric outpatient clinics, day clinics and memory clinics of six general and psychiatric hospitals in the Netherlands (Academic Medical Center (Amsterdam), Medical Center Alkmaar (Alkmaar), Slotervaart Hospital (Amsterdam), GGZ-Noord-Holland-Noord (Heiloo), and Geriant Noord-Kennemerland (Heerhugowaard)). Patients between 50 and 85 years of age were included if they reported a) complaints of decline in cognitive or behavioral functioning (as expressed by the patient or a close relative) not normal for age, and b) essentially intact instrumental activities of daily living. Patients were referred to the study by dementia specialists (neurologists, geriatricians, psychiatrists) after an initial consultation, which included recording of each patient’s history, collateral information from a relative, a clinical examination including a dementia screening instrument (The Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), laboratory analyses, MRI or CT scan if deemed necessary, and evaluation of the presence of clinical dementia criteria according to the Diagnostic and Statistical Manual of Mental Disorders–IV (DSM-IV-TR) criteria (American Psychiatric Association, 2000). For all participants the differential diagnosis included a possible preclinical stage of dementia at the time of referral. Exclusion criteria were a dementia syndrome as established during initial consultation by the dementia specialist according to the DSM-IV-TR criteria (American Psychiatric Association, 2000), other brain disease or systemic disease sufficient to cause the mental complaints, current substance abuse or addiction, a medical condition or handicap that prevented neuropsychological evaluation, preexistent mental retardation, contraindications for MRI scanning, and insufficient command of the Dutch language. Psychiatric (co-)morbidty on Axis I according to DSM-IV-TR, such as major depressive disorder, common anxiety disorder or adjustment disorder, was not an exclusion criterion.

2.2. PROCEDURE
Participants underwent a comprehensive neuropsychological examination at inclusion to evaluate several cognitive domains. Tests were administered in a fixed order (see next paragraph and Table 2). In intervals between verbal memory tests, non-verbal neuropsychological tests were administered (and vice-versa) in order to avoid interference. Furthermore, a high-resolution structural three-dimensional T1-weighted MR scan was
made. Neuropsychological assessment was carried out in the hospital or at the subjects’ home, in two sessions of two to three hours with suitable rest periods. MRI scans were made within a month of the neuropsychological examination. As part of the IDADO protocol, patients are followed up biannually until a clinical diagnosis is established. After two years, a neurologist evaluated all patients again. Next, a neuropsychologist or a trained neuropsychology master student, supervised by the neuropsychologist, administered a shortened neuropsychological test battery. If possible, a follow-up MRI scan was made.

The local ethics committees of participating hospitals approved the study. Written informed consent was obtained from all subjects after the nature of the study was fully explained.

2.3. MATERIALS
Memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT; immediate recall of a series of 15 unrelated nouns in five learning trials, 20-minute delayed free recall and recognition) (Rey, 1964), the Rivermead Behavioural Memory Test Logical Memory subtest (RBMT LM; immediate and 20-minute delayed recall of two news stories) (Wilson, Cockburn, & Baddely, 1985), the Visual Association Test (VAT; pictures of two common objects, representing an unusual combination, e.g. a monkey carrying an umbrella; recall is tested without a delay by showing one object and asking which other object is missing) (Lindeboom & Schmand, 2003), and the enhanced cued recall test (ECR; memorizing 16 items with help of category cues; after a short distraction task, subjects are asked to freely recall as many of the pictures as possible; category cues are provided for the remaining items) (Grober, Buschke, Crystal, Bang, & Dresner, 1988). Executive functions were examined with the Trail Making Test (TMT; connect numbers (part A) and connect numbers alternating with letters (part B)) (Reitan, 1992), the Stroop Color Word test (word reading, color naming and naming the ink color of color-words that are printed in a non-matching color (the interference condition)) (Stroop, 1935), the Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) for patients younger than 65 and the Modified Wisconsin Card Sorting Test (MWCST) (Nelson, 1976) for patients older than 65 (matching cards to one of four stimulus cards on color, design and quantity; participants are not told how to match the cards; however, they are told whether a particular match is right or wrong) and the Letter Digit Substitution Test (LDST; substitution of over-learned signs) (Jolles, Houx, Van Boxtel, & Ponds, 1995). Language function was assessed with the Visual Naming Test, which is an adapted, computerized 53-item
version of the Boston Naming Test in which the culturally unsuitable images were removed (BNT; naming line drawings of objects and animals) (Spaan & Schmand, 2010), Category fluency (naming as many animals and occupations as possible during one minute each) (Luteijn & Barelds, 2004) and the Controlled Oral Word Association Test (COWAT; naming as many words as possible that begin with a given letter (3 letters) during one minute each) (Benton, Hamsher, & Sivan, 1983). Visuospatial abilities were evaluated with the Clock Drawing Test (drawing the face of a clock on a blank piece of paper setting the hands at 1:45) (Royall, Cordes, & Polk, 1998), and the subtest Block Design of the Wechsler Adult Intelligence Scale-Third edition (WAIS-III; arranging blocks in increasingly difficult patterns) (Wechsler, 1997).

2.4. DATA ANALYSIS
Demographic and clinical data were analyzed with IBM SPSS Statistics for Windows (version 18.0). Significance was set at \( p < .05 \), two-tailed. To reduce the number of cognitive variables, four composite neuropsychological scores tapping the memory, executive, language and visuospatial domains were generated \textit{a priori}. These composite domain scores reflect the mean values for each participant of the raw scores of the neuropsychological tests (i.e. the raw scores were first z-transformed, if necessary negated, and then the mean z-score was calculated for each domain). Missing values (1.1% of all data points) were estimated by calculating the mean z-values of the remaining subtest scores for each domain (within subject) containing missing values. The composite memory score included the delayed free recall condition of the RAVLT, the delayed recall of the RBMT LM subtest, the VAT and the ECR. For the VAT, a short or a long version was administered, depending on the age of the participant. Scores on the short version were doubled to attain a similar distribution of test scores. The second composite measure, related to executive functions, included tests measuring divided attention, interference, concept formation and mental speed. It was generated by averaging z-scores of the TMT part B, the Stroop Color Word interference subtest, the percentage of errors on the (M) WCST, and the LDST score. The language composite score included the BNT, Category fluency and the COWAT. Finally, a visuospatial composite was generated by computing the mean z-values of the Clock Drawing Test and the subtest Block Design of the WAIS-III. The internal consistency reliability of this test classification was satisfactory: Cronbach’s \( \alpha \) was > 0.75 for each cognitive domain, except for the visuospatial composite where \( \alpha \) was 0.52. However, an additional analysis of the correlation between both tests of the visuospatial composite revealed a significant correlation coefficient of \( r = 0.44 \) (\( p = 0.01 \))
2.5. MRI ACQUISITION

Imaging was performed on a 3.0 Tesla MR system (Philips Intera, Best, The Netherlands) with a 6-channel SENSE head coil. A gradient echo 3D, T1-weighted, sagittal sequence was used with the following pulse sequence parameters: echo time [TE] = 3.5 ms, repetition time [TR] = 9 ms, scanning matrix = 256x231, flip angle = 8°, 170 partitions, voxel size = 1x1x1 mm.

2.6. IMAGING ANALYSIS

Imaging data were analyzed using VBM following unified segmentation using Statistical Parametric Mapping software (SPM8) implemented in Matlab 7.5.0.342(R2007b). VBM preprocessing included:

1) manual reorientation of the images to the anterior commissure (AC), mainly involving reorientation of the center point to the AC by changing the translation parameters. When necessary, images were however further adjusted in the rotation parameters to be in anterior commissure-posterior commissure alignment (pitch), or in the roll and jaw directions,

2) applying unified segmentation of the images into grey matter (GM), white matter and cerebrospinal fluid using the unified segmentation option implemented in SPM8,

3) normalization and modulation of the segmented GM images to the Montreal Neurological Institute (MNI) 152 space,

4) smoothing of the GM images using an 8mm full width at half maximum Gaussian kernel. In the resulting normalized and modulated images, each voxel represents an absolute amount of brain volume, equivalent to the brain volume per unit prior to normalization.

To assess associations between neuropsychological domains and regional GM volume, whole-brain multiple regression analyses were set up per domain with the GM volume maps as dependent variable and the domain score as main predictor. Correlations were explored at a voxel-wise height threshold of Z>3.09, and correlations had to meet p<.05, Family Wise Error (FWE) whole-brain corrected for multiple comparisons at the cluster level to be considered significant. To account for the non-stationary nature of the underlying neuroanatomy, we applied a non-stationarity correction at the cluster level as implemented in the WFU Non-Stationarity Cluster Extent Correction Toolbox of SPM8 (http://fmri.wfubmc.edu/cms/software#NS). Next, to investigate the independent relationship of neuropsychological tests capturing a specific domain with regional brain atrophy, whole-brain multiple regression analyses were set up with the GM volume maps as dependent variable and the composite scores of each domain as predictors. This way, the unique predicting value of each domain could be estimated. Again, effects had to
meet a threshold of $p<.05$, FWE cluster-wise corrected (following non-stationarity correction) to be considered significant (voxel-wise height threshold $Z>3.09$).

Age, gender, and total GM were entered as covariates in each model. To achieve maximal sensitivity, to optimize voxel residual smoothness estimation and to exclude false positives in non-GM tissue, voxel-wise comparisons were masked using a sample-specific explicit optimal threshold GM mask created with the Masking toolbox based on the whole sample (Ridgway et al., 2009). This mask was used in all analyses. All regions were identified with the use of the detailed brain atlas of Talairach and Tournoux (1988), after transforming MNI coordinates to Talairach and Tournoux space with the Münster T2T –converter (http://www.neuro03.uni-muenster.de/ger/t2tconv/).

Finally, to examine relations of several memory tasks with hippocampal volume, we first calculated hippocampal volume per patient as defined by the Anatomical Automatic Labelling system (AAL) implemented in the WFU-Pick Atlas and exported these to SPSS. Next, we correlated each memory test variable within the memory domain score with hippocampal volume. Furthermore, a stepwise multiple regression analysis was conducted to investigate which memory task(s) correlated significantly with hippocampal volume. Since there is a clear one-sided hypothesis for impairment, for these analyses, significance was set at $p<.05$, one-tailed.

3. RESULTS

The cohort consisted of 170 patients. MRI data were not available for 12 patients due to claustrophobia or the presence of MRI contraindications disclosed by a comprehensive MRI safety questionnaire. For 22 patients MRI scanning failed due to practical issues such as imaging and/or motion artifacts. Eight patients were excluded from further analyses due to non-credible performance at neuropsychological evaluation (see Rienstra et al., 2013). Non-credible performance is a threat to the validity of neuropsychological test results (Bush et al., 2005). If patients are unable or unwilling to invest the required amount of effort while doing the tests, it becomes uncertain whether the tests measure what they intend to measure, i.e. cognitive functioning or cognitive impairments. Therefore, investigating brain-behavior relationships in these patients is meaningless since it is uncertain if the neuropsychological test scores of these patients are valid. Finally, two patients withdrew consent. This resulted in a total sample of 126 participants. After consideration of the neuropsychological evaluation and the MRI scan at baseline, the clinical diagnoses of these patients varied. The majority satisfied either
the older (Petersen, 2004) or the more recent MCI criteria (Albert et al., 2011). However, a number of patients were also diagnosed with dementia, psychiatric diagnoses (mostly mood disorders), or diagnosis was deferred at the time of referral. Finally, a considerable number of patients were diagnosed as ‘worried well’. They were people who were cognitively normal, did not have cognitive test scores in the impaired range, and who did not meet criteria for a psychiatric disorder. Although they had cognitive complaints and were unsure about their mental stats, these worries appeared to be unjustified (see Table 1). Table 2 lists the demographic information of participants, including mean scores of the neuropsychological tests that were administered.

**TABLE 1**
Clinical diagnoses at baseline after consideration of the neuropsychological evaluation and the MRI scan

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI</td>
<td>48</td>
<td>38.1</td>
</tr>
<tr>
<td>dementia</td>
<td>19</td>
<td>15.1</td>
</tr>
<tr>
<td>psychiatric</td>
<td>16</td>
<td>12.7</td>
</tr>
<tr>
<td>worried well</td>
<td>34</td>
<td>27.0</td>
</tr>
<tr>
<td>deferred diagnosis</td>
<td>4</td>
<td>3.2</td>
</tr>
<tr>
<td>other</td>
<td>5</td>
<td>4.0</td>
</tr>
</tbody>
</table>

MCI= Mild Cognitive Impairment, other = organic disease other than MCI or dementia

### 3.1. COMPOSITE MEMORY CORRELATES
A positive relation between memory performance and regional GM volume was observed in bilateral parahippocampal gyrus extending to the uncus (BA 28, 34 & 36), indicating that patients with better memory performance had a larger volume in these regions. Additional significant clusters were observed in bilateral insula and superior temporal gyri (BA 13/38), the left middle temporal lobe (BA 21) and the superior parietal lobule (BA7) (Figure 1A). Correlation coefficients between memory composite scores and peak voxel for each cluster were in the range of 0.30 to 0.40. Also for the other cognitive domains correlations in this range were found. Whole-brain relations of memory performance with the left hippocampus were only observed at trend-level ($p<.08$ FWE corrected, $k=266$). Subthreshold, at $p<.001$ uncorrected, memory performance was also correlated with volume of the right hippocampus ($k=11$). How-
ever, when taking into account variance related to executive functioning, language, and visuoconstructive composite measures, the left hippocampus was the only region that showed a large and significant relation with memory performance ($p<.05$ FWE whole-brain cluster-corrected, $k=407$) (Figure 2).

**TABLE 2**

Demographic and cognitive characteristics (raw test scores and domain $z$-scores) of the sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total sample (N=126)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66.72 (10.04)</td>
<td>50-84</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>45.2</td>
<td></td>
</tr>
<tr>
<td>Education, years</td>
<td>12.10 (2.62)</td>
<td>6-18</td>
</tr>
<tr>
<td>MMSE</td>
<td>26.86 (2.63)</td>
<td>17-30</td>
</tr>
<tr>
<td>Composite Memory (N=119)$^*$</td>
<td>0.00 (0.85)</td>
<td>-2.14-1.35</td>
</tr>
<tr>
<td>RAVLT DR</td>
<td>6.27 (4.11)</td>
<td>0-14</td>
</tr>
<tr>
<td>RBMT LM DR</td>
<td>9.36 (7.33)</td>
<td>0-31.5</td>
</tr>
<tr>
<td>ECR</td>
<td>13.55 (3.08)</td>
<td>1-16</td>
</tr>
<tr>
<td>VAT</td>
<td>19.24 (5.97)</td>
<td>0-24</td>
</tr>
<tr>
<td>Composite EF (N=121)$^*$</td>
<td>0.00 (0.82)</td>
<td>-2.02-1.63</td>
</tr>
<tr>
<td>TMT part B (seconds)</td>
<td>197.36 (192.46)</td>
<td>35-952</td>
</tr>
<tr>
<td>Stroop part C (seconds)</td>
<td>142.88 (74.14)</td>
<td>58-938</td>
</tr>
<tr>
<td>LDST</td>
<td>25.89 (8.74)</td>
<td>3-53</td>
</tr>
<tr>
<td>WCST % errors</td>
<td>39 (19)</td>
<td>3-98</td>
</tr>
<tr>
<td>Composite language (N=126)$^*$</td>
<td>0.00 (0.83)</td>
<td>-2.61-1.90</td>
</tr>
<tr>
<td>Category fluency</td>
<td>33.68 (11.03)</td>
<td>9-67</td>
</tr>
<tr>
<td>COWAT</td>
<td>31.23 (12.28)</td>
<td>6-64</td>
</tr>
<tr>
<td>BNT</td>
<td>45.06 (6.25)</td>
<td>23-53</td>
</tr>
<tr>
<td>Composite visuoconstructive (N=117)$^*$</td>
<td>-0.04 (0.90)</td>
<td>-3.64-2.35</td>
</tr>
<tr>
<td>Block design (WAIS-III)</td>
<td>22.28 (12.14)</td>
<td>7-63</td>
</tr>
<tr>
<td>Clock drawing</td>
<td>10.74 (2.34)</td>
<td>1-14</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD). Values are raw scores unless otherwise indicated.

$^*$ values are $z$-scores

RAVLT = Rey Auditory Verbal Learning test; RBMT LM = Rivermead Behavioral Memory Test Logical Memory; ECR = Enhanced Cued Recall; VAT = Visual Association Test; TMT = Trail Making Test; LDST = Letter Digit Substitution Test; WCST = Wisconsin Card Sorting test; COWAT = Controlled Oral Word Association Test; BNT = Boston Naming Test; WAIS-III = Wechsler Adult Intelligence Scale version III
## TABLE 3

Positive correlations of grey matter values (MNI coordinates) and memory composite scores

<table>
<thead>
<tr>
<th>RA.</th>
<th>Region</th>
<th>BA</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T-value</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>uncus</td>
<td>28</td>
<td>312</td>
<td>-22</td>
<td>-14</td>
<td>-36</td>
<td>5.36</td>
<td>5.07</td>
</tr>
<tr>
<td>L</td>
<td>uncus</td>
<td>34</td>
<td>-14</td>
<td>2</td>
<td>-24</td>
<td></td>
<td>3.69</td>
<td>3.58</td>
</tr>
<tr>
<td>L</td>
<td>uncus</td>
<td>36</td>
<td>-18</td>
<td>0</td>
<td>-38</td>
<td></td>
<td>3.63</td>
<td>3.53</td>
</tr>
<tr>
<td>L</td>
<td>insula/ superior temporal gyrus</td>
<td>13</td>
<td>350</td>
<td>-42</td>
<td>2</td>
<td>-10</td>
<td>4.93</td>
<td>4.70</td>
</tr>
<tr>
<td>L</td>
<td>superior temporal gyrus</td>
<td>38</td>
<td>-40</td>
<td>14</td>
<td>-12</td>
<td></td>
<td>3.89</td>
<td>3.76</td>
</tr>
<tr>
<td>R</td>
<td>uncus</td>
<td>28</td>
<td>1053</td>
<td>22</td>
<td>-14</td>
<td>-36</td>
<td>4.52</td>
<td>4.34</td>
</tr>
<tr>
<td>R</td>
<td>uncus</td>
<td>34</td>
<td>8</td>
<td>-18</td>
<td>8</td>
<td>-10</td>
<td>4.49</td>
<td>4.31</td>
</tr>
<tr>
<td>R</td>
<td>uncus</td>
<td>34</td>
<td>16</td>
<td>-24</td>
<td>2</td>
<td>-24</td>
<td>4.43</td>
<td>4.26</td>
</tr>
<tr>
<td>R</td>
<td>insula</td>
<td>13</td>
<td>42</td>
<td>-4</td>
<td>2</td>
<td>-4</td>
<td>4.37</td>
<td>4.20</td>
</tr>
<tr>
<td>R</td>
<td>superior temporal gyrus</td>
<td>38</td>
<td>42</td>
<td>14</td>
<td>-12</td>
<td></td>
<td>3.83</td>
<td>3.71</td>
</tr>
<tr>
<td>L</td>
<td>superior parietal lobule</td>
<td>7</td>
<td>118</td>
<td>-32</td>
<td>-58</td>
<td>50</td>
<td>4.50</td>
<td>4.32</td>
</tr>
<tr>
<td>L</td>
<td>middle temporal gyrus</td>
<td>21</td>
<td>150</td>
<td>-68</td>
<td>-40</td>
<td>-2</td>
<td>4.42</td>
<td>4.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-64</td>
<td>-34</td>
<td>18</td>
<td>3.94</td>
<td>3.82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-60</td>
<td>-28</td>
<td>-22</td>
<td>3.69</td>
<td>3.58</td>
</tr>
</tbody>
</table>

R=L= Right/Left hemisphere; BA= Brodmann area; k= cluster size; MNI coordinate= the Montreal Neurological Institute coordinate; all results are reported at p<.05= Family Wise Error (FWE) whole-brain corrected for multiple comparisons at the cluster level (non-stationarity corrected); r= Pearson correlation coefficient (calculated over mean volume of the cluster).

### 3.2. COMPOSITE EXECUTIVE FUNCTION CORRELATES

A positive correlation between composite executive function scores and regional GM values was found in the post-central gyrus (BA 1), bilateral inferior temporal gyri (BA 20) extending into the middle temporal gyri (BA 21), and the left medial frontal gyrus (BA 6) extending to the anterior cingulate gyrus (BA 32) and the superior frontal gyrus (BA 6) (Figure 1B). There was a near-significant correlation in the right superior temporal gyrus (BA 22) projecting to the middle temporal gyrus (BA 37). After adjusting for variance related to memory, language and visuoconstructive composite measures, significant clusters were no longer observed.
3.3. COMPOSITE LANGUAGE CORRELATES

A positive correlation between language performance and regional GM volume was observed in an area covering the left inferior (BA 20) and middle temporal gyri (BA 21). An additional significant cluster was found in the right middle temporal gyrus (BA 21) (Figure 1C). After considering the variance of the other three composite measures, there were no longer any significant clusters.

TABLE 4

<table>
<thead>
<tr>
<th>R/L</th>
<th>Region</th>
<th>BA</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T-value</th>
<th>Z-score</th>
</tr>
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<tr>
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<td>-20</td>
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<td></td>
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<tr>
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<td>70</td>
<td>-34</td>
<td>-4</td>
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<td>-26</td>
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<td>4.01</td>
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<tr>
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<td>50</td>
<td>12</td>
<td>-40</td>
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<td>0</td>
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<td>50</td>
<td>4.40</td>
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<td>6</td>
<td>68</td>
<td>3.77</td>
<td>3.66</td>
<td></td>
</tr>
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</table>

R/L= Right/Left hemisphere; BA= Brodmann area; k= cluster size; MNI coordinate= the Montreal Neurological Institute coordinate; all results are reported at p<.05= Family Wise Error (FWE) whole-brain corrected for multiple comparisons at the cluster level (non-stationarity corrected); r= Pearson correlation coefficient (calculated over mean volume of the cluster).
### TABLE 5

Positive correlations of grey matter values (MNI coordinates) and language composite scores

<table>
<thead>
<tr>
<th>R/L</th>
<th>Region</th>
<th>BA</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T-value</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>inferior temporal gyrus</td>
<td>20</td>
<td>234</td>
<td>64</td>
<td>36</td>
<td>-22</td>
<td>5.15</td>
<td>4.89</td>
</tr>
<tr>
<td>L</td>
<td>middle temporal gyrus</td>
<td>21</td>
<td>235</td>
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<td>-12</td>
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<td>-24</td>
<td>-16</td>
<td>3.91</td>
<td>3.79</td>
<td></td>
</tr>
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</table>

R/L = Right/Left hemisphere; BA = Brodmann area; k = cluster size; MNI coordinate = the Montreal Neurological Institute coordinate; all results are reported at p < .05 = Family Wise Error (FWE) whole-brain corrected for multiple comparisons at the cluster level (non-stationarity corrected); r = Pearson correlation coefficient (calculated over mean volume of the cluster).

### 3.4. COMPOSITE VISUOCONSTRUCTIVE CORRELATES

A positive correlation between performance on visuoconstructive tasks and regional GM volume was observed in the right inferior parietal lobule (BA 40) and the left middle temporal gyrus (BA 21) (Figure 1D). Again, these clusters ceased to be significant after accounting for the variance related to the other composite measures.

### TABLE 6

Positive correlations of grey matter values (MNI coordinates) and visuoconstructive composite scores

<table>
<thead>
<tr>
<th>R/L</th>
<th>Region</th>
<th>BA</th>
<th>k</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T-value</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Inferior parietal lobule</td>
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<td>143</td>
<td>38</td>
<td>50</td>
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<tr>
<td>L</td>
<td>middle temporal gyrus</td>
<td>21</td>
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<td>-64</td>
<td>-32</td>
<td>-20</td>
<td>4.66</td>
<td>4.46</td>
</tr>
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</table>

R/L = Right/Left hemisphere; BA = Brodmann area; k = cluster size; MNI coordinate = the Montreal Neurological Institute coordinate; all results are reported at p < .05 = Family Wise Error (FWE) whole-brain corrected for multiple comparisons at the cluster level (non-stationarity corrected); r = Pearson correlation coefficient (calculated over mean volume of the cluster).
3.5. CORRELATIONS OF MEMORY TASKS WITH HIPPOCAMPAL VOLUME

In view of the above results, which appeared to be mainly driven by memory impairment and MTL atrophy, post hoc correlation analyses were performed between memory tests and hippocampal volume, again corrected for total GM (Table 7). Significant positive correlations were found between the volume of the left hippocampus and all individual memory measures.

Furthermore, a stepwise multiple regression analysis was conducted with the volume of the left hippocampus as dependent variable, the delayed free recall condition of the RAVLT, the recall of the RBMT LM subtest, the ECR, and the VAT as the predictors, and age and total GM as covariates. Results indicated that performance on the ECR made a significant contribution to the prediction of the left hippocampal volume, $F(3;115) = 24.16, p < .001$. Standardized coefficients beta were -0.18 for age, 0.69 for total GM, and 0.22 for the ECR. Together with age, total GM, and ECR explained 76% of the variance in left hippocampal volume, although age and total GM explained most variance.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Left hippocampal volume/ total GM</th>
<th>Right hippocampal volume/ total GM</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVLT DR</td>
<td>36**</td>
<td>19*</td>
</tr>
<tr>
<td>RBMT DR</td>
<td>18*</td>
<td>11</td>
</tr>
<tr>
<td>ECR</td>
<td>32**</td>
<td>23**</td>
</tr>
<tr>
<td>VAT</td>
<td>23*</td>
<td>15*</td>
</tr>
</tbody>
</table>

* Pearson r; * Spearman rho; * $p < 0.05$ (one-tailed), ** $p < 0.01$ (one-tailed)
RAVLT = Rey Auditory Verbal Learning test; DR= delayed recognition; RBMT LM = Rivermead Behavioral Memory Test Logical Memory; ECR= Enhanced Cued Recall test; VAT= Visual Association test.
Differential diagnosis in the memory clinic:

FIGURE 1

Statistical parametric maps (SPM) of whole brain (p<.001) correlations between grey matter volume and cognitive function following neurological (left to left and right to right) convention.

LH= Left hemisphere; RH= Right hemisphere.
4. DISCUSSION

The aim of the present study was to examine regional brain morphometric correlates of a range of neuropsychological deficits in a large, unselective sample of memory clinic patients. Psychiatric (co)morbidity was not an exclusion criterion, and people who appeared to be ‘worried well’ were not excluded either. The main exclusion criterion was a clear dementia syndrome that could be diagnosed by a dementia specialist without detailed neuropsychological assessment. Thus, the study sample was a naturalistic patient mix that is representative for first visitors of memory clinics, with a broad spectrum of cognitive functioning and impairments ranging from worried well to MCI and early dementia cases. The latter cases could be diagnosed as such only after proper neuropsychological evaluation and neuroimaging. We analyzed high-resolution MRI data using a VBM approach, which enabled us to identify potential changes in GM volume throughout the brain. In the following discussion we will first consider the regional GM correlates for each cognitive domain, followed by an overview of findings across domains.

In accordance with our hypotheses, memory performance correlated with GM volume in the MTL including the hippocampus, the parahippocampal gyrus and the entorhinal cortex, although the hippocampus was observed at a subthreshold level only when variation in other cognitive domains was not taken into account. These correlations involved both hemispheres, but were predominantly associated with the left MTL. Moreover, the left hippocampal cluster was the only cluster that remained significant when variance in other cognitive domains was accounted for. Medial temporal GM loss in the parahippocampal gyrus and hippocampus is a consistent finding.
Differential diagnosis in the memory clinic: in volumetric studies on MCI (Visser et al., 1999; Chételat et al., 2002; Seo et al., 2007; Ferreira, Diniz, Forlenza, Busatto, & Zanetti, 2011). Furthermore, our findings support the results of earlier studies in MCI patients that reported correlations of memory performance with GM values. For example, Chetelat et al. (2003) reported that hippocampal atrophy was related to deficits in both encoding and retrieval. Schmidt-Wilcke et al. (2009) found a correlation between immediate verbal recall and GM volume in the left perirhinal/entorhinal cortex, while delayed free recall correlated with GM volume in the left hippocampus. Dos Santos et al. (2011) showed that word list learning was associated with bilateral parahippocampal and right hippocampus volumes, and Nho et al. (2012) observed strong associations between memory scores and medial and lateral temporal lobe atrophy. In addition, functional MRI studies on MCI have demonstrated correlations between memory tests and hippocampal activity (e.g. Vogelaere, Santens, Achten, Boon, & Vingerhoets, 2012).

We also observed GM loss in the insula/superior temporal gyrus related to memory functioning, although when controlling for variance in the other domains, this region was no longer observed. GM loss in these areas has frequently been reported in previous studies that focused on MCI (Davatzikos, Bhatt, Shaw, Batmanghelich, & Trojanowski, 2011; Fan, Batmanghelich, Clark, & Davatzikos, 2008; Hääläläinen et al., 2007; Karas et al., 2004; Spulber et al., 2012). Furthermore, Xie et al. (2012) demonstrated that the intrinsic connectivity of the insula network was disrupted in amnesic MCI patients and that this altered connectivity was associated with episodic memory impairments. These findings suggest that the insula networks play an important additional role in the functional integration of episodic memory processes.

As expected, composite scores of executive function were significantly associated with brain morphology in the frontal regions (left superior and medial frontal gyri). These results are consistent with previous reports showing the importance of the frontal lobes in executive function in MCI patients as well as in healthy adults (Newman, Trivedi, Bendlin, Ries, & Johnson, 2007; Pa et al., 2009; Pa et al., 2010; Rabin et al., 2009; Rushworth, Hadland, Paus, & Sipila, 2002; Zakzanis, Mraz, & Graham, 2005). Moreover, significant correlations between executive dysfunction and GM loss were also found in the inferior parietal lobule, anterior cingulate gyrus, and bilateral temporal regions. Executive dysfunction in MCI has been associated with changes in the inferior parietal GM (Pa et al., 2010) and anterior cingulate white matter tracts (Grambaite et al., 2011). This suggests that besides parietal regions, anterior cingulate pathology may contribute to executive impairments in MCI (Johnson, Vogt, Kim, Cotman, & Head, 2004). Recently, associations between executive functions and bi-
lateral temporal regions have been reported in two studies investigating MCI populations (Nho et al., 2012; Shimada et al., 2012). Also in other patient groups, associations between temporal lobes and executive functioning have been demonstrated (Smith, Taylor, Brammer, & Rubia, 2004; Zakzanis et al., 2005).

In accordance with our expectations, impairments in language composite scores, including tests of naming and verbal fluency, were related to GM loss in bilateral middle temporal lobes (BA 20 and 21). These results are consistent with lesion studies, as well as functional neuroimaging and cortical stimulation studies (Baldo, Arévalo, Patterson, & Dronkers, 2013; Indefrey & Levelt, 2004). Furthermore, associations of deficits in naming and left temporal atrophy are in line with previous findings in MCI and AD patients (Pantel, Schönknecht, Essig, & Schröder, 2004; Dos Santos et al., 2011). In addition, Apostolova et al. (2008) demonstrated that impairments on the Boston naming test and animal fluency test correlated with cortical atrophy in the same Brodmann areas in the left temporal lobe in a sample of clinical and preclinical AD patients. In contrast with previous findings and with our hypothesis, however, we did not find associations between impaired performance on language related tasks and reduced GM volumes in frontotemporal and parietal sites (Pantel et al., 2004; Dos Santos et al., 2011; Apostolova et al., 2008). This is probably due to methodological differences, including sample and task selection, and methodological aspects related to imaging data acquisition. With respect to sample selection for example, Dos Santos et al. (2011) and Apostolova et al. (2008) used strictly defined MCI criteria highly predictive for the development of dementia while Pantel et al. (2004) investigated only patients with AD. Furthermore, tasks assessing verbal fluency were limited to animal naming (Apostolova et al., 2008; Dos Santos et al. 2011) or letter fluency. By contrast, our language composite score included, besides the BNT, category fluency (naming as many animals and occupations) and the COWAT letter fluency test. Finally, contrary to the covariates entered in the present study (age, gender, and total GM), all volumetric data were corrected for the subject's total intracranial volume in the study of Pantel et al. (2004) while no correction was applied in the study of Dos Santos et al. (2011).

Impairment in visuoconstructive abilities was related to GM densities in the left middle temporal gyrus (BA 21). This result confirms our hypothesis and is in line with previous findings on clock drawing performance in MCI (Thomann et al., 2008). Furthermore, the finding of a left hemispheric predominance for this task is supported by two studies, which investigated clock drawing performance and regional cerebral blood flow in AD (Ueda et al., 2002; Nagahama, Okina, Suzuki, Nabatame, & Matsuda, 2005). However, an earlier study relating volumetric measures to clock drawing...
Differential diagnosis in the memory clinic: performance in AD patients only found associations with right temporal lobe volumes (Cahn-Weiner et al., 1999). As opposed to the study of Dos Santos et al. (Dos Santos et al., 2011), who used the constructional praxis subtask of the CERAD neuropsychological test battery, we did not find a relation between constructional praxis and GM values in the left thalamus.

Taken together, it is notable that we found significant correlations in similar regions across the different cognitive domains, in particular the bilateral middle temporal lobes. This suggests that correlations of volumetric data and cognitive performance in our patients reflect the primary neurodegenerative pathology (i.e. middle temporal lobe atrophy) but not other known functional relationships of brain structures and cognitive domains. In other words, this fuels the idea that cortical changes do not correlate with cognitive impairments in a domain-specific way, but rather in a disease-specific way. Neuropathological changes in MCI patients are primarily restricted to the temporal lobe (Braak & Braak, 1991; McDonald et al., 2009) and are likely to underlie impaired cognitive functions. This assumption is supported by our analyses examining the associations between specific cognitive domains and regional brain volumes. Correlations between memory performance and GM values in the left hippocampus survived and if anything became more robust when variations in other neuropsychological domains were accounted for. Associations with bilateral middle temporal lobe GM volume were not specific for memory, or EF, language and visuoconstructive impairments, but rather seemed to reflect a general volume loss related to the severity of cognitive impairments. In contrast, GM loss in the insula or superior temporal gyrus was related to memory and executive functioning (subthreshold), but not when controlling for covariance between the domains. This pattern of results has also been found in a recent study evaluating associations between GM values and a measure of multiple cognitive domains capturing memory, language, visuospatial and executive abilities in a largely comparable mixed patient sample consisting of normal individuals, patients with MCI and subjects with dementia. In accordance with the present results these authors found that only hippocampal volume was uniquely associated with the various cognitive domain scores (Farias et al., 2013). Therefore, we propose that previous studies observed correlations between GM values and cognitive domains other than memory and executive function because they were examining a single cognitive domain instead of analyzing a battery of neuropsychological tests tapping multiple cognitive domains.

Our study also provides data on the relationship between individual memory tasks and left hippocampal volume. We found positive correlations for the majority of
Exploring the value of improved neuropsychological examination memory tests. Furthermore, our results showed that of the four memory tasks examined, the ECR was the most robust predictor of the left hippocampal volume. The cued recall technique of the ECR enhances spontaneous free recall by presenting the same semantic cues both at the encoding phase and at the retrieval phase of the test. Therefore, impairment of specific memory processes can be distinguished from apparent memory deficits due to use of inefficient strategies or impairment of other cognitive processes (Grober et al., 1988). It has been shown that the ECR is highly sensitive and specific in discriminating demented from non-demented elderly persons (Meulen et al., 2004). Yet, studies using the ECR in MCI populations are scarce. However, reports using comparable cued recall procedures demonstrated that this type of test performs at least equally to delayed free recall tests in the early detection of AD (Grober, Lipton, Hall, & Crystal, 2000; Ivanoiu et al., 2005).

Our study has a number of strengths. First, we evaluated a large, naturalistic sample of elderly patients referred to memory clinics. For all participants, the differential diagnosis included a possible preclinical stage of dementia at the time of referral. Unlike most previous studies on morphological correlates of neuropsychological deficits, we did not limit our sample to carefully selected patients without psychiatric comorbidity fulfilling MCI criteria highly predictive for the development of dementia. Instead, we only excluded cases with clear dementia at the time of referral, so that we retained a more representative mix of memory clinic patients who are a real diagnostic challenge. This aspect will enhance the generalizability of our findings to clinical practice in memory clinics. Second, to our knowledge, this is one of the first morphometric study analyzing a battery of neuropsychological tests tapping multiple cognitive domains in the same participants. Finally, the majority of previous reports utilized ROI methodologies to evaluate relationships between cognitive function and brain structure. The use of a whole-brain VBM analysis approach in our study does not depend on a priori hypotheses and may thus provide a more comprehensive assessment of brain areas associated with cognitive dysfunction.

There are also some methodological considerations that deserve mention. First of all, we did not use a healthy control group. However, our non-categorical correlational approach to investigate cerebral correlates of cognitive deficits in elderly persons may have advantages. The development of dementia is a continuous process without clear-cut borders between healthy, mildly impaired and demented. Therefore, a more accurate evaluation is possible if we assess both cortical atrophy and cognitive deficit in a graded manner (Tyler, Marslen-Wilson, & Stamatakis, 2005). Second, one might object that by examining a relatively unselected sample of memory clinic patients we
neglected the etiology of the impairments. Admittedly, brain – behavior relations may be different across diseases. However, our sample is too small to study these relationships in subgroups, and the resulting analyses would be underpowered. Yet, we do not think this objection is valid since we excluded other neurological causes than neurodegenerative brain disease. With a few exceptions, the large majority of patients who declined over the next two years satisfied either MCI or AD criteria at follow-up (Schmand et al., 2014). Thus, the baseline sample on which we report in the present paper mainly consisted of three main categories: worried well, patients who had a psychiatric disorder but were not in a dementia trajectory, and patients who had MCI or dementia due to a neurodegenerative disease. Since we also excluded patients with noncredible test performance, we assume that the subgroup of patients with a psychiatric disorder showed the usual brain – behavior relations of healthy elderly. Third, we reported correlations based on clusters that were identified as being those voxels showing strong associations. This implies some circularity, and the correlations might be inflated. However, these figures give an indication of the strengths of the brain-behavior relationships in this study. Fourth, to reduce the number of cognitive variables, we used composite neuropsychological scores to analyze relationships with brain structures. However, these composite measures disregard any differential relationships across different cognitive tasks within a single domain. Furthermore, the number of cognitive tests differed for the various domains, with the result that domain scores composed of more neuropsychological tests possibly provided a more representative measure of the underlying cognitive function. Finally, only baseline MRI scans and cross-sectional neuropsychological composite score were analyzed. To predict progressive atrophy from the neuropsychological profile in mild forms of the disease and vice versa, longitudinal studies examining correlations of GM values changes with the rate of decline of neuropsychological performance over time are needed (Arlt et al., 2012; Hua et al., 2008; Mungas et al., 2005).

In conclusion, in our naturalistic, unselective sample of memory-clinic patients, we found significant correlations with brain structure in similar regions, mainly located in the temporal lobes, across neuropsychological composite scores tapping different cognitive functions. Our analyses supported the assumption that these results are due to the primary neuropathology of memory dysfunction and do not reflect functional brain-behavior relationships, at least not in the non-memory domains.

It is important to keep in mind that, while we studied morphological data, VBM analysis does not provide direct evidence for functional impairments of a given brain region, and VBM results should thus be interpreted with caution in this respect.
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Longitudinal studies, combining morphometric with functional neuroimaging and neuropsychological methods are required to elucidate the functional consequences of regional cerebral changes in preclinical dementia stages.

References


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