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Mapping the brain pathways of declarative verbal memory: Evidence from white matter lesions in the living human brain ☆

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ABSTRACT

Understanding the contribution of the brain white matter pathways to declarative verbal memory processes has been hindered by the lack of an adequate model in humans. An attractive and underexplored approach to study white matter region functionality in the living human brain is through the use of non-aprioristic models which specifically search disrupted white matter pathways. For this purpose, we employed voxel-based lesion–function mapping to correlate white matter lesions on the magnetic resonance images of 46 multiple sclerosis patients with their performance on declarative verbal memory *storage* and *retrieval*. White matter correlating with storage was in the temporal lobe–particularly lateral to the hippocampus and in the anterior temporal stem–, in the thalamic region and in the anterior limb of the internal capsule, all on the left hemisphere, and also in the right anterior temporal stem. The same volumes were relevant for retrieval, but to them were added temporo-parieto-frontal paramedian bundles, particularly the cingulum and the fronto-occipital fasciculus. These 3D maps indicate the white matter regions most critically involved in declarative verbal memory in humans.

Introduction

Amnesia in humans has been described after bilateral lesions of the medial temporal regions or diencephalic grey matter structures (Scoville and Milner, 2000; Squire, 2004). Moreover, white matter lesions can impair memory because they disconnect critical components of the brain memory network, as it has been mainly supported by research on monkeys (Gaffan, 2005; Parker et al., 2002). The grey matter component of this network emphasizes the modular nature of distinct regions supporting memory and other cognitive functions, whereas the white matter component emphasizes the role of distributed networks characterized by marked cortical plasticity (Gaffan, 2005; Squire, 2004). Both views have been supported by experimental data and hindered by methodological limitations. Amnesia research on experimental animals has to contend with the differences between human amnesia, typically tested with declarative verbal memory paradigms, and monkey amnesia, tested with paradigms exploring behaviors that only approximate human memory (Squire, 2004). However, experimental work on monkeys has the advantage of allowing for selective damage of the cortex or white matter, both of which are injured in patients with stroke, encephalitis or head trauma, the classical lesion models in humans (Gaffan, 2002; Squire, 2004).

The role of the cortex in memory processes in humans has been greatly clarified by the powerful tools of functional neuroimaging. By contrast, the role and function of the white matter pathways continue to be elusive. Even white matter tractography with diffusion tensor imaging is primarily a structural technique, tricky to combine with functional techniques and that requires a priori knowledge of brain anatomy (Catani, 2006; Mori et al., 2005). Yet, the study of the white matter pathways involved in human cognition has been proposed as one of the next frontiers in cognitive neuroscience (Catani, 2006; Mesulam, 2005).

☆ Author contributions: JS has the original idea. JS, JM, MAP and PV contributed to the study design. JS, JSG, JG, BD and NVM performed the MRI protocol and analysis. JS performed the neuropsychological testing. JS, JM, and PV wrote the manuscript.

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In this study, we introduce a novel approach, based on a lesional model, to study in humans the contribution of white matter pathways to cognitive processes. It is based on five principles: 1) in the model, the white matter needs to be primarily and preferentially affected; 2) in each subject, the white matter has to be particularly damaged in discrete areas; 3) these areas need to vary in location and extent among different subjects, such that specific lesion locations can be correlated to specific cognitive impairments, and can be controlled by the lack of impairment in subjects with no lesions at a specific location; 4) in the sample studied, the sum total of the lesions of all the subjects needs to cover most of the brain, so that there are no unaffected volumes about which no information exists; and 5) the location and extent of the lesions should be measured with a method that does not presuppose any prior knowledge about relevant or target location to account for a given cognitive impairment. Thus, unbiased lesion–function correlations can be obtained between a type of measured cognitive impairment and the corresponding white matter lesions associated with it. Taking into account these principles, we measured declarative memory and correlated its impairment with the location of white matter lesions caused by a paradigmatic white matter disease, multiple sclerosis.

Multiple sclerosis affects predominantly the white matter, although the grey matter is also involved in the disease (Filippi, 2001; Hauser and Oksenberg, 2006; Rovaris et al., 2006; Sepulcre et al., 2006a). White matter lesions can disrupt brain connectivity anywhere in the CNS, leading to sensory-motor and cognitive impairment. Cognitive disturbances, mainly in declarative memory, attention and executive functions, are present in 45–65% of patients (Rao, 1995; Sepulcre et al., 2006b). Although with some regional predilection, the discrete white matter lesions of multiple sclerosis differ in location and extent among patients and offer the opportunity to explore the entire brain white matter. We used a white matter lesion–function correlation method, based on white matter lesion probability maps (see Fig. 1), for identifying brain regions involved in declarative verbal memory. The resulting 3D maps of this study provide the white matter regions most critically involved in this memory domain in humans.

Materials and methods

Patients

We studied forty six patients with multiple sclerosis (revised McDonald criteria) (Polman et al., 2005). Subject demographics are listed in Table 1. The local Research Ethics Committee approved the study and all subjects gave their informed consent according to the Declaration of Helsinki. Because our study was designed to identify the correlation between white matter lesion locations and verbal memory performance, with independence of the subtype of the disease, we included all evolution subtypes of multiple sclerosis. Only individuals with no history of psychiatric or neurological disease other than multiple sclerosis, as well as no history of visual or auditory deficits, alcohol or drug abuse, or any other major medical illness were included. Moreover, no patients with an active relapse, taking steroids or that had suffered a clinical relapse within the previous three months were included. Patients with psychiatric disturbances identified with the Cummings' Neuropsychiatric Inventory (Cummings, 1997), the Hamilton's Depression Rating Scale (Hamilton, 1960) (>8 points), the Hamilton's Anxiety Rating Scale (Hamilton, 1959) (>6 points) or taking psychoactive drugs were not studied. Finally, only right-handed (>70% Oldfield scale) (Oldfield, 1971) native Spanish-speakers took part in the study.

Table 1
Demographic, clinical, MRI and neuropsychological data of patients

N	46
Age (years)[a]	36.3±9.7
Sex ratio (male/female)	15/31
Education (years)[b]	14.5 (7 to 28)
Multiple sclerosis subtype	38RR/4SP/4PP
Disease duration (years)[b]	3.7 (0.75 to 36)
EDSS score[b]	2.5 (0 to 7.0)
MSCF score[b]	0.25 (−1.81 to 1.08)
Number of T2 lesions[b]	26 (5 to 178)
Vol. T2 lesion load (cm^3)[b]	34.64 (1.19 to 175.87)
Number of T1 lesions[b]	41 (5 to 204)
Vol. T1 lesion load (cm^3)[b]	8.11 (0.15 to 96.36)
Vol. GM (cm^3)[a]	522.76±54.19
Vol. WM (excluding lesion volume) (cm^3)[a]	501.4±49
SRT-S[a]	48.91±13.26
SRT-R[a]	39.28±13.74

RR: relapsing remitting; SP: secondary progressive; PP: primary progressive; EDSS: expanded disability status scale; MSFC: multiple sclerosis functional composite; GM: grey matter; WM: white matter; SRT-S: selective reminding test long-term storage; SRT-R: selective reminding test long-term retrieval. The data are expressed in mean± standard deviation[a] or median (range)[b] depending on the parametric or non-parametric distribution of the variable.

Neuropsychological testing

A trained neuropsychologist (JS), blinded to clinical and magnetic resonance image (MRI) data, performed the neuropsychological assessments. We used a classical declarative memory task, the 12-item Selective Reminding Test (SRT) (Buschke and Fuld, 1974), included in the Spanish translation of the validated Brief Repeatable Battery-Neuropsychology (Rao et al., 1991; Sepulcre et al., 2006b), to test declarative verbal memory. Two main memory scores were used: long-term SRT-*Storage* and long-term SRT-*Retrieval* (Buschke and Fuld, 1974), both of them performed over six trials. In order to confirm the brain anatomical specificity of our findings we also analyzed a non-verbal memory domain by using the spatial-visual test 10-36 Spatial Recall Test (Rao et al., 1991; Sepulcre et al., 2006b), and a non-cognitive domain by using the motor coordination score of the EDSS cerebellar score (Kurtzke, 1983). All subjects were naïve to the neuropsychological tests and, as the tests were administered only once, a training effect was avoided.

MRI acquisition

Subjects had a 3D T1-weighted MRI scan (1.5 T; TR 2140 ms; TE 5.04 ms, flip angle 15°; matrix size 256×256; 2-mm slice thickness; 88 contiguous axial slices; FOV 25 cm; in-plane resolution of 1×1 mm) of the whole head. We used T1-weighted images, rather than T2-weighted images, because they more accurately identify the existence of axonal damage (Comi et al., 2000), which has a stronger impact on the disruption of white matter pathways and brain function. The MRI assessment was performed within the month of the neuropsychological testing and blind to clinical and neuropsychological data. No subject suffered clinical reactivation of the disease between the period of the neuropsychological study and the MRI assessment.

Lesion probability maps

To obtain the 3D lesion probability maps (LPMs) (Charil et al., 2003; Lee et al., 1999) we outlined at voxel level all the white matter lesions on the 3D T1-weighted MRI scan of each patient using MRIcro software (Chris Rorden, University of Nottingham, Great Britain, UK). As it has been previously published, this method has an excellent inter-rater reliability (intraclass correlation coefficient=0.892; $p<0.001$; Esteban et al., 2007).

From this first step we obtained a 3D binary lesion mask for each patient (see Fig. 1-a). We then normalized T1 scans from a native to a stereotactic space using SPM2 software (Wellcome Department of Cognitive Neurology, University College of London, London, UK) and an optimized voxel-based morphometry protocol (Sepulcre et al., 2006a) running under Matlab v. 6.5 (Mathworks Inc., Natick, MA). Lesion masks of each patient were normalized applying the previously obtained parameters in the normalization of the T1 scans. To ensure that the location of white matter lesions in stereotactic space was correct, we matched the normalized lesion masks and the corresponding normalized T1 brains of each patient, and we carefully inspected all outputs. Finally, lesion masks were smoothed and converted to LPMs by applying an isotropic Gaussian kernel (12 mm full-width at half maximum) (Charil et al., 2003) (see Fig. 1-a).

As has been mentioned before, T1 studies were preferred because in multiple sclerosis they provide more accurate information about pathway disruption (Comi et al., 2000), and at the same time, multiple sclerosis lesions have a wider extension of tissue damage around the T1 lesions (Comi et al., 2000). So, to approximate the multiple sclerosis lesions to the real multiple sclerosis neuropathology, with deeper tissue damage in the centre of the lesions than in the periphery and greater extension than T1 lesion extension (Comi et al., 2000), and to statistically normalize the LPMs we used a high Gaussian filter (mentioned in the previous paragraph). Therefore, we obtained statistically and spatially normalized 3D LPMs where each voxel has a probability value of being classified as disrupted white matter pathway (ranging from 0 to 1), with a higher value at the centre of the lesion than in the periphery. By means of this voxel-by-voxel approach, we used all available information, avoiding reliance on cutoff scores or specified regions of interest (Bates et al., 2003). Finally, by comparing a normal segmented white matter template (Voitool; SPM extension toolbox; Sergei Pakomov http://www.ihb.spb.ru/~pet_lab/VTO/VTOMain.html) with the combined overlapping of LPMs of our sample, we determined that the combination of all voxels studied in the analysis covered 99.8% of the brain white matter.

Statistical analysis

To perform the statistical analyses, we employed the framework of the general linear model implemented in the SPM2 software. In particular, we used voxel-by-voxel multiple linear regressions models (Charil et al., 2003) to correlate the 3D LPMs and the memory scores. The normal distribution of memory scores was assessed using the Kolmogorov–Smirnov test (SPSS 13.0; SPSS Inc. Chicago, Illinois) ($p=0.68$ for SRT-Storage and $p=0.84$ for SRT-Retrieval). To ensure an unbiased

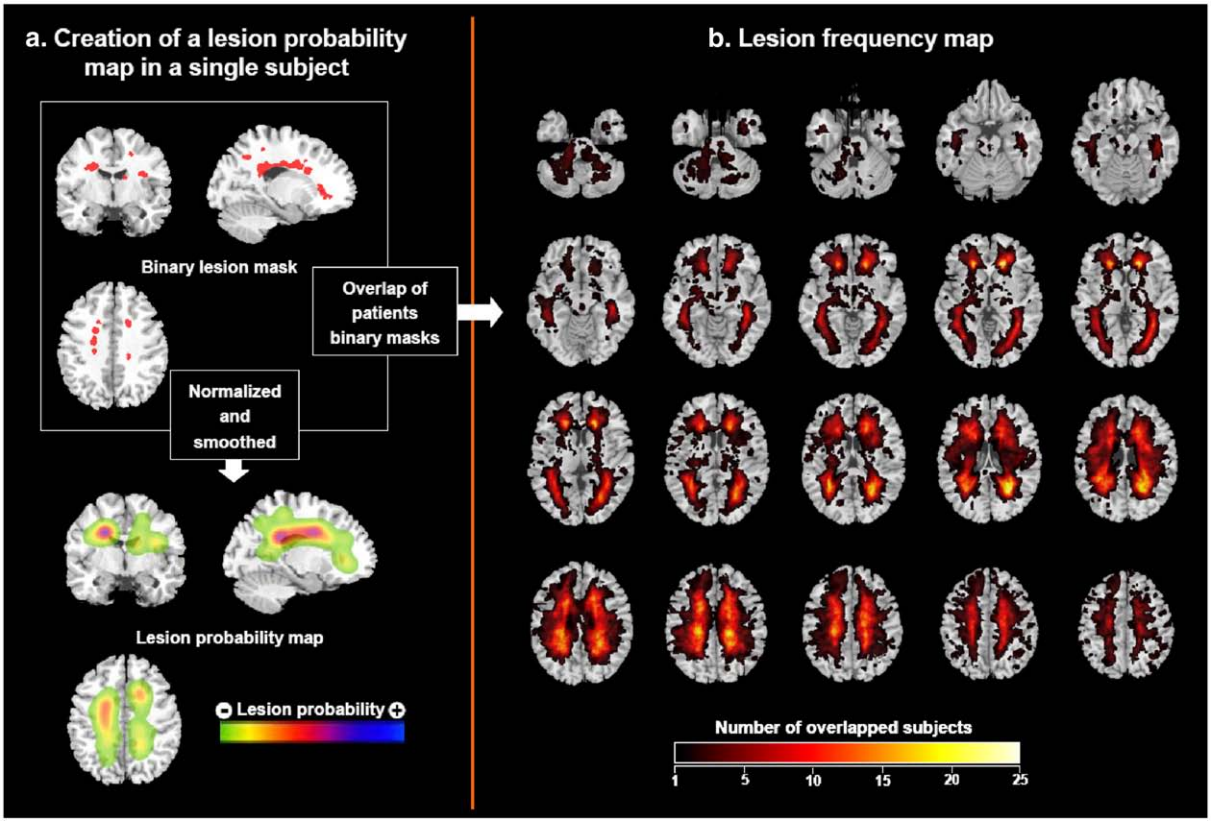

Fig. 1. (a) Creation of a lesion probability map in a single subject. Upper image: example of a binary lesion mask. Lower image: example of a final individual lesion probability map after applying an isotropic Gaussian kernel. (b) White matter lesion frequency map resulting from the overlap of the binary masks of the entire sample of subjects. This mask, with the highest lesion frequency in the periventricular region, was used in the statistical estimation process to correct for the bias posed by the lesion frequency factor in the study sample.

voxel-by-voxel statistical estimation, extracting the lesion frequency factor, which, in multiple sclerosis, would be important as lesions are more frequent in the periventricular region (see Fig. 1-b), we created a white matter lesion frequency mask using the average of the individual 3D binary masks (see Figs. 1-a and -b). This mask was used in the statistical estimation process to avoid the possible bias posed by lesion frequency in the study sample. Briefly, each voxel value of this lesion frequency mask was introduced in the multiple linear regression models as nuisance covariate to adjust the possible bias introduce by this factor at the final voxel-level result. In addition, an explicit binary white matter template (Voitool; Sergei Pakomov) was also used in this process to ensure that only white matter voxels were included in the analysis. The correlations between memory scores and white matter lesions were adjusted for gender, age and years of education. The level of significance for the SPM results was set at $p<0.05$ after correction for multiple comparisons to minimize type I error (False Discovery Rate method) (Genovese et al., 2002). To achieve consistent results only clusters with 100 or more voxels were retained (Grossman et al., 2004). The mean signal intensity values of each significant cluster were extracted with the VOI toolbox of SPM2 in order to show the global r and p values of every correlation (Supplementary table; Supplementary figure). Finally, the locations of the relevant clusters were compared with three white matter atlases (Dejerine, 1895; Mori et al., 2005; Schmahmann and Pandya, 2006), as well as with a source for the functional correlations of brain lesions (Brazis et al., 2006).

Results

Compared with normative data of healthy control population (Sepulcre et al., 2006b), almost half of the patients in our sample (46%) had memory impairment. Four white matter lesion clusters correlated with the score of verbal memory storage (Fig. 2-I; Supplementary table). Anatomically, they were located mainly in the left hemisphere, including (La) the white matter lateral to the hippocampus and amygdala, involving the cingulum and part of the inferior longitudinal fasciculus and extending to the anterior temporal stem (including a portion of the uncinate fasciculus, which connects the frontal and temporal lobes), as well as (Lb) perithalamic and thalamic white matter and (Lc) the anterior limb of the internal capsule. A cluster (R) in the anterior temporal region of the right hemisphere mirrored the similar cluster on the left

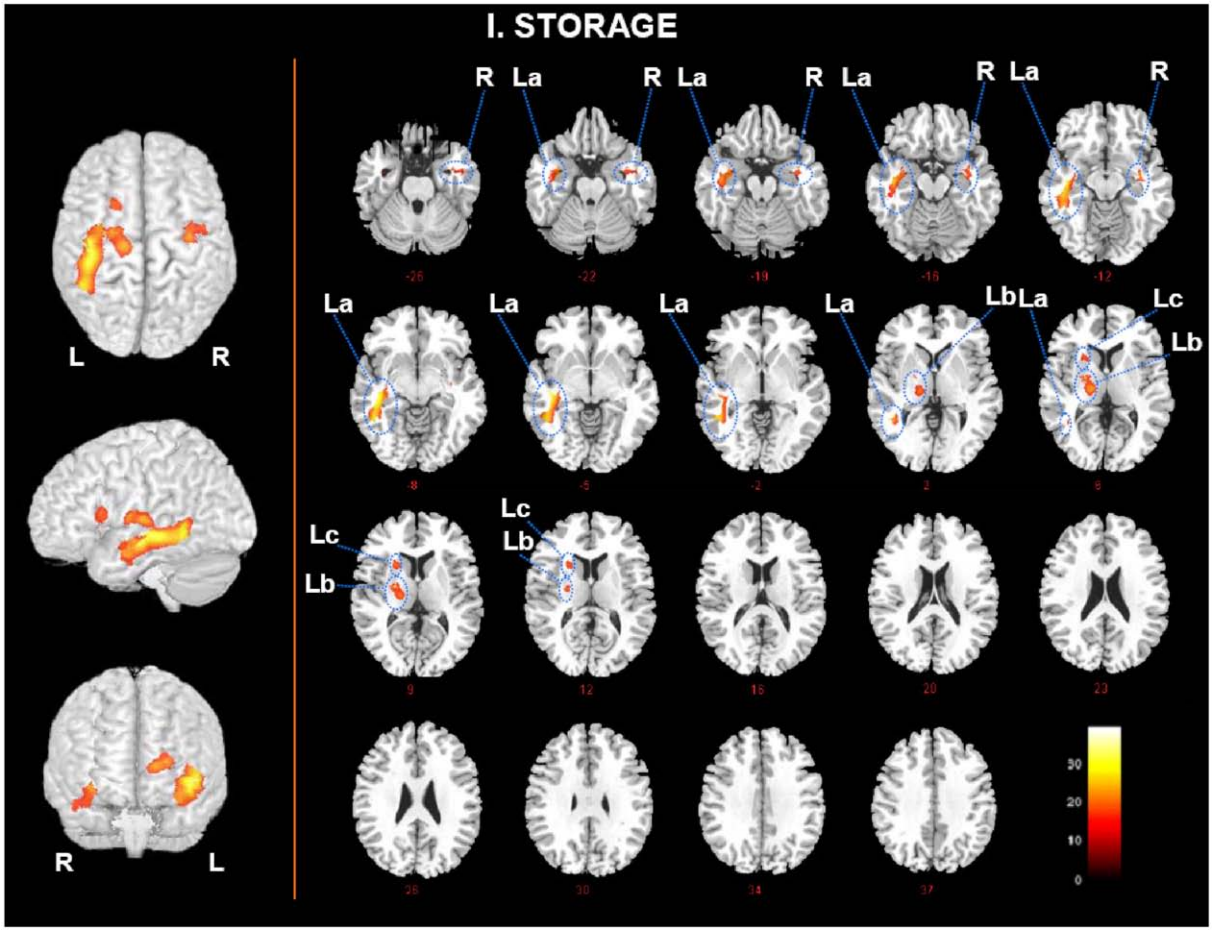

Fig. 2. Axial and 3D projections showing white matter clusters correlated with verbal declarative memory storage (I) and retrieval (II) (color bars indicate *F* statistic). I. Storage: Four white matter lesion clusters correlated with the score of verbal memory storage, three in the left hemisphere – (La) white matter in the temporal lobe, lateral to the hippocampus and amygdala and extending to the anterior temporal stem; (Lb) perithalamic and thalamic white matter; (Lc) the anterior limb of the internal capsule – and one (R) in the anterior temporal region of the right hemisphere. II. Retrieval: Five WM lesion clusters correlated with the score of verbal memory retrieval, three in the left hemisphere – (La) white matter in the temporal lobe, lateral to the hippocampus and amygdala and extending to the anterior temporal stem; (Lb) thalamic region; (Lc) a dorsal paramedian fiber system that run through the parietal into the frontal lobe and anterior limb of the internal capsule; – and two in the *right hemisphere* – (Ra) the paramedian parieto-frontal white matter and (Rb) the anterior limb of the internal capsule.

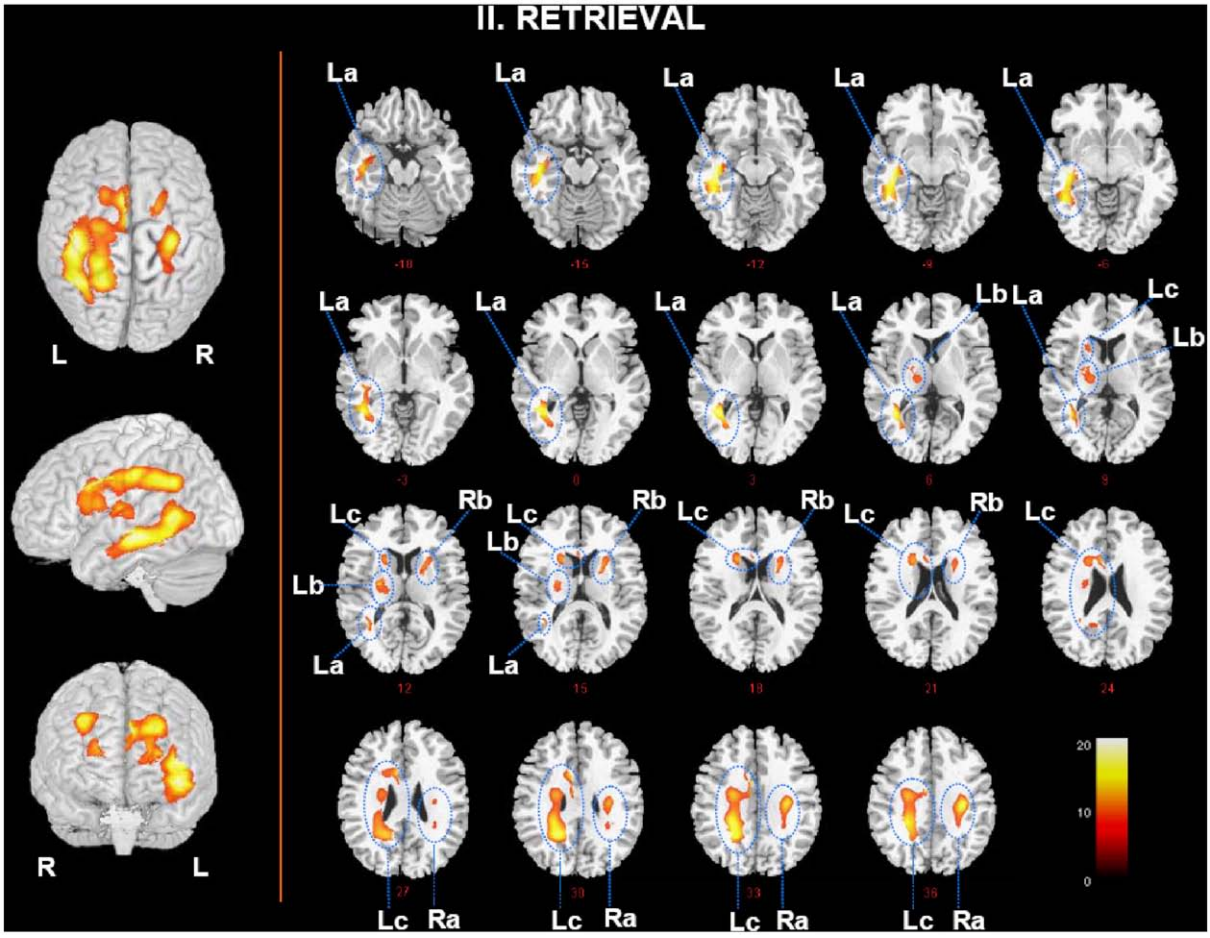

Fig. 2 (*continued*).

side, but it was only a fraction (18%) as large. These data highlight the importance of temporo-thalamo-frontal pathways in declarative memory storage (Fig. 3).

Five white matter lesion clusters correlated with the score of verbal memory retrieval (Fig. 2-II; Supplementary table). In the left hemisphere, some of them occupied the same regions as for storage, namely in the (La) temporal lobe, (Lb) thalamic region and (Lc) anterior limb of the internal capsule. But, in addition, the temporal cluster (La) extended posteriorly, lateral to the hippocampus, sweeping from the temporal into the parietal lobe around the forceps of the corpus callosum and, with some discontinuity, joining a dorsal paramedian fiber system that run through the parietal into the frontal lobe (Lc). The paramedian fiber system in the parieto-frontal region included mainly the cingulum, the parieto-frontal section of the superior fronto-occipital fasciculus, and the mid-anterior corpus callosum. The clusters in the right hemisphere were much smaller, involving only (Ra) the paramedian parieto-frontal white matter and (Rb) the anterior limb of the internal capsule. These data suggest that the circuitry for declarative memory retrieval overlaps that for storage, but in addition relies on temporo-parieto-frontal paramedian bundles (Fig. 3).

Finally, in order to confirm the specificity of these findings in declarative verbal memory we analyzed non-verbal memory and non-cognitive domains by using a spatial-visual test (10-36 Spatial Recall Test) and a motor coordination score (EDSS cerebellar function score). In both domains, we obtained significant brain locations related to each function and different of the white matter regions associated with declarative memory (Figs. 4a and b), reinforcing the specificity of our findings. In addition due to the inclusion of different types of multiple sclerosis in the study sample, we also did a new sub-analysis only including relapsing-remitting forms. Corre-

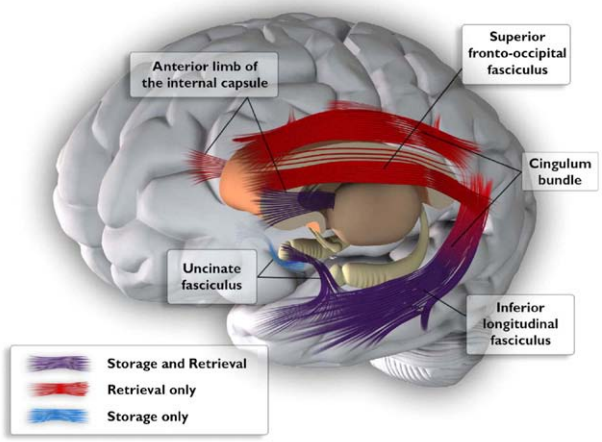

Fig. 3. Diagram of human brain pathways supporting declarative verbal memory. Temporo-thalamo-frontal pathways support both memory storage and retrieval (in mauve color). In addition, memory retrieval is also supported by temporo-parieto-frontal paramedian bundles, mainly including the cingulum and the fronto-occipital fasciculus (in red). The right uncinate fasciculus, involved in storage, is represented in blue.

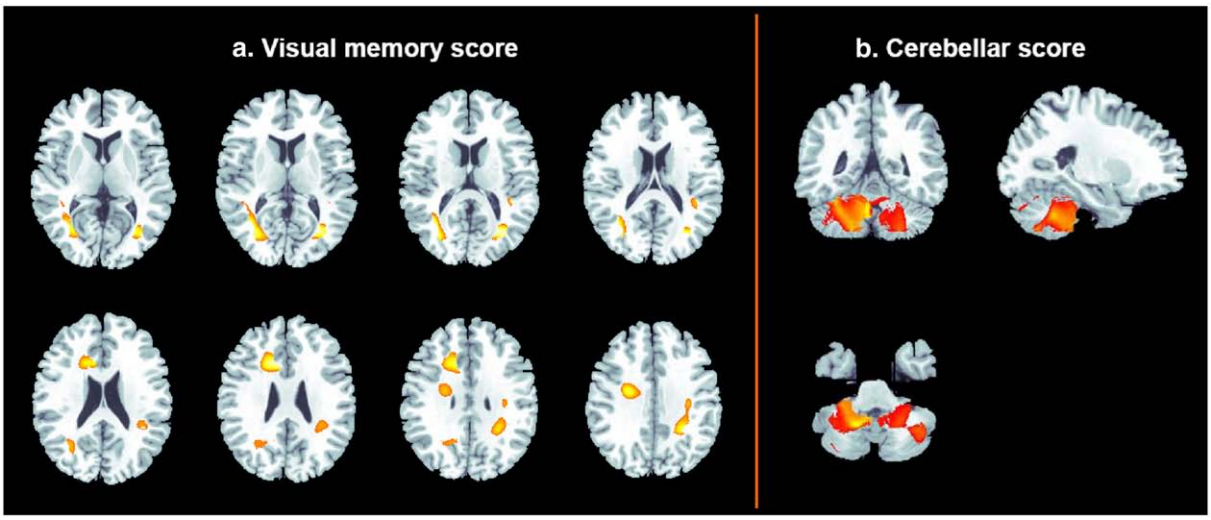

Fig. 4. (a) Axial projections showing white matter clusters correlated with spatial-visual memory (non-verbal memory domain). (b) Coronal, sagittal and axial projection showing white matter clusters correlated with cerebellar motor coordination (non-cognitive domain).

lations of the verbal memory results remained present even after removing non-relapsing-remitting patients.

Discussion

The importance for mnestic functions of some of the white matter regions shown in our study has been emphasized by experimental studies in monkeys. Severe and global memory impairment results from sectioning the white matter of the medial temporal lobe, and from combined lesions of the amygdala, the anterior temporal stem, and the fornix (Gaffan, 2005; Parker et al., 2002). Our results also show that fronto-temporal pathways, mainly via the anterior temporal stem (uncinate fasciculus), participate not only in memory storage but also in memory retrieval in humans, supporting the interplay of both structures in declarative verbal memory and the existence of top-down frontal modulation in the temporal lobe (Buckner et al., 1999; Dolan and Fletcher, 1997; Kroll et al., 1997; Takahashi et al., 2007). The novel finding in our study that the anterior limb of the internal capsule is involved in verbal memory storage and retrieval underlines the relevance of the thalamo-frontal connections for human memory. The anterior limb of the internal capsule contains the anterior thalamic peduncle, which connects the dorsomedial and anterior thalamic nuclei with the prefrontal cortex and the cingulate gyrus (Parent, 1996). The prefrontal cortex is involved in memory function (Buckner et al., 1999; Fletcher et al., 1997; Fuster, 2000) and the anterior cingulate region in task switching, error monitoring, and working memory, functions particularly related to memory retrieval (Baddeley, 2003; Muller and Knight, 2006; Rushworth et al., 2003). Thus, it is logical that damage of the anterior limb of the internal capsule could interfere with verbal memory, by disconnecting the thalamus from these cortical structures. However, frontal white matter was not highlighted in our study, suggesting that once the fibers have passed through the bottlenecks of the uncinate fasciculus (for the temporo-frontal fibers) and the anterior limb of the internal capsule (for the thalamo-frontal fibers), they fan out in the frontal lobe, requiring extensive lesions to interfere with verbal memory (Parker et al., 2002; Tanji et al., 2003). Moreover, such lesions cause other cognitive impairments that interfere with memory testing (Parker et al., 2002). Finally, our findings agree with data showing that temporal structures are essential for both memory storage and retrieval but with different regional distribution (Lepage et al., 1998), and that memory retrieval implies wider cortical participation than storage (Fletcher et al., 1997; Squire, 2004).

From a systems point of view, this study clarifies that declarative verbal memory mainly relies on two large-scale brain circuits, mostly in the left hemisphere, as would be expected for a verbal task. Temporo-thalamo-frontal pathways subserve both storage and retrieval (Fig. 3; blue and mauve color), suggesting that they are involved in the registration and local search of mnestic material (encoding and decoding processes). Temporo-parieto-frontal pathways are specific for the retrieval process (Fig. 3; red color), indicating a higher cognitive control and wider cortical processing for this memory component. Complementary interpretations are that retrieval process could also involve other cognitive systems such as attentional recruitment, working memory demands and overall task difficulty, and/or share common white matter pathways with other cognitive domains, such as fronto-parietal pathways. Finally, the storage and retrieval circuits of the right hemisphere, parallel to the ones on the left but normally less functionally important, seem to support the left hemisphere in declarative verbal memory and may explain why permanent amnesia results only from bilateral lesions (Scoville and Milner, 2000; Squire et al., 2004).

Our study has some limitations. First, in multiple sclerosis not only the white matter is targeted but there are also cortical plaques with inflammation and neuronal loss (Filippi, 2001; Hauser and Oksenberg, 2006; Rovaris et al., 2006; Sepulcre et al., 2006a). However, white matter lesions are much more extensive, particularly at the early phase of the disease, chosen for our study to minimize the effect of cortical involvement. Second, although T1 images provide the best correlation with axonal damage, they may not be as accurate as T2-weighted images on other pathological events, such as active inflammation, that also contribute to nerve conduction impairment. The use of a high Gaussian filter allowed us to approach the neuropathology of multiple sclerosis lesions (Comi et al., 2000) but at the price of losing some specificity. Third, we used a

memory test that is quick and easy to administer in the clinical setting, avoiding problems such as inattention, but it may not have enough power to separate entirely the storage and retrieval components of the verbal memory process, unlike other more accurate tasks used in functional neuroimaging. However, our model is remarkable in that, without any a priori information about memory localization, it has provided an anatomic rendition in the human of pathways known to be critical for memory processing in non-human primates.

For many decades, brain lesion-symptom studies have provided valuable insights into the relationship between brain areas and cognitive functions. In this study, we used a novel and unbiased lesion–function correlation approach to map the white matter regions implicated in the declarative verbal memory brain network. The application of this approach, which could also complement other neuroimage techniques, may show more clearly the wide outlines of the white matter systems subserving other cognitive functions in the human brain.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2008.05.038.

References

Baddeley, A., 2003. Working memory: looking back and looking forward. Nat. Rev. Neurosci. 4, 829–839.
Bates, E., Wilson, S.M., Saygin, A.P., Dick, F., Sereno, M.I., Knight, R.T., et al., 2003. Voxel-based lesion-symptom mapping. Nat. Neurosci. 6, 448–450.
Brazis, P., Masdeu, J., Biller, J., 2006. Localization in Clinical Neurology. Vol 1. Lippincott Williams and Wilkins, Philadelphia.
Buckner, R.L., Kelley, W.M., Petersen, S.E., 1999. Frontal cortex contributes to human memory formation. Nat. Neurosci. 2, 311–314.
Buschke, H., Fuld, P.A., 1974. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology 24, 1019–1025.
Catani, M., 2006. Diffusion tensor magnetic resonance imaging tractography in cognitive disorders. Curr. Opin. Neurol. 19, 599–606.
Charil, A., Zijdenbos, A.P., Taylor, J., Boelman, C., Worsley, K.J., Evans, A.C., et al., 2003. Statistical mapping analysis of lesion location and neurological disability in multiple sclerosis: application to 452 patient data sets. Neuroimage 19, 532–544.
Comi, G., Rovaris, M., Leocani, L., Martinelli, V., Filippi, M., 2000. Assessment of the damage of the cerebral hemispheres in MS using neuroimaging techniques. J. Neurol. Sci. 172, S63–S66.
Cummings, J.L., 1997. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology 48, S10–S16.
Dejerine, J., 1895. Anatomie des Centres Nerveux. Vol 1. Rueff et Cie, Paris.
Dolan, R.J., Fletcher, P.C., 1997. Dissociating prefrontal and hippocampal function in episodic memory encoding. Nature 388, 582–585.
Esteban, F.J., Sepulcre, J., de Mendizabal, N.V., Goni, J., Navas, J., de Miras, J.R., et al., 2007. Fractal dimension and white matter changes in multiple sclerosis. Neuroimage 36, 543–549.
Filippi, M., 2001. Multiple sclerosis: a white matter disease with associated gray matter damage. J. Neurol. Sci. 185, 3–4.
Fletcher, P.C., Frith, C.D., Rugg, M.D., 1997. The functional neuroanatomy of episodic memory. Trends Neurosci. 20, 213–218.
Fuster, J.M., 2000. Memory networks in the prefrontal cortex. Prog. Brain Res. 122, 309–316.
Gaffan, D., 2002. Against memory systems. Philos. Trans. R Soc. Lond. B Biol. Sci. 357, 1111–1121.
Gaffan, D., 2005. Neuroscience. Widespread cortical networks underlie memory and attention. Science 309, 2172–2173.
Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15, 870–878.
Grossman, M., McMillan, C., Moore, P., Ding, L., Glosser, G., Work, M., et al., 2004. What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. Brain 127, 628–649.
Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32, 50–55.
Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62.
Hauser, S.L., Oksenberg, J.R., 2006. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron. 52, 61–76.
Kroll, N.E., Markowitsch, H.J., Knight, R.T., von Cramon, D.Y., 1997. Retrieval of old memories: the temporofrontal hypothesis. Brain 120, 1377–1399.
Kurtzke, J.F., 1983. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 33, 1444–1452.
Lee, M.A., Smith, S., Palace, J., Narayanan, S., Silver, N., Minicucci, L., et al., 1999. Spatial mapping of T2 and gadolinium-enhancing T1 lesion volumes in multiple sclerosis: evidence for distinct mechanisms of lesion genesis? Brain 122, 1261–1270.
Lepage, M., Habib, R., Tulving, E., 1998. Hippocampal PET activations of memory encoding and retrieval: the HIPER model. Hippocampus. 8, 313–322.
Mesulam, M.M., 2005. Imaging connectivity in the human cerebral cortex: the next frontier? Ann. Neurol. 57, 5–7.
Mori, S., Wakana, S., van Zijl, P.C., Nagae-Poetscher, L.M., 2005. MRI Atlas of Human White Matter. Elsevier, Amsterdam.
Muller, N.G., Knight, R.T., 2006. The functional neuroanatomy of working memory: contributions of human brain lesion studies. Neuroscience 139, 51–58.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Parent, A., 1996. Carpenter's Human Neuroanatomy, 9th ed. Baltimore, Williams and Wilkins.
Parker, A., Wilding, E.L., Bussey, T.J., 2002. Cognitive Neuroscience of Memory: Encoding and Retrieval. Psychology Press Ltd, Hove, East Sussex, England.
Polman, C.H., Reingold, S.C., Edan, G., Filippi, M., Hartung, H.P., Kappos, L., et al., 2005. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”. Ann. Neurol. 58, 840–846.
Rao, S.M., 1995. Neuropsychology of multiple sclerosis. Curr. Opin. Neurol. 8, 216–220.
Rao, S.M., Leo, G.J., Bernardin, L., Unverzagt, F., 1991. Cognitive dysfunction in multiple sclerosis. I. Frequency, patterns, and prediction. Neurology 41, 685–691.
Rovaris, M., Judica, E., Gallo, A., Benedetti, B., Sormani, M.P., Caputo, D., et al., 2006. Grey matter damage predicts the evolution of primary progressive multiple sclerosis at 5 years. Brain 129, 2628–2634.
Rushworth, M.F., Hadland, K.A., Gaffan, D., Passingham, R.E., 2003. The effect of cingulate cortex lesions on task switching and working memory. J. Cogn. Neurosci. 15, 338–353.
Schmahmann, J.D., Pandya, D.N., 2006. Fiber pathways of the brain. Oxford University Press, Oxford.
Scoville, W.B., Milner, B., 2000. Loss of recent memory after bilateral hippocampal lesions. 1957. J. Neuropsychiatry Clin. Neurosci. 12, 103–113.
Sepulcre, J., Sastre-Garriga, J., Cercignani, M., Ingle, G.T., Miller, D.H., Thompson, A.J., 2006a. Regional gray matter atrophy in early primary progressive multiple sclerosis: a voxel-based morphometry study. Arch. Neurol. 63, 1175–1180.
Sepulcre, J., Vanotti, S., Hernandez, R., Sandoval, G., Caceres, F., Garcea, O., et al., 2006b. Cognitive impairment in patients with multiple sclerosis using the Brief Repeatable Battery-Neuropsychology test. Mult. Scler. 12, 187–195.
Squire, L.R., 2004. Memory systems of the brain: a brief history and current perspective. Neurobiol. Learn Mem. 82, 171–177.
Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annu. Rev. Neurosci. 27, 279–306.
Takahashi, E., Ohki, K., Kim, D.S., 2007. Diffusion tensor studies dissociated two fronto-temporal pathways in the human memory system. Neuroimage 34, 827–838.
Tanji, K., Suzuki, K., Fujii, T., Higano, S., Yamadori, A., 2003. A case of frontal network amnesia. J. Neurol. Neurosurg. Psychiatry 74, 106–109.