Resting state glucose utilization and the CERAD cognitive battery in patients with Alzheimer’s disease

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Abstract

The present study examined the cortical functional representation of neuropsychological domains in Alzheimer’s disease (AD) using positron emission tomography (PET) and the neuropsychological assessment battery of the Consortium to Establish a Registry of Alzheimer’s Disease (CERAD). Thirty patients with clinical probable AD and 10 elderly healthy controls underwent 18 FDG brain PET imaging during a resting state. Correlations between metabolic values and cognitive measures were determined using a region of interest analysis with NEUROSTAT (University of Michigan, USA) and a voxel-based analysis with SPM96 (Wellcome Department, London, UK). Specific correlations were seen between measures of episodic memory, verbal fluency and naming and left hemispheric temporal and prefrontal metabolism. Drawing was correlated with metabolism in left prefrontal and left inferior parietal regions. The presented data support the use of metabolic–cognitive correlations to demonstrate the neuronal substrates of cognitive impairment in AD. Subtests of the CERAD battery give a good representation of left, but not of right hemisphere function in AD.

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1. Introduction

Alzheimer’s disease (AD) is characterized by a heterogeneous profile of impaired cognitive functions. In general, episodic memory is first and most severely impaired, while language and visuo-spatial deficits follow later in the disease [28,76]. Some patients, however, show language or visuo-constructive impairment early in the course of the disease, often even preceding onset of memory dysfunction [5,6,41,46,55].

Studies using 18FDG-PET at rest show heterogeneity in the distribution of regional hypometabolism in AD [29]. Several studies investigated the relation between the regional pattern of cortical metabolism and the profile of cognitive impairment in AD patients. Patients with predominant left hemispheric hypometabolism showed greater impairment of language functions, whereas patients with predominant right hemispheric hypometabolism showed greater impairment of visuo-constructive abilities [33,34]. The individual profile of impairment across different domains of memory correlated with the regional distribution of hypometabolism in resting state PET [18,21,39]. These findings suggest that correlation analysis can be used to identify dysfunction of cortical regions underlying specific neuropsychological impairment in AD. This interpretation is based on the notion that PET-based measurement of resting state cerebral glucose consumption is closely related to regional synaptic activity which in turn
is the substrate of neuronal network [44,59,60]. In addition, correlation studies in AD have been used to draw conclusion on the cortical representation of domain specific neuropsychological functions in the human brain [21]. One widely used test battery to determine the profile of domain specific neuropsychological impairment in AD is the battery developed for the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) [22,52]. This battery comprises tests on memory, language and visuo-constructive ability.

In this study, we investigated correlations between cognitive domains assessed with the CERAD battery and the regional distribution of decreased cortical metabolism measured through resting state 18FDG-PET in 30 patients with clinically diagnosed AD. The aim of our study was to identify cortical regions that showed altered metabolism related to the decline of a specific cognitive function in AD. From a clinical perspective, this would allow us to assess whether the clinically established CERAD battery represents the entire range of regional cortical dysfunction in a group of AD patients.

We used two analysis strategies: (i) extraction of gray matter activity from a set of predefined regions, and (ii) voxel-based correlation analysis. The former technique allows to restrict statistical analysis to regions selected a priori based on the neuropsychological and neuroimaging literature. This renders the analysis sensitive and lowers the risk of spurious results. In contrast, voxel-based analysis allows searching the entire brain for significant correlations, including areas not covered by predefined regions.

2. Methods

2.1. Subjects

Thirty right-handed patients with the clinical diagnosis of AD (22 women, eight men; mean age 72.2 ± 7.9 years) and 10 right-handed healthy volunteers (six women, four men; mean age 62.0 ± 8.9 years) were recruited for the study. The National Institute of Neurological Disease and Stroke and Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable (n=27) and possible (n=2) Alzheimer’s disease [47] and the Petersen criteria [56] for mild cognitive impairment (n=1), later confirmed probable AD) were fulfilled at the time of the FDG-PET acquisition. The patient population included subjects with mild (MMSE > 19, n=17), moderate (MMSE > 9 and <20, n=12) and severe (MMSE < 10, n=1) cognitive impairment.

A written informed consent was obtained from all subjects. The Ethics committees of the Ludwig-Maximilian University and the Technical University Munich and the radiation protection authorities approved the studies.

2.2. Cognitive tests

Cognitive functions of the patients were evaluated using the neuropsychological test battery of the Consortium to Establish a Registry for Alzheimer’s Disease [52]. The CERAD battery included the following tests: learning of a visually presented list of 10 words (three trials), delayed word list recall, recognition of previously studied words among non-studied words, modified Boston naming test (naming of line drawings), animal category verbal fluency, drawing (copying figures of increasing complexity, visuo-constructional function) and MMSE (orientation, immediate and delayed memory, working memory, language and praxis) [53]. These tests are measures of semantic memory (the animal category verbal fluency test and the modified Boston naming test), visual–constructional functioning (drawing) and verbal episodic memory (word list learning, recognition and recall). The MMSE was utilized as a global measure of dementia severity.

2.3. PET imaging

PET images were obtained in 26 subjects using an EXACT PET scanner (CTI, Knoxville, TN) and in four subjects using a Siemens 951R/31 PET scanner. A transmission scan was performed using a 68Ga68Ge pin source for attenuation correction after each subject was positioned. Emission scan acquisitions were in two-dimensional mode with a total axial field of view of either 10.5 or 16.2 cm and no interplane dead space. Images were reconstructed by filtered back-projection with a Hanning filter (cutoff frequency 0.4 cycles/projection element), resulting in 31 (Siemens 951R/31) or 47 slices (EXACT PET scanner) with a 128 × 128 pixel matrix (pixel size 2.0 mm) and an inter-plane slice separation of 3.375 mm.

PET studies were performed with the subjects comfortably seated in a darkened and quiet room, with eyes closed and ears unplugged. All subjects had fasted for at least 4 h before PET scanning. Thirty minutes after injection of 370 MBq of 18FDG, a sequence of three 10-min frames was acquired and later summed into a single frame.

2.4. Data processing and analyses

Anatomic standardization of 18FDG PET image sets was performed using NEUROSTAT (Department of Radiology, University of Michigan, Seattle). This procedure generates
standardized three-dimensional stereotactic surface projections (3D-SSP) data sets for individual data, normalized to an ¹⁸F-FDG-PET template in Talairach space, as previously described [40]. The resulting standardized image set had a cubic voxel size of 2.25 mm, 60 slices and a matrix size of 128 x 128. The standardized data were processed in two different ways: (i) extraction of gray matter activity from a set of predefined regions, and (ii) voxel-based analysis.

Gray matter activity in the brain was extracted using 3D-SSP [49]. The pixel counts were normalized to the thalamic hemisphere with the higher value, to reduce effects of functional deactivation induced by the more severely affected hemisphere in AD. A set of regions of interest (ROI) was defined according to the stereotactic space of Talairach and Tournoux [71]. The ROI were defined to re-

Cluster extension represents the number of contiguous voxels passing the threshold of \( p < 0.01 \). Bold markings delineate a cluster and the peak \( z \)-value within the cluster. Subsequent non-bold markings identify further peaks within the same cluster. Brain regions are indicated by Talairach and Tournoux coordinates, \( x, y \) and \( z \) [71]: \( x \) the medial to lateral distance relative to midline (positive: right hemisphere); \( y \) the anterior to posterior distance relative to the anterior commissure-posterior commissure line (positive: superior); BA: Brodmann area; Lpi: inferior parietal lobe; Supramarg: Gyrus supramarginalis; GTm: medial temporal gyrus; GTs: superior temporal gyrus; and PCC: posterior cingulate cortex.

The predefined set of ROI was then positioned on the individual anatomically standardized 3D-SSP images in a fully automated and user-independent way. The average gray matter activity extracted from each ROI was correlated with cognitive performance scores, using Spearman’s rank correlation coefficient. We considered the level of \( p < 0.05 \) as statistically significant. Contribution of age and gender to correlations between neuropsychological scores and regional metabolism was investigated in a multiple regression model.

Voxel-based statistical analysis was performed using SPM96 (Wellcome Department of Neurology, Institute of Neurology, UK). The images were smoothed using an isotropic gaussian kernel (12 mm FWHM), which accommodates inter-individual anatomical variability and has been shown to improve the sensitivity of the statistical analysis [26]. Individual global counts were normalized by proportional scaling across the entire data set to the group mean value. The normalized data set was compared between the healthy control group and the AD patients by computing a voxel-based two-sampled \( t \)-statistic. Within the patient group, relative metabolic activity in each single voxel was regressed on neuropsychological test performance. Significance threshold was assessed based on the peak value (corrected for multiple comparisons by Bonferroni method, 14 resels, \( p < 0.0036 \), one-sided). We assessed correlations in the positive direction (i.e. impaired cognitive performance was predicted to be related to decreased CMRGlc). Cluster size was set to a minimum of 100 contiguous voxels above a peak height of \( p = 0.01 \).

### Table 1

Peak metabolic reductions in AD patients compared to controls

<table>
<thead>
<tr>
<th>Location</th>
<th>BA</th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>Peak ( z )-value</th>
<th>( p )-value, uncorrected</th>
<th>Cluster extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lpi, right</td>
<td>40</td>
<td>40</td>
<td>-54</td>
<td>-54</td>
<td>4.18</td>
<td>( p &lt; 0.001 )</td>
<td>2130</td>
</tr>
<tr>
<td>Supramarg, right</td>
<td>39/40</td>
<td>-56</td>
<td>29</td>
<td>3.90</td>
<td>( p &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTm, right</td>
<td>22</td>
<td>61</td>
<td>-40</td>
<td>-2</td>
<td>3.30</td>
<td>( p &lt; 0.001 )</td>
<td></td>
</tr>
<tr>
<td>LPi, left</td>
<td>40</td>
<td>-45</td>
<td>-45</td>
<td>36</td>
<td>4.06</td>
<td>( p &lt; 0.001 )</td>
<td>2413</td>
</tr>
<tr>
<td>GTm/GTm, left</td>
<td>22/39</td>
<td>-52</td>
<td>20</td>
<td>3.65</td>
<td>( p &lt; 0.001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTm, left</td>
<td>21</td>
<td>-56</td>
<td>-47</td>
<td>-7</td>
<td>3.62</td>
<td>( p &lt; 0.001 )</td>
<td></td>
</tr>
<tr>
<td>Parietal, medial</td>
<td>7/31</td>
<td>0</td>
<td>-65</td>
<td>36</td>
<td>3.54</td>
<td>( p &lt; 0.001 )</td>
<td>2588</td>
</tr>
<tr>
<td>PCC</td>
<td>23</td>
<td>0</td>
<td>-29</td>
<td>27</td>
<td>3.44</td>
<td>( p &lt; 0.001 )</td>
<td></td>
</tr>
<tr>
<td>PCC</td>
<td>31</td>
<td>0</td>
<td>-50</td>
<td>27</td>
<td>3.33</td>
<td>( p &lt; 0.001 )</td>
<td></td>
</tr>
</tbody>
</table>

3. Results

#### 3.1. Between groups comparison of regional metabolism

In voxel-based analysis, relative metabolism was significantly reduced in bilateral temporal and parietal association cortex and in posterior cingulate cortex in AD patients compared to healthy controls (Table 1 and Fig. 2).

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**Fig. 1.** Region of interest template according to [19] projected onto the 3D-SSP of an AD patient.
3.2. Correlation between cognitive tests and regional grey matter activity within the AD group

In voxel-based analysis, memory scores were correlated with left temporal (recall and recognition) and left lateral prefrontal brain activity (recall and total number of words learned over three trials). Correlations with naming were limited to left medio-temporal metabolism, whereas fluency showed additional correlations with metabolic impairment in the left prefrontal cortex and, albeit non-significantly, with left parietal association areas. Performance on the drawing test was correlated with activity in the left temporo-parietal transition and prefrontal cortex. The results of the correlation analyses are summarized in Fig. 3 and Table 2.

ROI analysis showed correlations between memory scores and metabolic values in left temporal and left prefrontal regions. Correlations between learning ability and regional metabolism were significant, when learning was measured as the sum of successfully learned words across all three trials and as the number of words learned at the third trial. Correlations were not significant for the number of words learned at trials 1 and 2. Naming was correlated with left temporal and left superior parietal activity, whereas word fluency was
4. Discussion

In this study, we investigated correlations between cognitive domains assessed with the CERAD battery and regional decrease of cortical metabolism measured with resting state 18FDG-PET. Against the background of previous observations of inter-individual variance of cognitive performance and regional hypometabolism in AD patients, our aim was to identify cortical regions that may underlie the decline of specific cognitive functions in AD.

We found that AD patients had bilateral hypometabolism in temporo-parietal association and posterior cingulate cortex compared to controls. The regional pattern of hypometabolism in AD patients remained unchanged after controlling for age differences between groups. The regional distribution of hypometabolism in our patients is consistent with findings of a large number of previous PET studies [35,43,50] and the regional pattern of neuropathology in AD [8,45].

We correlated cognitive performance scores with regional metabolism across subjects to elucidate the cortical substrate of cognitive impairment. For the interpretation of the results, it is important to keep in mind that observed correlations between task-performance and resting state PET may reflect impairment only in isolated brain regions rather than the entire neuronal network involved in task performance. As an example, a specific task may involve hippocampus and leave prefrontal cortex relatively intact. In this case, the correlation between task performance and resting state glucose metabolism would reveal main correlations with hippocampus metabolism despite a significant involvement of left prefrontal cortex in this task. Therefore, the resting PET correlation approach may be more comparable to neuropsychological lesion studies than to functional activation studies.
Table 3

Correlations (Spearman’s ρ) between neuropsychological scores and ROI derived regional metabolic values in AD patients

<table>
<thead>
<tr>
<th>Region/test</th>
<th>Learning</th>
<th>Recall</th>
<th>Recognition</th>
<th>Naming</th>
<th>Fluency</th>
<th>Drawing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left prefrontal</td>
<td>0.38**</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right prefrontal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior–temporal</td>
<td>0.37*</td>
<td>NS</td>
<td>0.48***</td>
<td>0.44*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right anterior–temporal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left medial–temporal</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>0.44*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right medial–temporal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left posterior–temporal</td>
<td>0.46***</td>
<td>NS</td>
<td></td>
<td>0.64 ***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right posterior–temporal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left lateral–temporal</td>
<td>0.40*</td>
<td>NS</td>
<td></td>
<td>0.49**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right lateral–temporal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left superior–parietal</td>
<td>0.38*</td>
<td>0.51**</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right superior–parietal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left inferior–parietal</td>
<td>0.48**</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right inferior–parietal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Spearman’s ρ correlation coefficients. NS indicates correlations expected a priori, but not reaching significance. Blank cells indicate correlations not reaching significance and not expected a priori.

∗ p < 0.05.
∗∗ p < 0.01.
∗∗∗ p < 0.001.

4.1. Memory

4.1.1. Learning

In voxel-based analysis, the total score of word list learning correlated with activity in the left medial frontal lobe, ROI-analysis showed additional correlations with left temporal lobe regions (Table 3). The correlations were significant for the number of words learned on trial 3, but not for the number of words learned on trials 1 and 2. Previous imaging evidence suggests left prefrontal activation in verbal episodic encoding and in semantic memory [9,73]. The left middle temporal region of the lateral temporal lobe represents a part of the verbal semantic and phonological loop, involved in the processing of verbal information [4].

4.1.2. Recall

Recall correlated with left lateral temporal and left prefrontal metabolism in voxel-based analysis, whereas correlations in ROI analysis did not reach significance. In previous studies, left prefrontal activation occurred in healthy subjects during encoding of verbal material [73]. According to the HERA model of Tulving et al. [73] the left prefrontal cortex is also engaged in retrieval from semantic memory, whereas episodic memory retrieval is related to right prefrontal activation. Recent studies have found a shift from right to left prefrontal activation during retrieval of verbal material in older compared to younger subjects [11,12,65]. The left hemispheric predominance of prefrontal correlations in learning and recall in our study suggests that in AD patients the ability to additionally engage left prefrontal regions may be critical not only for encoding but also for retrieval performance. This hypothesis is further supported by the observation of left prefrontal activation of Brodman areas 9 and 10 in AD patients and elderly controls during free word recall [7].

4.1.3. Recognition

Recognition of verbal material correlated with metabolism in the left hippocampus and adjacent entorhinal cortex, when voxel-based analysis was used. In ROI analysis, additional correlations with left lateral and anterior temporal lobe were observed.

Activation of left medial temporal lobe has been demonstrated in healthy subjects during recognition of previously learned words [20,53], the extent of activation being related to retrieval success. As yet, evidence is not conclusive in regard to hippocampus activation in recognition of verbal material, with several studies showing parahippocampal but not hippocampal activation [2,72]. However, fMRI studies showed evidence for left hippocampal activation during word recognition [62,69].

Several imaging studies showed activation of prefrontal cortex in association with recognition memory [63,74]. In contrast, neuropsychological studies suggest that recognition task performance may be relatively preserved even in presence of widespread frontal lobe damage [70]. Activation of prefrontal cortex during memory retrieval has been connected to top-down activation of memorized material [32]. The correlation between free recall and left prefrontal metabolism suggests an active process of top-down memory retrieval that fails with increasing functional impairment of this region. Recognition memory poses less demand on retrieval processes than free recall. Therefore, impaired function of prefrontal cortex in AD may be less related to performance in recognition than to performance in free recall. This agrees with the typical finding that patients even with widespread...
impairment of fronto-temporal systems show a dissociation be-
 tween severely impaired free recall and moderately impaired
or even unimpaired recognition memory, as demonstrated in fronto-temporal degeneration and progressive supranuclear
palsy [57,77].

4.2. Language

Category fluency as a measure of semantic fluency
was significantly correlated with left tempo-parietal and
prefrontal metabolism. Left prefrontal activation has been
demonstrated in semantic retrieval [10,73] and impaired cat-
egory fluency occurred in patients with left prefrontal lesions
[15]. Lesions of cortical areas surrounding the tempo-parietal
junction are found in patients with impaired word comprehen-
sion and retrieval [14,30] and in semantic demen-
tia [36]. Semantic processing impairment was also correlated
with hypoperfusion in inferior parietal and superior temporal
regions in AD patients [31].

In the voxel-based analysis, naming showed peak corre-
lations with fusiform gyrus and with left medial temporal
gyrus. ROI analysis showed an additional correlation with
left superior parietal lobe. Activation of fusiform gyrus has
been shown in several functional imaging studies on naming
of objects [58,66,67]. The correlation is also consistent with
the early involvement of fusiform gyrus in AD related atro-
phy and neurodegeneration [13] and naming deficits as one
early sign of AD related cognitive impairment.

4.3. Drawing

In voxel-based analysis, drawing was correlated with
left inferior parietal lobe and left inferior frontal gyrus
metabolism in our patients. ROI-based analysis showed no
correlations of drawing performance with any predefined re-
gion. The role of cortical impairment in drawing deficits in
AD has not been thoroughly studied so far. A large range
of neuropsychological studies on patients with focal cere-
bral lesions suggest the involvement of bilateral or right
parietal lobe in drawing performance [62,75]. Predominant
parietal or parieto-occipital lesions have also been reported
in patients with progressive visuo-spatial and constructional
impairment due to neurodegenerative disease [3,16,25].
In PET studies, impairment in copying of line-drawings cor-
related with right parietal hypometabolism in AD [24,33].
Another study, investigating different aspects of drawing
performance in AD patients, showed correlations with left
and right tempo-parietal hypometabolism in resting state
PET [54]. Additionally, attention to details of drawings was
correlated with bilateral fronto lobe metabolism. In agree-
ment with these findings, in an earlier neuropsychological
study, drawings of AD patients had features in common
with those of patients with left or right-sided focal cere-
bral lesions. In contrast to the drawings of patients with
focal lesions, however, the spontaneous drawings of AD
patients were not only simplified, but often incoherent and
lacked essential features, and the spatial relationships were
lost not only in spontaneous drawings but also when copy-
ing an object [51]. The authors suggested that deficits in
demented patients on copying tasks might be partially at-
tributable to attention deficits whereby the patients fail to
integrate separate features of an object into a coherent
whole.

The correlation between drawing and metabolic activity
in left inferior parietal lobe in our patients may, therefore,
in part reflect attention deficits contributing to impaired per-
formance in the CERAD drawing test in our AD patients.
The left inferior parietal lobe subserves the allocation of
attention to locations in the visual field [61]. For example,
compared to the range drawing test used in earlier studies
[33], the CERAD drawing test comprises only a small range
of four presented items with a very uneven distribution of task
difficulties (copying of a circle, a rhombus and two overlap-
ing rectangles compared to copying of a three-dimensional
cube). Two recent studies suggest that among all subtests of
the CERAD battery this test has the least power to discrim-
inate mild to moderate AD patients from healthy controls
[1,64]. This finding indicates that only a minor part of vari-
ations in task performance across mild to moderate AD pa-
tients may be specifically related to the disease process, and
hence correlations with this test will not be able to uncover
disease related regional functional deficits.

4.4. Limitations

There are two methodological caveats, which have to be
considered with our data. First, metabolic values determined
using PET are affected by partial volume effects, i.e. con-
tamination of grey matter counts by counts from CSF and/or
white matter spaces which cannot be resolved with the lim-
ited resolution of the PET camera. Several studies showed
that MRI-based atrophy correction leads to a mean increase
of global cortical metabolism of about 19% in patients with
mild to moderate clinical stages of AD [38,48]. Therefore, it
is likely that correcting for atrophy has an influence on cor-
relations between cortical metabolism as measured by PET
and cognitive function. The ROI analysis in our study was
based on standardized three-dimensional stereotactic surface
projections (3D-SSP) as described in [40,49]. This technique
reduces partial volume effects, because each cortical surface
pixel is represented by the maximum value along its pro-
jection into the cortex. It is not resolved, however, how this
approach compares to atrophy correction based on individual
MRI scans.

Second, the a priori determined level of significance has
an effect on the interpretation of our findings. The ROI-based
analyses were not corrected for multiple comparisons. Strict
Bonferroni correction would have implied a \( p \)-value < 0.0006
(0.05/84, 6 neuropsychological tests by 14 regions), cor-
responding to a Spearman’s \( \rho \) of about 0.7. Therefore, no
significant correlations would have remained. Comparisons,
however, are not independent, but there is a high correlation
both between the neuropsychological subtests and between the regional metabolic values. Moreover, specific correlations were expected a priori, e.g. between verbal fluency and metabolism in left prefrontal cortex. Finally, the lack of correlations in the right hemisphere is equally important as the specific left hemispheric correlations because this finding suggests that the CERAD battery might not be useful to detect right hemispheric dysfunction. Therefore, in our study it was important to achieve a trade-off between the error of the first kind (to erroneously assume a correlation) and the error of the second kind (to erroneously reject a correlation). Because we had selected 14 independent regions of primary interest in the ROI-based analysis, the level of significance for the voxel-wise analysis was determined as 0.05/14 = 0.0036. The limitation of the above approach is that we may not interpret the exact coordinate location too heavily, i.e. if we find a significant activation in the left inferior parietal lobe, we cannot put emphasis on the specific function of a subdivision of the left inferior parietal lobe. The advantage is that we can state with relative confidence that the dissociation between left and right hemispheric correlations is not solely due to an error of the second kind, and at the same time control the risk of spurious positive findings.

4.5. Summary

Regional correlation coefficients ranged from 0.35 to 0.64 over all sub scores and regions (Table 3). This indicates that neuropsychological measures accounted for 12–40% of variance of metabolic measures in the respective regions. This amount of common variance is comparable to a previous study correlating metabolic and neuropsychological measures in AD [18].

Our findings support the notion that correlations between profiles of cognitive impairment and regional cortical metabolism can identify cortical regions that are affected by AD pathology, leading to specific cognitive dysfunction. Comparing these findings to results derived from healthy control subjects allows drawing conclusions on compensatory reallocation of cortical resources to maintain task performance. This may be helpful for the planning and interpretation of functional imaging studies in AD. From a clinical perspective, the CERAD battery gives a good representation of left hemisphere dysfunction in AD patients. Impairment of right hemisphere function, however, appears to be only poorly represented in the battery. A subgroup of AD patients clinically presents with initial right hemispheric impairment, for example Balint syndrome [27,37,42]. These symptoms might be undetected using a screening battery, which is mainly sensitive to left hemispheric dysfunction. Therefore, if this result can be confirmed in an independent sample, we recommend adding an additional test of visuo-constructive impairment to the CERAD battery that provides a wider and more homogeneously distributed range of task difficulty, e.g. the range drawing test [33].

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