Cortical Responses to a Graded Working Memory Challenge Predict Functional Decline in Mild Cognitive Impairment

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Background: Early detection of progressive cognitive decline offers an opportunity for preventative interventions with enormous public health implications. Functional neuroimaging during cognitive activity in individuals at risk of dementia has the potential to advance this objective. In a prior study, we evaluated the utility of a novel functional magnetic resonance imaging paradigm that incorporated a graded working memory (WM) task to detect changes associated with mild cognitive impairment (MCI). We observed greater deactivation of posteromedial cortex (PMC) under conditions of increased WM load in MCI compared with control subjects. Our objective here is to test whether this paradigm can predict ensuing functional decline.

Methods: Thirty individuals with MCI who underwent baseline functional magnetic resonance image scanning were followed clinically for 2 years. Multiple linear regression analyses were used to determine whether deactivation in PMC under increased load at baseline independently predicted decline in instrumental activities of daily living (IADL).

Results: Greater deactivation in PMC to increased load predicted greater decline in IADL after controlling for baseline clinical severity, MCI subtype, apolipoprotein $\varepsilon 4$ carrier status, gray matter, PMC and hippocampal volumes, and task performance.

Conclusions: Increased deactivation observed at baseline was a harbinger of subsequent functional decline as measured by IADL in a cohort with MCI. This graded WM challenge may operate like a memory stress test by producing a threshold effect beyond which abnormal deactivation is elicited in MCI subjects who are at greatest risk of functional decline.

Key Words: Alzheimer disease, default mode network, functional MRI, mild cognitive impairment, prospective study, working memory

Prediction of cognitive decline in the elderly before the onset of dementia is of major importance, as it could allow the targeted introduction of preventive interventions. Research has focused on mild cognitive impairment (MCI), a term used to characterize individuals who have memory or other cognitive impairments beyond that expected for their age and who are at increased risk of developing dementia. Mild cognitive impairment, commonly thought to be a transitional state between healthy aging and Alzheimer's disease (AD) and other dementias (1), is a heterogeneous syndrome and only a proportion of individuals progress to dementia (2). Task-activated functional magnetic resonance imaging (fMRI) may provide key prognostic information in these individuals because of its sensitivity to alterations in synaptic function that occur very early in the disease process, preceding neuronal loss and cortical atrophy detectable on structural magnetic resonance imaging (MRI) (3).

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Research using task-activated fMRI suggests that alterations in brain activity in a number of neural networks are already present in individuals with MCI. Numerous fMRI studies using a range of memory tasks have demonstrated that the medial temporal lobe (MTL) system, including the hippocampus and surrounding structures, is functionally altered in MCI. However, comparisons of MCI and cognitively normal subjects have been inconsistent, with some showing increased (4–7) and others decreased (8–12) MTL activity. We have demonstrated that this variability may be due, in part, to task difficulty (13), a factor that determines how well an individual can perform the task. Clinical severity (14,15) and hippocampal volume (16) may also contribute to the varying patterns of MTL activity observed in fMRI studies.

The functional integrity of a large, distributed network of functionally connected regions known as the default mode network (DMN) (17) is significantly disrupted in MCI (18,19). In healthy individuals, the DMN is active during rest and deactivated during task performance across a wide range of cognitive tasks (20–22). The posteromedial cortex (PMC)—consisting of medial precuneus, posterior cingulate, and retrosplenial cortex—is a major node of the DMN and is among the earliest affected regions in AD (23), presumably because of its selective vulnerability to early amyloid deposition (24). Recent fMRI studies have reported alterations in task-induced deactivation in regions of the PMC during performance of memory tasks (10,15,25,26). While most studies reported less deactivation in MCI and AD subjects than in healthy elderly subject (10,25,27), our group and others found that task difficulty and clinical severity influence deactivation as well as activation patterns (13,15).

Overall, findings from cross-sectional studies remain equivocal. Prospective fMRI studies are needed to examine the prognostic significance of functional alterations in MCI, while controlling for factors such as clinical severity, task difficulty, and performance and the effect of potential volume loss that may influence fMRI signal.

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To date, few prospective studies have been reported (4,28–31) and most have investigated positive task-related activity in MTL using episodic memory tasks. These have consistently shown that greater baseline hippocampal activity predicted greater subsequent clinical decline, independent of hippocampal volume, clinical severity, and apolipoprotein E (APOE) $\varepsilon 4$ genotype (4,29,31). In the only study that has examined task-related deactivation in MCI individuals prospectively, loss of functional deactivation in PMC during task performance was predictive of conversion to AD after adjusting for clinical severity (30).

We have previously found that after careful individual calibration of task difficulty, adults with MCI showed greater deactivation in PMC during encoding of a visuospatial associative working memory (WM) task compared with healthy age-controlled subjects under conditions of increasing memory load (13). Our multiple-level WM paradigm represents an advance over most previous studies that have used a single fixed condition, because it allows examination of dynamic brain responses to changes in load. Hence, this paradigm could potentially operate like a memory stress test by eliciting abnormal activity when an individual is under conditions of increasingly high cognitive challenge. To explore this idea, we tested the ability of our fMRI paradigm to predict decline in everyday function in adults with MCI, because this may be a marker of future dementia (32,33). We hypothesized that greater deactivation in PMC in response to increasing load at baseline would be predictive of decline in instrumental activities of daily living (IADL) over 2 years. We tested this predictive model after controlling for a number of known risk factors and potential confounding factors. Measures of total gray matter and hippocampal volume were included in our model to compare the predictive utility of cortical activity changes on fMRI with volumetric changes.

Methods and Materials

Participants

Participants were drawn from the Sydney Memory and Ageing study, a longitudinal study of nondemented community-living older adults (34). Subjects were aged 70 to 85 years, right-handed, from an English-speaking background, and diagnosed with MCI. Exclusion criteria included diagnosis of dementia or other psychiatric or central nervous system disorder. Of 35 MCI subjects with a baseline scan, 30 subjects who had a 2-year follow-up assessment with no missing data were included. At baseline and follow-up, participants underwent comprehensive neuropsychological assessment, medical examination, blood collection, and APOE genotyping (baseline). Informants provided information about cognitive difficulties and functional activities. Details of these procedures have been previously reported (34). Diagnosis of MCI was made by a panel of neuropsychiatrists, psychogeriatricians, and neuropsychologists based on current international consensus criteria (35) and included all subtypes (1) (amnestic: 12 single-domain, 9 multiple-domain; nonamnestic: 6 single-domain, 3 multiple-domain). Participants gave written informed consent and the study was approved by the University of New South Wales Human Research Ethics Committee.

Longitudinal Functional IADL Changes

Functional decline was defined as the difference between the baseline and 2-year follow-up scores on the Bayer Activities of Daily Living Scale (B-ADL), an informant-based instrument measuring instrumental activities of daily living (36,37). Informants who had at least weekly contact of $\geq$ 1 hour were administered the B-ADL via telephone interview, rating 25 everyday activities on a 10-point scale. Ratings were made by the same informant at both time points. Informants were asked if difficulty for an item was due to cognitive or physical reasons. If attributed to physical reasons alone or to both, the item was not included in the total to ensure that the score reflected cognitive reasons for difficulty rather than physical reasons (36). The total score represented an average of all valid items and was reversed so that lower scores represented greater difficulty with IADLs, with a negative change score reflecting worsening of function.

Task and fMRI Procedures

Functional MRI data were acquired while participants performed a visuospatial associative WM paradigm with parametric increases in load, as detailed in a previous publication (13). Briefly, participants were presented with pictures (abstract designs) and filler items on a 5 $\times$ 5 grid and instructed to remember the pictures and the positions they appeared in (i.e., remember targets not filler items). The WM load was manipulated by altering the number of targets presented for encoding. Three WM load conditions were presented: low, medium, and high. Figure 1 depicts the events and timing of a single fMRI trial.

Working Memory Load Calibration. An important feature of our experimental design was individualized calibration of WM load. In a prescan session, we determined for each participant the number of targets to be presented during scanning to achieve approximately 75% to 85% accuracy for the medium-load condition and 60% to 70% for the high-load condition. One target was presented for all participants in the low-load condition. Our aim was to provide comparable task challenge for all subjects by controlling for individual differences in ability and minimizing potential floor effects at high load.

Imaging Protocol

Subjects were scanned using a Philips (Achieva X) 3.0-Tesla scanner (Philips Medical Systems, Best, The Netherlands). Functional images were acquired using T2*-weighted gradient echo-planar sequences (29 axial slices, repetition time/echo time: 2000/30 msec, 90° flip angle, matrix size: 112 $\times$ 128, field of view: 240 mm, voxel size: 2.14 $\times$ 2.73 $\times$ 4.5 mm, no gap). The T1-weighted structural images were acquired coronally (repetition time/echo time: 6.39/2.9 msec, 8° flip angle, matrix size: 256 $\times$ 256, field of view: 256 $\times$ 256 $\times$ 180 mm, voxel size: 1 $\times$ 1 $\times$ 1 mm, no gap).

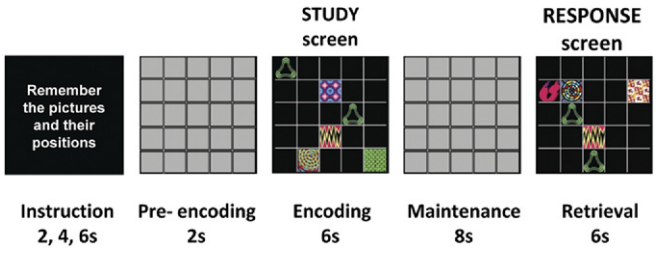

Figure 1. Paradigm sequence, stimuli, and timing in a single trial. This is a schematic representation of a true positive trial. Each box represents a trial component with duration of each (in seconds) indicated. During the study screen, targets were presented for participants to remember. During the response screen, another set of stimuli were displayed and participants indicated with a button press (yes/no) if any one of the targets were repeated from the immediately preceding study screen. Multicolored abstract designs represent target stimuli to be remembered, including their position on the grid. Curved green shape represents nontarget (filler) items. Filler items were included in the study and response screens so the total number of stimuli presented was always six items, thereby holding overall visual input constant over load conditions.