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

Nicole A. Kochan, Michael Breakspear, Michael Valenzuela, Melissa J. Slavin, Henry Brodaty, Wei Wen, Julian N. Trollor, Andrew Turner, John D. Crawford, and Perminder S. Sachdev

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).

From the Brain and Ageing Research Program (NAK, MV, MJS, HB, WW, JNT, JDC, PSS), Dementia Collaborative Research Centre (MJS, HB), Department of Developmental Disability Neuropsychiatry (JNT), Regenerative Neuroscience Group (MV, AT), School of Psychiatry, Faculty of Medicine, University of New South Wales; Neuropsychiatric Institute (NAK, WW, PSS) and Academic Department for Old Age Psychiatry (HB), Prince of Wales Hospital; and The Black Dog Institute (MB), Sydney, New South Wales, Australia; and Queensland Institute of Medical Research (MB), Brisbane, and Royal Brisbane and Women's Hospital (MB), Herston, Queensland, Australia.

Address correspondence to Nicole A. Kochan, M.Sc., University of New South Wales, School of Psychiatry, Brain and Ageing Research Program, Sydney, NSW 2031, Australia; E-mail: n.kochan@unsw.edu.au.

Received Nov 27, 2010; revised Feb 7, 2011; accepted Mar 2, 2011.

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.

0006-3223/$36.00
doi:10.1016/j.biopsych.2011.03.006

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).

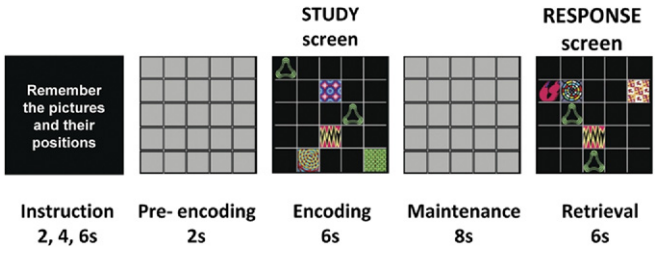

Figure 1. Paradigm sequence, stimuli, and timing in a single trial. This is a schematic representation of a true positive trial. Each box represents a trial component with duration of each (in seconds) indicated. During the study screen, targets were presented for participants to remember. During the 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.

fMRI Processing and Analysis

Functional MRI (blood oxygenation level-dependent) images were preprocessed and analyzed using statistical parametric mapping SPM5 software (http://www.fil.ion.ucl.ac.uk/spm/). Preprocessing included realignment of time series, co-registration to structural T1 image, normalization into standard Montreal Neurological Institute space, and 8 mm spatial smoothing. Statistical analysis of the time series of images was conducted using the general linear model (38) in an event-related design. Only correct trials were modeled. An a priori functional region of interest (ROI) analysis was conducted (39) using the PMC region that previously demonstrated cross-sectional differences in load-dependent brain activity between MCI and healthy control subjects during encoding (13) (see Figure S1 in Supplement 1, which depicts the load-related functional responses separately for MCI and control groups). To test our hypothesis that magnitude of deactivation under conditions of increasing load in this PMC region predicts decline in IADL, we first created an anatomical mask from the cluster that showed a significant group (MCI vs. control group) by load (high < medium) interaction effect in our previous study. To establish that a load main effect (high < medium) was present in the MCI group, a random-effects analysis was performed within the defined mask. The statistical map was thresholded at $p < .001$ uncorrected (one-tailed). Parameter estimates (β values) for each load averaged over all voxels in the functional mask were extracted for each participant. A difference score (high minus medium), representing the change in β values over increased load, was entered subject-wise as an independent predictor in a linear regression analysis. An exploratory whole brain analysis was also conducted to complement our a priori ROI analysis. The whole brain random-effects analysis investigated load-related activity differences between MCI subjects who declined over 2 years and those who did not decline. The two groups were defined by upper and lower quartile values of the B-ADL change score ($n = 8/8$). Individual subject contrast images were entered into a two-way factorial analysis of variance with group (MCI-decline/MCI-no decline) as a between-subjects factor and load as a within-subjects factor. Clusters were considered significant at $p < .05$ (family-wise error [FWE]-corrected) after initial whole brain threshold of $p < .01$ (uncorrected).

Structural MRI Volumetry

The T1-weighted images were segmented into gray matter (GM), white matter, and cerebrospinal fluid (40), and total GM was used as an index of generalized brain atrophy. Gray matter volumes were also extracted from the PMC ROI mask. First, GM was modulated and normalized to Montreal Neurological Institute space, then the PMC mask image was resliced to match the T1 GM images and GM volumes were extracted. A manual tracing protocol was used for measuring hippocampal volumes on T1-weighted images, as has been previously published (41). Hippocampal volumes represent averages across right and left sides after rigid body co-registration and reslicing images perpendicular to the long axis of the hippocampus. Total intracranial volume (GM + white matter + cerebrospinal fluid) was used as a control variable for the structural MRI variables in the regression analysis.

Statistical Analysis

Linear regression analyses were conducted with the difference score of the β values (high minus medium) extracted from the functional ROI as an independent variable and B-ADL change score (baseline to 2 years) as the dependent variable. Following a univariate analysis, multiple regression analyses using the enter and backward elimination procedures were conducted to evaluate the predictive ability of this fMRI parameter, while controlling for a number of variables that have been shown in the literature to be predictive of decline in individuals with MCI, namely baseline cognitive status (42) (Mini-Mental State Examination score), profile of cognitive impairment (MCI subtypes: amnestic vs. nonamnestic, single vs. multiple domain),(43,44), baseline functional status (42) (B-ADL score), APOE genotype (ε4 carrier vs. noncarrier) (45), total hippocampal volume (left + right) (46), and total GM volume (47). Age, years of education, total intracranial volume, PMC GM volume, and accuracy on high load were also included as control variables, the latter included to control for the relationship between task performance and brain activity (48,49). Analyses were conducted using PASW 18.0 Statistical Package (SPSS, Inc., Chicago, Illinois). Distributions of variables to be entered in the regression were inspected for normality and extreme values. To minimize the influence of extreme values on statistical outcomes, scores were Winsorized where necessary so that upper and lower values were reduced to three standard deviations above or below the mean. Potential outliers in regression analyses were investigated by examining residual statistics (studentized deleted residuals) and distance statistics (Mahalanobis distance, Cook's distance). Bivariate associations between variables included in the regression and B-ADL change score were examined by Pearson correlation coefficients.

Results

Sample Characteristics

Summary statistics for baseline demographic, clinical variables, and behavioral test scores are shown in Table 1. Over an average of 23.1 ± 2.1 months of follow-up, change in B-ADL score ranged from an increase of 1.0 points to a decline of 1.68 points. A single participant was diagnosed with probable AD (50) over the follow-up interval. Table 2 lists correlations among variables in the regression analysis and B-ADL change score.

Load-Dependent Deactivation in Posteromedial Cortex

Figure 2 depicts the PMC mask that incorporated medial precuneus and posterior cingulate cortices. Within this PMC ROI, stronger

Table 1. Baseline Characteristics of Mild Cognitive Impairment Sample ($n = 30$)

Characteristic	Mean (SD) or % of Sample
Age (years)	78.3 (4.0)
Sex (M) (%)	36.7
Education (years)	12.6 (4.0)
MMSE-Adjusted Baseline	27.8 (1.6)
Bayer-ADL Baseline	1.4 (.5)
Accuracy Low Load	94.5 (8.1)
Accuracy Medium Load	79.8 (13.3)
Accuracy High Load	74.0 (13.8)
MCI Subtype (amn-sd/amn-md/namn-sd/nam-md) (%)	40/30/20/10
APOE ε4 (1 or 2 alleles) (%)	26.7
Total Gray Matter Volume (liters)	.63 (.07)
Hippocampal Volume (mm^3)	2428.7 (506.8)

Values presented for task accuracy are expressed as percentage correct. Hippocampal volume represents the average of left and right volumes. Data for age and education adjustments were derived from Anderson *et al.* (70).

amn-md, amnestic multiple domain; amn-sd, amnestic single domain; APOE, apolipoprotein E; Bayer-ADL, Bayer-Activities of Daily Living Scale; M, male; MCI, mild cognitive impairment; MMSE-adjusted, Mini-Mental State Examination adjusted for age and education; namn-md,nonamnestic multiple domain; namn-sd nonamnestic single domain; SD, standard deviation.

Table 2. Correlations Between Control Variables, Hypothesized Predictors, and 2-Year Change in Bayer-ADL Scale

	Age	Education	MMSE-Adjusted	Bayer-ADL	Accuracy High Load	PMC High Minus Medium[a]	Total GM Volume	PMC GM Volume[b]	Total Hippocampal Volume
2-Year Bayer-ADL Change	.08 $p = .67$	−.16 $p = .39$	.36 $p = .05$	−.09 $p = .62$	.56 **$p = .001$**	.49 **$p = .006$**	−.13 $p = .49$	.02 $p = .93$	−.31 $p = .10$
Age		−.10 $p = .61$	−.10 $p = .95$	.05 $p = .79$	.27 $p = .16$	.05 $p = .79$	−.07 $p = .71$	−.19 $p = .33$	−.35 $p = .07$
Education			.19 $p = .31$	.06 $p = .77$	−.10 $p = .61$	.02 $p = .93$	−.09 $p = .65$	−.04 $p = .85$	.10 $p = .61$
MMSE-Adjusted				.40 **$p = .03$**	.29 $p = .11$	.40 **$p = .03$**	−.11 $p = .58$	.10 $p = .62$	−.07 $p = .71$
Bayer-ADL					.26 $p = .16$	.16 $p = .40$	.14 $p = .48$	.18 $p = .35$	.20 $p = .31$
Accuracy High Load						.34 $p = .07$	.19 $p = .33$	.34 $p = .07$	−.07 $p = .71$
PMC High Minus Medium[a]							−.04 $p = .84$	−.03 $p = .87$	.15 $p = .45$
Total GM Volume								.50 **$p = .01$**	.39 **$p = .04$**
PMC GM Volume[b]									.36 $p = .05$

Partial correlations were performed for structural volumetric measures controlling for total intracranial volume and bivariate correlations for all other variables. Apolipoprotein E carrier status, MCI subtype—nonamnestic/amnestic and single domain/multiple domain (categorical variables) are not included in this analysis.

Significant findings ($p < .05$) are shown in bold.

Bayer-ADL, Bayer-Activities of Daily Living Scale; GM, gray matter; MCI, mild cognitive impairment; MMSE-adjusted, Mini-Mental State Examination adjusted for age and education; PMC, posteromedial cortex.

[a]β values extracted from the posteromedial cortex functional region of interest.

[b]Gray matter volume extracted from the posteromedial cortex functional region of interest.

negative responses (greater deactivation) were observed as load increased from medium to high ($t = 3.85$, $p = .00013$). This increased load-related deactivation is clearly seen in the plot of the parameter estimates (Figure 2). No clusters reached significance using FWE correction in our exploratory whole brain analysis examining load-dependent activity differences between MCI-decline and MCI-no decline groups. However, a group × load effect, significant only at uncorrected thresholds (peak voxel: 15 –57 37; $t = 3.69$; cluster size = 139 voxels; $p = .189$ FWE corrected, $p = .006$ uncorrected), was observed in a region of the PMC closely corresponding to the PMC ROI. In this region, increased load had a stronger effect on task-induced deactivation in the MCI-decline compared with MCI-no decline group. The lack of significance is at least partly due to the loss of power implicit in this approach, although collapsing a continuous measure into two categorical states may have also contributed. No other brain regions approached significance either for load-related deactivation or positive activation group comparisons.

Posteromedial Cortex Deactivation and Future Decline in Functional Activities

In the univariate regression analysis, greater deactivation under conditions of increased load in PMC significantly predicted decline in B-ADL score ($\beta = .49$, $p = .006$) (Figure 3). To further examine this while controlling for other potential predictors of decline, a multiple linear regression analysis was conducted with all variables entered into the model simultaneously (Table 3: Model 1). The main effect of load-related deactivation (high minus medium) remained a significant predictor of B-ADL decline. Task accuracy for high load was the only other significant predictor in the model; lower accuracy was associated with greater decline. One subject with the lowest B-ADL change score (diagnosed with AD at 2-year follow-up) met formal criteria for an outlier observation in the multiple regression analysis and may have been overly influencing the findings. Therefore, the analysis was repeated after removal of this subject. The overall model remained significant ($R = .0853$ $p = .02$) with the fMRI parameter still a significant predictor ($p = .018$).

A backward elimination procedure was used to remove variables to produce a more parsimonious model. The previous results for deactivation (high minus medium) and accuracy were confirmed, with these two variables comprising the simplest model. We present results for the penultimate solution that includes a third variable (MCI subtype), which showed a trend for significance ($p = .16$) because of the potential clinical significance of this model, noting that the small sample size may give rise to type II error in this analysis (Table 3: Model 2). Thus, in addition to the main effects for deactivation and task performance, a trend toward greater decline in everyday function was present for persons with multiple domain MCI relative to single domain MCI.

Load-Dependent Deactivation and Task Performance

We examined the relationship between load-dependent deactivation and task performance, observing a significant correlation between change in deactivation magnitude as load increased from medium to high and change in accuracy ($r = .41$, $p = .024$) but not change in reaction time ($r = -.20$, $p = .31$). The MCI subjects who showed the largest increase in deactivation with load also showed the largest decline in accuracy.

Discussion

Consistent with our hypothesis, stronger deactivation in PMC in response to increasing memory load from medium to high level was predictive of greater decline in everyday function over 2 years. This relationship was still present after controlling for a number of

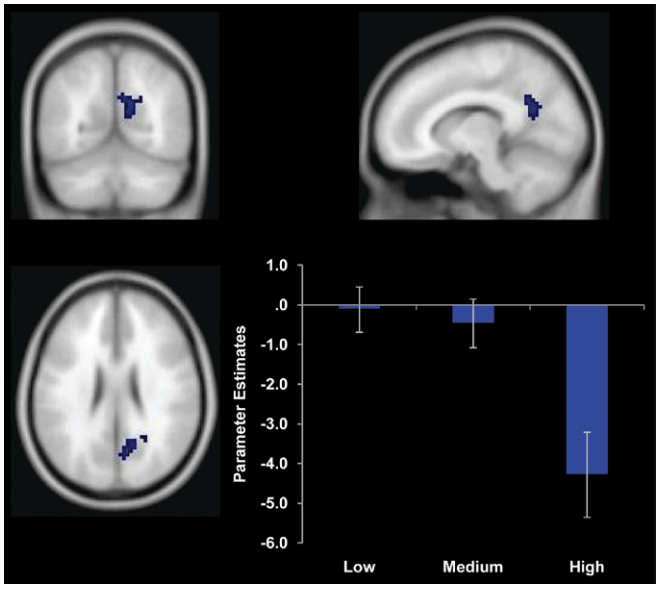

Figure 2. Posteromedial cortex region from which working memory load-related parameter estimates were extracted for each mild cognitive impairment (MCI) subject to use as predictor variables in the linear regression analyses. This region was selected as an a priori functional region of interest because deactivation in this region was greater in MCI subjects compared with healthy control subjects as load increased from medium to high level in a previous cross-sectional study. The posteromedial cortex region of interest (blue) is overlaid on a statistical parametric mapping high-resolution averaged T1-weighted image. Lower right: Plot of the mean parameter estimates averaged over the depicted posteromedial cluster for the MCI group at each load.

factors associated with decline in MCI, namely baseline clinical and functional status, MCI subtype, APOE ε4 carrier status, and GM and hippocampal volumes. Hence, in a randomly selected cohort of community living adults with broadly defined MCI, our task-related functional brain measure was a better predictor of decline on IADL than structural volumetric measures, genotyping, and clinical severity ratings. Task accuracy at high load also independently predicted decline—subjects with weaker in-scanner performance were more likely to decline.

This is the first study to demonstrate that increasing cognitive demand can elicit brain responses in persons with MCI—specifically deactivation—that are predictive of subsequent functional decline in everyday activities. One of the strengths of this study is that we controlled for a number of important risk factors and potential confounders such as volumetric atrophy in the fMRI region of interest and task performance levels. The importance of controlling performance levels in fMRI studies of MCI, both between and within groups of interest, has been discussed by our group (13) and others (51,52) in light of reported associations between brain activity and task performance (48,49). Using an individualized calibration method to set load levels, in-scanner performance variability was reduced among our subjects (13); however, task performance at the highest cognitive challenge was still found to be an independent predictor of functional decline. Importantly, load-related deactivation in PMC independently predicted decline and could not be accounted for by performance differences.

Using a backward elimination procedure, we retained a reduced model (Model 2) that, in addition to the fMRI and behavioral variables, also included clinical diagnostic information, suggesting a trend for the multiple-domain MCI subtype to better predict future decline than the single-domain subtype. This is consistent with observations from community-based prospective studies (43,53) and so inclusion of this clinical variable may enhance the potential clinical usefulness of our findings. By combining these three variables, functional decline over a 2-year period was predicted with a high level of confidence ($p < .001$). Functional brain response to increasing cognitive challenge is therefore an important factor in predicting longitudinal decline. Moreover, our task-related fMRI measure performed better than structural volumetric measures when predicting IADL decline. Reduced hippocampal and GM volumes are observed during the predementia stage (54–59) and have been shown to have some prognostic value (46,47); however, in the presence of fMRI parameters, volumetric measures did not independently predict decline, consistent with findings from other fMRI studies (4,29,31).

Few studies have investigated the prognostic significance of altered brain activity in MCI. Greater medial temporal lobe activity during memory tasks has been consistently found to predict clinical decline (4,29,31), and increased superior parietal lobe activity during spatial task performance has been observed in MCI subjects who progressed to AD compared with those who remained stable (28). The prognostic implications of alterations in task-induced deactivation in MCI have only recently been investigated. Petrella *et al.* (30) found that MCI subjects who progressed to AD had relatively reduced deactivation in PMC during memory task performance compared with those who remained stable. A progressive reduction of PMC task-induced deactivation was observed across the spectrum of healthy elderly to AD, a trend observed in some cross-sectional studies (10,25) but not others (60). Contrary to this, increased task-induced deactivation was predictive of functional decline in our study. Important methodological differences may account for these different results. In our study, the degree of task challenge was a key factor because increased deactivation was observed in the context of increased WM load, using individually calibrated load levels to minimize performance differences. In previous studies, a uniform task condition is typically presented to all

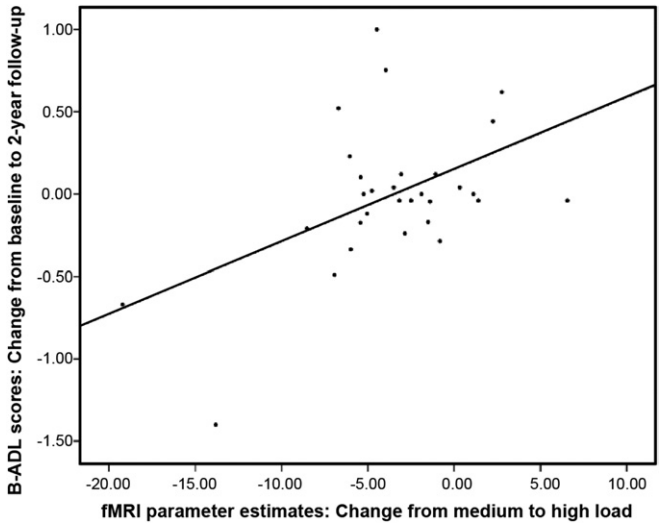

Figure 3. Association of load-related change in brain activity and change in Bayer-Activities of Daily Living Scale scores from baseline to 2-year follow-up. Scatter plot reveals that greater deactivation in response to increasing load from medium to high predicts greater decline in everyday functioning. Points on the graph represent values after the distributions were Winsorized so that all values fell within three standard deviations above or below the mean. B-ADL, Bayer-Activities of Daily Living Scale; fMRI, functional magnetic resonance imaging.

Table 3. Multiple Linear Regression Models Predicting Change in Bayer-ADL Score over Two Years

	Model 1			Model 2		
	β	*t*	*p*	β	*t*	*p*
Sociodemographic						
Age	−.12	−.68	.504	—	—	—
Education	−.19	−1.03	.319	—	—	—
Clinical						
MMSE-adjusted	.11	.55	.588	—	—	—
Bayer-ADL	−.10	−.46	.654	—	—	—
Amnestic/non-amnestic[a]	−.12	−.68	.509	—	—	—
Single/multiple domain[a]	−.21	−1.09	.290	−.23	−1.44	.163
APOE ε4 absent/present	.21	1.01	.326	—	—	—
Task Performance						
Accuracy high load	.48	2.48	**.025**	.38	2.42	**.023**
fMRI Parameter[b]						
High minus medium load	.42	2.22	**.041**	.45	2.63	**.014**
Structural MRI						
Total intracranial volume	.24	1.21	.245	—	—	—
Total gray matter volume	−.21	−.99	.338	—	—	—
PMC gray matter volume[c]	.03	.12	.910			
Total hippocampal volume	−.23	−1.14	.270	—	—	—
Overall Model		$R = .825$ ($p = .035$)			$R = .675$ ($p = .001$)	

Multiple linear regression analyses were used to test each model. Model 1 used the enter procedure and model 2 used the backward elimination procedure on the same set of variables shown for model 1. Significant findings ($p < .05$) are shown in bold.

APOE, apolipoprotein E; Bayer-ADL, Bayer-Activities of Daily Living Scale; fMRI, functional magnetic resonance imaging; MMSE-adjusted, Mini-Mental State Examination adjusted for age and education; MRI, magnetic resonance imaging; PMC, posteromedial cortex.

[a]Profile of cognitive impairments.

[b]β values extracted from the posteromedial cortex functional region of interest.

[c]Gray matter volume extracted from the posteromedial cortex functional region of interest.

participants. Few prior studies have controlled for performance differences.

A number of alternative neurobiological explanations can be hypothesized for why greater load-dependent deactivation in PMC was observed in persons with MCI who went on to decline functionally. In healthy young adults, greater deactivation is observed in PMC and other regions of the DMN in line with task increasing difficulty (61) or WM load (62). This has been interpreted as reflecting greater suppression of default activity during demanding tasks to reallocate finite processing resources toward task-relevant processes (17,63). In our MCI group, individuals who showed stronger PMC deactivation with increased load were less accurate. Therefore, one interpretation is that some individuals experienced greater subjective task difficulty because they were reaching the limits of their WM capacity (64), hence performing poorly despite greater deactivation. According to one theoretical model (65), increasing task demands may have uncovered a dysfunctional cognitive system because of accumulating neuropathology.

It is also possible that our findings reflect the outcome of compensatory processes, as has been proposed by others to explain increased task-positive activity in medial temporal lobe regions and other brain regions in MCI and AD (4,7,15,66,67). Compensatory mechanisms are processes engaged to mitigate against compromised cortical processes through reorganization of functional brain activity that lessen the cognitive impact of a primary neuropathological process. We cannot rule out that increased PMC deactivation may be reflective of a partially successful compensatory mechanism relating to use of general cognitive resources or task effort rather than task-specific processes. However, it is not possible, given the cross-sectional nature of the present imaging data, to predict how those subjects would have performed without recourse to such a putative compensatory strategy. Such a question could only be resolved by re-challenging the same subjects at a later time and examining intrasubject variance in performance and deactivation.

At this time, a definitive conclusion about the mechanism(s) underlying increased deactivation in decliners is not possible. A complex interplay of multiple factors is implicated, including cortical responses to increasing task demands, task performance, and, of course, a potentially variable level of disease burden among individuals with MCI. In future studies, the relationship between these factors may be more clearly demonstrated using longitudinal imaging with multiple modalities, such as Pittsburgh Compound-B positron-emission tomography together with fMRI to directly assess disease burden together with functional response within the same subjects. Recent evidence of reduced resting state connectivity within the DMN in cognitively normal elderly with high amyloid burden suggests a mechanism by which this network could be disrupted in MCI (68,69).

There are some limitations to this study. Firstly, the sample size was relatively small considering the expected heterogeneity of MCI samples drawn from the community. Multiple regression analyses are susceptible to potential outliers that may influence results. Importantly, our model was still robust upon removal of a subject who was the most clinically severe and had the greatest decline on B-ADL. Secondly, our follow-up period was relatively brief and given that the cohort was a heterogeneous group drawn from a community sample, it included very few who converted to dementia. Therefore, it is not possible to relate our fMRI measures to eventual conversion to dementia. The current findings do suggest, however, that fMRI may predict early decline before an individual reaches the threshold for a clinical diagnosis at a stage of disease when they may most benefit from future therapeutic interventions.

In this study, we have demonstrated that a graded WM task that allows examination of dynamic brain responses to changes in load is a good prototype of an fMRI paradigm that can predict decline in

everyday function over a brief follow-up period of 2 years. Our findings suggest that increased deactivation in PMC is evoked when faced with the highest working memory challenge. Akin to a cardiac stress test, this fMRI paradigm may be operating like a memory stress test, whereby the effort required to perform close to capacity uncovers cortical responses that are predictive of functional decline.

The study was supported by a James S. McDonnell Foundation Grant Brain Network Recovery Group (JSMF22002082) to MB; an Australian Rotary Health Research Grant to NAK, MB, and MJS; and a National Health and Medical Research Council of Australia Program Grant (350833) to PSS and HB.

We thank Dr. Anthony R. McIntosh of the Rotman Research Institute, Baycrest Center, Toronto, Canada, for helpful discussions regarding aspects of the experimental design. The scans were conducted at the Neuroscience Research Australia Imaging facility, Sydney, Australia; we thank the staff for their help with acquisition of the scans. The apolipoprotein E genotyping was performed by Arezoo Assareh and Dr. Karen Mather in the laboratory of Professor Peter Schofield and Dr. John Kwok at Neuroscience Research Australia. We thank the participants for their enthusiastic support.

Professor Henry Brodaty has served as a consultant and received speaker honararia for Pfizer, Lundbeck, Novartis, and Janssen. He has received funding from Pfizer, Eisai, Janssen, Novartis, Lundbeck, Voyager, and GlaxoSmithKlein and has served as a board member for Pfizer, Lundbeck, Wyeth, Novartis, and Janssen. Dr. Michael Valenzuela has received honoraria for scientific presentations from Pfizer Australia and The Brain Department and research funds from The Brain Department. Professor Henry Brodaty and Dr. Michael Valenzuela report no conflicts of interest relevant to the subject matter of this manuscript. All other authors report no biomedical financial interests or conflicts of interest.

Supplementary material cited in this article is available online.

1. Petersen RC (2004): Mild cognitive impairment as a diagnostic entity. *J Intern Med* 256:183–194.
2. Dubois B, Albert ML (2004): Amnestic MCI or prodromal Alzheimer's disease? *Lancet Neurol* 3:246–248.
3. Selkoe DJ (2002): Alzheimer's disease is a synaptic failure. *Science* 298: 789–791.
4. Dickerson BC, Salat DH, Bates JF, Atiya M, Killiany RJ, Greve DN, *et al.* (2004): Medial temporal lobe function and structure in mild cognitive impairment. *Ann Neurol* 56:27–35.
5. Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, *et al.* (2005): Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology* 65:404–411.
6. Kircher TT, Weis S, Freymann K, Erb M, Jessen F, Grodd W, *et al.* (2007): Hippocampal activation in patients with mild cognitive impairment is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry* 78:812–818.
7. Hämäläinen A, Pihlajamäki M, Tanila H, Hänninen T, Niskanen E, Tervo S, *et al.* (2007): Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiol Aging* 28:1889–1903.
8. Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, *et al.* (2006): Activation of brain regions vulnerable to Alzheimer's disease: The effect of mild cognitive impairment. *Neurobiol Aging* 27:1604–1612.
9. Petrella JR, Krishnan S, Slavin MJ, Tran TT, Murty L, Doraiswamy PM (2006): Mild cognitive impairment: Evaluation with 4-T functional MR imaging. *Radiology* 240:177–186.
10. Petrella JR, Wang L, Krishnan S, Slavin MJ, Prince SE, Tran TT, Doraiswamy PM (2007): Cortical deactivation in mild cognitive impairment: High-field-strength functional MR imaging. *Radiology* 245:224–235.
11. Machulda MM, Ward HA, Borowski B, Gunter JL, Cha RH, O'Brien PC, *et al.* (2003): Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. *Neurology* 61:500–506.
12. Mandzia JL, McAndrews MP, Grady CL, Graham SJ, Black SE (2009): Neural correlates of incidental memory in mild cognitive impairment: An fMRI study. *Neurobiol Aging* 30:717–730.
13. Kochan NA, Breakspear M, Slavin MJ, Valenzuela M, McCraw S, Brodaty H, Sachdev PS (2010): Functional alterations in brain activation and deactivation in mild cognitive impairment in response to a graded working memory challenge. *Dement Geriatr Cogn Disord* 30:553–568.
14. Clément F, Belleville S (2010): Compensation and disease severity on the memory-related activations in mild cognitive impairment. *Biol Psychiatry* 68:894–902.
15. Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, *et al.* (2006): Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: An independent component analysis. *J Neurosci* 26:10222–10231.
16. Woodard JL, Seidenberg M, Nielson KA, Antuono P, Guidotti L, Durgerian S, *et al.* (2009): Semantic memory activation in amnestic mild cognitive impairment. *Brain* 132:2068–2078.
17. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001): A default mode of brain function. *Proc Natl Acad Sci U S A* 98:676–682.
18. Sorg C, Riedl V, Mühlau M, Calhoun VD, Eichele T, Läer L, *et al.* (2007): Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* 104:18760–18765.
19. Bai F, Zhang Z, Yu H, Shi Y, Yuan Y, Zhu W, *et al.* (2008): Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: A combined structural and resting-state functional MRI study. *Neurosci Lett* 438:111–115.
20. Binder JR, Frost JA, Hammeke TA, Bellgowan PS, Rao SM, Cox RW (1999): Conceptual processing during the conscious resting state. A functional MRI study. *J Cogn Neurosci* 11:80–95.
21. Mazoyer B, Zago L, Mellet E, Bricogne S, Etard O, Houdé O, *et al.* (2001): Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res Bull* 54:287–298.
22. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, *et al.* (1997): Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *J Cogn Neurosci* 9:648–663.
23. Minoshima S, Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE (1997): Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. *Ann Neurol* 42:85–94.
24. Kemppainen NM, Aalto S, Wilson IA, Någren K, Helin S, Brück A, *et al.* (2007): PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. *Neurology* 68:1603–1606.
25. Pihlajamaki M, Sperling RA (2009): Functional MRI assessment of task-induced deactivation of the default mode network in Alzheimer's disease and at-risk older individuals. *Behav Neurol* 21:77–91.
26. Rombouts SA, Barkhof F, Goekoop R, Stam CJ, Scheltens P (2005): Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: An fMRI study. *Hum Brain Mapp* 26:231–239.
27. Lustig C, Snyder AZ, Bhakta M, O'Brien KC, McAvoy M, Raichle ME, *et al.* (2003): Functional deactivations: Change with age and dementia of the Alzheimer type. *Proc Natl Acad Sci U S A* 100:14504–14509.
28. Vannini P, Almkvist O, Dierks T, Lehmann C, Wahlund LO (2007): Reduced neuronal efficacy in progressive mild cognitive impairment: A prospective fMRI study on visuospatial processing. *Psychiatry Res* 156: 43–57.
29. Miller SL, Fenstermacher E, Bates J, Blacker D, Sperling RA, Dickerson BC (2008): Hippocampal activation in adults with mild cognitive impairment predicts subsequent cognitive decline. *J Neurol Neurosurg Psychiatry* 79:630–635.
30. Petrella JR, Prince SE, Wang L, Hellegers C, Doraiswamy PM (2007): Prognostic value of posteromedial cortex deactivation in mild cognitive impairment. *PLoS ONE* 2:e1104.
31. O'Brien JL, OKeefe KM, LaViolette PS, DeLuca AN, Blacker D, Dickerson BC, Sperling RA (2010): Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. *Neurology* 74:1969–1976.
32. Nygård L (2003): Instrumental activities of daily living: A stepping-stone towards Alzheimer's disease diagnosis in subjects with mild cognitive impairment? *Acta Neurol Scand Suppl* 179:42–46.

33. Artero S, Touchon J, Ritchie K (2001): Disability and mild cognitive impairment: A longitudinal population-based study. *Int J Geriatr Psychiatry* 16:1092–1097.
34. Sachdev PS, Brodaty H, Reppermund S, Kochan NA, Trollor JN, Draper B, *et al.* (2010): The Sydney Memory and Ageing Study (MAS): Methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70-90 years. *Int Psychogeriatr* 22:1248–1264.
35. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, *et al.* (2004): Mild cognitive impairment--beyond controversies, towards a consensus: Report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 256:240–246.
36. Hindmarch I, Lehfeld H, de Jongh P, Erzigkeit H (1998): The Bayer Activities of Daily Living Scale (B-ADL). *Dement Geriatr Cogn Disord* 9(suppl 2):20–26.
37. Erzigkeit H, Lehfeld H, Peña-Casanova J, Bieber F, Yekrangi-Hartmann C, Rupp M, *et al.* (2001): The Bayer-Activities of Daily Living scale (B-ADL): Results from a validation study in three European countries. *Dement Geriatr Cogn Disord* 12:348–358.
38. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ (1995): Statistical parametric maps in functional imaging: A general linear approach. *Hum Brain Mapp* 2:189–210.
39. Brett M, Anton JL, Valabregue R, Poline JB (2002): Region of interest analysis using an SPM toolbox. Presented at the 8th International Conference on Functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan. [Available on CD-ROM in *Neuroimage*, Vol 16].
40. Ashburner J, Friston KJ (2005): Unified segmentation. *Neuroimage* 26: 839–851.
41. Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H (2008): Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS ONE* 3:e2598.
42. Devanand DP, Liu X, Tabert MH, Pradhaban G, Cuasay K, Bell K, *et al.* (2008): Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. *Biol Psychiatry* 64:871–879.
43. Busse A, Bischkopf J, Riedel-Heller SG, Angermeyer MC (2003): Subclassifications for mild cognitive impairment: Prevalence and predictive validity. *Psychol Med* 33:1029–1038.
44. Busse A, Hensel A, Gühne U, Angermeyer MC, Riedel-Heller SG (2006): Mild cognitive impairment: Long-term course of four clinical subtypes. *Neurology* 67:2176–2185.
45. Tierney MC, Szalai JP, Snow WG, Fisher RH, Tsuda T, Chi H, *et al.* (1996): A prospective study of the clinical utility of ApoE genotype in the prediction of outcome in patients with memory impairment. *Neurology* 46: 149–154.
46. Kovacevic S, Rafii MS, Brewer JB, Alzheimer's Disease Neuroimaging Initiative (2009): High-throughput, fully automated volumetry for prediction of MMSE and CDR decline in mild cognitive impairment. *Alzheimer Dis Assoc Disord* 23:139–145.
47. Smith EE, Egorova S, Blacker D, Killiany RJ, Muzikansky A, Dickerson BC, *et al.* (2008): Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Arch Neurol* 65:94–100.
48. Rypma B, D'Esposito M (2000): Isolating the neural mechanisms of age-related changes in human working memory. *Nat Neurosci* 3:509–515.
49. Grady CL, Yu H, Alain C (2008): Age-related differences in brain activity underlying working memory for spatial and nonspatial auditory information. *Cereb Cortex* 18:189–199.
50. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984): Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34:939–944.
51. Han SD, Bangen KJ, Bondi MW (2009): Functional magnetic resonance imaging of compensatory neural recruitment in aging and risk for Alzheimer's disease: Review and recommendations. *Dement Geriatr Cogn Disord* 27:1–10.
52. Dickerson BC, Sperling RA (2008): Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: Insights from functional MRI studies. *Neuropsychologia* 46:1624–1635.
53. Ganguli M, Snitz BE, Saxton JA, Chang C-C, Hall KS, Lee C-W, *et al.* (in press): Outcomes of mild cognitive impairment depend on definition: A population study. *Arch Neurol*.
54. Becker JT, Davis SW, Hayashi KM, Meltzer CC, Toga AW, Lopez OL, *et al.* (2006): Three-dimensional patterns of hippocampal atrophy in mild cognitive impairment. *Arch Neurol* 63:97–101.
55. Karas GB, Scheltens P, Rombouts SA, Visser PJ, van Schijndel RA, Fox NC, Barkhof F (2004): Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 23:708–716.
56. Trivedi MA, Wichmann AK, Torgenson BM, Ward MA, Schmitz TW, Ries ML, *et al.* (2006): Structural MRI discriminates individuals with mild cognitive impairment from age-matched controls: A combined neuropsychological and voxel based morphometry study. *Alzheimers Dement* 2:296–302.
57. Wolf H, Hensel A, Kruggel F, Riedel-Heller SG, Arendt T, Wahlund LO, Gertz HJ (2004): Structural correlates of mild cognitive impairment. *Neurobiol Aging* 25:913–924.
58. Slavin MJ, Sandstrom CK, Tran TT, Doraiswamy PM, Petrella JR (2007): Hippocampal volume and the Mini-Mental State Examination in the diagnosis of amnestic mild cognitive impairment. *AJR Am J Roentgenol* 188:1404–1410.
59. Shi F, Liu B, Zhou Y, Yu C, Jiang T, Shi F (2009): Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. *Hippocampus* 19:1055–1064.
60. Gould RL, Brown RG, Owen AM, Bullmore ET, Howard RJ (2006): Task-induced deactivations during successful paired associates learning: An effect of age but not Alzheimer's disease. *Neuroimage* 31:818–831.
61. McKiernan KA, Kaufman JN, Kucera-Thompson J, Binder JR (2003): A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J Cogn Neurosci* 15:394–408.
62. Tomasi D, Chang L, Caparelli EC, Ernst T (2007): Different activation patterns for working memory load and visual attention load. *Brain Res* 1132:158–165.
63. Gusnard DA, Raichle ME (2001): Searching for a baseline: Functional imaging and the resting human brain. *Nat Rev Neurosci* 2:685–694.
64. Cowan N (2005): *Working Memory Capacity*. New York: Psychology Press.
65. Prvulovic D, Van de Ven V, Sack AT, Maurer K, Linden DE (2005): Functional activation imaging in aging and dementia. *Psychiatry Res* 140:97–113.
66. Grady CL, McIntosh AR, Beig S, Keightley ML, Burian H, Black SE (2003): Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *J Neurosci* 23:986–993.
67. Bokde AL, Lopez-Bayo P, Born C, Dong W, Meindl T, Leinsinger G, *et al.* (2008): Functional abnormalities of the visual processing system in subjects with mild cognitive impairment: An fMRI study. *Psychiatry Res* 163:248–259.
68. Hedden T, Van Dijk KR, Becker JA, Mehta A, Sperling RA, Johnson KA, Buckner RL (2009): Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *J Neurosci* 29:12686–12694.
69. Sheline YI, Raichle ME, Snyder AZ, Morris JC, Head D, Wang S, Mintun MA (2010): Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. *Biol Psychiatry* 67:584–587.
70. Anderson TM, Sachdev PS, Brodaty H, Trollor JN, Andrews G (2007): Effects of sociodermographic and health variables on Mini-Mental State Exam scores in older Australians. *Am J Geriatr Psychiatry* 15:467–476.