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MRI correlates of episodic memory in Alzheimer's disease, mild cognitive impairment, and healthy aging

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ABSTRACT

Episodic memory is a core feature of Alzheimer's disease (AD) and mild cognitive impairment (MCI). Impaired episodic memory in AD results from the dysfunction of an integrated network and involves both gray and white matter pathologies. We explored the neural correlates of episodic memory in AD, MCI and healthy aging by correlating a measure of episodic memory with hippocampal volume and fractional anisotropy (FA) and mean diffusivity (MD) of the cingulum and fornix. Episodic memory was associated with hippocampal volume and MD of the cingulum and fornix. In contrast, there were fewer significant associations between episodic memory and FA. These findings support a relationship between episodic memory and hippocampal circuitry, and suggest that MD is a more sensitive marker of decreased white matter integrity in the study of AD and MCI than FA. Furthermore, MD was significantly associated with hippocampal volume, indicating that white matter pathology is not completely independent of gray matter pathology. However, the pattern of diffusivity differences in AD and MCI implies a more complex pathology than simply Wallerian degeneration.

1. Introduction

Impaired episodic memory is a core feature of both Alzheimer's disease (AD) and mild cognitive impairment (MCI) (Dubois et al., 2007), although the continuous nature of decline results in an overlap between diagnostic groups (Petersen, 2004). It is hypothesised that impaired episodic memory in AD results from the dysfunction of an integrated network that includes the medial temporal lobe, mamillary bodies, dorsomesial thalamus, posterior cingulate, and the connecting white matter tracts (Nestor et al., 2006). Correlations between episodic memory and elements of this limbic–diencephalic network have been detected across the spectrum of healthy aging, MCI and AD. For example, impaired verbal episodic memory has been associated with reduced hippocampal volume, measured using structural magnetic resonance imaging (MRI) (Choo et al., 2010; Leube et al., 2008), and also impaired integrity of the cingulum and fornix, measured with diffusion tensor imaging (DTI) (Choo et al., 2010; Fellgiebel et al., 2005; Mielke et al., 2009).

DTI characterises the orientation and integrity of white matter tracts by measuring the diffusion of water molecules in living neural tissue (Le Bihan, 2003). The three-dimensional water diffusivity obtained from the diffusion tensor can be modelled as an ellipsoid whose orientation is defined by the three eigenvectors (ε_1, ε_2, and ε_3), which represent the major, medium, and minor principal axes and whose shape is defined by the three eigenvalues (λ_1, λ_2, and λ_3), which represent the diffusivities in the three eigenvector directions. As the major eigenvector reflects the direction of maximum diffusivity, it is assumed to reflect the orientation of the white matter tract. The degree of diffusion anisotropy and the overall displacement of water molecules can be examined using fractional anisotropy (FA) and mean diffusivity (MD) values, respectively. In addition, diffusivity can be studied in greater detail using axial diffusivity (DA, λ_1, diffusivity parallel to the white matter tract) and radial diffusivity (DR, $(\lambda_2+\lambda_3)/2$, diffusivity perpendicular to the white matter tract). Although FA is the most commonly used DTI metric, it lacks sensitivity when diffusivity in all three directions displays similar changes. This may be particularly relevant in AD, where several degenerative processes may be at play. For example, white matter degradation may result from myelin breakdown in line with the retrogenesis hypothesis, Wallerian degeneration occurring secondary to gray matter pathology, and also local microvascular changes. Indeed, MD has been found to be more sensitive than FA in detecting group differences between AD and control participants (Acosta-Cabronero

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et al., 2010) and in reflecting Mini-Mental State Examination (MMSE) decline within AD (Nakata et al., 2009; Yoshiura et al., 2002).

Tract-based spatial statistics (TBSS) is a DTI analysis technique that projects all subjects' FA data onto a tract skeleton which represents the centres of all tracts common to the group. The TBSS protocol minimises the effects of misregistration, which is especially important when studying patient groups that can display significant atrophy. In the present work we use neuroimaging measures obtained from structural MRI and DTI in order to thoroughly examine the neural correlates of episodic memory. With regard to structural MRI, we use an automatic segmentation tool to examine the volume and shape of hippocampus. With DTI, we utilise the TBSS processing strategy to determine a white matter skeleton, then create cingulum and fornix regions of interest (ROIs) overlaid on the skeleton. Due to the complex pathology of AD, we hypothesised that MD would be a more sensitive marker of episodic memory than FA.

2. Methods

2.1. Participants

The study was conducted with approval from the Lothian Research Ethics Committee (Ref: LREC/06/S03/36). Informed written consent was obtained from all participants.

Three groups of participants were enrolled in the study: AD, MCI and controls. Participants with early AD were recruited from patient lists of the Lothian Old Age Psychiatry Services. Participants with MCI were identified from a longitudinal study, which recruited via tertiary referrals to the Edinburgh Older Adult Neuropsychological Assessment Service (Lonie et al., 2008; Terrière et al., 2008). Healthy control participants were recruited from the community, e.g. participants' friends and relatives.

Participants with early Alzheimer's disease fulfilled National Institute of Neurological and Communicative Disorders and Stroke — Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann et al., 1984) and Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (DSM-IV) criteria.

All participants completed a comprehensive battery of neuropsychological tests valid for use within an elderly population with cognitive impairment. The tests examined pre-morbid IQ, general cognition, semantic memory, processing speed, executive function, visuospatial ability, and episodic memory (details available from the authors on request).

MCI was defined by a performance of 1S.D. or more below previously published matched control age means on two or more measures assessing a single cognitive domain (A), or 1.5S.D. or more below published normative age means on at least one test (B) (Lonie, 2010) and met revised criteria for MCI as specified by Petersen et al. (2005).

All MCI participants underwent comprehensive clinical neuropsychological and psychiatric evaluations, and medical screening as part of their clinical work-up. Healthy control participants had no history of memory impairment, depression or other psychiatric illness. The clinical exclusion criteria for all participants included potentially confounding co-morbid medical, psychiatric or neurological conditions, including stroke or cerebrovascular disease, head injury, alcoholism, schizophrenia, major depression, and epilepsy. In addition to the clinical exclusion criteria, participants with metallic implants were excluded as required by local standard MRI protocols.

2.2. Neuropsychological assessment

Verbal and visual episodic memory was assessed using the Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt, 1991) and the Rey Complex Figure Test (RCFT) (1941), respectively.

2.3. Data acquisition

All MRI scans were obtained at the Scottish Higher Education Funding Council Brain Imaging Research Centre in the Western General Hospital, Edinburgh using a GE Signa HDX 1.5 Tesla MRI scanner.

2.3.1. Structural imaging protocol

The exam included standard structural imaging (field of view (FOV) 220×220 mm, 24 contiguous slices, 5.6 mm thickness in all cases), i.e. T2-weighted (acquisition matrix: 256×128, TR 6300 ms, TE 102.0 ms), Fluid Attenuation Inversion Recovery (FLAIR) (acquisition matrix: 256×128, TR 9000 ms, TE 140.0 ms, TI 2200.0) and gradient echo (acquisition matrix: 256×192, TR 625 ms, TE 15.0 ms) scans to characterise cerebral white matter lesions and microbleeds, and a 3D Inversion Recovery Preparation (IR-PREP) scan in the coronal plane with slices perpendicular to the long axis of the hippocampus (acquisition matrix: 256×128, 128 slices, 1.7 mm thickness, TE Min Full, TI 600 ms) for volumetric measurements.

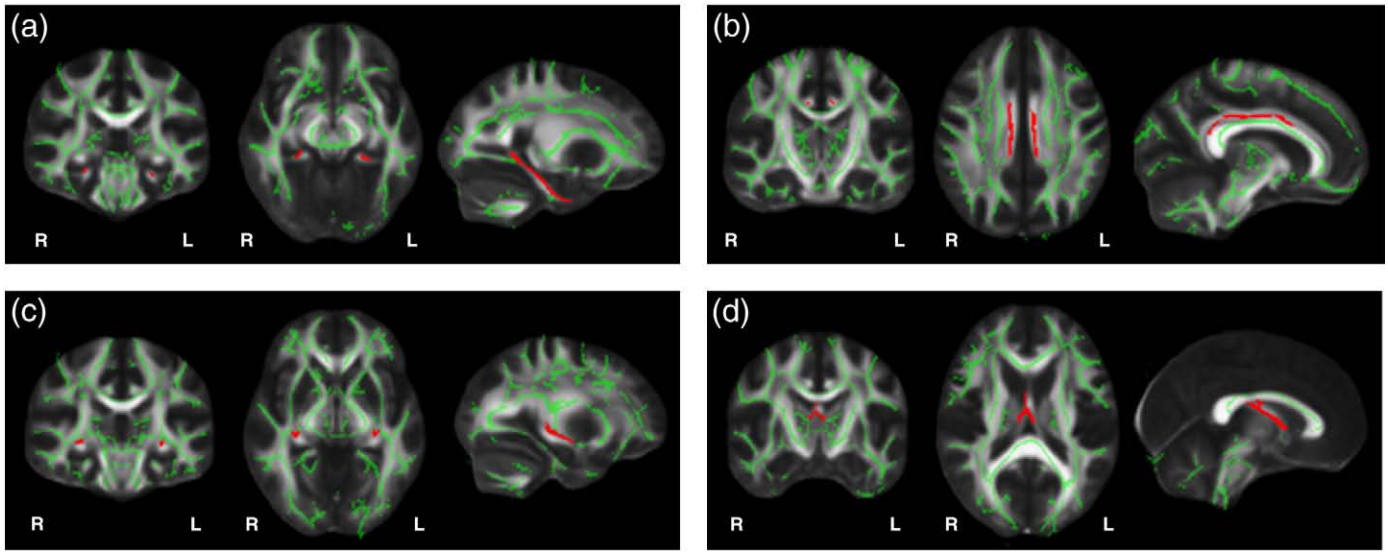

Fig. 1. Regions of interest. Regions of interest (red) overlaid on the skeleton (green) (a) Cingulum: hippocampal portion (b) Cingulum: cingulate gyrus portion (c) Fornix: crus (d) Fornix: body and column.