Deficits in episodic memory retrieval reveal impaired default mode network connectivity in amnestic mild cognitive impairment

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ABSTRACT

Amnestic mild cognitive impairment (aMCI) is believed to represent a transitional stage between normal healthy ageing and the development of dementia. In particular, aMCI patients have been shown to have higher annual transition rates to Alzheimer's Disease (AD) than individuals without cognitive impairment. Despite intensifying interest investigating the neuroanatomical basis of this transition, there remain a number of questions regarding the pathophysiological process underlying aMCI itself. A number of recent studies in aMCI have shown specific impairments in connectivity within the default mode network (DMN), which is a group of regions strongly related to episodic memory capacities. However to date, no study has investigated the integrity of the DMN between patients with aMCI and those with a non-amnestic pattern of MCI (naMCI), who have cognitive impairment, but intact memory storage systems. In this study, we contrasted the DMN connectivity in 24 aMCI and 33 naMCI patients using seed-based resting state fMRI. The two groups showed no statistical difference in their DMN intra-connectivity. However when connectivity was analysed according to performance on measures of episodic memory retrieval, the two groups were separable, with aMCI patients demonstrating impaired functional connectivity between the hippocampal formation and the posterior cingulate cortex. We provide evidence that this lack of connectivity is driven by impaired communication from the posterior cingulate hub and does not simply represent hippocampal atrophy, suggesting that posterior cingulate degeneration is the driving force behind impaired DMN connectivity in aMCI.

1 Introduction

Mild cognitive impairment (MCI) is a clinical state of cognitive decline "greater than expected for an individual's age and education level" (Gauthier et al., 2006) and has been proposed to represent an intermediate stage between normal ageing and dementia (Petersen et al., 2009). The annual rate of progression from MCI to Alzheimer's Disease (AD) is approximately 14%, which is markedly greater than the expected 1–2% annual incidence of AD (Petersen et al., 2009). Thus, MCI has been hypothesised to represent a transitional phenotype for future dementia states (Villain et al., 2008).

Patients with MCI can be further sub-divided based on patterns of cognitive impairment observed on neuropsychological testing. Impaired performance on neuropsychological tests of episodic memory retention and retrieval (Petersen and Morris, 2005) is consistent with an amnestic profile (aMCI) and this sub-group is thought to share a common pathophysiological mechanism with AD (Dubois and Albert, 2004). In contrast, non-amnestic (naMCI) patients have preserved episodic memory and as such are more likely to transition to other forms of dementia (Petersen et al., 2009). In regard to neurobiological markers, patients with aMCI have decreased grey matter volume in the hippocampus (Shi et al., 2009) along with impairments in hippocampus connectivity whilst completing memory tasks (Bai et al., 2009). Furthermore, these differences have been localised to the left hippocampus (Lye et al., 2006), with decreased grey matter volume associated with specific impairments in episodic memory function, as measured by the Rey Auditory Verbal Learning Test (RAVLT) (Hickie et al., 2005). Despite these insights, uncertainty remains concerning the pathophysiological processes underlying aMCI and AD (Sperling et al., 2010).

To delineate the pathophysiological mechanisms underlying aMCI, a number of recent studies have adopted functional neuroimaging approaches (for a review, see Sperling et al., 2010). Earlier studies had focused on task related increases in neural activity as determined using traditional techniques, however more recent approaches have employed resting state functional connectivity MRI (rsfcMRI) measures to examine the coordinated patterns of the brain responses in

the absence of explicit tasks. Activity in rsfcMRI is thought to reflect both direct and indirect synaptic activities and provides insight into the information processing capacity of the human brain (Greicius et al., 2009). This method has documented the organisation of the brain into multiple large-scale neural networks (Fox et al., 2005) that retain their functional organisation during task performance (Smith et al., 2009) as well as sleep (Horovitz et al., 2009).

The default mode network (DMN) is one such network and this is of particular interest in aMCI and AD. The DMN has been shown to underpin self-referential and episodic memory capacities (Andrews-Hanna et al., 2010; Spreng and Grady, 2010) and as such, several groups have explored the patterns of intrinsic functional connectivity during the resting state in both MCI and AD (Greicius et al., 2004; Rombouts et al., 2005). Studies have consistently identified reduced intrinsic connectivity amongst MCI patients in the posterior cingulate cortex (PCC), a core hub of the DMN (De Vogelaere et al., 2012). Interestingly, several studies have reported hyperactivation of medial temporal lobe (MTL) structures in MCI patients, yet these findings remain variable (Sperling et al., 2010). Further, increased MTL functional connectivity with the hippocampus is observed during successful memory formation (Ranganath et al., 2005). Impaired DMN activity has been directly related to altered cognitive processing through correlation with neuropsychological data (De Vogelaere et al., 2012). The findings from these studies thus support the notion that the episodic memory impairments in aMCI and AD may be directly related to impairments in connectivity between the MTL and the core regions of the DMN.

To our knowledge, rsfcMRI has not been utilised to compare DMN connectivity between a cohort of patients with aMCI and those with naMCI. We hypothesised that the two groups would differ based on functional connectivity within the DMN, with specific impairments relating to the communication between the MTL and the core regions of the DMN. To explore this hypothesis, we examined the seed-based resting-state functional connectivity in the left hemisphere hubs of the DMN between the aforementioned patient groups. In addition, we sought to determine how these regions coordinated their activity as a function of performance on the RAVLT, a robust test of episodic memory capacity (Andersson et al., 2006).

2 Methods

2.1 Participants

A total of 57 health seeking older adults meeting criteria for MCI were recruited from the Healthy Brain Ageing Clinic, at the Brain and Mind Research Institute, Sydney, Australia. All participants received a comprehensive medical assessment by an old age psychiatrist, and exclusion criteria included: diagnosed dementia; neurological disease (e.g., Parkinson's, epilepsy); psychosis; prior stroke or head injury (with loss of consciousness >30 min); and, inadequate English for neuropsychological assessment. This study was approved by the University of Sydney Institutional Ethics Committee, and all participants gave written informed consent.

2.2 Neuropsychological assessments

As part of a comprehensive assessment battery (Duffy et al., 2014), a neuropsychologist administered the RAVLT (Lezak, 1995), a test which has been linked to hippocampal atrophy (Hickie et al., 2005) and predictive of conversion to dementia in MCI (Andersson et al., 2006). This task required patients to learn a list of 15 unrelated words over 5 trials. The total number of words recalled over the first 5 trials was calculated as a measure of episodic memory encoding (RAVLT$_{1-5}$). After a 20-minute delay, patients were asked to again recall the words,

and memory retention was calculated as a percentage of words retained (i.e., trial 7 divided by trial 5 * 100; RAVLT$_{7/5}$). For descriptive purposes, a neuropsychologist also administered the Mini Mental State Examination (MMSE) (Folstein et al., 1983) and the Wechsler Test of Adult Reading as an estimate of predicted IQ (Hartman, 2009). Additionally, patients completed the Geriatric Depression Scale (GDS) (Yesavage et al., 1982).

A diagnosis of MCI was determined using Petersen's criteria requiring cognitive decline of at least 1.5 standard deviations on at least one neuropsychological test, relative to age- and education-adjusted normative data (Petersen and Morris, 2005). Per criteria, each participant was required to have subjective and objective cognitive decline, but with the general preservation of function. MCI diagnoses were consensus rated by an old age psychiatrist and two neuropsychologists, based on clinical profile and neuropsychological assessment and with reference to structural MRI scans where possible. The broad clinical definition of MCI was further categorised into amnestic and non-amnestic subtypes (Petersen and Morris, 2005). In order to be categorised as aMCI, participants were required to demonstrate clear evidence of deficits in memory retention, which was not considered to be merely due to poor encoding. Patients were diagnosed with naMCI if deficits were present on cognitive domains other than memory (e.g., processing speed, working memory, language, visuospatial and executive functioning). As detailed elsewhere (Duffy et al., 2014), the broader neuropsychological test battery included psychomotor speed (Part A of the Trail Making Test [TMT]), working memory (Digit Span subtest of the Wechsler Adult Intelligence Scale — Third Edition), verbal learning and memory (Logical Memory subtest of the Wechsler Memory Scale — Third Edition), language (Boston Naming Test), visuospatial skills (Rey Complex Figure Test, Clock drawing), and executive functioning (Part B of the TMT, DKEFS Stroop and Controlled Oral Word Association Test).

2.3 Neuroimaging analysis

2.3.1 Image acquisition

Imaging was conducted on a GE 3 Tesla MRI (General Electric, Milwaukee, USA). T2*-weighted echo planar functional images were acquired in sequential order with repetition time (TR) = 3 s, echo time (TE) = 32 ms, flip angle = 90°, 32 axial slices covering the whole brain, field of view = 220 mm, inter-slice gap = 0.4 mm, and inplane voxel size = 3.4 mm by 3.4 mm by 4 mm thick. A T1-weighted Magnetisation Prepared Rapid Gradient-Echo (MPRAGE) sequence producing 196 sagittal slices with TR = 7.2 ms, TE = 2.8 ms, flip angle = 10°, matrix 256 × 256 and 0.9 mm isotropic voxels was also obtained for localisation of functional resting state loci via co-registration with echo planar functional images. The T1-weighted images were also used to calculate the hippocampal volumes for each participant. A single rsfcMRI run was performed in the scanner by each patient and consisted of patients lying supine with their eyes closed. Patients were also instructed to allow their mind to wander freely.

2.4 Resting state functional connectivity fMRI analysis (rsfcMRI)

In order to determine whether the regions identified in the functional analysis formed consistent functional networks, rsfcMRI analyses were applied to task-independent T2*-weighted data. Statistical parametric mapping software (SPM8, Wellcome Trust Centre for Neuroimaging, London, UK) was used for image processing and analysis. Of 127 individual volumes collected from each subject, the first five whole brain scans were discarded to eliminate spurious T2*-equilibration effects. Resting state images were then pre-processed according to a standard pipeline: a) scans were slice-time corrected to the median (17th) slice in each TR; b) scans were then realigned to create a mean realigned image and measures of six degrees of rigid head movements were calculated for later use in the correction of