Neuropsychology
2010, Vol. 24, No. 6, 757–774

0894-4105/10/$12.00 DOI: 10.1037/a0020314

Task Switching Performance Reveals Heterogeneity Amongst Patients With Mild Cognitive Impairment

Marco Sinai
Concordia University

Natalie A. Phillips
Concordia University and Lady Davis Institute for Medical Research/Jewish General Hospital

Howard Chertkow
Lady Davis Institute for Medical Research/Jewish General Hospital

Noor Jehan Kabani
Sunnybrook and Women's College Health Sciences Centre

Objective: To assess executive function in patients with mild cognitive impairment (MCI) and to determine whether task switching ability is associated with transition to Alzheimer's disease. ***Methods:*** Twenty-seven MCI patients and 19 older controls were tested using a cued letter-digit classification switching task. Sixteen patients could perform the task (MCI-able), 6 could not (MCI-unable), and 5 were able only with cognitive support (MCI-cue). Demographic, neuropsychological, event-related potential (ERP), MRI, and genetic data were also collected. ***Results:*** The four groups did not differ on age, gender, and APO E4 frequency. Compared to the controls, the MCI-unable group had significantly poorer performance on the Trail Making task ($\eta^2 = .430$), lower education ($\eta^2 = .234$), and smaller cortical volume ($\eta^2 = .245$). Most MCI patients exhibited task-switching deficits but to vastly different degrees and with varying outcomes. The combined pattern of neuropsychological and task switching performance indicates that the MCI-able patients displayed memory retrieval difficulties ($F(2,39) = 3.6$, $p = .036$, $MSE = 1.44$), generally preserved task switching abilities, and had a high probability of remaining dementia-free at follow-up. The MCI-cue patients had increased mixing costs, $F(2,39) = 11.0$, $p < .001$, $MSE = .07$; the MCI-unable patients showed episodic memory deficits, and both groups had a high probability of poor outcome (i.e., developing AD or dying within four years). ***Conclusion:*** This study demonstrates that variability in performance on measures of task-switching can highlight important heterogeneity in the MCI population.

Keywords: mild cognitive impairment (MCI), executive functions, task switching, cognitive reserve, event-related brain potentials (ERPs)

Mild cognitive impairment (MCI) has been proposed to be a transitional state between healthy aging and dementia and is characterized by a decline in memory function (i.e., excess of 1.5 *SD* from the norm) without the full range of cognitive deficits and functional decline observed in Alzheimer's disease (AD; Petersen & Negash, 2008). The MCI diagnostic classification has shown clinical utility because individuals with MCI are at greater risk for conversion to AD than their age peers in the general population. Estimates of MCI progression to AD are in the 10–15% per year range compared with healthy elderly controls who progress at a rate of 1–2% per year (Petersen & Negash, 2008). However, this high risk population has proved to be highly heterogeneous, with a significant minority of MCI patients returning to a normal profile and another sizable subgroup remaining stable even up to a 10-year follow-up (e.g., Ganguli, Dodge, Shen, & DeKosky, 2004). The ability to distinguish those MCI patients who are more likely to imminently progress to AD from those who will remain stable or will improve to normal status is of obvious clinical importance.

There is evidence that MCI patients with isolated episodic memory deficits have significantly lower risk of transitioning to dementia relative to MCI patients with deficits in multiple cognitive domains. For example, Rasquin, Lodder, Visser, Lousberg, and Verhey, (2005) found very high negative predictive validity of the MCI subtype comprising patients with isolated memory deficits (aMCI-s), indicating that the likelihood that these patients would transition to AD in the following two years was low. Similarly, Artero, Petersen, Touchon, and Ritchie (2006) found that, at two year follow-up, aMCI-s patients showed a less than 1% rate of AD conversion compared to a 13% rate of conversion for MCI patients with deficits in memory and other cognitive areas.

This article was published Online First October 4, 2010.

Marco Sinai, Department of Psychology/Centre for Research in Human Development, Concordia University; Natalie A. Phillips, Department of Psychology/Centre for Research in Human Development, Concordia University, and Lady Davis Institute for Medical Research/Jewish General Hospital; Howard Chertkow, Lady Davis Institute for Medical Research/Jewish General Hospital; Noor Jehan Kabani, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada.

A portion of these data was reported previously at the *11th Biennial Cognitive Aging Conference*, April 20–23, Atlanta. GA, U.S.A. We thank L. Ingenito for her assistance in subject testing and data processing, S. Solomon for her assistance in participant recruitment, and V. Penhune for helpful discussions. We are grateful to our study participants for their time and effort. This study was supported by Grant 04-29 awarded to Natalie A. Phillips from the Alzheimer Society of Canada. Marco Sinai was supported by a Canadian Institutes of Health Research (CIHR) Doctoral Fellowship.

Correspondence concerning this article should be addressed to Natalie A. Phillips, Ph.D., Centre for Research in Human Development, Department of Psychology, Concordia University, 7141 Sherbrooke Street West, Montréal, Québec, Canada, H4B 1R6. E-mail: Natalie.Phillips@concordia.ca

Also, Bozoki, Giordani, Heidebrink, Brent, and Foster (2001) found a 6% conversion rate for aMCI-s patients compared to a 50% conversion rate for MCI patients with deficits in memory and other cognitive domains. Of all the nonmemory cognitive domains affected in MCI, attention and executive functions have been shown to be the best predictors of MCI conversion to AD (Belleville, Chertkow, & Gauthier, 2007; Perry, Watson, & Hodges, 2000).

Although a defining characterization of executive functions remains elusive, most authors agree that the inherent nature of executive functions is to organize and control other functions, such as memory, attention, and motor responses (Royall et al., 2002). As such, executive functions are never seen in isolation but rather emerge "on top" of the primary functions, a characteristic that complicates the task of measuring them. The fractionation of separable, although not totally independent executive functions has received support from several studies using factor analysis with various populations (Miyake et al., 2000; Royall et al., 2002). Miyake et al. (2000) showed three basic executive functions that were clearly separable, namely inhibition (i.e., the ability to override dominant or prepotent responses), working memory updating (i.e., monitoring and processing of incoming information and the continuous updating of its relevance to the task at hand), and shifting (i.e., the ability to rapidly switch between two tasks or mental sets).

The ability to switch flexibly between tasks, locations, or objects is emerging as one of the most ubiquitous cognitive functions, implicated not only in spatial and visual tasks but also in motor tasks (Rushworth, Hadland, Paus, & Sipila, 2002) and language (Gurd, Weiss, Amunts, & Fink, 2003; Jackson, Swainson, Mullin, Cunnington, & Jackson, 2004). Several tasks have been used to study switching ability. The covert attention task (Posner, 1980) was designed to study shifts of visual attention between different locations whereas the Wisconsin Card Sorting Task is thought to require shifts of mental sets between stimulus dimensions (Milner, 1963). Further, several studies have shown significant group differences between MCI patients and normal controls on the Trail Making B test, a widely used clinical test of shifting abilities in which the participants must connect points on a sheet of paper alternating between numbers and letters in ascending order (Albert, Moss, Tanzi, & Jones, 2001; Blacker et al., 2007; Chen et al., 2000; Daly et al., 2000; Lopez et al., 2006; Rapp & Reischies, 2005; Silveri, Reali, Jenner, & Puopolo, 2007; Zhang, Han, Verhaegen, & Nilsson, 2007). Although easily administered and widely used, this clinical test taps into general switching ability and does not lend itself easily to the exploration of the specific component processes involved in task switching.

Task Switching Paradigm

In contrast to clinical measures, experimental versions of the task switching paradigm (Allport, Styles, & Hsieh, 1994; Meiran, Chorev, & Sapir, 2000; Rogers & Monsell, 1995) have been widely used to study set-shifting in the cognitive psychology literature. In the cued task switching design, the order of each task to perform is random and the participant is cued on every trial as to which task to perform next. In this context, the need to switch from one task to another involves a series of events, such as disengaging from the old task, engaging the new task, processing the stimulus, and selecting the appropriate response. It likely involves a combination of both primary (e.g., perceptual, memory, and motor processes) and control processes, with the latter serving to coordinate the former. Distinct control processes are thought to be involved in the two main cost types, the mixing cost and the switch cost, defined as follows.

The broadest measure of switching ability is the contrast between repeat trials during blocks where the participant has to switch between two tasks (i.e., a mixed block of trials) and trials in blocks where the participant has to perform only one task (i.e., a homogeneous block of trials); this contrast is referred to as the mixing cost. The cost, usually expressed in reaction time (RT) or error rates (ER), is believed to reflect the engagement of extra monitoring processes during mixed as opposed to single task blocks (Meiran et al., 2000) and has been seen as a measure of working memory resources required to manage more than one task in rapid succession (Kray & Lindenberger, 2000).

The second, more widely studied aspect of the task switching paradigm is the contrast between trials where the participant must switch between performing a different task and trials where the participant is able to repeat a task. The reaction time difference, which typically results from slower switch trials and faster repeat trials, has been termed the switch cost (Rogers & Monsell, 1995). Although debate about the nature of the switch cost still remains, there is consensus that it reflects at least two distinct set of processes. The first is a goal-directed, endogenous set of processes that reconfigure the task-set in anticipation of the performance of the upcoming task. The second is a stimulus-driven, exogenous set of processes evoked by the target that complete the reconfiguration process (Meiran, 2000; Rogers & Monsell, 1995; Rubinstein, Meyer, & Evans, 2001; Rushworth, Passingham, & Nobre, 2002).

Notwithstanding the ongoing debate regarding the exact nature of the control processes underlying the switch cost, Mayr and Kliegl (2000) have proposed that much of what a subject can do to prepare for an upcoming task is to retrieve the task rules[1] from long-term memory. According to this view, memory retrieval processes are recruited during task switching but are not control processes per se. Thus, there could be multiple explanations for task switching difficulty in MCI. It could be due to impairment in the processes indexed by the mixing and/or switch costs or, given the episodic memory deficits of MCI patients, it could be due to impairment in that domain.

Task Switching and ERPs

One technique that has successfully been used in conjunction with more classical performance measures in the exploration of cognitive phenomena is the recording of event-related potentials (ERPs). The ERP is a measure derived from the human electroencephalogram (EEG) and is time-locked to specific events. The usefulness of the ERP technique in the study of task switching processes is enhanced by the cued task switching paradigm. It can be argued that brain activity time-locked to the cue presentation reflects processes tied to task preparation in anticipation of the

[1] An example of a rule for Task A might be, if the stimulus is a letter and is a vowel then press the right button, if it is a consonant then press the left button; for Task B, the rule might be, if the stimulus is a number and is even then press the right button, if it is odd then press the left button.

target which, as was reviewed above, likely includes the retrieval of task rules from long term memory (Mayr & Kliegl, 2000).

A growing number of studies have used ERPs to examine the different control processes involved in task switching with differing task switching designs (Goffaux, Phillips, Sinai, & Pushkar, 2006, 2008; Karayanidis, Coltheart, Michie, & Murphy, 2003; Karayanidis et al., 2010; Lorist et al., 2000; Poulsen, Luu, Davey, & Tucker, 2005; Sinai, Goffaux, & Phillips, 2007). Despite methodological differences, all studies show the presence of a negative slow wave over posterior scalp regions in the later part of the cue-target interval. This is possibly a stimulus preceding negativity (SPN), which is believed to reflect attentional processes in anticipation of the upcoming target stimulus (Brunia & van Boxtel, 2001). This posterior negativity has been shown to be enhanced on homogeneous trials versus repeat trials, which in turn are enhanced relative to switch trials and has been interpreted as facilitated processing during repeat trials relative to switch trials (Goffaux et al., 2006).

Current Study

To summarize thus far, there is mounting evidence that task switching ability may be one of the first functions outside of episodic memory to be affected in very early AD and MCI. However, because most of the evidence comes from traditional paper-and-pencil tests, it is unclear which of the several component processes of task switching might be affected in MCI.

The current study is divided into two parts. The first part was an in-depth analysis of behavioral and ERP data designed to explore whether task switching deficits in MCI patients are due to reduced performance in primary functions, such as retrieval of information from long-term memory, or rather are due to failures in control processes as indexed by the mixing and switch costs. We expected the MCI group to be slower overall on mixed trials relative to their age-matched controls. Whether these performance deficits come in the presence or absence of mixing and/or switch costs would be very informative regarding the exact nature of task-switching deficits in MCI. Simply put, observing performance deficits in the absence of group differences in mixing and switch costs would argue against the involvement of control processes and would suggest that nonexecutive processes like processing speed or memory retrieval could account for any observed task-switching deficits. In contrast, group differences in mixing cost would suggest the presence of working memory deficits. Further, the presence of group differences in switch costs would argue in favor of increased MCI difficulty in task-set reconfiguration.

The second part of the study was an effort to identify the variables associated with poor task switching ability in MCI. To this end, we present demographic, genetic and neuroanatomical data associated with MCI patients with varying levels of task switching performance. We collected structural magnetic resonance imagery (MRI) data from MCI and controls. Since both frontal and parietal areas have been implicated in task switching (Wager, Jonides, & Reading, 2004) and some studies have shown significant atrophy in these areas in MCI compared to controls (Bell-McGinty et al., 2005; Chételat et al., 2005), we expected to find significant differences between MCI patients with poor task switching abilities and controls in both parietal and frontal areas.

Regarding genetic data, we compared the frequency of occurrence of the Apolipoprotein E (ApoE) 4 allele in MCI patients and controls. To our knowledge, no study has directly examined the relationship between ApoE polymorphism and task switching performance; however, the presence of ApoE4 has been widely recognized as a significant risk factor for AD pathology (Corder et al., 1995; Slooter et al., 1998) and has been associated with working memory and covert attention deficits in nondemented individuals (Parasuraman, Greenwood & Sunderland, 2002; Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002). Given this evidence, we expected to find higher frequency of ApoE 4 carriers in the MCI patients with poor task switching ability compared to MCI with good switching ability and with controls.

Finally, we present 4-year follow-up data on the participants' diagnostic status to determine the possible predictive utility of this executive function deficit in this MCI group. Given previous reports of increased risk of AD conversion in MCI patients with deficits in multiple cognitive domains (Artero et al., 2006; Bozoki et al., 2001; Rasquin et al., 2005), we expected a larger proportion of conversions to AD in the MCI patients with poor task switching ability relative to MCI patients with good task-switching ability.

Methods

Participants

MCI sample. MCI subjects were recruited from the Memory Clinic of the Sir Mortimer B. Davis–Jewish General Hospital (JGH), a tertiary care referral center of McGill University, Montreal. Their investigations included full medical, neuropsychological, and neuroradiological evaluations.

Twenty-seven individuals identified as having mild cognitive impairment (MCI) participated. They all received CDR scores of 0.5, indicating mild forgetfulness, minimal word finding difficulties, and a slight impairment in mental efficiency (Hughes, Berg, Danzinger, Cohen, & Martin, 1982). All patients met the original (Petersen et al., 1999) criteria for mild cognitive impairment that included a reported decline (by either the individual or family) in memory function that was gradual and of at least 6 months duration, a documentation of impaired performance (i.e., ± 1.5 *SD*) on objective neuropsychological tests with appropriate norms for age and/or education, the absence of significant impairment in activities of daily living, and failure to meet the criteria for dementia, as determined by the assessing physician in the Memory Clinic.

Of these 27 MCI patients, 16 were able to perform the task switching task and were classified as the "MCI-able" group for the purpose of this study. The remaining 11 MCI patients were not able to perform the original task as described below in the Experimental Task Switching Paradigm section. Their difficulties are described below in more detail; however, for now we note that of these 11 patients, six were not even able to complete the homogeneous blocks and are referred to as the "MCI-unable" group. The remaining five MCI patients, referred to as the "MCI-cue" group, were able to complete the homogeneous blocks but could not perform on mixed blocks. In an effort to collect data from these patients, the original design was modified slightly as described in the Experimental Task Switching Paradigm section below.

Control group. Nineteen healthy elderly adults were recruited from the Herzl Family Medicine Clinic of the JGH and screened at the JGH Memory Clinic to ensure they had no symptoms of dementia and their neuropsychological profile was normal (Clinical Dementia Rating, CDR = 0).

All participants gave informed consent for their participation. The study was approved by the Jewish General Hospital and Concordia University Human Ethics committees.

Experimental Task Switching Paradigm

Materials. All stimuli in the experimental task were presented in 24 font size, Times New Roman white font, on a black background in the middle of a standard 15 in. CRT computer screen. A cue (either the word "Number" or "Letter") instructed the participants on the upcoming task for each trial. The experimental stimuli consisted of bivalent letter/digit pairs (e.g., 5G,A2, etc.) and letter or digit/neutral pairs (e.g., %A). The compound stimuli were constructed from the following stimulus pools: letters: A, E, I, U, L, M, G, K; numbers: 2, 3, 4, 5, 6, 7, 8; and neutral symbols: %, #, &, $.

Procedure. The experimenter visited the patient's home one or two days prior to the experimental session. The home session consisted of a cognitive screening battery and an extensive training session for the experimental task lasting 30 minutes to teach the patients the stimulus–response associations.

The experimental procedure is depicted in Figure 1. Participants were asked to perform either a letter or number classification task on any given trial. Participants held a standard mouse in their hands and responded by pressing the mouse keys with either the left or right thumb. Responses were bivalent, meaning that the same response keys were used for both tasks. The letter task entailed classifying a letter being as a vowel or a consonant and responding with either the right or the left key. The digit task entailed classifying a digit as being either an even or odd number and responding with either the right or left key. Each trial began with the presentation of a cue (i.e., letter or number) that instructed the participant as to which task to perform next. The cue remained on the screen for 1000 ms and was replaced by the presentation of the compound stimulus that remained on the screen until the participant responded or up to a maximum of 10 seconds. The following trial began following a 200 ms interval after the response or time-out.

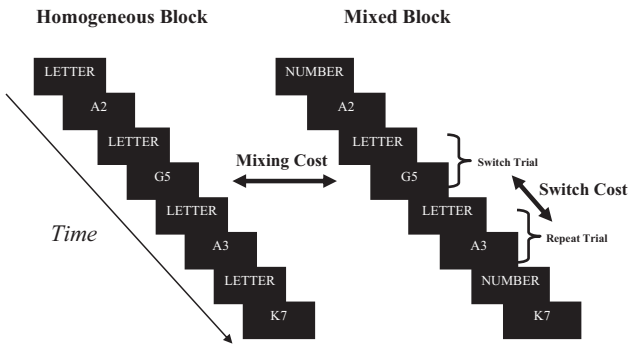

Figure 1. Time course of stimulus presentation for homogeneous (left side) and mixed (right side) blocks. Each trial started with the presentation of a cue followed by a blank screen, followed by the presentation of a target that remained on the screen until the participant responded.

Following the ERP set-up (approximately 40 minutes) of the experimental session, each participant was given three 48-trials practice blocks consisting of "letter" only, "number" only, and "mixed" trials respectively. After the practice blocks, each participant was presented with eight experimental blocks of 90 trials each (the first six trials of each experimental block was not retained for analysis). The first two blocks, called homogeneous blocks, consisted of trials cued by only one task, either "Letter" or "Number," the order of which was counterbalanced across participants. In other words, no switching between tasks was required in these blocks. The following six blocks, called mixed blocks, consisted of a semirandom mixture of letter (50%) and number (50%) task trials in response to the compound stimuli. Thus, switch and repeat trials occurred with equal probability. The sequence was semirandom in the sense that there were no more than three of the same trial type (either switch or repeat) allowed in a row.

Participants held the mouse with both hands and responded by pressing either the left or right button with their thumbs. In case of a response error, feedback was signaled by a 400 Hz 100 ms tone immediately following the response and the following trial began after an 800 ms delay. Participants were instructed to respond as quickly as possible while keeping errors to a minimum.

As stated previously, 16 MCI participants were able to complete the task under these conditions, but 11 MCI patients were classified as unable to perform the task when they exceeded a 20% error rate on any one block. In most of these cases, the participant would start the block correctly but would then become confused after the first few errors and would subsequently perform at near chance accuracy despite multiple repetitions of the instructions and additional practice. Of these 11 participants, five were able to complete the homogeneous blocks but had difficulty in the mixed condition. In an effort to collect behavioral and ERP data on these patients, the design was slightly modified in order to minimize working memory demands by leaving the cue on the screen along with the target until the response (see Figure 2). Under these conditions, these five MCI patients were able to complete the mixed blocks. However, the remaining six MCI patients were unable to accurately perform the task regardless of the amount of support provided.

Neuropsychological Evaluation

As part of their diagnostic clinical examination, the MCI participants underwent a neuropsychological evaluation with the following tests:

Global cognition. Global cognition was evaluated by the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) and the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005).

Episodic memory. Episodic memory was evaluated by the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958) to assess immediate and delayed verbal learning, recall, and recognition.

Working memory. Working memory was evaluated by Letter Number Sequencing from the WMS-III (Wechsler, 1997).

Executive functions. Executive functions were evaluated by the Clock Drawing Test (Shulman, Shedletsky, & Silver, 1986);

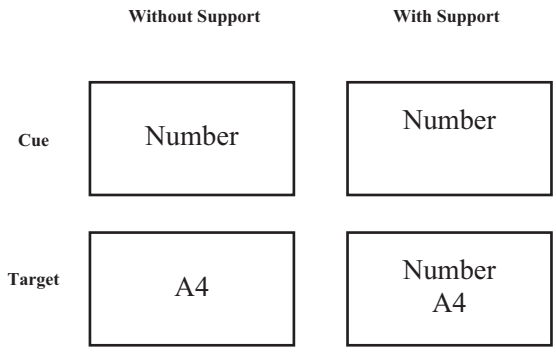

Figure 2. Illustration of cue and target presentation in the original and modified design. Left panel: normal controls and MCI-able participants were able to perform the task when the cue disappeared just prior to target presentation. Right panel: five MCI participants were able to perform the task when the cue remained on the screen along with the target until response.

phonological (letters *F*, A, and S) and semantic (animal) fluency (Strauss, Sherman & Spreen, 2006); Digit Symbol Coding from the Wechsler Adult Intelligence Scale III (WAIS–III; Wechsler, 1997); and the Color Stroop Test (Victoria version; Lezak et al., 2004) to assess selective attention and response inhibition. We also used the Trail Making Test A and B (Lezak et al., 2004) to provide convergent validity on the ability to switch between tasks. We also report the Trails ratio (Trails B/Trails A), which takes into account each participant's baseline visual processing speed.

Language functions. Language functions were evaluated by Similarities (WAIS–III; Wechsler, 1997) to assess verbal abstract reasoning abilities and the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) to assess confrontation naming skills.

This same neuropsychological battery was also administered to the normal control participants.

Other Study Variables

Depression. Symptomatic depression was estimated with the Geriatric Depression questionnaire (GDS; Yesavage et al., 1982) and was measured at the time of the neuropsychological evaluation.

Time since diagnosis. This variable represents the number of months elapsed between the date of the diagnosis of mild cognitive impairment and the task switching session. It is used in this study as an estimate of disease progression.

Years since symptom onset. This variable represents the number of years elapsed between the chart-recorded onset of symptoms of memory loss as reported by the patient and the date of the task switching session.

Genetic data. Genotyping of apolipoprotein E was carried out using DNA extracted from peripheral leukocytes. DNA was amplified by polymerase chain reaction (PCR), digested with Hhal, and separated by electrophoresis on an 8% polyhacrylaamide nondenatured gel. DNA fragments were viewed by ultraviolet illumination after the gel was treated with ethidium bromide for 30 minutes. Subjects were categorized as e4 carriers if they carried at least one copy of the e4 allele. One participant in the MCI-unable group had a 2/4 genotype and was not considered in the analyses.

Four-Year Follow-Up

We obtained the diagnostic status of each participant approximately four years after the task switching session ($M = 49$ months, $SD = 4.9$). Two MCI-unable patients were lost to follow-up.

Magnetic Resonance Image Acquisition and Processing

MRI scans at the Montreal Neurological Institute were acquired on a Philips Gyroscan ACS, 1.5 Tesla superconducting magnet system. T1-weighted images were obtained using three-dimensional spoiled gradient-echo acquisition with sagittal volume excitation (TR518, TE510, flip angle 308, 1 mm isotropic voxels, 140–180 sagittal slices). The scans were then processed using a standard set of image processing algorithms (Zijdenbos, Forghani, & Evans, 2002). Briefly, this first entailed correcting for intensity inhomogeneity in the images using the N3 algorithm (Sled, Zijdenbos, & Evans, 1998) and then linearly registering the images to a standardized space (Collins, Neelin, Peters, & Evans, 1994).

The Automatic Nonlinear Image Matching and Anatomical Labeling (ANIMAL) volumetric registration package and the Intensity Normalized Stereotaxic Environment for the Classification of Tissue (INSECT) procedure were used to quantify 16 cortical regions (see Table 4 for a list) by registering the T1-weighted images to a probabilistic atlas (Collins, Zijdembos, Baare, & Evans, 1999). We chose these 16 areas according to two main principles. First, temporal lobe areas were included because they are the earliest regions affected in AD and are therefore relevant to the question of MCI-AD conversion. Second, selected parietal and frontal areas were included because of their relevance in executive functions in general and task switching in particular (Wager et al., 2004).

Electrophysiological Recording and Data Analysis

The EEG was recorded from 74 Ag/AgCl electrodes mounted in an elastic cap (Easycap). A forehead location was used as ground. All sites were referenced to the left ear and rereferenced offline to linked ears. Electro-oculogram activity (EOG) was recorded from electrodes placed at the outer canthi of both eyes (horizontal EOG) and above and below the left eye (vertical EOG). Vertical and horizontal EOG artifacts were corrected off-line for all participants using the spatial filter procedure as implemented by the Neuroscan software (Edit 4.3, Neuroscan, 2003, p. 246). Electrode impedances were kept below 5 kΩ and EEG data were amplified using Neuroscan Synamps in a DC-30 Hz bandwidth and sampled at 500 Hz.

ERPs were recorded time-locked to the cue onset. Consistent with the behavioral data, trials following an incorrect answer or trials tagged as statistical outliers on the basis of RT data were excluded from analysis. Cue-locked epochs spanned −100 to 1000 ms and employed a baseline 100 ms interval before cue presentation. Statistical analyses were performed on mean waveform amplitudes averaged across the following intervals: 200–400 ms, 400–600 ms, 600–800 ms, and 800–1000 ms.

The six midline electrode sites (FPz, Fz, FCz, Cz, CPz, Pz) were chosen for the analyses since effects were most prominent there.[2]

Behavioral Data Analysis

Behavioral data were obtained simultaneously with ERP data. Participants' RTs were measured as the time taken to respond to the target stimulus after it appeared on the screen. RTs were analyzed for correct trials only and the trials that followed an incorrect response were also excluded from analysis. RTs longer than three standard deviations from the mean and trials with RT less than 200 ms were excluded from analysis; these rejected outliers consisted of fewer than 2% of total trials.

Statistical Analysis

For behavioral data, mixing cost RT and error rate (ER) data were analyzed with a mixed ANOVA with mixing (repeat vs. homogeneous trials) as the within subject factor and group (Controls vs. MCI-able vs. MCI-cue) as the between subject factor. Switch cost RT and ER data were each analyzed with a mixed ANOVA with switch (switch vs. repeat trials) as the within subject factor and group as the between subject factor.

ERP cue-locked data were not only analyzed with two mixed ANOVAs with similar designs as above but also including two additional within factors, namely electrode site (five levels: FPz, Fz, FCz, Cz, CPz, Pz) and time interval (six levels: 200–400 ms, 400–600 ms, 600–800 ms, and 800–1000 ms).

Neuropsychological data were analyzed using a multivariate analysis of covariance (MANCOVA) on 14 measures (see Table 2) derived from the 13 neuropsychological tests described above, with years of education and GDS scores as covariates. Statistical significance was followed up by Bonferroni corrected post hoc comparisons.

Sociodemographic variables were analyzed with the chi-square (χ^2) statistic in the case of discrete variables and with a multivariate analysis of variance (MANOVA) in the case of interval data. In the case of χ^2 analyses, $\alpha = .025$ level was used for post hoc comparisons between the control group and the two MCI groups.

Neuroanatomical data were analyzed using a repeated-measures mixed ANOVA with laterality and region as within subject factors, group as the between subject factor, and gray matter volume expressed in mm^3 as the dependent variable.

In the repeated measures analyses, the Greenhouse-Geisser (1959) correction for nonsphericity was employed when appropriate. Following convention, unadjusted degrees of freedom are reported, along with the Greenhouse-Geisser adjusted p value. Mean square error (*MSE*) values reported are those corresponding to the Greenhouse-Geisser correction. The main effect of variables are reported first but described only if they did not interact with other variables. In the case of significant interactions, post hoc Bonferroni-corrected ANOVAs were conducted where appropriate. Statistical significance is assumed at the $\alpha = .05$ level unless otherwise specified.

Results

Sociodemographic Results

Table 1 summarizes the sociodemographic results for the four groups (i.e., the three MCI subgroups and the Controls). The overall MANOVA was significant ($F_{(9,126)} = 3.0$, $p = .003$, $\eta^2 = .176$). Post hoc analyses revealed significant effects on two variables. With respect to education ($F_{(3,42)} = 4.3$, $p = .01$, $\eta^2 = .234$), the MCI-unable group had fewer years of education ($M = 10.1$ year, $SE = 1.2$) than the control group ($M = 14.5$ years, $SE = .7$; $p = .017$), but there was no significant difference between the controls and MCI-able or between the MCI-able and MCI-cue groups ($p > .187$). There was also a significant effect for depression ($F_{(3,42)} = 6.7$, $p = .001$, $\eta^2 = .325$) with MCI-cue patients reporting higher symptoms ($M = 13.0$, $SE = 2.0$) than MCI-able patients ($M = 4.8$, $SE = 1.1$) and than controls ($M = 2.9$, $SE = 1.0$). It is important to note, however, that the four groups did not differ on age ($F_{(3,42)} = .1$, $p = .96$). Further, the three MCI groups did not differ in time since diagnosis ($F_{(2,24)} = 1.3$, $p = .27$) and years since symptom onset ($F_{(2,24)} = 2.6$, $p = .09$). Chi-square analyses indicated no group differences in gender and Apo E4 distribution (all ps $> .12$).

Neuropsychological Results

Table 2 summarizes neuropsychological test performance for all four groups. A MANCOVA was performed with years of education and GDS scores as covariates because some of the MCI subgroups differed on these variables, which can influence cognitive function.

The overall MANCOVA was significant ($F_{(48,81)} = 2.2$, $p = .001$, $\eta^2 = .567$). Post hoc analyses revealed significant effects on two global measures of cognitive function; in the MMSE ($F_{(3,40)} = 3.9$, $p = .015$, $\eta^2 = .229$), the MCI-unable group had lower scores than controls ($p = .044$) and the MCI-able group ($p = .013$); in the MoCA ($F_{(3,40)} = 3.6$, $p = .02$, $\eta^2 = .216$), the MCI-unable group had lower scores than controls ($p = .024$).

In the episodic memory domain significant group differences were found in RAVLT Immediate Recall ($F_{(3,40)} = 6.9$, $p = .001$, $\eta^2 = .343$), with MCI-able ($p = .002$) and MCI-unable ($p = .003$) groups having lower scores than the controls; RAVLT Delayed Recall ($F_{(3,40)} = 7.9$, $p < .001$, $\eta^2 = .373$), with the MCI-able ($p = .001$) and MCI-unable ($p < .001$) groups having lower scores than controls; RAVLT Recognition memory ($F_{(3,40)} = 12.9$, $p < .001$, $\eta^2 = .492$), with the MCI-unable group having lower scores than the control ($p < .001$), MCI-able ($p < .001$), and MCI-cue ($p < .001$) groups.

In the executive domain, there was a main effect of group in Trail Making B/A completion time Ratio ($F_{(3,40)} = 10.0$, $p < .001$, $\eta^2 = .430$), with the MCI-unable group having higher ratios than the control ($p < .001$), and MCI-able ($p < .001$) groups and the MCI-cue group showed a trend toward significantly higher ratios relative to the control group ($p = .07$); finally, in the Similarities test ($F_{(3,40)} = 2.9$, $p = .044$, $\eta^2 = .182$), the MCI-cue group had lower scores than the MCI-unable group ($p = .036$).

In sum, the MCI-unable group showed significantly lower scores on two global cognitive measures, recall and recognition verbal memory, and task switching ability. The MCI-cue group showed a trend toward significantly poorer performance on the

[2] Preliminary analyses were conducted on lateral electrodes FP1, FP2, F3, F4, FC3, FC4, C3, C4, CP3, CP4, P3, and P4 were also selected to analyze laterality effects. No group by laterality effects were found ($p > .38$) and, thus, are not reported further.

Table 1
Sociodemographic and Health Related Characteristics of the Control, MCI-Able, MCI-Cue, and MCI-Unable Groups

	Controls	MCI-able	MCI-cue	MCI-unable
N	19	16	5	6
Continuous variables, Mean (SE)				
Demographics				
Age (years)	75.7 (1.5)	75.5 (1.7)	77.0 (2.9)	76.5 (2.6)
Education (years)	14.5 (.7)[1]	12.2 (.7)	11.4 (1.3)	10.1 (1.2)[1]
Depression (GDS)	2.9 (1.1)[2]	4.8 (1.2)[*]	13 (2.0)[2,*]	6.3 (1.8)
Years since symptom onset	n.a.	6.1 (.6)	3.6 (1.0)	6.5 (1.0)
Months since diagnosis	n.a.	42.9 (6.5)	21.8 (11.6)	43.2 (10.6)
Discrete variables, Frequency (%)				
Demographics				
Sex, Female	12 (63)	10 (62)	2 (40)	4 (66)
Apolipoprotein e4 carrier	3 (16)	2 (12)	1 (20)	3 (50)

Note. SE = Standard Error; GDS = Geriatric Depression Scale; n.a. = not available.
[1] Significant difference between Controls and MCI-unable. [2] Significant difference between Controls and MCI-cue.
[*] Significant difference between MCI-able and MCI-cue.

Trails B test, a measure of task switching ability, and the MCI-able group did not differ from the control group on any measure except for verbal memory recall scores.

Experimental Task Switching Test – Behavioral Results

Next, data are presented for the three groups that successfully completed the experimental session, namely the controls, the MCI-able, and the MCI-cue groups.

Reaction Time

Overall performance speed on heterogeneous blocks differed significantly between groups ($F_{(2,37)} = 22.8$, $p < .001$, $\eta^2 = .552$) with the MCI-cue group responding more slowly ($M = 2064.3$ ms, $SE = 133.0$) than the control ($M = 1055.4$ ms, $SE = 68.2$; $p < .001$) and the MCI-able ($M = 1263.3$ ms, $SE = 74.3$; $p < .001$) groups. Also, there was a significant group effect on homogeneous block performance ($F_{(2,39)} = 9.7$, $p < .001$, $MSE = 1012558$), with the MCI-cue group responding more slowly ($M = 1046.1$ ms,

Table 2
Mean (and SE) Scores and Group Differences on Neuropsychological Tests Among Controls, MCI-Able, MCI-Cue, and MCI-Unable Groups

	Controls	MCI-able	MCI-cue	MCI-unable
N	19	16	5	6
Global functioning				
MOCA (/30)	26.5 (.5)[1]	24.3 (.5)	21.4 (1.0)	20.7 (.9)[1]
MMSE (/30)[ſ]	28.6 (.4)[1]	28.4 (.4)[†]	26.2 (.8)	25.17 (.8)[1†]
Episodic Memory				
RAVLT (Immediate recall)	9.3 (.6)[1,3]	5.1 (.6)[3]	5.4 (1.2)	2.83 (.1.1)[1]
RAVLT (Delayed recall)	8.5 (.6)[1,3]	4.5 (.7)[3]	3.8 (1.3)	.7 (.1.2)[1]
RAVLT (Recognition)	12.9 (.6)[1]	12.4 (.7)[†]	12.6 (1.2)[^]	5.8 (.1.1)[1†^]
Executive functions				
Letter number sequencing	8.7 (.6)	8.6 (.6)	6.20 (1.2)	5.8 (.1.1)
Clock	8.7 (.3)	8.8 (.3)	8.60 (.6)	8.7 (.5)
Digit symbol coding (/133)	51.2 (1.9)	48.7 (2.1)	36.0 (4.4)	37.5 (3.9)
Trail making ratio (B/A)	1.1 (.3)[1,2]	1.3 (.4)[†]	3.2 (.6)[2]	4.4 (.6)[1†]
Victoria Stroop (C-A)/A	2.0 (.2)	2.2 (.2)	2.5 (.4)	2.0 (.4)
Language functions				
Fluency (Letter, FAS)	46.1 (3.1)	41.1 (3.2)	25.6 (6.8)	33.8 (6.1)
Fluency (Category, Animals)	17.0 (1.1)	15.8 (1.1)	13.6 (2.2)	13.2 (2.0)
Boston	54.1 (1.8)	50.8 (1.8)	47.0 (3.8)	44.0 (3.4)
Similarities	23.3 (1.0)	21.4 (1.0)	17.0 (2.1)[^]	22.5 (1.9)[^]

Note. SE = Standard Error; MMSE = Mini Mental State Examination; MoCA = Montreal Cognitive Assessment; RAVLT = Rey Verbal Learning Test.
Multivariate analysis on all neuropsychological data used education and MMSE as covariates. The means presented are unadjusted; however, post-hoc tests were performed on adjusted means.
[1] Significant difference between Controls and MCI-unable. [2] Trend toward significance between Controls and MCI-cue. [3] Significant difference between Controls and MCI-able.
[†] Significant difference between MCI-able and MCI-unable. [^] Significant difference between MCI-cue and MCI-unable.

$SE = 105.5$) than the control ($M = 751.6$ ms, $SE = 22.6$; $p < .001$) and the MCI-able ($M = 834.6$ ms, $SE = 33.5$; $p = .011$) groups. To control for these differences in baseline performance, all subsequent analyses were performed on data transformed as a proportion of the baseline performance (i.e., Condition RT/homogeneous RT). However, we report raw reaction time (RT) data along with error rate data in Table 3 and Figure 3 rather than transformed data to allow comparison with other studies.

There was a significant main effect of group mixing cost ($F_{(2,39)} = 11.0$, $p < .001$, $MSE = .07$) with the MCI-cue group showing a larger mixing cost ($M = 2.0$, $SE = .21$) than the control ($M = 1.4$ ms, $SE = .19$; $p < .001$) and the MCI-able ($M = 1.5$ ms, $SE = .27$; $p = .001$) groups.

With respect to the switch cost, there was a switch factor main effect ($F_{(1,37)} = 12.5$, $p = .001$, $MSE = .006$, $\eta^2 = .253$) with repeat trials faster (transformed $M = 1.61$, $SE = 0.05$) than switch trials (transformed $M = 1.68$, $SE = .06$). There was a significant main effect of group ($F_{(2,37)} = 9.7$, $p < .001$, $\eta^2 = .344$), with the MCI-cue group (transformed $M = 2.04$, $SE = .13$). performing more slowly than the Controls (transformed $M = 1.42$, $SE = .06$). or MCI-able group (transformed $M = 1.49$, $SE = .07$). However, no main effect of group was found in the switch cost contrast, $F_{(2,39)} = .1$, $p = .93$, and there was no Group by Switch interaction ($F_{(1,37)} = .07$, $p = .93$, $MSE = .006$, $\eta^2 = .004$; see Table 3 and Figure 3 for the nontransformed means).

Error Rate

There was an overall main effect of group on heterogeneous blocks ($F_{(2,39)} = 4.2$, $p < .022$, $MSE = 3.6$) with the MCI-cue group showing more errors ($M = 6.3$, $SE = 1.2$) than the control ($M = 3.6$, $SE = .4$; $p = .024$) and the MCI-able ($M = 3.6$, $SE = .5$; $p = .025$) groups. However, the three groups did not differ in regards to the mixing cost, ($F_{(2,39)} = .7$, $p = .49$) nor to the switch cost, ($F_{(2,39)} = 1.1$, $p = .34$).

Experimental Task Switching Test – ERP Results

As before, data are only presented for the three groups that successfully completed the experimental session, namely the controls, the MCI-able, and the MCI-cue groups. Figure 4 shows, for the CPz site,[3] ERP grand average waveforms collapsed across subjects in control (top panel), MCI-able (middle panel), and MCI-cue (bottom panel) groups. Starting at approximately 300 ms for all groups, one can observe a generally negative sloping waveform for all groups and conditions.

Mixing Cost

There was no main effect of group ($F_{(2,37)} = 0.6$, $p = .56$). However, there was a trend toward a significant interaction between the group, mix, and time factors ($F_{(6,111)} = 2.5$, $p = .06$, $\eta^2 = .121$), which we explored with a Bonferroni corrected post hoc analysis. This revealed a significant mixing cost effect such that repeat waveforms (solid line) were more negative than homogeneous waveforms (dotted line) for the control and MCI-able groups between 600 and 1000 ms (ps between .034 to .004) but not for the MCI-cue group ($p > .51$).

Switch Cost

Although there was no main effect of group ($F_{(2,37)} = .22$, $p = .81$), the group factor significantly interacted with the switch factor ($F_{(2,37)} = 4.3$, $p = .02$, $\eta^2 = .189$). Bonferroni corrected post hoc analyses showed no significant switch cost (i.e., a difference between the repeat and switch waveforms) for the control group ($F_{(1,37)} = .56$, $p = .81$) but a significant switch cost for the MCI-able ($F_{(1,37)} = 11.6$, $p = .002$, $\eta^2 = .239$) and MCI-cue ($F_{(1,37)} = 7.9$, $p = .008$, $\eta^2 = .177$) groups.

Upon visual inspection of the waveforms, a distinct difference in the morphology of the three participant groups' waveforms is clearly visible toward the end of the recording epoch. Whereas the control group showed a flattening of the negative sloping wave, waveforms for the two MCI groups showed a sustained negativity throughout the latter part of the Cue-Target interval (see Figure 4). To quantify this effect, we calculated a more fine-grained average amplitude over this period in three 100 ms intervals (t1: 700–800 ms, t2: 800–900 ms, t3: 900-1000ms) for repeat waveforms (solid line, Figure 4) at CPz where the effect was most prominent. We then calculated the slope of the curve for each group by subtracting the average amplitudes in the 1st time interval (700–800 ms) from the average amplitude from the 3rd interval (900–1000 ms) and performed a one-way ANOVA to compare the slope in all three groups. Results showed a significant effect ($F_{(2,39)} = 3.6$, $p = .036$, $MSE = 1.44$), with MCI-able patients showing a larger amplitude slope ($M = 1.27$ μV, $SE = .40$) relative to normal controls ($M = .2$ μV, $SE = .19$; $p = .03$). Although the MCI-cue group waveform exhibited a similar slope amplitude as the MCI-able group ($M = 1.03$ μV, $SE = .26$), it was not significantly different from the control group slope ($p = .36$), probably due to low power due to the MCI-cue small sample size.

Structural MRI Results

Returning to data available from all four groups, brain volume data were analyzed using a mixed ANOVA with group (control, MCI-able, MCI-cue, and MCI-unable) as the between subject factor and laterality (right and left hemisphere) and 16 cortical regions as within subject factors (see Table 4 for list of brain regions included in the analysis). There was a main effect of laterality ($F_{(1,43)} = 13.7$, $p < .001$, $\eta^2 = .243$) with the right hemisphere ($M = 12156$ mm^3, $SE = 332$) larger than the left ($M = 11976$ mm^3, $SE = 331$). However, the laterality factor did not interact with group ($p = .68$). Therefore, the two hemispheres were collapsed for all subsequent analyses.

There was a significant main effect of group ($F_{(3,42)} = 4.5$, $p = .008$, $\eta^2 = .245$). The MCI-unable patients ($M = 20642$ mm^3, $SE = 1858$) had significantly lower volumes than the control group ($M = 27193$ mm^3, $SE = 1044$; $p = .022$); the MCI-cue group ($M = 21115$ mm^3, $SE = 2036$) showed a trend in the same direction ($p = .067$). The MCI-able ($M = 25294$ mm^3, $SE = 1138$) and control groups did not differ ($p = 1$; See Figure 5).

There was a significant interaction between the group and region factors ($F_{(48,672)} = 2.9$, $p = .004$, $\eta^2 = .173$). Bonferroni-corrected post hoc analyses revealed a pervasive pattern of lower

[3] The CPz site was chosen for presentation because it is representative of centro-parietal (Cz, CPz, PZ) activity along the midline.

Table 3
Mean Raw Reaction Times (RT in Ms) and Percent Error Rates (ER) With Their Standard Error (SE) for Homogeneous, Repeat, and Switch Trials for Control, MCI-Able, and MCI-Cue Groups

	Controls	MCI-able	MCI-cue
Homogeneous trials	RT: 751.6 (22.6)	RT: 834.6 (33.5)	RT: 1046.1 (105.5)
	ER: 2.2 (.3)	ER: 1.8 (.4)	ER: 3.7 (.7)
Repeat trials	RT: 1028.6 (66.9)	RT: 1237.6 (72.9)	RT: 2020.6 (128.4)
	ER: 2.5 (.4)	ER: 2.9 (.4)	ER: 4.8 (.7)
Switch trials	RT: 1082.9 (71.9)	RT: 1290.2 (77.2)	RT: 2114.8 (140.9)
	ER: 4.7 (.7)	ER: 4.3 (.6)	ER: 7.7 (.9)
Mixing cost	RT: 277.0 (53.2)[1]	RT: 402.9 (57.9)[*]	RT: 974.4 (103.6)[1,*]
	ER: 1.4 (.4)	ER: 1.8 (.4)	ER: 2.5 (.8)
Switch cost	RT: 54.3 (21.1)	RT: 52.6 (23.1)	RT: 94.8 (41.3)
	ER: 2.3 (.6)	ER: 1.4 (.5)	ER: 2.9 (.5)

[1] Significant difference between Controls and MCI-cue.
[*] Significant difference between MCI-able and MCI-cue.

volumes in the MCI-unable group relative to the control group in all regions (except the superior and inferior frontal gyri, the parahippocampal gyrus, the supramarginal gyrus and occipital lobe) and smaller hippocampal volume relative to the MCI-able group. The MCI-cue group showed significantly lower volumes in medial and lateral orbital gyri, the middle frontal gyrus, the hippocampus, and the insula relative to controls. No significant differences were noted between the MCI-able and control groups.

Status at 4-Year Follow-Up

Table 5 shows the diagnostic status of all participants at 4-year follow-up. Normal controls were largely unaffected, showing a stable status between baseline and follow-up, except for two deceased participants. Of the 16 MCI-able patients, five reverted to normal status, eight remained stable and maintained the MCI diagnosis, two transitioned to AD, and one patient died. In contrast, in the MCI-cue group, there were no improved patients, two patients remained stable, one transitioned to AD, and two were deceased. A similar pattern was found in the MCI-unable group, where no patients showed improvement, one remained stable, two transitioned to AD, one was deceased, and two could not be contacted by the examiner and were therefore lost to follow-up. Based on these data, the three MCI groups differed in diagnostic status distribution ($\chi^2 = 15.6$, $df = 8$, $p = .048$).

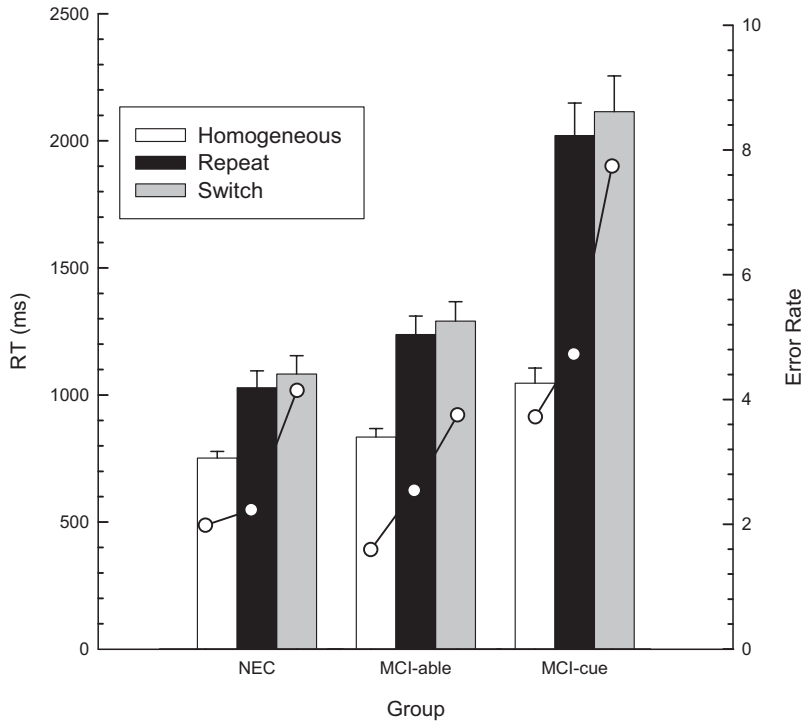

Figure 3. Mean Reaction Time (Bar graph, Left Axis) and Error Rate (Line graph, Right Axis) for Homogeneous, Repeat, and Switch trials for Controls, MCI-able, and MCI-cue groups. Error bars represent the condition's Reaction Time standard error.

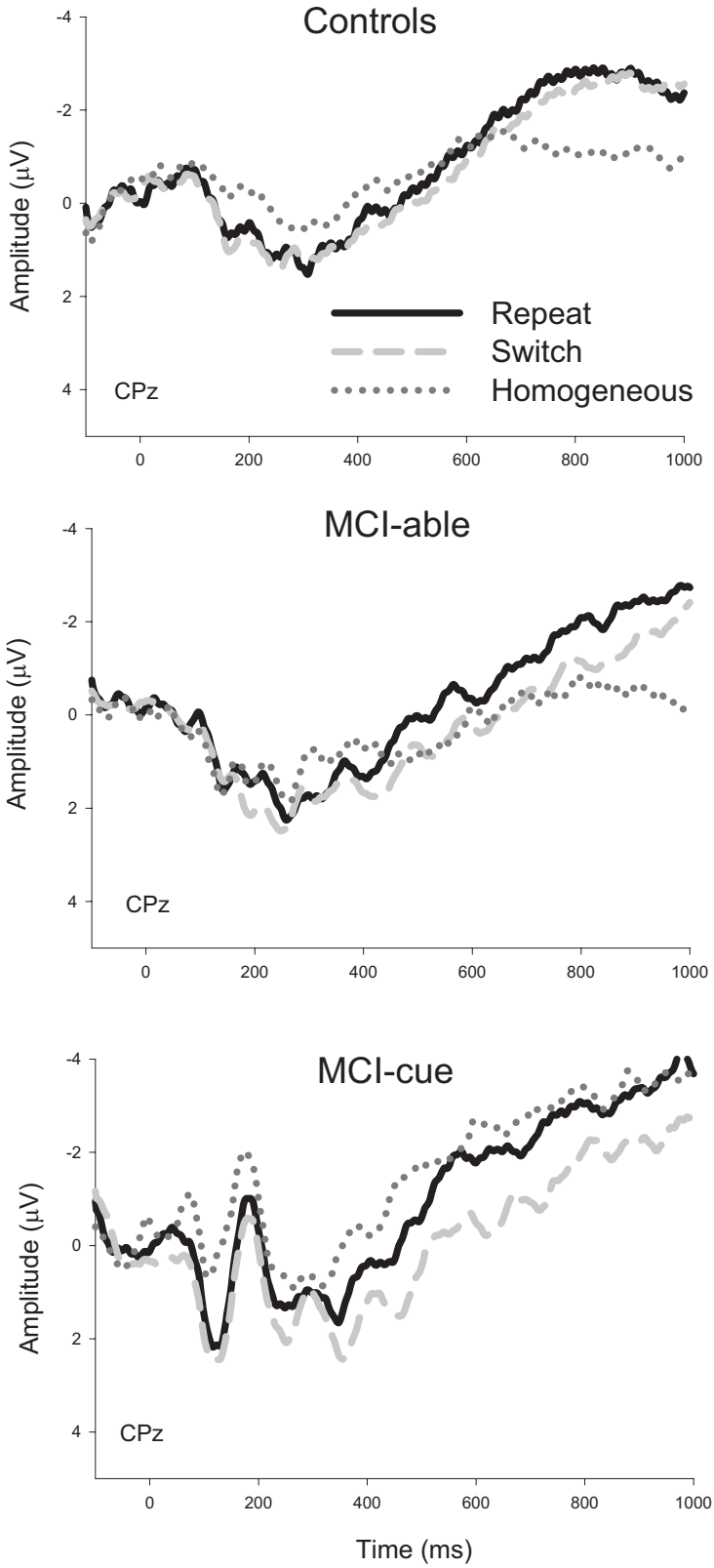

Figure 4. Cue-locked ERP grand average waveforms at CPz. Top panel: Normal controls. Middle panel: MCI-able patients. Bottom Panel: MCI-cue patients. Repeat trials are represented in black, switch trials are represented in gray dashed line, and homogeneous trials are represented in black dotted line.

Table 4
Selected Regions Volume (Mm^3) With Their Standard Deviation (SD) for Control, MCI-Able, MCI-Cue, and MCI-Unable Groups

Region	Control	MCI-able	MCI-cue	MCI-unable
Medial orbital gyrus	4788 (817)[1,2]	4176 (974)	3394 (791)[2]	3467 (770)[1]
Lateral orbital gyrus	27037 (3283)[1,2]	24113 (5191)	19956 (5110)[2]	20089 (4796)[1]
Superior frontal gyrus	23780 (4836)	23256 (5042)	19087 (5393)	17739 (4897)
Middle frontal gyrus	52907 (7601)[1,2]	46179 (12179)	37054 (8978)[2]	37452 (10712)[1]
Inferior frontal gyrus	27980 (5110)	25518 (6793)	20980 (7413)	20109 (5879)
Medial frontal gyrus	31022 (4982)[1]	29857 (6541)	23653 (5140)	23390 (6899)[1]
Cingulate gyrus	33056 (3625)[1]	30675 (6415)	26886 (5193)	25962 (5827)[1]
Precentral gyrus	33707 (5738)[1]	31255 (7279)	25710 (5899)	24499 (7028)[1]
Superior temporal gyrus	39385 (6362)[1]	36903 (8006)	29622 (6232)	29461 (6558)[1]
Middle temporal gyrus	61940 (9456)[1]	58024 (10702)	52067 (13511)	47704 (11367)[1]
Inferior temporal gyrus	16507 (2232)[1]	14987 (2635)	13897 (2845)	13252 (1753)[1]
Hippocampus	9790 (1296)[1,2]	9222 (1628)[†]	7860 (1164)[2]	7382 (1218)[1†]
Parahippocampal gyrus	12629 (1398)	12311 (2226)	11189 (1532)	11042 (2085)
Insula	18617 (2439)[1,2]	17136 (2895)	14227 (3423)[2]	14412 (3373)[1]
Superior parietal gyrus	26613 (6048)[1]	24659 (6811)	20011 (5045)	18580 (5782)[1]
Supramarginal gyrus	11065 (1818)	10756 (2896)	8925 (2066)	8976 (2447)
Occipital lobe	31463 (5889)	30982 (8842)	24450 (7476)	27408 (8633)

[1] Significant difference between Controls and MCI-unable. [2] Significant difference between Controls and MCI-cue.
[†] Significant difference between MCI-able and MCI-unable.

In an effort to understand this significant effect, diagnostic categories were collapsed into three levels: Improved, Stable, and Declined. As discussed later, an association between cognitive decline and increased mortality has been observed (Frisoni, Fratiglioni, Fastbom, Viitanen, & Winblad, 1999; Palmer, Wang, Bäckman, Winblad, & Fratiglioni, 2002; Tuokko et al., 2003); therefore, the Declined category included patients who transitioned to AD or who were deceased. Also, because the diagnostic distribution of the MCI-cue and MCI-unable were similar, the two groups were combined to increase power. One χ^2 test evaluated the data in two categories: improved versus not improved. This revealed that 31.3% of MCI-able patients returned to normal status, but no MCI-unable or MCI-cue patients did so ($\chi^2 = 3.5$, $df = 1$, $p = .06$). The second χ^2 test focused on the number of patients who had declined at follow-up using the categories "declined" versus "not declined." The two groups showed a significant difference ($\chi^2 = 5.7$, $df = 1$, $p = .016$) with only 19% of MCI-able patients having declined compared to 67% of MCI-unable and MCI-cue patients.

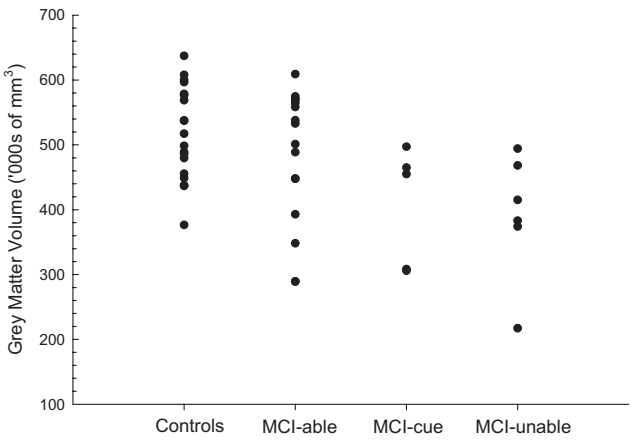

Figure 5. Vertical scatter plot of whole gray matter volume by group.

Discussion

This article had two major goals. The first was to explore the possible contribution of memory processes (i.e., retrieval of information from long-term memory) and control processes (as indexed by the mixing and switch costs) to MCI patients' expected task switching deficits. The second goal was to describe which factors are associated with poor task switching performance in MCI patients.

The experimental task switching paradigm we used revealed several subgroups in our MCI participants. There were the majority of patients (16) who were able to complete the task and who displayed subtle behavioral and ERP differences from controls. Their data are further discussed below. However, there was a significant number of MCI patients, namely 11 out of 27, who attempted the switching task but were not able to complete it with the original design. Five of these, referred to as the MCI-cue group, were able to perform on homogeneous blocks and on a modified mixed block design that we believe minimized working memory demands. The remaining six patients were referred to as the MCI-unable group. This paper characterizes these two groups of MCI patients and describes how they differ from those patients who were able to perform the task (MCI-able) and controls, using neuropsychological and neuroradiological information as well as sociodemographic and health related variables.

Our results suggest that despite ERP and neuropsychological evidence of mild retrieval difficulties, the MCI-able group had largely intact switching abilities as evidenced by their ability to complete the task and by their similar mixing and switching costs relative to controls. In contrast, the MCI-cue group showed dramatically increased mixing costs despite the availability of addi-

Table 5
Status of Participants at Four-Year Follow Up for the Control and Three MCI Groups

Diagnosis at follow-up, Frequency (%)	Diagnosis at time of testing			
	Controls	MCI-able	MCI-cue	MCI-unable
Normal	17 (89)	5 (31)	0	0
MCI	0	8 (50)	2 (40)	1 (17)
AD	0	2 (12)	1 (20)	2 (33)
Deceased	2 (11)	1 (6)	2 (40)	1 (17)
Lost to follow-up	0	0	0	2 (33)

tional cue support. This suggests that they had difficulty maintaining the task cue in working memory. Finally, because the MCI-unable group proved unable to perform the task even with cognitive support, it is difficult to determine which component process failure underlies their performance deficit although converging results from our neuropsychological and neuroradiological data point to widespread functional deficits including both primary and control processes. We will return to all of these results in detail below.

Relative to patients who successfully performed the experimental task, we also expected that patients with task switching difficulty would show significant differences on most of the variables we looked at, including significant frontal and parietal lobe atrophy, longer time since receiving the MCI diagnosis or since symptom onset, a higher frequency of ApoE 4 carriers, a higher risk of AD conversion at follow-up, and/or a deteriorating cognitive profile. As summarized in Table 6, our results generally support the hypotheses. The MCI-unable group had significant frontal, temporal, and superior parietal lobe atrophy relative to the control group. They also had poorer scores on neuropsychological tests measuring switching ability relative to the MCI-able and control groups, lower education compared to the controls, and increased risk of transition to AD or mortality. The MCI-cue group exhibited more depressive symptoms and showed some frontal and medial temporal lobe atrophy relative to controls, although not to the same extent as the MCI-unable group. We now discuss these findings in more detail.

Encoding and Retrieval Profiles

In this section, we attempt to interpret the overall pattern of results as evidence for the presence of different patterns of cognitive deficits in our MCI subgroups. In our task switching experiment, participants first had to learn arbitrary stimulus–response associations through extensive practice prior to the experimental session. This process relies on adequate episodic memory function, which is presumably compromised in most MCI patients; this was certainly the case for our sample, based on their neuropsychological performance. It is therefore important to examine how such difficulties in episodic memory might affect task switching abilities. Optimal performance on standard episodic memory tests like the word list recall task used here requires at least three intact mechanisms. The first two are the encoding and consolidation of information into long term-memory (LTM) and the third mechanism is the retrieval of information from LTM when needed. It has been argued that contrasting performance on free recall and recognition recall on episodic memory tests can differentiate between deficits due to encoding and consolidation failures versus deficits due to retrieval failures. A so-called "retrieval" profile is characterized by poor free recall but normal performance following a cue whereas a profile of poor free recall and poor cued recall is indicative of a problem with encoding. As expected, several studies with AD patients (Grober, Buschke, Crystal, Bang, & Dresner, 1988; Tounsi et al., 1999) and MCI patients who will convert to AD (Sarazin et al., 2007) show impaired recall without a cue and minimal benefit of cueing, suggesting that the memory trace was poorly encoded into LTM; this is consistent with Medial Temporal Lobe (MTL) atrophy. In one study (Sarazin et al., 2007), MCI patients who did or did not convert to AD differed significantly in total recall with converters showing an "encoding" profile and nonconverters showing a "retrieval" profile. This suggests that nonconverters' did encode the words but had difficulty retrieving them from LTM whereas converters showed an encoding failure (i.e., the memory trace was not accessed even with a cue).

As in most task switching studies, the current study employed a design in which participants were asked to learn arbitrary stimulus–response associations (e.g., if the number is even, press the left key; if the number is odd, press the right key), which would then need to be rapidly retrieved from LTM during the experimental conditions. Our ERP results support the interpretation of less-than-optimal retrieval of rules from LTM. As depicted in Figure 4, there were significant group differences between the MCI-able and MCI-cue groups and the controls in the cue-locked waveforms during the period in which the task has been cued and response rules should be retrieved. First, there was no difference between the switch and repeat waveforms in the control group; however, a switch effect was observed for the two MCI groups in the form of an enhanced negativity to repeat waveforms relative to switch waveforms at centro-parietal sites from 400 ms to 1000 ms after

Table 6
Summary of Results

	Affected processes	Associated characteristics	Prognosis
MCI-able	Mild retrieval difficulties	None	Positive
MCI-cue	Retrieval difficulties, working memory deficit	None	Negative
MCI-unable	Encoding and maintenance of task rules	Low education, small cortex, weak cognitive profile	Negative

cue presentation. This posterior negativity has been previously interpreted as an index of attentional resources allocated in preparation for target processing (Goffaux et al., 2006). Work from our lab suggests that this effect is due to the activation of task rules required for optimal processing of the upcoming target (Goffaux et al., 2008), rather than task-set inhibition (Sinai et al., 2007). Accordingly, enhanced negativity during repeat trials suggests that the activation of task rules is facilitated due to the fact that task rules from the previous trial remain primed in the system.

The lack of differences in the late negativity associated with switch and repeat trials in our control group is likely due to the fact that the time between the cue and the target (1000 ms) was long enough to allow ample time for retrieval of task set rules and optimal allocation of resources even on switch trials. This explanation is supported by the fact that the waveform flattens during the late period of the cue-target interval in the normal, suggesting that optimal preparation may have been reached before the end of the cue-target period. In contrast, the MCI patients continue to show an upward slope to the negativity, suggesting that preparation processes were ongoing by the time the target was presented.

Even though they appear to have some retrieval difficulty, the ERP results suggest that the MCI-able and MCI-cue patients properly encoded the task rules in LTM. This is supported by the results of the neuropsychological battery administered to all participants that contained a measure of word list free recall and recognition (from the RAVLT). The MCI-able group indeed showed a "retrieval" profile characterized by impaired free recall but normal recognition performance. MCI-cue group had similar scores to the MCI-able group although differences in recall scores relative to the control group did not reach statistical significance due to several factors including low sample size and statistical corrections due to group differences in depression scores (please see discussion below). Therefore, our results are in line with reports of "retrieval" profiles in many MCI patients (Pike, Rowe, Moss, & Savage, 2008). In contrast to the MCI-able group, the MCI-unable participants, who could not perform the experimental switching task at all, demonstrated an "encoding" profile on the RAVLT characterized by poor free recall and poor recognition. In fact, the RAVLT recognition score was the only memory measure that differentiated the MCI-unable and the MCI-able groups. This suggests that the MCI-unable participants had encoding difficulties. Our neuroanatomical data support this interpretation insofar as we found significant lower hippocampal volumes in the MCI-unable group relative to controls and the MCI-able group, an area that is crucial to the encoding of newly acquired memory traces (Squire, 1987).

Working Memory

Table 3 shows reaction time (RT) results for the five MCI-cue as well as the MCI-able and control groups. Although direct comparisons between the five MCI-cue patients and the other two groups should be made with caution due to design differences and the small sample size, the results show that despite the cognitive support the MCI-cue patients received, their RT on mixed blocks were dramatically increased relative to the other two groups. It is important to note that the MCI-cue group showed a significantly larger mixing cost that was also manifested in the cue-locked ERP data but no increased behavioral switch costs. This argues in favor of a difficulty in holding more than one task rule in working memory.

We argue that this deficit is consistent with the neuroanatomical findings for these patients and with the neuroimaging literature. With respect to the latter, there are several converging lines of evidence suggesting that the lateral prefrontal cortex is essential to the ability to maintain a set of goals (i.e., intention to act) "on line" even in the absence of external cues (Funahashi & Takeda, 2002; Fuster, 1997; Fuster, 2000; Goldman-Rakic, 1987). Converging evidence from fMRI studies confirms that the human lateral prefrontal cortex (LatPFC) is involved in the maintenance of information regardless of the modality of the information received to guide action (Wallis, Anderson, & Miller, 2001). However, there is debate as to which part of the LatPFC is involved in task maintenance, and other areas have also been implicated in the maintenance of information in working memory.

Bunge, Kahn, Wallis, Miller, & Wagner (2003) required subjects to maintain a specific motor plan over a delay period until a target was presented and found activation in the dorsal premotor cortex as well as in presupplemental motor area (SMA). Cavina-Pratesi et al. (2006) also showed that pre-SMA and left inferior parietal lobule were more active when subjects maintained two S–R mappings (e.g., press A if target is a house; press B if target is a face) instead of one (press A if target is any stimulus). These results suggest that pre-SMA and parietal cortex can maintain representations of possible responses online. Another PFC area that has often been implicated in task maintenance is the dorsolateral prefrontal cortex (DLPFC). This area has been implicated in response selection when task rules must be maintained in working memory (Goldman-Rakic, 1987; Passingham & Rowe, 2002). DLPFC activation is observed in brain imaging studies in which demands on response selection have been manipulated (Hazeltine, Poldrack, & Gabrieli, 2000; Schumacher, Elston, & D'Esposito, 2003). This area may therefore be preferentially activated in mixed block situations in which two sets of task rules have to be selected from, relative to single task blocks in which response selection is less demanding.

Returning to the neuroanatomical findings for our patients, the MCI-cue group showed lower volumes in the lateral orbitofrontal cortex and middle frontal gyrus. Although the orbitofrontal cortex has not, to our knowledge, been involved in task switching, the middle frontal gyrus, which corresponds to the DLPFC, has been shown to be activated in task switching studies (MacDonald, Cohen, Stenger, & Carter, 2000). This supports the hypothesis that the significantly larger mixing cost observed in the MCI-cue group relative to the control and MCI-able groups may be due to increased difficulty selecting the appropriate task rule in working memory.

In contrast, the MCI-unable group showed lower volumes in almost all analyzed regions, including areas known to be important in task switching, such as the middle and medial frontal gyri, precentral gyrus, cingulate gyrus, and the superior parietal gyrus relative to the control group. The medial frontal gyrus includes the SMA and has been reliably activated in task switching studies. As discussed previously, this area has been implicated in studies where participants have to maintain two sets of task rules in working memory (Brass et al., 2003; Cavina-Pratesi et al., 2006) suggesting that this area is crucial in maintaining S–R mappings

online while subjects prepare to respond. It is interesting to note that observation of the MCI-unable patients during the experiment showed that although they tended to start the experimental block correctly, they were likely to become confused as soon as they made one error and lost the correct task rule, from which they could no longer recover. Although we interpret this as an encoding deficit, this apparent set loss could also be interpreted as a difficulty in maintaining the S-R mappings in working memory.

To sum up, our effort to integrate neuropsychological, neuroradiological, and electrophysiological data from the four groups suggests a high degree of heterogeneity in the extent to which task switching processes are affected in MCI. The MCI-able group exhibited difficulties limited to mild retrieval deficits. In contrast, the MCI-cue group showed difficulties in working memory in addition to retrieval deficits. Finally, patients in the MCI-unable group could not perform the task even with cognitive support, probably due to episodic memory and set maintenance difficulties. Given these group differences in the affected component processes, it is tempting to see an intensification of deficits as patients move closer to a negative outcome (including dementia or death). Although plausible, this interpretation should be made with caution because the number of patients is too small, especially in the MCI-cue and MCI-unable subgroups, to reach strong conclusions. Nevertheless, our follow-up data do suggest that MCI-able participants represent the mildest formulation of mild cognitive impairment, which included some individuals who reverted back to normal status. In contrast, the MCI-cue and MCI-unable groups who did have task switching difficulties appear to consist of patients who had negative outcomes during the follow-up period. This notion is elaborated upon next.

The Reserve Hypothesis

Consistent with the episodic memory deficits that are the hallmark of MCI, medial temporal lobe structures are the brain regions most likely to show atrophy in MCI patients (Soininen et al., 1994; Wolf et al., 2001). However, recent studies have shown that the extent of brain atrophy in MCI patients extends beyond the medial temporal lobe areas to include the middle and inferior temporal lobes, the posterior cingulate and precuneus (Chételat et al., 2005; Whitwell et al., 2007) as well as aspects of the inferior, middle, and superior frontal gyri (Bell-McGinty et al., 2005). However, our results of significantly lower volumes in frontal regions observed in the MCI-unable and the MCI-cue patients are much more severe and widespread than what has been previously reported (Bell-McGinty et al., 2005) and raise the possibility that the MCI-unable and MCI-cue participants may possess individual characteristics that predate the onset of cognitive symptoms.

Although the four groups did not differ on gender or age, they showed significant differences in the level of education such that the MCI-unable group had significantly fewer years of formal education than the controls. Because of a well-established link between cognitive impairment and lower level of education (Feil, Marmon, & Unutzer, 2003; Fischer et al., 2007), most studies attempt to match cases and controls in terms of education levels. Nevertheless, several studies have reported significantly less education in MCI relative to controls (Hunderfund et al., 2006; Loewenstein, Acevedo, Agron, & Duara, 2007; Lopez et al., 2006), including one large-scale prospective community study (Chen et al., 2000). Of special relevance here, three of these studies (Hunderfund et al., 2006; Loewenstein et al., 2007; Lopez et al., 2006) compared MCI patients with isolated memory impairment, MCI with multiple domains impairments, and controls and found that MCIs with little impairment outside of episodic memory had similar education levels to controls whereas MCI patients with deficits in multiple domains tended to have lower levels of education. In particular, Lopez et al. (2006) found that MCI patients with lower levels of education had impairments in multiple cognitive domains based on a battery of age- and education-adjusted neuropsychological tests.

We speculate that the fact that our MCI-unable group had lower education and smaller brain volumes reflects the presence of premorbid constitutional factors that left these patients more vulnerable to neuropathological changes presaging AD. This interpretation fits well with the brain/cognitive reserve hypothesis of cognitive decline that has been invoked to explain often dramatic differences in cognitive functioning between patients with similar brain lesions or brain atrophy. This reserve is believed to be the capacity of the brain to withstand ageing or pathology, after which deficits appear (Katzman, 1993; Stern, 2002; Valenzuela & Sachdev, 2006).

It could be argued that the neuroanatomical and neuropsychological differences observed between the MCI-unable and control groups are simply an artifact of lower education in the MCI-unable group. The effect of education on cognitive ability in normal aging has been the subject of some debate. Whereas some have shown moderate effects of education on cognitive function (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006; Van Hooren et al., 2007), others have found this relationship to be minimal (Christensen et al., 2007; Rabbitt, Chetwynd, & McInnes, 2003; Van Gerven, Meijer, & Jolles, 2007). Therefore, we believe it is unlikely that the moderately lower level of education observed in our MCI-unable group relative to the control group could, by itself, account for the severe task switching deficits exhibited by the MCI-unable group. This interpretation is bolstered by the fact that significant group differences in cognitive functioning remained even after statistically controlling for education, suggesting that the pronounced neuropsychological and neuroanatomical differences between the MCI-unable and control groups exceeded what would be expected from simple differences in education.

We were able to rule out a number of possible health-related factors that might explain the cognitive differences between the groups. First, the MCI-unable group was not likely further along in a progression to AD relative to symptom onset in a strict temporal sense because the three MCI groups did not differ on the time elapsed since their MCI diagnoses. Also, the three groups did not differ on Apo E4 frequency.

Several limitations of this study should be noted. First, we employed a rather simple cued paradigm that was tolerable and suited to the abilities of our patient sample. Nevertheless, a number of manipulations could be explored in future research, including using more variable cue-target intervals, the examination of cue and repetition priming, restart costs, and so forth Thus, there remain possible additional contributions to the performance difficulties of the MCI patients. Second, we attempted to modify our design by providing a constant cue to minimize working memory demands and provide cognitive support to the MCI-unable patients. However, this effort was limited and admittedly ad hoc.

Thus, the interpretation of the cue-locked ERPs in this group should be taken cautiously due to the difference in the presentation of cue. However, we note that the presence of additional cue support in this group should have worked against finding group differences (i.e., it should have lessened differences between the MCI-able and MCI-cue groups). In fact, we observed the opposite; striking differences remained in the mixing costs. Future studies could further investigate the processes underlying the MCI-unable group inability to perform the task. Other informative manipulations could be attempted such as allowing S-R associations on the screen for the duration of the trial so to decrease task rule retrieval demands. Third, our results show that the MCI-unable group had significantly lower education levels than the controls. There is a need for more investigation regarding the possible association between task-switching ability and level of education in MCI and to find out whether severe task switching deficits are limited to patients with relatively low education or whether it also applies to higher educated MCI patients. Fourth, although we did show that poor task switching performance was associated with a negative long-term outcome during follow-up, we must remember that patients with two very different outcomes were combined (i.e., those patients who declined to dementia and those who died); thus, the factors underlying the relationship between poor cognitive function and the different negative outcomes may not be the same. Finally, our sample size, especially for the two MCI groups that showed switching difficulties was quite small and may limit the ability to generalize these results to the broader MCI population.

The Nature of MCI

One of the most interesting results of this study is the association between poor task switching ability and a higher risk of functional decline, defined as a transition to dementia or death, whereas adequate task switching performance was associated with a higher likelihood of a return to normal cognitive profile at 4-year follow-up. It is possible that these patients who reverted to normal status may have been misdiagnosed as MCI; however, we do not believe this is likely since these patients had been repeatedly diagnosed as MCI at multiple evaluations ($M = 2.8$, $SD = 1.1$) prior to testing. Our rate of MCI-able patients (31.25%) who returned to normal is in the upper range of what has previously been reported (Busse, Hensel, Guhne, Angermeyer, & Reidel-Heller, 2006; Ganguli et al., 2004; Palmer, Fratiglioni, & Winblad, 2003).

There is a lack of consensus in the literature as to the nature of MCI. Some authors have conceptualized MCI as simply the prodromal phase of AD (Morris et al., 2001). However, this position minimizes the documented heterogeneity of MCI. With respect to diagnostic outcome, four groups have been described in the literature: patients who have incipient dementia and will transition to AD within 3 to 5 years, patients who remain stable over long periods of time, patients who will revert to normal status, and patients who fluctuate between MCI and normal functioning. Clearly, not all amnestic MCIs—up to 40% in some large scale studies—represent prodromal AD. Some have argued that this heterogeneity casts doubts on the validity of MCI as a diagnostic category (Dubois, 2000). We would argue that, on the contrary, this heterogeneity actually validates the usefulness of the MCI concept. Put simply, if there was a one-to-one correspondence between amnestic MCI and AD, there would be no need for such an intermediate classification. As it stands, the MCI classification fulfills its intended purpose, which is to detect individuals at increased risk of developing AD. Once identified as a high risk population, these individuals can be followed more closely for signs of cognitive and functional deterioration, contributing to early detection of AD.

The observation that some MCI patients remain stable or even revert to normal status while some are destined to progress to AD has led to the emergence of the concept of "stable" (SMCI) versus "progressive" MCI (PMCI). Several studies have sought to explore the cognitive (Bozoki et al., 2001), neuroanatomical (Wang et al., 2009), neurofunctional (Stefani et al., 2009), and electrophysiological (Giannakopoulos, Missonnier, Kovari, Gold, & Michon, 2009) markers that distinguish these two MCI categories. Results from the current study support the concept of stable versus progressive MCI and adds detail to the specific cognitive functions that may be affected in both stable and progressive MCI. Aside from the obvious episodic memory impairment that warranted the MCI diagnosis, our MCI-able participants showed an overall performance deficit in the form of significant longer reaction time on the experimental task that, coupled with the ERP findings, indicates a difficulty retrieving task rules from long-term memory. Whereas a significant minority of individuals in this group reverted to normal status at follow-up, the vast majority of the remaining participants retained a stable MCI diagnosis four years later. These MCI individuals possessed characteristics that distinguished them from both controls and AD patients. As such, they may represent the quintessential MCI profile, a true intermediate state between normal cognitive aging and dementia. In contrast, the poor task switching ability and weak cognitive profile of the MCI-unable group was clearly qualitatively different from the control group and included a high proportion of patients who converted to AD as well as higher mortality rates.

Conclusions

This study demonstrated that measures of task-switching ability can highlight important heterogeneity in the MCI population. We found that most MCI patients exhibit some form of task-switching deficits but to vastly different degrees. On the one hand, there were individuals closer to the normal aging side of the cognitive spectrum; these individuals may present with memory deficits relative to their normal age peers but appeared to compensate these with quasi-intact executive functions. On the other side of the spectrum were individuals who performed poorly on executive tasks as well as having significant episodic memory deficits. These individuals appeared to have a high probability of developing AD or dying within four years.

There are also some clinical implications of these findings. It has been proposed that standardized tests should reflect not only the age of the patient but also his or her level of education. Although we agree in principle with this sensible approach, we would caution against the over reliance on education-adjusted scores, especially when it relates to the assessment of executive functions in low educated individuals. A clinician assessing an MCI patient may interpret low scores on executive function tests as normal given the patient's low average intelligence and low levels of education. However, the results of this study suggest that impaired

task switching ability and executive functions in general should be treated as an additional risk factor of MCI transition to AD regardless of the patient's level of education.

References

Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *Journal of the International Neuropsychological Society, 7,* 631–639.

Allport, D. A., Styles, E. A., & Hsieh, S. (1994). Shifting intentional set: Exploring the dynamic control of tasks. In C. Umilta & M. Moscovitch (Eds.), *Attention and performance XV* (pp. 421–452). Cambridge, MA: MIT Press.

Altmann, E. M., & Gray, W. D. (2008). An integrated model of cognitive control in task switching. *Psychological Review, 115,* 602–639.

Artero, S., Petersen, R., Touchon, J., & Ritchie, K. (2006). Revised criteria for mild cognitive impairment: Validation within a longitudinal population study. *Dementia and Geriatric Cognitive Disorders, 22,* 465–470.

Belleville, S., Chertkow, H., & Gauthier, S. (2007). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology, 21,* 458–469.

Bell-McGinty, S., Lopez, O. L., Meltzer, C. C., Scanlon, J. M., Whyte, E. M., Dekosky, S. T., & Becker, J. T. (2005). Differential cortical atrophy in subgroups of mild cognitive impairment. *Archives of Neurology, 62,* 1393–1397.

Blacker, D., Lee, H., Muzikansky, A., Martin, E. C., Tanzi, R., McArdle, J. J., . . . Albert, M. (2007). Neuropsychological measures in normal individuals that predict subsequent cognitive decline. *Archives of Neurology, 64,* 862–871.

Bozoki, A., Giordani, B., Heidebrink, J. L., Berent, S., & Foster, N. L. (2001). Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. *Archives of Neurology, 58,* 411–416.

Brass, M., Ruge, H., Meiran, N., Rubin, O., Koch, I., Zysset, S., . . . von Cramon, D. Y. (2003). When the same response has different meanings: Recoding the response meaning in the lateral prefrontal cortex. *NeuroImage, 20,* 1026–1031.

Brunia, C. H., & van Boxtel, G. J. (2001). Wait and see. *International Journal of Psychophysiology, 43,* 59–75.

Bunge, S. A., Kahn, I., Wallis, J. D., Miller, E. K., & Wagner, A. D. (2003). Neural circuits subserving the retrieval and maintenance of abstract rules. *Journal of Neurophysiology, 90,* 3419–3428.

Busse, A., Hensel, A., Gühne, U., Angermeyer, M. C., & Riedel-Heller, S. G. (2006). Mild cognitive impairment: Long-term course of four clinical subtypes. *Neurology, 67,* 2176–2185.

Cavina-Pratesi, C., Valyear, K. F., Culham, J. C., Köhler, S., Obhi, S. S., Marzi, C. A., & Goodale, M. A. (2006). Dissociating arbitrary stimulus-response mapping from movement planning during preparatory period: Evidence from event-related functional magnetic resonance imaging. *The Journal of Neuroscience, 26,* 2704–2713.

Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., & Ganguli, M. (2000). Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology, 55,* 1847–1853.

Chételat, G., Landeau, B., Eustache, F., Mézenge, F., Viader, F., de la Sayette, V., . . . Baron, J. C. (2005). Using voxel-based morphometry to map the structural changes associated with rapid conversion in MCI: A longitudinal MRI study. *Neuroimage, 27,* 934–946.

Christensen, H., Anstey, K. J., Parslow, R. A., Maller, J., Mackinnon, A., & Sachdev, P. (2007). The brain reserve hypothesis, brain atrophy and aging. *Gerontology, 53,* 82–95.

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized talairach space. *Journal of Computer Assisted Tomography, 18,* 192–205.

Collins, D. L., Zijdembos, A. P., Baare, W. F. C., & Evans, A. C. (1999). ANIMAL+INSECT: Improved cortical structure segmentation. In A. Kuba (Ed.), *Information processing in medical imaging* (pp. 210–223). Berlin, Germany: Springer.

Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Jr., Rimmler, J. B., . . . Haines, J. L. (1995). Apolipoprotein E, survival in Alzheimer's disease patients, and the competing risks of death and Alzheimer's disease. *Neurology, 45,* 1323–1328.

Daly, E., Zaitchik, D., Copeland, M., Schmahmann, J., Gunther, J., & Albert, M. (2000). Predicting conversion to Alzheimer disease using standardized clinical information. *Archives of Neurology, 57,* 675–680.

Dubois, B. (2000). "Prodromal Alzheimer's disease": A more useful concept than mild cognitive impairment? *Current Opinion in Neurology, 13,* 367–369.

Feil, D., Marmon, T., & Unützer, J. (2003). Cognitive impairment, chronic medical illness, and risk of mortality in an elderly cohort. *American Journal of Geriatric Psychiatry, 11,* 551–560.

Fischer, P., Jungwirth, S., Zehetmayer, S., Weissgram, S., Hoenigschnabl, S., Gelpi, E., . . . Tragl, K. H. (2007). Conversion from subtypes of mild cognitive impairment to Alzheimer dementia. *Neurology, 68,* 288–291.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12,* 189–198.

Frisoni, G. B., Fratiglioni, L., Fastbom, J., Viitanen, M., & Winblad, B. (1999). Mortality in nondemented subjects with cognitive impairment: The influence of health-related factors. *American Journal of Epidemiology, 150,* 1031–1044.

Funahashi, S., & Takeda, K. (2002). Information processes in the primate prefrontal cortex in relation to working memory processes. *Reviews in the Neurosciences, 13,* 313–345.

Fuster, J. M. (1997). *The prefrontal cortex: Anatomy, physiology, and neuropsychology of the frontal lobe*. New York, NY: Lippincott-Raven.

Fuster, J. M. (2000). Prefrontal neurons in networks of executive memory. *Brain Research Bulletin, 52,* 331–336.

Ganguli, M., Dodge, H. H., Shen, C., & DeKosky, S. T. (2004). Mild cognitive impairment, amnestic type: An epidemiologic study. *Neurology, 63,* 115–121.

Giannakopoulos, P., Missonnier, P., Kövari, E., Gold, G., & Michon, A. (2009). Electrophysiological markers of rapid cognitive decline in mild cognitive impairment. *Frontiers of Neurology and Neuroscience, 24,* 39–46.

Goffaux, P., Phillips, N. A., Sinai, M., & Pushkar, D. (2006). Behavioural and electrophysiological measures of task switching during single and mixed-task conditions. *Biological Psychology, 72,* 278–290.

Goffaux, P., Phillips, N. A., Sinai, M., & Pushkar, D. (2008). Neurophysiological measures of task-set switching: Effects of working memory and aging. *The Journals of Gerontology Series B, Psychological Sciences and Social Sciences, 63,* 57–66.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In J. M. Brookhart &. V. B. Mountcastle (Series Eds.) & F. Plum (Vol. Ed.), *Handbook of physiology: Section 1. The nervous system: Vol. 5. Higher functions of the brain* (pp. 373–417). Washington, DC: American Physiological Society.

Greenhouse, S. W., & Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrica, 24,* 95–112.

Grober, E., Buschke, H., Crystal, H., Bang, S., & Dresner, R. (1988). Screening for dementia by memory testing. *Neurology, 38,* 900–903.

Gurd, J. M., Weiss, P. H., Amunts, K., & Fink, G. R. (2003). Within-task switching in the verbal domain. *Neuroimage, 20,* S50–S57.

Hazeltine, E., Poldrack, R., & Gabrieli, J. D. (2000). Neural activation during response competition. *Journal of Cognitive Neuroscience, 12,* 118–129.

Hughes, C. P., Berg, L., Danzinger, W. L., Cohen, L. A., & Martin, R. L. (1982). American Psychiatric Association. Clinical Dementia Rating [CDR] scale. Task force for the *Handbook of Psychiatric Measures*. (2000). *Handbook of psychiatric measures* (pp. 446–450). Washington, DC: American Psychiatric Association.

Hunderfund, A. L., Roberts, R. O., Slusser, T. C., Leibson, C. L., Geda, Y. E., Ivnik, R. J., . . . Petersen, R. C. (2006). Mortality in amnestic mild cognitive impairment: A prospective community study. *Neurology, 67,* 1764–1768.

Jackson, G. M., Swainson, R., Mullin, A., Cunnington, R., & Jackson, S. R. (2004). ERP correlates of a receptive language-switching task. *The Quarterly Journal of Experimental Psychology A, Human Experimental Psychology, 57,* 223–240.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston Naming Test.* Philadelphia, PA: Lea & Febiger.

Karayanidis, F., Coltheart, M., Michie, P. T., & Murphy, K. (2003). Electropsychological correlates of anticipatory and poststimulus components of task switching. *Psychophysiology, 40,* 329–348.

Karayanidis, F., Jamadar, S., Ruge, H., Phillips, N., Heathcote, A., & Forstmann, B. U. (2010). Advance preparation in task-switching: Converging evidence from behavioral, model-based and brain activation approaches. Manuscript submitted for publication.

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology, 43,* 13–20.

Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychology and Aging, 15,* 126–147.

Lezak, M. D., Howieson, D. B., & Loring, D. W. (2004). *Neuropsychological Assessment* (4th ed.). New York, NY: Oxford University Press.

Loewenstein, D. A., Acevedo, A., Agron, J., & Duara, R. (2007). Stability of neurocognitive impairment in different subtypes of mild cognitive impairment. *Dementia and Geriatric Cognitive Disorders, 23,* 82–86.

Lopez, O. L., Becker, J. T., Jagust, W. J., Fitzpatrick, A., Carlson, M. C., DeKosky, S. T., . . . Kuller, L. H. (2006). Neuropsychological characteristics of mild cognitive impairment subgroups. *Journal of Neurology, Neurosurgery, and Psychiatry, 77,* 159–165.

Lorist, M. M., Klein, M., Nieuwenhuis, S., De Jong, R., Mulder, G., & Meijman, T. F. (2000). Mental fatigue and task control: Planning and preparation. *Psychophysiology, 37,* 1–12.

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science, 288,* 1835–1838.

Mayr, U., & Kliegl, R. (2000). Task-set switching and long-term memory retrieval. *Journal of Experimental Psychology: Learning Memory & Cognition, 26,* 1124–1140.

Meiran, N. (2000). The reconfiguration of the stimulus task-set and the response task-set during task switching. In S. Monsell & J. S. Driver (Eds.), *Control of cognitive processes: Attention and performance XVIII* (pp. 377–400). Cambridge, MA: MIT Press.

Meiran, N., Chorev, Z., & Sapir, A. (2000). Component processes in task switching. *Cognitive Psychology, 41,* 211–253.

Milner, B. (1963). Effect of different brain lesions on card sorting. *Archives of Neurology, 9,* 90–100.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: A latent variable analysis. *Cognitive Psychology, 41,* 49–100.

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-stage Alzheimer disease. *Archives of Neurology, 58,* 397–405.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53,* 695–699.

Palmer, K., Fratiglioni, L., & Winblad, B. (2003). What is mild cognitive impairment? Variations in definitions and evolution of nondemented persons with cognitive impairment. *Acta Neurologica Scandinava Supplementum, 179,* 14–20.

Palmer, K., Wang, H. X., Bäckman, L., Winblad, B., & Fratiglioni, L. (2002). Differential evolution of cognitive impairment in nondemented older persons: Results from the Kungsholmen Project. *American Journal of Psychiatry, 159,* 436–442.

Parasuraman, R., Greenwood, P. M., & Sunderland, T. (2002). The apolipoprotein E gene, attention, and brain function. *Neuropsychology, 16,* 254–274.

Passingham, R. E., & Rowe, J. (2002). Dorsal prefrontal cortex: Maintenance in memory or attentional selection? In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe function* (pp. 221–232). Oxford, England: Oxford University Press.

Perry, R. J., Watson, P., & Hodges, J. R. (2000). The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: Relationship to episodic and semantic memory impairment. *Neuropsychologia, 38,* 252–271.

Petersen, R. C., & Negash, S. (2008). Mild cognitive impairment: An overview. *CNS Spectrums, 13,* 45–53.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Archives of Neurology, 56,* 303–308.

Pike, K. E., Rowe, C. C., Moss, S. A., & Savage, G. (2008). Memory profiling with paired associate learning in Alzheimer's disease, mild cognitive impairment, and healthy aging. *Neuropsychology, 22,* 718–728.

Posner, M. I. (1980). Orienting of attention. *Quarterly Journal of Experimental Psychology, 32,* 3–25.

Poulsen, C., Luu, P., Davey, C., & Tucker, D. (2005). Dynamics of task sets: Evidence from dense-array event-related potentials. *Cognitive Brain Research, 24,* 133–154.

Rabbitt, P., Chetwynd, A., & McInnes, L. (2003). Do clever brains age more slowly? Further exploration of a nun result. *British Journal of Psychology, 94,* 63–71.

Rapp, M. A., & Reischies, F. M. (2005). Attention and executive control predict Alzheimer disease in late life: Results from the Berlin Aging Study (BASE). *American Journal of Geriatric Psychiatry, 13,* 134–141.

Rasquin, S. M., Lodder, J., Visser, P. J., Lousberg, R., & Verhey, F. R. (2005). Predictive accuracy of MCI subtypes for Alzheimer's disease and vascular dementia in subjects with mild cognitive impairment: A 2-year follow-up study. *Dementia and Geriatric Cognitive Disorders, 19,* 113–119.

Rey, A. (1958). *L'examen clinique en psychologie.* Paris, France: Presse Universitaire de France.

Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General, 124,* 207–231.

Rosen, V. M., Bergeson, J. L., Putnam, K., Harwell, A., & Sunderland, T. (2002). Working memory and apolipoprotein E: What's the connection? *Neuropsychologia, 40,* 2226–2233.

Royall, D. R., Lauterbach, E. C., Cummings, J. L., Reeve, A., Rummans, T. A., Kaufer, D. I., . . . Coffey, C. E. (2002). Executive control function: A review of its promise and challenges for clinical research. A report from the Committee on Research of the American Neuropsychiatric Association. *Journal of Neuropsychiatry and Clinical Neurosciences, 14,* 377–405.

Rubinstein, J., Meyer, E. D., & Evans, J. E. (2001). Executive control of cognitive processes in task switching. *Journal of Experimental Psychology: Human Perception and Performance, 27,* 763–797.

Rushworth, M. F., Hadland, K. A., Paus, T., & Sipila, P. K. (2002). Role of the human medial frontal cortex in task switching: A combined fMRI and TMS study. *Journal of Neurophysiology, 87,* 2577–2592.

Rushworth, M. F. S., Passingham, R. E., & Nobre, A. C. (2002). Components of switching intentional set. *Journal of Cognitive Neuroscience, 14,* 1139–1150.

Sarazin, M., Berr, C., De Rotrou, J., Fabrigoule, C., Pasquier, F., Legrain, S., . . . Dubois, B. (2007). Amnestic syndrome of the medial temporal type identifies prodromal AD: A longitudinal study. *Neurology, 69,* 1859–1867.

Schumacher, E. H., Elston, P. A., & D'Esposito, M. (2003). Neural evidence for representation-specific response selection. *Journal of Cognitive Neuroscience, 15,* 1111–1121.

Shulman, K. I., Shedletsky, R., & Silver, I. (1986). The challenge of time: Clock drawing and cognitive function in the elderly. *International Journal of Geriatric Psychiatry, 1,* 135–140.

Silveri, M. C., Reali, G., Jenner, C., & Puopolo, M. (2007). Attention and memory in the preclinical stage of dementia. *Journal of Geriatric Psychiatry and Neurology, 20,* 67–75.

Sinai, M., Goffaux, P., & Phillips, N. A. (2007). Cue- versus response-locked processes in backward inhibition: Evidence from ERPs. *Psychophysiology, 44,* 596–609.

Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A non-parametric method for automatic correction of intensity non-uniformity in MRI data. *IEEE Transactions on Medical Imaging, 17,* 87–97.

Slooter, A. J., van Duijn, C. M., Bots, M. L., Ott, A., Breteler, M. B., De Voecht, J., . . . Hofman, A. (1998). Apolipoprotein E genotype, atherosclerosis, and cognitive decline: The Rotterdam Study. *Journal of Neural Transmission, 53,* 17–29.

Soininen, H. S., Partanen, K., Pitkanen, A., Vainio, P., Hänninen, T., Hallikainen, M., . . . Riekkinen, P. J., Sr. (1994). Volumetric MRI analysis of the amygdale and the hippocampus in subjects with age-associated memory impairment: Correlation to visual and verbal memory. *Neurology, 44,* 1660–1668.

Squire, L. R. (1987). *Memory and brain.* New York, NY: Oxford University Press.

Stefani, A., Sancesario, G., Pierantozzi, M., Leone, G., Galati, S., Hainsworth, A. H., & Diomedi, M. (2009). CSF biomarkers, impairment of cerebral hemodynamics and degree of cognitive decline in Alzheimer's and mixed dementia. *Journal of Neurological Sciences, 283,* 109–115.

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society, 8,* 448–460.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). New York, NY: Oxford University Press.

Tounsi, H., Deweer, B., Ergis, A. M., Van der Linden, M., Pillon, B., Michon, A., & Dubois, B. (1999). Sensitivity to semantic cuing: An index of episodic memory dysfunction in early Alzheimer disease. *Alzheimer Disease and Associated Disorders, 13,* 38–46.

Tuokko, H., Frerichs, R., Graham, J., Rockwood, K., Kristjansson, B., Fisk, J., . . . McDowell, I. (2003). Five-year follow-up of cognitive impairment with no dementia. *Archives of Neurology, 60,* 577–582.

Valenzuela, M. J., & Sachdev, P. (2006). Brain reserve and dementia: A systematic review. *Psychological Medicine, 36,* 441–454.

Van der Elst, W., Van Boxtel, M. P., Van Breukelen, G. J., & Jolles, J. (2006). The Stroop color-word test: Influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment, 13,* 62–79.

Van Gerven, P. W., Meijer, W. A., & Jolles, J. (2007). Education does not protect against age-related decline of switching focal attention in working memory. *Brain and Cognition, 64,* 158–163.

van Hooren, S. A., Valentijn, A. M., Bosma, H., Ponds, R. W., van Boxtel, M. P., & Jolles, J. (2007). Cognitive functioning in healthy older adults aged 64–81: A cohort study into the effects of age, sex, and education. *Neuropsychology Development and Cognition Section B, Aging, Neuropsychology, and Cognition, 14,* 40–54.

Wager, T. D., Jonides, J., & Reading, S. (2004). Neuroimaging studies of shifting attention: A meta-analysis. *Neuroimage, 22,* 1679–1693.

Wallis, J. D., Anderson, K. C., & Miller, E. K. (2001). Single neurons in prefrontal cortex encode abstract rules. *Nature, 411,* 953–956.

Wang, H., Golob, E., Bert, A., Nie, K., Chu, Y., Dick, M. B., . . . Su, M. Y. (2009). Alterations in regional brain volume and individual MRI-guided perfusion in normal control, stable mild cognitive impairment, and MCI-AD converter. *Journal of Geriatric Psychiatry and Neurology, 22,* 35–45.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale—Third edition: Administration and scoring manual.* San Antonio, TX: Psychological Corporation.

Whitwell, J. L., Przybelski, S. A., Weigand, S. D., Knopman, D. S., Boeve, B. F., Petersen, R. C., & Jack, C. R., Jr. (2007). 3D maps from multiple MRI illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to Alzheimer's disease. *Brain, 130,* 1777–1786.

Wolf, H., Grunwald, M., Kruggel, F., Riedel-Heller, S. G., Angerhöfer, S., Hojjatoleslami, A., . . . Gertz, H. (2001). Hippocampal volume discriminates between normal cognition: Questionable and mild dementia in the elderly. *Neurobiology of Aging, 22,* 177–186.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research, 17,* 37–49.

Zhang, Y., Han, B., Verhaeghen, P., & Nilsson, L. G. (2007). Executive functioning in older adults with mild cognitive impairment: MCI has effects on planning, but not on inhibition. *Neuropsychology, Development and Cognition Section B, Aging Neuropsychology and Cognition, 14,* 557–570.

Zijdenbos, A. P., Forghani, R., & Evans, A. C. (2002). Automatic "pipeline" analysis of 3-D MRI data for clinical trials: Application to multiple sclerosis. *IEEE Transactions of Medical Imaging, 21,* 1280–1291.

Received March 2, 2009
Revision received April 8, 2010
Accepted April 23, 2010 ■