Neural correlates of visual memory in Diffuse Axonal Injury patients

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Abstract

In this study, 39 patients spanning the full range of traumatic brain injury (TBI) severity and a group of 53 matched healthy controls (HC) were evaluated on CANTAB tests of visual-spatial short-term recognition memory and learning. ANCOVAs and Cohen's d estimations of effect sizes were used to test between-group differences in the measures of memory function. Partial correlations and multiple regression analyses were used to examine relationships between cognitive variables and MRI volumetric findings. Patients with TBI performed significantly worse than controls in all the tasks assessed. Performance in the tests was associated with reductions in grey and white matter volume of several cortical and subcortical structures as well as with CSF space enlargement in accordance with previous studies of memory in patients with TBI and cognitive models that suggest memory problems involve the alteration of multiple systems. Our results propose that compromised visual memory in patients with TBI is related to a distributed pattern of volume loss in regions mediating memory and attentional processing.

Keywords

Traumatic Brain Injury, Visual Memory, Magnetic Resonance Imaging

1. Introduction

Traumatic brain injury (TBI) is associated with a wide variety of cognitive and emotional deficits that can persist several years after injury and have an effect on psychosocial recovery. Common cognitive problems associated with mild, moderate and severe TBI include difficulties with memory, attention, information processing and executive function [1,2]. Memory is one of the functions most frequently impaired following TBI [3,4]. Such problems, noted by patients and family members [5], significantly influence an individual's rehabilitation and have been associated with poorer functional outcome (e.g. employment status, emotional functioning and overall quality of life) [6].

It is currently accepted that memory is not a unitary system but a set of systems with different neuroanatomical substrates [7]. Memory has been classified into different subtypes depending on its persistence (short or long-term memory), the contents of its stored material (episodic or semantic), and the presence or not of consciousness during learning and memory (declarative or nondeclarative). Deficits in declarative memory – the capacity for conscious recollection of facts and events – are a common consequence of head trauma that is disproportionately suffered in comparison with other types of memory [8]. Neuroanatomically, this kind of memory has been associated with the integrity of the prefrontal cortex and medial temporal lobes [9-11] the fusiform [12,13], the parietal [14,15] and the premotor cortex [16,17]. These regions are thought to be involved in the encoding and transformation of sensory input into internal representations (inferior frontal and fusiform gyrus) [18], storage of the internal representations into memory (medial temporal lobe and hippocampal formation) [19,20] and attentional processing during encoding (parietal and premotor cortex) [21]. In patients with TBI, reductions in the volume of grey and white matter of the temporal, frontal, parietal and occipital lobes, as well as in the cingulate gyrus, the cerebellum and subcortical structures such as the basal ganglia and the thalamus have been associated with impaired memory functions [22-29]. Research

into the neurobiological correlates of memory in TBI patients can increase our understanding of the underlying changes that occur in the brain following injury and identify potential targets for pharmacological modulations of disrupted neurotransmitter systems. However, many of the studies conducted so far are compromised by small sample sizes, variability in imaging methods or tests used and the use of samples with a mixture of focal and diffuse brain injuries [30]. Furthermore, previous work has typically focused on a limited number of regions of interest [31] and since most of the functions commonly impaired depend on the coherent activity of widely distributed networks [32,33], such approaches limit the scope for uncovering a complete picture for the structural causes of the pathology studied.

This study investigated the neural substrates of visual recognition memory in a sample of 39 patients with TBI. This study complements and extends previous studies by performing volumetric comparisons on a variety of resolution levels, from whole brain to voxel-based level analysis. Moreover, only patients with diffusion axonal injury (DAI), as opposed to focal lesions, were included, enabling us to study TBI-related memory impairment as a consequence of axonal damage and therefore compromised connectivity. We hypothesised that patients with decreased grey and white matter volume in the temporal, frontal, parietal and occipital lobes as well as in subcortical areas and the cerebellum would perform poorly on the tests of memory function analysed.

2. Materials and Methods

2.1. Participants

Thirty-nine patients with TBI were included in this study. Patients were referred from the Addenbrooke's Neurosciences Critical Care Unit Follow-Up Clinic, the Addenbrooke's Traumatic Brain Injury Clinic and the Royal London Hospital Intensive Care Unit. Only patients with DAI – as confirmed by the Marshall Score [34]– were included in this study. They were at least 6 months

post TBI (mean 14.09 ± 9.17 months) and were not receiving any acute hospital interventions. They sustained mild to severe TBI –as measured by the Glasgow Coma Scale (GCS) [35]. A group of 53 healthy controls (HC) recruited for studies running in parallel to ours, was used as a control group for comparison with the TBI patients in the neuropsychological tasks used. HC were recruited via advertisements in Addenbrooke’s Hospital and in the local Cambridge area and were paid for their participation. Both TBI patients and HC were screened by exclusion criteria including National Adult Reading Test <70 , Mini Mental State Exam <23 , left-handedness, history of psychiatric or neurologic disorders, taking medication that may affect their physical or cognitive performance, history of drug or alcohol abuse and pregnancy or breast feeding. Additionally, patients were excluded if they had a physical disability that could prevent them from completing the tasks either in the screening or scanning stages. This study was approved by the local Research Ethics Committee. All participants gave written informed consent before participation according to the 1991 Declaration of Helsinki.

2.2. Neuropsychological assessment

Participants completed a series of computerised tasks, taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (<http://www.cantab.com>). Specifically, the Patter recognition memory (PRM), the Spatial recognition memory (SRM) and the Paired associates learning (PAL) were used.

2.2.1. Pattern Recognition Memory

The PRM task employs a two-choice forced discrimination paradigm. One at a time, 12 different visual patterns, which are designed in a way that makes it difficult to assign verbal labels to them, appear on a computer screen. Subsequently, the participant is asked to discriminate between previously presented and novel patterns. This procedure is repeated with 12 new patterns. The test is a good indicator of overall visual short-term recognition memory, which is impaired in disorders

such as mild to moderate Alzheimer's disease [36,37]. Here, TBI patients' performance was evaluated based on the number of correct trials, expressed as a percentage (i.e. percentage of correct trials). Higher percentage indicates better performance.

2.2.2. Spatial Recognition Memory

The second task designed to test participants' visual memory was the SRM. This task is based on a two-choice discrimination paradigm: a white square appears sequentially at different locations on the screen. Following this, in the recognition phase, the participant is presented with a series of pairs of squares, with one of those being in a previously seen position. The other square is in a novel position on the screen. This test is repeated three more times, each time with new locations. The outcome measure chosen for this task was the participants' speed (mean latency for correct responses). Latency is scored in milliseconds with lower latency indicating better performance. SRM has previously shown higher latency scores in TBI compared to healthy controls [38].

2.2.3. Paired Associates Learning

PAL combines the different visual memory components evaluated by the PRM and SRM tasks. It assesses visual memory and new learning and is sensitive to mild cognitive impairment and Alzheimer's disease [23,39]. Since TBI has been associated with increased risk of these disorders [40-42], the combination of neuroimaging and the PAL may provide insights into one of the possible mechanisms by which risk for neurodegenerative disorders is increased following TBI.

The PAL involves boxes displayed on the screen opening in a random order, with one or more of them containing a pattern. Subsequently, the patterns appear in the middle of the screen, one at a time. The participant is asked to touch the box in which the pattern was initially presented. Should the participant make a mistake, the patterns are presented again as a reminder of the original locations. Task difficulty increases with the number of patterns presented (up to eight). The analysis of PAL focused on the number of errors made at the 6-pattern stage. The 6-

pattern condition has been found to be reliable in distinguishing between individuals with memory impairments and healthy controls, as well as differentiating between various neurodegenerative conditions [e.g. 36,37,43]. Lower number of errors indicates better performance.

2.3. MRI acquisition and preprocessing

The imaging session started with a localiser followed by a high resolution T1-weighted, magnetization-prepared 180 degrees radio-frequency pulses, rapid gradient-echo (MPRAGE) structural scan (TR = 2300 ms, TE = 2.98 ms, TA = 9.14 min, flip angle = 9°, FOV = 256 mm, voxel size = 1.0 x 1.0 x 1.0 mm, slices = 176), acquired on a 3T Siemens Trio scanner (Siemens AG, Erlangen, Germany) at the Wolfson Brain Imaging Centre (WBIC), University of Cambridge.

The images were preprocessed and analysed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>). Initially, the T1 images were segmented into grey matter, white matter and cerebrospinal fluid (CSF) using the VBM8-toolbox (<http://dbm.neuro.uni-jena.de/vbm/download/>). The images were entered into the DARTEL framework and high resolution study-specific grey matter, white matter and CSF templates were created and used as tissue probability maps in an additional normalisation and segmentation of the original T1 scans. Segmented images were subjected to Jacobian modulation to sensitise the analyses to true volumetric differences between patients. Although this cohort suffered diffuse injuries and therefore did not present with anatomical distortions we used study specific templates to optimise spatial normalisation. We visually inspected the images following spatial normalisation to ascertain the algorithm transformed the images to standard space. Finally, the images were smoothed with a 3-D Gaussian filter of 8 mm full width at half maximum (FWHM).

Individual grey matter, white matter and CSF volumes were calculated for the whole brain, the left and right hemispheres (separated into brainstem, cerebellum and cerebrum), the midbrain (including the pons, medulla and midbrain) and separate lobes (fronto-temporal space, the frontal,

limbic, occipital, parietal and temporal lobe, as well as the medulla, pons, sublobar region and anterior and posterior cerebellum). Additionally, a volumetric analysis was performed using the areas defined by Automated Anatomical Labeling (AAL) atlas [44]. Finally, a more detailed voxel-level analysis was performed [45]. Because there can be differences in results when ROI vs. voxel-based approaches are employed, the use of different approaches in the same dataset could help to establish structural differences that converge across analysis methods, as well as, the level of resolution sufficient to detect behavioural/structural associations (see Supplementary Figure 1 for an illustration of the different levels of resolution used).

2.4. Analyses

2.4.1. Behavioural analysis

Behavioural data were analysed with the SPSS 21 (Chicago, IL, USA). Independent-sample t-test and chi-square tests were used to compare the groups on relevant socio-demographic variables. ANCOVAs and Cohen's d estimations of effect sizes were used to test between-group differences in the measures of memory functioning. Due to the large variance in the age of the participants and previously reported age effects in brain morphometry [28,46] and neuropsychological performance [47-49], age at assessment was used as a covariate in our analyses. Significance threshold was set at $p < 0.05$.

2.4.2. Imaging analysis

Analyses were conducted using the SPSS 21 in the cases of whole brain, hemisphere, lobe and gyri volume comparisons and SPM8 for the voxel-based correlations between regional grey matter, white matter and CSF and the scores of the different memory scales. Partial correlations and multiple regression analyses were used to examine possible relationships between cognitive variables and MRI volumetric findings. Age was used as a covariate in all the analyses. Significance threshold was set at $p < 0.05$ in the first set of analysis (SPSS) and at a p value of

<0.001 uncorrected for voxels and <0.05 at cluster-level with correction for family-wise error (FWE) in the second one.

3. Results

3.1. Behavioural analyses

The groups were statistically matched in terms of gender ($\chi^2=0.694$, $p=0.405$), age ($t_{89}=-0.425$, $p=0.672$), and premorbid IQ ($t_{89}=-1.526$, $p=0.132$), as estimated by the National Adult Reading Test (NART). Demographic and characteristics of the samples are summarized in Table 1. The results of the analyses showed that patients with TBI had significantly poorer performance than HC on all neuropsychological tests administered (Table 2). Calculation of effect sizes showed large effect sizes ($d>0.8$) for the PAL and medium effect sizes ($d>0.5$) for the PRM and the SRM (Table 2).

Please insert Tables 1 and 2 here

3.2. Imaging analyses

3.1. Pattern Recognition Memory

Amounts of grey and white matter in the temporal lobe were found to be significantly correlated with percent of correct responses. Patients with more intact tissue outperformed patients with lower amounts of grey ($r=0.36$, $p<0.05$) and white matter ($r=0.38$, $p<0.05$). Positive correlations between tissue volume and performance were also found at the gyral level (see Table 3). Specifically, we found significant positive correlations between the percentage of correct trials and gray matter volume in the temporal and occipital lobes, the angular gyrus and the putamen and white matter volume in the hippocampus, the temporal and frontal lobes, the angular gyrus and the cerebellum. Furthermore, a negative correlation between CSF volume in the right hippocampus and PRM accuracy was found, which is in line with the positive association found between

performance and amount of intact white matter in this region. Finally, we found a significant positive correlation between accuracy and CSF volume in the areas 4 and 5 of the vermis. The analysis at the voxel-levels did not show significant correlations at the threshold level used.

Please insert Table 3 here

3.2. Spatial Recognition Memory

Lower resolution level analyses did not yield any significant results. Analyses on gyral-level were more informative (Table 4). Patients with higher amounts of grey matter in the hippocampus and parts of the vermis responded faster. The same was true for more intact white matter volume in a number of bilateral frontal structures. Additionally, more intact white matter in the left cuneus was positively related to mean latency. Finally, a negative correlation between CSF volume in the right cerebellum (area 10) and speed was found, indicating a correlation between greater grey or white matter atrophy and slower responses.

Please insert Table 4 here

3.3. Paired Associates Learning

Patients with more intact grey matter in the frontal ($r=-0.43$, $p<0.01$), temporal ($r=-0.44$, $p<0.01$), parietal ($r=-0.46$, $p<0.01$) and limbic lobes ($r=-0.34$, $p<0.05$), as well as sublobar regions ($r=-0.46$, $p<0.01$) were found to make significantly fewer errors. The association between sublobar tissue volume and errors made was also found in the white matter analysis ($r=-0.34$, $p<0.05$). Also, higher CSF volume in the parietal ($r=-0.42$, $p<0.05$) and occipital lobe ($r=-0.40$, $p<0.05$), and thus potentially lower grey or white matter amounts, were linked to poorer performance.

The importance of intact tissue for successful PAL performance emerged again when analysing the data on a gyral level (Table 5). Lower grey and white matter volume in the temporal and frontal lobes, as well as in the hippocampus, supplementary motor area and basal ganglia were

associated with impaired performance on this task. Similarly, patients with higher amounts of grey matter in the parietal and occipital cortex, rolandic operculum, cingulum, precentral, fusiform and angular gyrus, in addition to the white matter volume of the thalamus and the cerebellum made fewer errors on this task. In contrast, there was a significant positive correlation between more intact white matter in the middle temporal gyrus (temporal pole) and the number of errors made. The correlation results of PAL performance and CSF volume on gyral level are consistent with the grey and white matter findings at this level of analysis. In this sense, less CSF, and therefore probably higher amounts of brain tissue, was associated with better performance. Significant results for this relationship were found in parts of the hippocampus, temporal, frontal and occipital lobes and the cerebellum.

The voxel based analysis revealed significant negative correlations between the number of errors and grey matter volume in the medial part of the superior frontal gyrus, the precentral gyrus, and the precuneus. Similarly, more intact white matter in the right sagittal stratum and near the inferior and middle temporal gyri, with the cluster extending to the fusiform gyrus, was associated with better performance. The importance of intact brain tissue for good PAL performance was echoed in the CSF VBM results. Increased CSF near temporal, frontal and occipital regions was linked with poorer performance (Fig. 1).

Please insert Table 5 and Fig. 1 here

4. Discussion

Consistent with a body of literature on the presence of memory deficits in patients with TBI [4,50], our patients showed significant impairments in the measures of visual memory analysed. When the neural correlates of memory function were analyzed, memory performance was associated with reductions in the volume of grey and white matter of several cortical and subcortical structures as well as with ventricular enlargement. This finding is in accordance with

previous studies of memory in patients with TBI and theoretical models proposing that memory problems in patients with TBI involve the alteration of multiple systems [25,32]. Along these lines, it has been suggested that memory deficits in this population may result from difficulties in the application of active or effortful strategies in learning or retrieval processes [4,51]. Moreover, the involvement of numerous regions in memory performance in this population might indicate the use of compensatory mechanisms to optimize performance [52,53]. Our data therefore suggest that memory impairments persist following TBI highlighting the chronic nature of this condition [54-57].

The first task we used to assess patients' visual memory abilities was the PRM test. The results of our study implicate the hippocampus and the temporal lobe in PRM performance. The hippocampus and the temporal lobe have been consistently associated with memory functioning. Specifically, evidence indicates that both structures are involved in the storage of internal representations into memory [19,20].

Furthermore, both structures have been associated with visual recognition memory in previous studies of healthy individuals and patients with temporal lobe damage [47,49-51,53-60]. We also found a positive correlation between the volume of white matter of the inferior frontal gyrus and performance in this task. This finding is in line with the role of this region in the encoding and recognition of visual and verbal information [61-65]. The memory deficits we found in the patients with TBI and their association with structures of the temporo-parietal network, are comparable to the abnormalities reported in patients with Alzheimer's disease and mild cognitive impairment [e.g. 23,66]. This finding provides some insight into the increased dementia risk documented in TBI patients [67,68]. Future research should explore the sensitivity and specificity of neuropsychological and neuroimaging biomarkers in this population and provide differential treatment pathways and rehabilitation strategies.

Our findings also suggest that intact tissue in the left angular gyrus is critical for successful PRM performance. This result overlaps with previous findings demonstrating the importance of this structure in learning and memory processes [69]. For example, it has been postulated that the angular gyri may directly support episodic retrieval through their anatomical and functional connections with the medial temporal lobe [70-73]. The analyses at the gyral-level also implicated the occipital cortex and the cerebellum in this task. Both structures have showed increased activation during a visual memory task [74]. The involvement of the middle occipital gyrus might reflect its known role in visual processing and object recognition [75].

The cerebellum, on the other hand, has been found to be involved in memory function, among other cognitive domains [76-78]. Further evidence for this association was found in a study of twenty-three children with severe traumatic brain injury [22]. According to the authors, cerebellar lesions can lead to reduced performance in tasks that require sustained attention such as tasks of visual recognition memory [22,79]. We also found a link between lower grey matter in the putamen and PRM performance. This association coincides with recent studies showing the role of the basal ganglia in feedback-based learning [38].

Investigation of the neural correlates of the SRM suggested that more intact grey matter volume in the hippocampus and cerebellar areas support faster correct responses on this task, consistent with the studies that show that TBI patients with compromised tissue in these areas responded significantly slower when compared to HC [38]. White matter volume in the inferior and middle frontal gyri was associated with better performance, in accordance with the role of these structures in the encoding and recognition of visual and verbal information [61-65]. We also found a positive correlation between the volume of white matter in the cuneus (a region of the default mode network) and the participants' speed in line with studies that show that disrupted structural grey and white-matter integrity in the default mode network. These findings suggest a potential mechanism for the structural changes found in this population [80,81].

Finally, the PAL results showed that performance in this task relies on a wide range of structures, including the frontal, temporal, parietal and occipital lobes, as well as medial (i.e. cingulate, precentral gyrus and supplementary motor area) and subcortical regions (i.e. basal ganglia, thalamus and pallidum), the default mode network (i.e. precuneus and angular gyrus) and the cerebellum. In addition to the role of the regions found associated with memory performance in the PRM and SRM tests, the number of errors in the PAL was associated with grey matter volume in the parietal gyrus. The role of the parietal cortex in memory function has been emphasized in previous studies. For example, greater activations in specific parietal regions have been associated with better episodic memory retrieval, recognition of old items, as well as familiarity of events [82-84]. Alterations in the parietal cortex are known to cause attentional dysfunction during processes that support memory retrieval, searching, monitoring and verification [85]. Reduced grey matter volume in medial structures such as the cingulate, precentral gyrus and the supplementary motor area were associated with a higher number of errors. These regions have been associated with attentional processing, an important element of memory encoding [16,17,21]. We also found a negative correlation between the volume of white matter of several subcortical structures and the performance in this task, in line with recent studies showing the involvement of subcortical structures in memory functioning [86-88]. Finally, the volume of grey matter of the rolandic operculum and the fusiform gyrus were associated with PAL performance in accordance with the role of these structures in somatosensory processing [12,13,18,89].

This study investigated the neural substrates of visual recognition memory in a sample of 39 patients with TBI. Strengths of this study include the use of an optimized VBM protocol, as well as the use of several resolution levels in the analyses. We found the voxel-level analyses were not very informative, a result that could reflect the differences in statistical power between voxel-based and ROI analyses [90] but also the heterogeneity inherent in TBI. Limitations of this study

include the heterogeneity of our sample and the exploratory nature of the analyses. In this sense, our study included individuals with a wide range of injury severities and time since injury. Nevertheless, although the sample studied was heterogeneous, the patients were characterized as having DAI and age at assessment was included as covariate.

Declaration of interest

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Tables

Table 1. Demographic and clinical characteristics of the samples.

	TBI patients (n=39)						HC (n=53)	
	Mild (n=4)		Moderate (n=6)		Severe (n=29)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Gender (male/female)	2/2		2/4		19/10		26/27	
Age (years)	44.75	18.77	49	17.50	30.97	13	35.74	10.94
NART	108.50	8.85	113.60	11.52	108.96	10.54	112.57	7.40
ISS	12	7.62	24.17	10.96	22.52	10.16		
APACHE II	10.75	6.13	17.17	7.73	16.22	4.08		
Time-post injury (months)	20.75	13.38	14.33	8.36	14.21	8.78		
	Median	IQR	Median	IQR	Median	IQR		
GCS	14.50	2	10.50	2	5	3		
GOS	4	1.50	3.5	2	4	1		

NART: National Adult Reading Test; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; ISS: Injury Severity Scale; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 2. Descriptive scores for the different indices of memory functioning.

	TBI patients (n = 38)		HC (n = 53)		Test		
	Mean	SD	Mean	SD	F	<i>p</i>	<i>d</i>
PRM	84.32	14.74	90.72	9.83	3.939	0.023	-0.51
SRM	2589.10	1470.70	1983.53	556.32	5.041	0.008	0.54
PAL	5.71	8.50	0.23	3.22	11.954	0.000	0.85

PRM: Patter Recognition Memory percentage of correct trials; SRM: Spatial Recognition Memory mean latency for correct responses; PAL: Paired Associates Learning Total errors made at the 6-pattern stage.

Table 3. Significant correlations between the measure of PRM and the volume of grey, white matter and CSF in the TBI sample.

Location	R score	P value
Grey matter		
Left middle temporal gyrus	0.33	0.044
Right middle occipital gyrus	0.33	0.044
Left angular gyrus	0.34	0.040
Left putamen	0.38	0.021
White matter		
Right hippocampus	0.46	0.004
Left middle temporal gyrus	0.34	0.039
Right middle temporal gyrus	0.38	0.020
Left inferior frontal gyrus	0.40	0.014
Left angular gyrus	0.40	0.013
Left cerebellum (area 3)	0.36	0.030
Left cerebellum (area 10)	0.41	0.013
Vermis (areas 1 and 2)	0.36	0.028
CSF		
Right hippocampus	-0.43	0.007
Vermis (areas 4 and 5)	0.37	0.026

Table 4. Significant correlations between performance the measure of SRM and the volume of grey, white and CSF in the TBI sample.

Location	R score	P value
Grey matter		
Left hippocampus	-0.37	0.023
Right hippocampus	-0.40	0.013
Vermis (areas 1/2)	-0.33	0.045
Vermis (area 3)	-0.39	0.017
White matter		
Left middle frontal gyrus	-0.47	0.003
Right middle frontal gyrus	-0.34	0.043
Left inferior frontal gyrus	-0.33	0.046
Right inferior frontal gyrus	-0.43	0.007
Left cuneus	0.39	0.018
CSF		
Right cerebellum (area 10)	0.35	0.032

Table 5. Significant correlations between the measure of PAL and the volume of amount of grey, white and CSF in the TBI sample.

Location	R score	P value
Grey matter		
Right hippocampus	-0.42	0.011
Right inferior temporal gyrus	-0.48	0.003
Right superior temporal gyrus	-0.33	0.049
Right middle temporal gyrus	-0.36	0.031
Right middle temporal pole	-0.37	0.026
Left superior medial frontal gyrus	-0.33	0.047
Right rolandic operculum	-0.38	0.022
Right middle cingulum	-0.34	0.043
Right precentral gyrus	-0.49	0.002
Left supplementary motor area	-0.37	0.023
Right supplementary motor area	-0.38	0.022
Left superior parietal gyrus	-0.37	0.026
Left angular gyrus	-0.37	0.024
Right angular gyrus	-0.33	0.048
Right fusiform gyrus	-0.45	0.005
Right middle occipital gyrus	-0.39	0.017
Right caudate nucleus	-0.38	0.022
Right putamen	-0.37	0.025
White matter		
Right hippocampus	-0.55	0.000
Right middle temporal gyrus	-0.48	0.003
Right inferior temporal gyrus	-0.46	0.00
Left middle temporal pole	0.33	0.045
Left inferior frontal gyrus	-0.34	0.038
Right inferior frontal gyrus	-0.34	0.040
Right superior frontal gyrus	-0.33	0.047
Left supplementary motor area	-0.35	0.033
Left caudate	-0.33	0.045
Left putamen	-0.36	0.030
Left pallidum	-0.43	0.009
Right pallidum	-0.47	0.004
Right thalamus	-0.37	0.024
Left cerebellum (area 10)	-0.38	0.022
Vermis (area 3)	-0.35	0.036
CSF		
Right hippocampus	0.41	0.013
Right middle temporal gyrus	0.36	0.029
Right inferior temporal gyrus	0.52	0.001
Right inferior frontal gyrus	0.43	0.009
Left middle occipital gyrus	0.40	0.015
Left superior occipital gyrus	0.45	0.005
Left cerebral crus 2	0.39	0.019
Right cerebellum (area 3)	-0.33	0.048

Figures

Figure 1. Clusters of significant correlations found between the measure of PAL and the volume of grey, white and CSF. Cluster of correlations between the volume of grey matter of the left superior medial frontal gyrus (peak at $x, y, z = 0, 54, 45$; $t=4.76$) and precuneus (peak at $x, y, z = -12, -67, 61$; $t=4.77$) and the right precentral gyrus (peak at $x, y, z = 36, -22, 64$; $t=5.02$) (negative correlation) (green), the volume of white matter near the sagittal stratum (includes inferior fronto-occipital fasciculus and inferior longitudinal fasciculus) (peak at $x, y, z = 42, -24, -8$; $t=4.41$) (negative correlation) (red) and the CSF of the right inferior temporal (peak at $x, y, z = 52, -61, -14$; $t=4.82$) and middle frontal gyrus (peak at $x, y, z = 44, 54, 12$; $t=5.44$) and left superior parietal gyrus (peak at $x, y, z = -16, -70, 54$; $t=5.17$) (positive correlation) (blue). Results are overlaid on axial and sagittal sections of a normalized brain.

Supplementary Material

Figure S1. Illustration of analyses of different levels of resolution, including whole brain-, hemisphere-, lobe-, gyral- and voxel-level.