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Fornix damage limits verbal memory functional compensation in multiple sclerosis

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ABSTRACT

Selective atrophy of the hippocampus, in particular the left CA1 subregion, is detectable in relapsing-remitting MS (RRMS) and is correlated with verbal memory performance. We used novel high-resolution imaging techniques to assess the role that functional compensation and/or white matter integrity of mesial temporal lobe (MTL) structures may play in mediating verbal memory performance in RRMS. High-resolution cortical unfolding of structural MRI in conjunction with functional magnetic resonance imaging (fMRI) was used to localize MTL activity in 18 early RRMS patients and 16 healthy controls during an unrelated word-pairs memory task. Diffusion tensor imaging (DTI) and Tract-Based Spatial Statistics (TBSS) were used to assess the integrity of the fornix and the parahippocampal white matter (PHWM), the major efferents and afferents of the hippocampus. RRMS patients showed greater activity in hippocampal and extra-hippocampal areas during unrelated word-pair learning and recall. Increased hippocampal activity, particularly in the right anterior hippocampus and left anterior CA1 was associated with higher verbal memory scores. Furthermore, increased fractional anisotropy (FA) in the fornix was correlated with both greater fMRI activity in this region and better memory performance. Altered hippocampal fMRI activity in RRMS patients during verbal learning may result from both structural damage and compensatory mechanisms. Successful functional compensation for hippocampal involvement in RRMS may be limited in part by white matter damage to the fornix, consistent with the critical role of this pathway in the clinical expression of memory impairment in MS.

Introduction

Multiple sclerosis (MS) is an autoimmune disorder causing demyelination of the central nervous system. Early symptoms often include sensory disturbances, limb weakness, and fatigue. A hallmark of MS-related imaging findings is focal, inflammatory, white matter plaques in the brain and spinal cord (Noseworthy et al., 2000). Although most clinical measures of disease severity reflect sensorimotor function, 40 to 65% of MS patients also demonstrate cognitive dysfunction (Amato et al., 2006).

Cognitive deficits in MS vary, but affected domains can include memory, attention, processing speed, visuospatial and executive functions, but usually not intellectual or language functions (Bobholz and Rao, 2003). Among the earliest reported are memory deficits in both retrieval (Rao, 1986) and encoding (DeLuca et al., 1994) abilities. Although memory impairment in MS is progressive (Thornton and Raz, 1997), it develops independently of traditional disease markers such as relapse-rate or total lesion load (Duque et al., 2008). Recent studies have shown that cognitive impairment in MS is best predicted by degenerative changes beyond white matter damage such as global atrophy (Chard et al., 2002), cortical lesions (Geurts et al., 2005), cortical thinning (Sailer et al., 2003), and subcortical atrophy (Cifelli et al., 2002).

The hippocampus is a subcortical structure essential for memory function (Milner, 1958) and is impacted in MS as evidenced by decreased glucose metabolism (Paulesu et al., 1996), increased inositol levels suggesting gliosis (Geurts et al., 2006), and demyelination detected in vivo and verified on pathological sections (Geurts et al., 2005; Roosendaal et al., 2008). We recently demonstrated early selective hippocampal volume loss in the Cornu Ammonis 1 (CA1) subregion as well as overall hippocampal volume loss, both of which correlated with decreased performance on a verbal learning task,

Abbreviations: RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary-progressive multiple sclerosis; MTL, mesial temporal lobe; fMRI, functional magnetic resonance imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; TBSS, tract-based spatial statistics; CA1, cornu ammonis 1; CA23DG, cornu ammonis 2–3 and dentate gyrus; AntCADG, Anterior CA1–3 and dentate gyrus; Sub, subiculum; PHC, parahippocampal cortex; PRC, perirhinal cortex; ERC, entorhinal cortex; Fus, fusiform gyrus; PHWM, parahippocampal white matter; TR, repetition time; TE, echo time; NEX, number of excitations; FOV, field of view; TI, inversion time; EPI, echo planar imaging; BOLD, blood oxygen level dependent.

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but not information processing speed, in relapsing-remitting MS (RRMS) and secondary-progressive MS (SPMS) patients (Sicotte et al., 2008). Post-mortem histological analysis suggests that hippocampal atrophy may result from decreased neuronal numbers in the cornu ammonis subfields, as well as decreased neuron size in the CA1 region, although these studies were limited to SPMS patients (Papadopoulos et al., 2008).

White matter damage to hippocampal efferents and afferents may also contribute to memory impairment in MS. A voxel-based lesion-function study found that declarative verbal memory deficits in MS were associated with visible lesions in several frontal-temporal-limbic pathways (Sepulcre et al., 2008) and altered white matter diffusion metrics have been detected in the inferior longitudinal fasciculi and the fornix (Roosendaal et al., 2009). White matter lesions have also been detected in the fornix post-mortem in MS (Huitinga et al., 2001). The fornix is the major output of the hippocampus, but it also allows reciprocal connections with the septal nuclei, the anterior thalamic nucleus and the hypothalamus, which modulate hippocampal activity (Duvernoy, 2005). Fornix damage can cause severe memory deficits (Gaffan and Gaffan, 1991), though its role in MS-related memory impairment has not been studied in detail. The parahippocampal white matter (PHWM) consists of several hippocampal afferents such as the perforant pathway and the cingulum bundle in addition to reciprocal projections relaying multimodal sensory information primarily through the entorhinal cortex.

The presence of MS-related structural changes in the mesial temporal lobe (MTL) is evident, but the link between structure and function has not been fully elucidated. Functional magnetic resonance imaging (fMRI) can be used to localize changes in regional blood flow during cognitive tasks as a surrogate for neural activity. Traditional fMRI techniques are challenging to apply to the hippocampus given the convoluted neuroanatomical structure and susceptibility to signal distortion that occurs particularly in the anterior MTL. To overcome these limitations, we used high-resolution structural and functional imaging in conjunction with a novel cortical unfolding technique (Zeineh et al., 2000) to accurately detect subregional functional activity in the hippocampus and MTL in RRMS patients and controls. Furthermore, we evaluated the fornix and the PHWM using diffusion tensor imaging (DTI) to assess the relation between white matter damage to hippocampal efferents and afferents, MTL fMRI activity, and verbal memory performance in MS.

Subjects, materials and methods

Subjects

Subjects included 18 patients with clinically definite (Poser et al., 1983) RRMS and 17 healthy controls. The UCLA Human Subjects Protection Committee approved the protocol and informed consent was obtained. RRMS patients had disease duration less than 5 years from diagnosis and had not relapsed nor received steroids within the previous 3 months. No subject had a history of drug or alcohol abuse in the last 3 years. Controls did not suffer from any neurological conditions, were not taking any medications, and had normal neurological exams and normal ($\geq$28) scores on the mini-mental status exam. All subjects were right handed, had no significant visual deficits, and were able to perform the verbal memory task. A single control subject was identified as an outlier due to very poor performance on the verbal memory task and was excluded from the analyses reported here, leaving a total of 16 controls and 18 patients. These subjects represent a subgroup of those reported previously (Sicotte et al., 2008).

Verbal memory task

To assess hippocampal function, subjects were tested with an unrelated word-pairs task known to engage the hippocampus and be sensitive to hippocampal damage (Rausch and Babb, 1993). Seven different pairs of unrelated words (e.g. shelf:noisy) were presented one pair at a time in sequence for 30 s during the encoding phase. A 20 s rest period preceded the recall phase, in which one word from each pair was presented in sequence and the subject tried to remember the other word. The same 7 word-pairs were repeated over 6 trials. The number of words successfully recalled in each trial was recorded. The number of word-pairs successfully recalled in each of the 6 trials was added to create an overall performance score with a maximum of 42 (i.e. a subject who immediately recalls all 7 words in the first trial and subsequently in all the remaining trials receives a score of 42). This score reflects both speed and quantity of memory acquisition.

Before scanning, the test was administered and scored by a trained researcher to familiarize the subject with the task and accurately assess performance. In the scanner, a different set of 7 word-pairs was presented through earphones and displayed visually using MR compatible goggles and MacStim software (Darby, 2004). During the encoding phase, the first word of a pair was presented for approximately 1 s, and then the second word was presented adjacent to it for about 2 s, followed by a blank screen for 1 s before the next word pair presentation. During the recall phase, one word of each pair was presented for about 3 s and subjects were instructed to recall the second word silently (to avoid head motion) and press a button with their index finger to indicate if they remembered the second word, or to press a different button with their middle finger if they could not recall the second word. Word pair order was randomized across trials. The rest phase involved a distracter task in which subjects pressed a button whenever the presented symbol changed about every 6 s. All subjects were able to successfully perform the distracter task. A trained researcher assessed actual memory performance in the scanner with a post-test of a single recall block of the same 7 word-pairs presented in the scanner obtained immediately following the scan. The fMRI paradigm is shown in Fig. 1F.

MRI acquisition

Subjects were scanned on a Siemens Allegra 3.0 T MRI scanner. DTI was obtained with one b0 with no diffusion weighting and 12 non-collinear diffusion encoded spin echo EPI images with a single b-value of 900 s/mm^2. Seventy-five contiguous axial slices were acquired (TR = 10,200 ms, TE = 84 ms, Matrix = 128 × 128, FOV 256 mm, 2NEX, 2 mm^3). The DTI scan was administered twice and the images were averaged to increase signal to noise. A sagittal localizer was used to identify the long axis of the hippocampus. All subsequent 3.0 T scans were aligned in the same oblique coronal plane perpendicular to the long axis of the hippocampus.

A high-resolution T2 SE pulse sequence (TR = 5200, TE = 105, 2 NEX, FOV = 200 mm, Matrix = 512 × 512, 3.00 mm, no gap) was acquired for structural hippocampal segmentation and unfolding. This scan (0.391 mm × 0.391 mm × 3 mm) encompassed the head, body, and most of the tail of the hippocampus. A functional high-resolution echo planar imaging (EPI) sequence (TR = 3000, TE 39, FOV = 200 mm, Matrix = 128 × 128, 1.6 mm × 1.6 mm × 3.0 mm slices, no gap), was used to detect blood-oxygen level dependent (BOLD) signal during the unrelated word-pairs task. An EPI matched bandwidth sequence (TR = 5000, TE = 66) was acquired to facilitate alignment of functional images to structural images. A GRE field-mapping scan (TR = 500, TE1 = 4.88, TE2 = 7.3) was acquired to correct for magnetic field inhomogeneities.

On the same scanning day, each subject underwent a second sequence in a Siemens 1.5T Sonata Scanner that was part of an ongoing longitudinal natural history study. A T1-weighted scan (TR = 1900, TE = 4.38,1 mm^3) was acquired to determine total brain volume. Brain volume percentage was calculated for each subject using SIENAX