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Model-based assessment and neural correlates of spatial memory deficits in mild cognitive impairment

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Abstract

Mild cognitive impairment (MCI) is characterized by subjective and objective memory impairments within the context of generally intact everyday functioning. Such memory deficits are typically thought to arise from medial temporal lobe dysfunction; however, differences in memory task performance can arise from a variety of altered processes (e.g., strategy adjustments) rather than, or in addition to, “pure” memory deficits. To address this problem, we applied the linear ballistic accumulator (LBA: Brown & Heathcote, 2008) model to data from individuals with MCI (n=18) and healthy older adults (HOA; n=16) who performed an object-location association memory retrieval task during functional magnetic resonance imaging (fMRI). The primary goals were to 1) assess between-group differences in model parameters indexing processes of interest (memory sensitivity, accumulation speed, caution and time spent on peripheral perceptual and motor processes) and 2) determine whether differences in model-based metrics were consistent with fMRI data. The LBA provided evidence that, relative to the HOA group, those with MCI displayed lower sensitivity (i.e., difficulty discriminating targets from lures), suggestive of memory impairment, and displayed higher evidence accumulation speed and greater caution, suggestive of increased arousal and strategic changes in this group, although these changes had little impact on MCI-related accuracy differences. Consistent with these findings, fMRI revealed reduced activation in brain regions previously linked to evidence accumulation and to the

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BH and KS designed the empirical study and collected and curated the data. AW and BH conceptualized the study goals and analysis plan. AW carried out the model-based analyses under supervision by BH. AW and BH carried out the functional neuroimaging analyses. All authors contributed to the interpretation of the study results. AW wrote the original draft of the manuscript and BH and KS provided critical reviews and edits.

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implementation of caution reductions in the MCI group. Findings suggest that multiple cognitive mechanisms differ during memory performance in MCI, and that these mechanisms may explain neuroimaging alterations outside of the medial temporal lobes.

Keywords

mild cognitive impairment; cognitive modeling; linear ballistic accumulator; fMRI

Introduction

Older adults who meet diagnostic criteria for mild cognitive impairment (MCI), a condition primarily characterized by subjective and objective memory deficits but preserved everyday functioning, have a high likelihood of progressing to a dementia of the Alzheimer's type (Petersen et al., 2009). Hence, MCI has been proposed to be a prodromal marker for dementia that can be used to facilitate prediction of Alzheimer's disease progression (Petersen, 2002; Tramutola et al., 2015) as well as early intervention (Hampstead, Gillis, & Stringer, 2014; Kinsella et al., 2009; Petersen, 2004, Ströhle et al., 2015). Research on the neural locus of memory deficits in MCI has generally focused on medial temporal lobe structures (Bakker, Albert, Krauss, Speck, & Gallagher, 2015; Dickerson & Sperling, 2008; England, Gillis & Hampstead, 2014; Loewenstein et al., 2009; Stelmokas et al., 2017). However, accumulating evidence suggests that this focus may be based on an overly simplistic view of cognitive dysfunction. For example, recent neuroimaging work has found evidence for widespread neocortical abnormalities in MCI that extend beyond the medial temporal lobe; individuals with MCI appear to display hypo-activation of a broad range of frontal, parietal and subcortical areas during episodic memory encoding and retrieval tasks (Hampstead et al., 2011; Wang, et al., 2016; but see: Miller et al., 2008; Dickerson et al., 2005). We recently reported marked shifts in MCI patients' pattern of task-related effective connectivity during encoding and retrieval that were primarily focused outside of medial temporal lobe structures (Hampstead et al., 2016). This evidence for diffuse neural abnormalities in MCI suggests that processes beyond the basic mnemonic functions of medial temporal lobe structures may contribute to aberrant memory task performance in the disorder.

Typical behavioral summary statistics (e.g., mean response time [RT], accuracy) are insensitive to the potential multifactorial nature of memory (or other cognitive) dysfunction since they assume the construct of interest is uniform. Consequentially, findings of reduced accuracy and/or longer RTs on an episodic memory task could emerge from impaired memory, other cognitive deficits (e.g., attention), and/or the individuals' cognitive strategies (e.g., emphasizing response speed over accuracy). Due to this problem of measurement impurity, researchers' claims about the causes, and neural correlates, of memory deficits in MCI may need to be reconsidered. Recently, multiple research groups have addressed this problem by using formal cognitive models, first developed in the field of mathematical psychology, to better characterize the underlying contributors of cognitive deficits in clinical populations (e.g., Heathcote et al., 2015; Mulder et al., 2010; Pe, Vandekerckhove, & Kuppens, 2013; Weigard, Huang-Pollock & Brown, 2016; White, Ratcliff, Vasey, &

McKoon, 2010a). Such models specify mechanistic descriptions of the underlying processes that individuals use to perform cognitive tasks. Hence, fitting such models to task data allows estimation of model parameters that distinguish targeted cognitive abilities (e.g., mnemonic associations) from other mechanistic processes (White, Ratcliff, Vasey, & McKoon, 2010b; Wiecki, Poland, & Frank, 2015; Voss, Nagler & Lerche, 2013). The current report uses this method of model-based measurement to evaluate the various factors that may contribute to test performance in MCI.

We focus on sequential sampling models (Brown & Heathcote, 2008; Rae et al., 2014; Ratcliff, 1978; Starns & Ratcliff, 2014), because they have been demonstrated to provide some of the most robust and fullest descriptions of both RT and accuracy data from memory tasks. Basic assumptions of such models hold that individuals discriminate between target stimuli (e.g., previously-studied items or item-location associations) and lure (or novel) stimuli by gradually gathering evidence over time. In the commonly-used linear ballistic accumulator (LBA) model framework (Brown & Heathcote, 2008; Osth, Bora, Dennis & Heathcote, 2017), the accumulation (or “drift”) rates of evidence for a “target” response and evidence for a “lure” response on a given trial are sampled from normal distributions that represent variability in the strength of memory evidence for targets vs. lures (Figure 1a). As these distributions represent between-trial variability in the strength of evidence, they can be thought of as analogous to the “signal + noise” and “noise” distributions in signal detection theory (Starns & Ratcliff, 2014; Ratcliff, 1978). Once drift rates for a given trial are sampled from the distributions, evidence for each response accumulates at these rates over time until a critical threshold of evidence is reached (Figure 1b), which results in the selection of either a “target” or “lure” response. Metrics derived from the parameters of the full LBA model (detailed in Figure 1c) can be used to index several processes of clinical interest, which are explained in detail in Table 1.

Prior model-based work aimed at understanding the influence of normal and pathological aging on mechanisms that underlie memory task performance has typically used the diffusion decision model (DDM: Ratcliff, 1978), a sequential sampling model framework that frames two-choice decisions as a noisy evidence accumulation process that drifts between two response boundaries. Although the parameters of DDM and LBA do not necessarily have a one-to-one mapping, the two models typically provide highly similar explanations for behavioral effects in task performance (Donkin, Brown, Heathcote & Wagenmakers, 2011; Dutilh et al., 2018). The DDM line of work has generally found that healthy older adults show significantly higher levels of caution and longer non-decision times (i.e., time spent on peripheral sensory and motor processes) than their younger counterparts on memory tests. Yet, they only show subtle, and in some cases non-significant, reductions in sensitivity (i.e., discrimination between targets and lures) that are most pronounced for associative material (Ratcliff, Thapar & McKoon, 2006; Ratcliff & McKoon, 2015; McKoon and Ratcliff, 2012). However, older adults with a family history of Alzheimer’s disease showed reduced sensitivity relative to those without a family history (Aschenbrenner, Balota, Gordon, Ratcliff, & Morris, 2016). Hence, the limited available evidence suggests that sequential sampling models may be sensitive to early pathological decline and provide a method through which to parse confounding factors like more a

conservative response style and an increase in the time needed for basic perceptual and/or motor processes.

The current study used the LBA to evaluate the mechanistic differences underlying impaired object-location association (OLA) memory in individuals with MCI, relative to their cognitively-intact counterparts. Furthermore, we used functional magnetic resonance imaging (fMRI) data collected during the OLA memory task to test whether mechanistic differences identified by the model were consistent with group differences in activation, given previous research on fMRI correlates of LBA parameters. Since MCI patients in clinical settings typically complain of misplacing objects, the OLA task was designed to be ecologically relevant (Hampstead et al., 2011), making it an appropriate paradigm with which to parse the mechanisms behind commonly-reported everyday problems. On the basis of prior work by Aschenbrenner et al (2016), we predicted that individuals with MCI would display lower sensitivity than their cognitively intact counterparts. We also predicted that differences in sensitivity, and other model-based metrics, would be accompanied by between-group differences in fMRI activation in regions previously linked to the same cognitive mechanisms (e.g., the anterior insula and inferior parietal lobule, which are associated with the accumulation of evidence to discriminate between responses: Ho, Brown & Serences, 2009; Kühn et al., 2011).

Materials and Methods

Archival Data Analysis Approach

The current study re-analyzed behavioral data from Hampstead et al. (2011) in which participants underwent fMRI scanning as they encoded and then later recalled OLAs. The current report focuses on the cognitive/behavioral and fMRI aspects of the memory retrieval data, given our goal of determining whether model-based analyses can clarify the underlying neurocognitive mechanisms of memory impairment in MCI. Specifically, RT data from the memory retrieval task were fit to the LBA model. Although analyses of this dataset were reported in prior work (Hampstead et al., 2011; 2012; 2016), our analyses of LBA parameter estimates and univariate fMRI results from the retrieval task are novel. One of these studies (Hampstead et al., 2016) previously reported the results of a connectivity analysis of neuroimaging data from the retrieval task. However, the current study's focus on univariate activations from this task is both novel and, as previous work on neuroimaging correlates of LBA parameters has focused on univariate activations (Forstmann et al., 2008; Ho, Brown & Serences, 2009), crucial for our goal of linking the current study's results to these previous neuroimaging findings.

Participants

A total of 18 patients with MCI (mean age = 71.2, SD = 8.5, 12 males) and 16 comparably aged cognitively intact ("healthy") older adults (mean age = 72.1, SD = 7.3, 6 males) participated in the study. Demographic, neuropsychological and brain volumetric characteristics of each group are reported in Table 2, and full descriptions of recruitment methods and diagnostic procedures are reported in Hampstead et al. (2011). Briefly, individuals with MCI were recruited from two major medical centers and were diagnosed

according to Petersen's (2004) criteria via a consensus conference that included neurologists, neuropsychologists, geriatricians and other clinical staff. Healthy older adults (HOA) were recruited from a research registry and the community surrounding the medical centers, were free of objective memory impairment, and were functionally independent in their activities of daily living. All participants were right-handed, and exclusion criteria for both groups included a known history of neurological disease (other than MCI), psychiatric disorder, or substance abuse. Participants provided written informed consent, and all study procedures were approved by Emory University's Institutional Review Board and the Research and Development Committee of the Atlanta VAMC.

OLA Task

The OLA task, previously described in detail (Hampstead et al., 2011), was designed to emulate real-world associative memory problems that patients with MCI and Alzheimer's type dementia often report (Hamilton, Fay & Rockwood, 2009). Briefly, we used a virtual design program (www.Plan3d.com) to create 18 different 3-dimensional rooms (e.g., bedroom, garage, office). Within each environment, we identified 5 locations that spanned the height and width of each environment. A single object was placed in each of these locations in order to create the specific OLAs. Ninety images were selected from an established database (<http://www.psy.uwa.edu.au/mrcdatabase/mrc2.html>) and were then pseudorandomly assigned to each of the target locations in each room. All OLAs were checked to minimize implicit associations. These 90 OLAs are referred to hereafter as "Novel" stimuli. Two additional rooms (kitchen and bathroom) were assigned only a single object in a single location; these OLAs served as control stimuli and are referred to hereafter as the "Repeated" stimuli. The repetition of these simple associations served as an fMRI control condition; neural responses related to the retrieval of specific object-location associations were distinguished from those evoked by basic perceptual properties of the stimuli by subtracting "Repeated" stimulus activation from "Novel" stimulus activation.

During encoding, participants were first presented with an image of an object for 2 seconds (in order to facilitate identification), followed immediately by a 4-second display of the object in its target location within the room. Each trial was followed by an inter-stimulus interval (ISI) of 8 seconds, during which a fixation cross was presented. Participants completed a total of five functional imaging runs, each containing 18 Novel and 9 Repeated trials in a pseudorandom order. Six 10-second periods of baseline fixation were also included in each run to allow signal normalization. Run order was randomized for each participant. Participants were simply instructed to remember the location of each object presented and no response was required during the encoding scan. Results of the encoding data were previously reported by Hampstead et al. (2011).

Participants were removed from the scanner for a one-hour break before re-entering the scanner to complete the retrieval portion of the paradigm. During retrieval, participants were again presented with an image of the object for 2 seconds, followed by a 4-second presentation of the room that originally contained the object, and a subsequent 8-second ISI. During the presentation of the room, participants were instructed to choose which of three locations (marked with rectangles containing the numbers "1", "2" and "3") was the object's

actual target location. Importantly, each available option (including the 2 “lures”) was an actual target location. Therefore, the task required participants to use recollection to retrieve the specific object-location association rather than mere familiarity that something had been placed in that location, in the absence of specific memory for the correct item. Retrieval runs mirrored parameters of those used during encoding, but with a different stimulus order. Runs were randomized for each participant.

Imaging Parameters

All images were collected using a Siemens Trio 3-Tesla MRI scanner and a 12-channel head coil. Each functional imaging run included 219 T2*-weighted whole-brain images, collected in interleaved order using an echoplanar imaging (EPI) pulse sequence with the following parameters: TR = 2000ms, TE = 30ms, flip angle = 90°, field of view 220mm, 29 axial slices of 4mm each, an in-plane resolution of 3.4mm × 3.4mm, and an in-plane matrix of 64 × 64. In addition, a whole-brain, high-resolution, T1-weighted, 3D MPRAGE structural image was collected with the following parameters: TR = 2300ms, TE = 3.9ms, TI = 1100 ms, flip angle = 8°, 176 sagittal slices, 1mm slice thickness, 256mm field of view, in-plane resolution of 1mm × 1mm, and an in-plane matrix of 256 × 256. Stimuli were displayed using Presentation (Neurobehavioral Systems Inc., Albany, CA), and were synchronized to image acquisition using the scanner trigger.

Model-Based Analyses

Pre-analyses.—Prior to model-fitting, RT data from the OLA retrieval task were first inspected for quality. It is standard practice in sequential sampling model analyses to remove both long outlier RTs and possible “fast-guesses” (i.e., responses completed before most individuals would be able to make decisions at accuracy rates greater than chance) since both types of contaminant RTs can bias parameter estimation (Ratcliff & Tuerlinckx, 2002). RTs <0.500 seconds were removed as fast guesses because preliminary analyses revealed close-to-chance accuracy rates below this cutoff. An upper exclusion bound of 5.498 seconds was then determined by adding 3 standard deviations to the mean of RT data for both groups. These exclusion procedures removed <1% of trials (i.e., about 1 trial per person) in each group.

Model structure.—The LBA model was specified and fit using Dynamic Models of Choice (DMC: Heathcote, Lin, & Gretton, 2017; Heathcote et al., 2018: <https://osf.io/pbwx8/>), a free set of R (R Core Team, 2013) functions for model-based choice RT analyses in a Bayesian framework. The model assumed that each trial was a race between three accumulators: one accumulator for the correct response, with a rate drawn from a distribution with a mean of νc and a standard deviation of $s_{\nu c}$, and two accumulators for the error responses (one for each of the possible error responses in the three-choice task), with rates drawn separately from a distribution with a mean of νe and a standard deviation of $s_{\nu e}$. Although allowing these drift rate parameters to vary by different features of the stimuli (e.g., type of room, spatial location of the target) may have improved model fit, we chose to simplify the model due to the relatively low number of trials per person. The threshold (b) parameter, which was operationalized as the distance of the threshold above the top of the start point distribution (A), was allowed to vary by response key ($b.1$, $b.2$, and $b.3$) because

preliminary analyses revealed that participants likely displayed a response bias away from the “3” option. A single non-decision time ($t0$) parameter was estimated across all trials. Although the standard implementation of the LBA does not include a parameter for between-trial variability in $t0$, we estimated such a parameter ($st0$) which assumed variability following a uniform distribution, akin to the non-decision time variability parameter from the diffusion decision model (Ratcliff, Smith, Brown & McKoon, 2016). We did so because of indications that estimation of this parameter improves recovery of other model parameters when likelihood is used for fitting (Lerche, Voss & Nagler, 2017). Finally, a single start-point variability (A) parameter was estimated across all trials.

Sequential sampling models of RT suffer from a “scaling” problem, such that if their mean rate, rate variability, and threshold parameters are all multiplied by an arbitrary number, the predictions of the model do not change. To address this problem, models can be constrained by fixing one of these parameters to an arbitrary value (Donkin, Brown & Heathcote, 2009). In the current study, we decided to fix the drift rate variability parameter for correct responses (sve) to 1. Hence, we estimated a total of 9 free parameters for each individual: vc , ve , sve , $b.1$, $b.2$, $b.3$, $t0$, $st0$, and A .

We used a hierarchical Bayesian version of the LBA (Turner, Sederberg, Brown & Steyvers, 2013), which simultaneously estimates posterior distributions over individual-level parameter values and the values of group-level parameters, which describe the group distributions. Group distributions of each parameter value were described by two hyper-parameters: a mean (μ) and standard deviation (σ) parameter. This method is advantageous in situations with relatively low numbers of trials at the individual level for two reasons. First, the group-level parameter estimates can provide robust summaries of group data, even with high levels of uncertainty in the individual-level parameter estimates. Second, the group-level parameters act as priors for the individual-level estimates, preventing extreme outlier estimates of individual-level parameters, which may otherwise occur with sparse data.

Estimation.—Broad and uninformative priors were posited for group-level parameters, following previous hierarchical LBA implementations; we used the same priors as Turner et al. (2013), with the exception of some additional restrictions on the variability parameter priors (A , sve) that were helpful for obtaining convergence during parameter estimation. All group-level σ priors were exponential distributions with a scale of 1. Group-level μ priors were truncated normal (TN) distributions with the following means (μ), standard deviations (σ), and bounds:

$$A \sim TN(\mu = 1, \sigma = .5, 0, 3)$$

$$b.1 \sim TN(\mu = 1, \sigma = .5, 0, \infty)$$

$$b.2 \sim TN(\mu = 1, \sigma = .5, 0, \infty)$$

$$b.3 \sim TN(\mu = 1, \sigma = .5, 0, \infty)$$

$$vc \sim TN(\mu = 2, \sigma = 1, 0, \infty)$$

$$ve \sim TN(\mu = 2, \sigma = 1, 0, \infty)$$

$$sve \sim TN(\mu = 1, \sigma = .2, .25, \infty)$$

$$t0 \sim TN(\mu = 1, \sigma = .5, .1, \infty)$$

$$st0 \sim TN(\mu = 1, \sigma = .5, 0, \infty)$$

Differential evolution Markov Chain Monte Carlo simulations (DE-MCMC: Turner et al., 2013) were then used to estimate posterior distributions over group-and individual-level parameter values. A total of 27 chains were used for sampling, and simulations were run for a burn-in period until convergence was indicated by both the Gelman-Rubin statistic (< 1.1 for all parameters: Gelman & Rubin, 1992) and visual inspection of the chains. Following the burn-in period, 2,000 iterations of the simulation, thinned by 20 to save file space, were retained for analysis, leaving a total of 2,700 posterior samples for each model parameter.

Following parameter estimation, the primary measures of interest were calculated at the both the group level (using group μ parameters) and the individual level. Sensitivity and accumulation speed were calculated by entering posterior samples into the respective formulas displayed in Table 1. As response biases were not of interest in the current study, caution was calculated by simply averaging posterior samples for all three b parameters. Non-decision time was operationalized using samples for the single $t0$ parameter.

Hypothesis testing.—To test for group differences in the primary model-based measures of interest, group μ samples for the MCI group were subtracted from those of the HOA group to obtain difference distributions. Odds ratios (ORs) were then used to quantify evidence for the presence of group differences. ORs were calculated by first subtracting the posterior distribution for the MCI group's mean from that of the HOA group's mean to obtain a difference distribution. Next, for tests in which the majority of samples in the difference distribution fell above 0 (suggesting lower parameter values in the MCI group), the number of samples above 0 was divided by the number of samples below 0 to calculate an OR. For tests in which the majority of samples in the difference distribution fell below 0 (suggesting higher parameter values in the MCI group), the number of samples below 0 was divided by the number of samples above 0 to calculate an OR. Following previous research using Bayesian models of choice RT (Winkel, Hawkins, et al., 2016), ORs were interpreted

using the guidelines proposed by Jeffreys (1961) for Bayes factors: ORs > 3:1 were considered “positive” evidence for a difference, ORs > 10:1 were considered “substantial” evidence, ORs > 30:1 were considered “strong” evidence, and ORs > 100:1 were considered “decisive”.

fMRI Analyses

Functional images were motion-corrected in real time using Siemens 3D-PACE during data acquisition. All subsequent neuroimaging analyses were conducted within BrainVoyager QX v2.2 (Brain Innovation, Maastricht, The Netherlands). Pre-processing included intra-session alignment and motion correction of functional images to the first image of the series (trilinearsinc interpolation), slice timing correction (sinc interpolation), and high-pass filtering to 2 cycles/run to remove low frequency noise. Functional images were then co-registered with high-resolution anatomical images, spatially smoothed with a 4mm full-width half maximum Gaussian kernel, and normalized across runs and subjects using BrainVoyager’s z-baseline normalization option.

For general linear model (GLM) analysis, regressors for all trial events consisted of the time series for the entire 6-second event (the 2-second presentation of the object followed by the 4-second presentation of the room), convolved with a canonical hemodynamic response function. Although previous analyses of similar tasks excluded Novel trials for which stimuli were incorrectly encoded (e.g., Hampstead et al., 2011), we collapsed across correct and incorrect Novel trials for two reasons. First, as the LBA model explains performance on both correct and incorrect trials, we were broadly interested in how neural activity differed between groups during all trials of the task, which would be more relevant to differences in model parameters between groups. Second, analysis of all trials, rather than a subset, increases the statistical power of the contrasts used. Regressors for the baseline of each run and motion parameters were also included in individual-level models. The AR(1) approach was used to control for temporal autocorrelation. For group-level random effects analyses, we were primarily interested in between-group differences in the value of the within-subjects Novel > Repeated contrast, which was aimed at controlling for neural responses related to basic perceptual properties of the stimuli. Hence, the primary contrast of interest was a Novel > Repeated by Group interaction: (HOA Novel > HOA Repeated) > (MCI Novel > MCI Repeated). Whole-brain statistical maps for this contrast were held to a per-voxel cluster-forming threshold of $p < .005$ and adjusted for multiple comparisons using 1,000 Monte Carlo simulations implemented in BrainVoyager within the whole-brain analysis mask. Simulations determined that a cluster-forming threshold of >16 functional voxels was necessary to obtain a family-wise error rate of .05.

Results

Behavioral Summary Statistics

Although analyses of mean RT, collapsed across correct and incorrect trials, and accuracy rates from this data set have been previously reported (Hampstead et al., 2011), we report new analyses of behavioral summary statistics here for two reasons. First, our use of exclusion criteria for individual trials in the current study altered these statistics. Second,

following previous work with sequential sampling models (Ratcliff et al., 2016), we were interested in whether there were differences between the latencies of correct and incorrect RTs from each group, and whether the model we used could account for these differences.

As expected, both groups displayed higher accuracy rates than would be expected from chance responding (.33 for a 3-choice task), but the HOA group had a significantly higher accuracy rate (mean = .50) than the MCI group (mean = .39), $t(32)=2.94$, $p=.006$, $d=1.01$. There was not a significant group difference in RT when all trials were included (i.e., mean of correct and incorrect), $t(32)=0.18$, $p=.859$, $d=0.06$. However, a significant Group x Accuracy interaction was detected, $F(1,32)=19.53$, $\eta^2=.18$, $p<.001$, in which the HOA group displayed faster correct RTs (HOA mean=2.486, MCI mean=2.654) but slower incorrect RTs (HOA mean=2.897, MCI mean=2.757) than the MCI group. However, neither the group effect in correct RTs, $t(32)=0.98$, $p=.335$, $d=0.34$, nor the group effect in incorrect RTs, $t(32)=0.83$, $p=.416$, $d=0.28$, was significant on its own, suggesting that these group differences may not be reliable.

Model-Based Analyses

Before investigating group differences in model parameters, posterior predictive checks (Gelman, Meng, & Stern, 1996), which are standard practice for assessing the absolute fit of Bayesian cognitive models (Lee & Wagenmakers, 2014), were used to ensure that the model provided an adequate description of key effects in the empirical data (e.g., RT and accuracy differences between groups). Such checks compare the empirical data to data predicted by values sampled from posterior distributions of model parameters, which should closely approximate the empirical data if model fit is good. Rather than a discrete value, the posterior predictive data are distributions of values produced by many individual samples from the posterior, and the spread of these distributions therefore represents uncertainty in predicted data values, which, in turn, reflects uncertainty about model parameter estimates. Figure 2a plots empirical group means of accuracy rates and selected quantiles (.1, .5, .9) of correct and incorrect RTs for each group against density plots of the same group means from posterior predictive data. The model describes accuracy rates in each group very well and, although there is some misfit in the absolute values of the RT quantiles, the model captures the general pattern of the RT data well. Specifically, the model appears to describe the Group x Accuracy interaction effect reported above, in which the HOA group had marginally faster correct RTs, but marginally slower incorrect RTs, than the MCI group. Therefore, we decided that the model fit the empirical data adequately.

One potential pitfall of model-based analyses is that the LBA, like many other models in the cognitive and biological sciences, can display highly-correlated parameters, especially in situations where there are sparse data at the individual level (Kolossa & Kopp, 2018; Gutenkunst et al., 2007). These parameter intercorrelations can result in “trade-offs” between model parameters, in which increases in a given parameter for a given condition may lead to artificial increases or decreases in other model parameters for the same condition, which are due to parameter correlations rather than true differences in underlying mechanisms (Boehm et al., 2018). We investigated the possibility of parameter trade-offs by inspecting within-group correlations between individual-level parameter values, and found

that, particularly for the HOA group, sensitivity and accumulation speed were positively correlated, and both of these parameters were negatively correlated with caution (Supplemental Materials). Although the presence of these trade-offs is not surprising given the relatively low number of trials at the individual level (which was the primary reason we decided, prior to analyses, to focus on inferences drawn from group-level parameters), it suggests that 1) individual-level parameter estimates are likely not reliable enough to be used in analyses, and that 2) these trade-offs will not necessarily affect group-level inferences, but may have some implications for their interpretation, as discussed below.

Group-level posterior distributions for parameters of interest are displayed in Figure 2b as violin plots, which include box plots of the posterior samples surrounded by density plots of the same samples. Figure 2b also displays density plots of the difference distributions obtained by subtracting the posterior of the HOA group from that of the MCI group. Consistent with our initial predictions, there was positive evidence that the MCI group displayed poorer sensitivity than the HOA group ($OR=3.56:1$). However, there was also decisive evidence that the MCI group both had faster evidence accumulation speed ($OR=191.86:1$) and was more cautious ($OR>1000:1$) than the HOA group. There was little evidence for a group difference in non-decision time ($OR=2.05:1$).

Simulation Study to Determine Parameter Contributions

Even though the model-based analyses described above provide evidence for which processes measured by the model plausibly differ between groups, the individual contribution of these processes to key effects in the behavioral data can often be difficult to discern. Therefore, following methods used in recent work (Boag, Strickland, Heathcote, Neal and Loft, 2019; Strickland et al., 2019; Weigard, Heathcote, Matzke & Huang-Pollock 2019) we conducted a simulation study to evaluate the average contributions of sensitivity, accumulation speed, and caution to explaining the primary behavioral difference found between the groups: reduced accuracy rates in the MCI group. Of the parameters found to be different between groups, sensitivity and caution would be most expected to impact accuracy rate, although caution is less likely to impact accuracy when sensitivity is very low (e.g., in the MCI group), as waiting for additional evidence has little benefit when the evidence is generally poor.

First, we simulated data from “average” subjects in each group using median values of the group mean (μ) parameter posteriors. 1.5 million trials were simulated for each group to allow for stability in estimates of predicted accuracy rates, and the predicted between-group accuracy rate difference obtained was compared to the empirical difference in accuracy rates between groups (roughly equal to .11). We then repeated this procedure while “normalizing” different summary parameters of interest (sensitivity, accumulation speed, and caution) in the MCI group by setting the parameter values of the “average” MCI subject to be equal to those of the “average” HOA subject. For caution, this was accomplished by simply setting all b parameter values to those of the HOA group. As sensitivity and accumulation speed are both determined by values of vc and ve , while the former is also determined in this model by values of sve , all three of these parameters were set to HOA group values when both sensitivity and accumulation speed were normalized in the same simulation. When

sensitivity was normalized without accumulation speed, we set sve to the HOA group's value and solved algebraically for values of vc and ve that would equate sensitivity between groups but allow accumulation speed to remain at the typical MCI group value (see Table 3). Similarly, when accumulation speed was normalized without sensitivity, we kept sve at the MCI group's average value and solved algebraically for values of vc and ve that would equate accumulation speed between groups while leaving the MCI group's sensitivity level unchanged.

In Table 3, we report both the raw predicted between-group accuracy rate differences in each simulation condition and the percentage of the empirical between-group accuracy rate difference that model parameters in each condition explained. These percentages can exceed 100% if the model parameters used in a given simulation condition predict a group difference in accuracy rates that exceeds the empirical accuracy rate difference. Results indicated that, in the simulation condition where none of the parameters of the “average” MCI subject were normalized (i.e., all parameter values for each group were identical to those obtained in the original model fit), the model slightly over-predicted the magnitude of group differences in accuracy (109%, or .12 versus an empirical value of .11). Models in which sensitivity was normalized substantially underestimated the size of the accuracy effect (18%–45% of the empirical effect) and all models in which group sensitivity differences were left intact, but accumulation speed and caution were normalized, predicted the same magnitude of accuracy effect as the original model parameters (109%). Although normalizing accumulation speed only did not reduce estimates of the accuracy effect magnitude, the simulation condition in which all parameters other than accumulation speed were normalized (S+C) predicted a somewhat larger accuracy effect (45%) than the condition in which all parameters of interest were normalized (27%), suggesting that accumulation speed increases, by themselves, may play a minor role in reducing accuracy rates in this context. Normalizing caution had little effect, suggesting that adjustments to caution do not benefit individuals with MCI by increasing their accuracy rates on the task.

Taken together, these findings suggest that although there is evidence that individuals with MCI display altered levels of accumulation speed and caution on the task, the main MCI-related performance deficit on the task (reduced accuracy) is primarily driven by MCI-related group differences in sensitivity

Whole-Brain fMRI Analysis of Retrieval Data

The planned Novel > Repeated by Group interaction contrast revealed numerous regions that displayed greater activation in the HOA group than in the MCI group during OLA retrieval (Table 4, Figure 3), but no regions that displayed the opposite effect. Of the areas identified, one large medial cluster (displayed in the top left panel of Figure 3) spanned multiple anatomical regions, including the rostral anterior cingulate cortex (rACC), middle anterior cingulate cortex (mACC), and pre-supplementary motor area (pre-SMA). Notably, many of the regions identified in this analysis also displayed greater activity in HOA during encoding (Hampstead et al., 2011), including the caudate, globus pallidus, medial frontal (present within the large cluster noted above), and right anterior insular cortical regions. Contrary to our expectations, significant clusters in the medial temporal lobe (e.g., hippocampus) were

not identified. However, we note that this may be the result of a Type II error, given the relatively low statistical power of whole-brain analyses using cluster-extent thresholding for detecting effects in small anatomical regions (Woo et al., 2014). Hence, the pattern of results from this analysis is generally consistent with previous research suggesting that individuals with MCI display widespread abnormalities in neocortical function extending beyond structures in the medial temporal lobe.

Several of the regions identified have previously been associated with parameters in sequential sampling models. In particular, there is evidence that the anterior insula is involved in domain-general accumulation of sensory evidence for decisions (Ho et al., 2009), suggesting that activity in this region may be related to individuals' sensitivity. Activity in pre-SMA and caudate has been previously associated with reductions in caution (Forstmann et al., 2008; van Veen et al., 2008), consistent with the fact that the HOA group, which showed increased activity in these regions, had lower levels of caution.

Discussion

The current study used the LBA, a formal model of choice RT tasks, to 1) clarify the mechanistic processes that are altered during memory performance in MCI and 2) provide preliminary evidence that MCI-related patterns of neural activation during memory retrieval are consistent with these mechanistic processes, given previous model-based neuroscience research. Comparisons of group-level model parameters provided evidence that individuals with MCI displayed reduced sensitivity on the OLA task, consistent with the hypothesis that these individuals display a core memory deficit. These comparisons also suggested that MCI patients displayed higher levels of caution (greater emphasis on accuracy relative to speed) relative to the HOA group, as well as a faster overall speed of evidence accumulation. As overall accumulation speed as previously been interpreted as an index of arousal or task engagement (Forstmann et al., 2011; van Maanen et al., 2016), and has been linked to arousal in studies of sleep deprivation (Racliff & Van Dongen, 2011), the latter result may indicate that individuals with MCI are more aroused or engaged during the task. However, simulation studies to determine parameter contributions to group differences in behavior indicated that MCI-related differences in sensitivity appeared to be the primary driver of poorer accuracy rates in this group, and that adjustments to accumulation speed and caution had little effect on accuracy rate. Analyses of fMRI data revealed that individuals with MCI exhibited reduced activity in a wide variety of brain regions, a subset of which were consistent with expectations based on between-group differences in LBA model parameters, as described in more detail below.

The finding that accumulation speed and caution displayed convincing evidence of MCI-related changes in parameter difference tests but did not appear to contribute to the most salient behavioral difference between groups, the large MCI-related reduction in accuracy, has two possible implications. First, it is possible that these parameter differences reflect trade-offs between parameters, in which increases in a given parameter are associated with artificial increases or decreases in others. Second, it is possible that group differences in accumulation speed and caution are present, but do not substantially impact accuracy rate in the MCI group, and instead cause more subtle changes to behavior (e.g., changing features

of response time distributions) that were not easily captured by analyses of group differences in behavioral summary statistics. Although there was evidence of trade-offs in the individual-level parameter values (Supplemental Materials), this evidence does not necessarily indicate that group parameter differences were due to trade-offs, both because individual-level parameters are likely more difficult to estimate due to low trial numbers on this task (hence our primary focus on group-level parameters) and because of the direction of the observed trade-offs; individual estimates of sensitivity and accumulation speed were positively correlated with one another, and both parameters were negatively correlated with caution. However, the MCI group showed, in addition to greater accumulation speed, *lower* sensitivity and *higher* caution, indicating that group differences are generally in the opposite direction of what would be expected if they were due to trade-offs alone.

A formal model comparison analysis, in which parameters are fixed between conditions (typically within-subject conditions), and model fit is evaluated with a metric that penalizes for model complexity (e.g., DIC: Spiegelhalter, Best, Carlin, & Van Der Linde, 2002), may have provided more definitive evidence that changes in accumulation speed and caution account for key behavioral differences between the groups. However, we did not conduct such an analysis because we were unaware of previous examples where these analyses were applied to test for between-group parameter differences in a hierarchical model, and it was therefore unclear how such an analysis would be optimally conducted to provide a sensitive test of between-group differences. The lack of a formal model comparison analysis is a limitation of the current study and prevents us from making stronger claims about accumulation speed and caution differences in MCI. However, given the evidence presented above that parameter trade-offs were unlikely to have resulted in the specific pattern of group-level parameter differences observed, our findings suggest that group differences in accumulation speed and caution reflect true mechanistic differences between the groups, although this inference must be further tested in future work.

If the inference that accumulation speed and caution, in addition to sensitivity, differ in MCI is assumed to be valid, the findings of the model-based analyses have several key implications. The finding that individuals with MCI displayed evidence of both reduced sensitivity and increased caution is notable in the context of the existing literature on DDM analyses of memory tasks, which has found modest reductions in sensitivity and large increases in caution on associative memory tasks in “normal” aging (Ratcliff & McKoon, 2015; McKoon and Ratcliff, 2012). A previous study which applied the LBA to a perceptual decision task also found evidence of faster accumulation speed in older, relative to younger, adults, and interpreted this increase as evidence of older participants’ increased arousal or engagement (Forstmann et al., 2011). The fact that the LBA’s accumulation speed index does not have a one-to-one mapping to DDM parameters may explain why only this latter study presents evidence for arousal differences in older adults. Importantly, the current analysis found comparable non-decision time between the MCI and HOA groups, which indicates that memory performance differences in MCI are not reflective of slowing in the peripheral sensory and motor processes that are indexed by this parameter. In contrast, non-decision time differences play a large role in age-related declines in DDM analyses of memory task performance (Ratcliff, Thapar & McKoon, 2006; 2007; Ratcliff & McKoon, 2015). Consistent with this dissociation between the effects of normative aging and those of

clinical phenotype, Aschenbrenner et al. (2016) also reported reduced sensitivity, but intact non-decision time, in a DDM analysis of individuals with familial risk factors for Alzheimer's disease. Although the differences in findings between this previous study and the current results may be due to our use of the LBA, our results suggest that, relative to individuals with only family risk factors, those who meet diagnostic criteria for MCI may display increased caution and accumulation speed in addition to poorer sensitivity.

Consideration of prior work on age-related increases in caution may be informative for understanding the reasons for increased caution in MCI. Such age-related differences have been attributed to two plausible mechanisms: 1) a strategic tendency for older adults to minimize avoidable errors, even though it results in non-optimal reward rates (Starns & Ratcliff, 2010), and 2) age-related decrements in the structural integrity of neural systems that mediate voluntary reductions in caution (e.g., direct connections between the striatum and pre-SMA: Forstmann et al., 2011). The latter mechanism is consonant with the MCI group's observed patterns of reduced activation in these regions, which suggests that neuropathology in MCI may exacerbate age-related decrements in their structural integrity or the integrity of connections between them, leading to even greater inflexibility in caution than that caused by normal aging. However, it is also plausible that this increase in caution, along with the parallel increase in accumulation speed observed in MCI, is related to strategic or attentional changes individuals with MCI make to compensate for poor sensitivity. Specifically, if individuals with MCI are aware that they are struggling with the task, they may attempt to improve their performance by implementing a more error-averse strategy (increasing caution) and/or by dedicating more effort or attention to the task (increasing accumulation speed).

Despite the fact that our simulation studies indicated that the observed group differences in accumulation speed and caution did not directly contribute to MCI-related memory deficits, these group differences have two important implications for the study of MCI. First, as noted above, effects in these parameters suggest that individuals with MCI may approach the task differently from individuals without memory deficits because they recognize that their performance is poor and try to compensate by increasing their engagement in the task or their level of caution. It is therefore notable that individuals with MCI continue to display poorer accuracy even after such possible "adjustments", suggesting that they are unable to effectively compensate for their reduced memory integrity, and that accumulation speed and caution are unlikely to be productive compensatory strategies or targets for interventions. Second, robust group differences in these latent mechanisms may provide useful information for classification algorithms, even if they are unrelated to group differences in accuracy. Recent work applying machine learning to cognitive task data to predict clinical outcomes in Parkinson's and Huntington's diseases has demonstrated that classification algorithms display superior performance when parameters of computational models are used in place of summary statistics like accuracy (Wiecki, Poland & Frank, 2015; Wiecki et al., 2016). Therefore, LBA parameters may ultimately provide richer information for MCI diagnostic algorithms than accuracy scores because these parameters index more varied and precise mechanistic dimensions.

Reduced activation in several brain regions was particularly meaningful given group differences in LBA model parameters. Specifically, the anterior insular reduction in those with MCI is consistent with prior work indicating this region plays a role in the accumulation of sensory evidence for decisions (Ho et al., 2009). In contrast, as the striatum and pre-SMA have both been linked to individuals' ability to modulate their level of caution in choice RT tasks (Forstmann et al., 2008; 2011), lower activity of these regions in MCI is consistent with their higher level of caution. When viewed within the context of the wider literature on cognitive (McLaughlin et al., 2014; Zheng et al., 2012; Levinoff et al., 2005) and neuroimaging (Hampstead et al., 2011; Zhang et al., 2015; Wang, et al., 2016) deficits in MCI, the current findings support the notion that aberrations in cognitive performance in MCI are related to widespread dysfunction that extends beyond the medial temporal lobes.

As individual-level LBA parameter estimates were based on relatively sparse data (90 trials per person), and displayed evidence of intercorrelations that likely reflect trade-offs between individual-level parameters (Supplemental Materials), brain-behavior correlation analyses using data from the current study would be difficult to interpret. Therefore, a key limitation of the current study is that we were unable to use such analyses to provide additional evidence for these preliminary links between the mechanisms indexed by the LBA and neural activations in MCI. Future work using larger samples of participants and tasks with greater numbers of trials per-person will be essential for investigating these possible links through the use of brain-behavior correlation analyses.

Additional limitations of the study, beyond those noted above, include the heterogeneous nature of the clinical MCI phenotype, which means that evidence for mechanistic differences in this condition may not apply to all individuals with the diagnosis. Second, the task was not optimized for the LBA approach, so future studies should include more trials and modify other relevant parameters (e.g., shortening the response timeframe) in order to ensure LBA assumptions are met. We attempted to mitigate such paradigm limitations by using hierarchical modelling to obtain group-level parameter estimates (the main estimates of interest) and by evaluating posterior predictive plots – which suggested that our application of the LBA described the data well and did not violate major assumptions of the model. We are already planning a follow-up study in which a task designed to better meet the assumptions of sequential sampling models will be performed by a large sample of biomarker-confirmed participants in order to overcome the above limitations and determine the stability/reliability of the observed findings and their ability to predict clinical conversion.

In sum, the current study provided evidence that individuals with MCI 1) display “core” memory deficits, 2) also display differences in other key factors (i.e., accumulation speed and caution) relative to their cognitively intact peers, although these differences do not appear to contribute to MCI-related accuracy differences on the task, and 3) that group differences in these processes are generally consistent, given prior research, with observations of reduced neural activity across a number of brain regions. If replicated by future studies, the results support the further incorporation of mathematical cognitive modeling methods in clinical and research contexts relevant to MCI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- The linear ballistic accumulator model was used to evaluate memory deficits in MCI
- Individuals with MCI displayed evidence of core memory deficits
- Individuals with MCI also displayed increased arousal and caution
- Group differences in neural activation were consistent with those in model parameters

Figure 1.

Outline of sequential sampling explanations of memory task performance and the LBA model. **a)** Sequential sampling models assume that individuals gather evidence for each possible response by sampling bits of evidence over time from partially overlapping distributions of memory representations for “target” and “lure” stimuli. **b)** Example of a single trial in the LBA model framework. As the LBA assumes a linear, deterministic rate of evidence accumulation, the accumulation rates for the “target” and “lure” response accumulators are determined by a single sample from the respective distributions. The accumulators gather evidence at these set rates over time on the trial until one reaches threshold, and the corresponding response occurs. **c)** Schematic of the full LBA model, which describes this “race” by assuming that the rate of each accumulator at a given trial, or “drift rate”, is drawn from a normal distribution with a mean of ν and a standard deviation (SD) of $s\nu$. Typically, the distribution of drift rates for correct responses (e.g., a “target” response) is described by a mean of ν_c and an SD of $s\nu_c$, while the distribution of drift rates for error responses (e.g., “lure” responses) is described by a mean of ν_e and an SD of $s\nu_e$. The starting point for each accumulator is drawn from a uniform distribution bounded at 0 and the A parameter. Accumulators for each response race until one reaches a threshold, denoted by the b parameter, which initiates the corresponding response. A t_0 parameter accounts for the amount of time spent on peripheral processes that occur before and after decision making.

Figure 2.

Plots of model fit and group mean differences in model parameters of interest. **a)** Empirical data (black lines and points) plotted against posterior predictive distributions generated by the model (grey density plots) for overall accuracy rates and selected quantiles (.1, .5, .9) of correct and error RTs. **b)** Violin plots of posterior distribution samples for group μ parameters from the HOA and MCI groups (top) and density plots of the difference distributions (HOA – MCI) calculated from these samples (bottom). Violin plots display box plots of samples surrounded by density plots of the same samples.

Figure 3.

Results of the whole-brain fMRI analysis for the Novel/Repeated by Group interaction contrast (HOA Novel/Repeated > MCI Novel/Repeated) displayed as maps of t -statistics visualized on a participant-specific template. We used this template to create an anatomical mask to constrain the whole brain analysis. Statistical maps are thresholded at a voxel-wise $p < .005$ and corrected for multiple comparisons using the procedures described in the text.

Table 1.

List of model-based measures derived from the LBA, including details of their calculation using basic LBA model parameters and previous studies which where the basis of our choice to use these measures in the current study.

Measure	Calculation	Description	Previous Studies
Sensitivity	$\frac{(vc - ve)}{\sqrt{(svc^2 + sve^2)}/2}$	Ability to discriminate between target (correct) stimuli and lure (incorrect) stimuli in the memory task, similar to d' in signal detection theory	Heathcote et al., 2015; Winkel, Hawkins, et al., 2016
Accumulation Speed	$(vc + ve)/2$	Absolute accumulation speed of both correct and incorrect information from the stimulus, which appears to reflect arousal and task engagement	Ratcliff & Van Dongen, 2011; van Maanen et al., 2016; Forstmann et al., 2011
Caution	b	Degree to which individuals emphasize accuracy over response speed by waiting for additional information to accumulate before making a decision	Rae et al., 2014; van Maanen et al., 2016; Winkel, Hawkins, et al., 2016
Non-decision time	$t0$	Time taken up by processes peripheral to decision making (e.g., perceptual encoding, motor response)	Rae et al., 2014; van Maanen et al., 2016; Winkel, Hawkins, et al., 2016

Table 2.

Demographic, neuropsychological and brain volumetric data for each group, copied with permission from Hampstead et al. (2011). Standard deviations are provided in parentheses. MMSE = mini-mental state exam; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; GDS = Geriatric Depression Scale; FAQ = Functional Activities Questionnaire.

	HOA (n=16)	MCI (n=18)	<i>t</i> (32)	<i>p</i> -value
Age	72.1 (7.3)	71.2 (8.5)	0.33	.74
Education (years)	16.1 (2.7)	17.1 (2.1)	1.19	.25
MMSE	27.8 (1.97)	26.7 (2.3)	1.47	.15
RBANS Indices (Standard Scores)				
Immediate Memory	105.8 (13.5)	87.1 (13.2)	4.1	<.001
Visuospatial/construction	99.5 (14.4)	94.9 (16.8)	0.84	.41
Language	103.3 (15.2)	92.2 (7.1)	2.77	.009
Attention	110.4 (11.8)	105.9 (11.8)	1.11	.28
Delayed Memory	103.8 (8.9)	74.9 (15.1)	6.68	<.001
Total Score	106.5 (14.4)	87.8 (10.4)	4.39	<.001
Trails A (T-scores)	49.0 (8.7)	45.8 (12.1)	0.87	.39
Trails B (T-scores)	50.4 (9.0)	47.7 (6.7)	0.98	.34
GDS (raw scores)	1.1 (1.9)	1.6 (1.9)	0.74	.46
FAQ (raw scores)	0.4 (0.7)	3.6 (3.9)	3.07	.005
Brain Volumetrics (% intracranial volume; ICV)				
Cortical gray	30.1 (2.1)	29.1 (1.6)	1.57	.13
Lateral ventricles	2.2 (0.8)	2.8 (1.0)	1.95	.06
Inferior lateral ventricles	0.16 (0.05)	0.19 (0.07)	1.73	.09
Hippocampus (Total)	0.49 (0.06)	0.46 (0.06)	1.39	.18
Left	0.24 (0.03)	0.23 (0.03)	1.0	.32
Right	0.25 (0.03)	0.24 (0.04)	1.5	.14
Amygdala	0.23 (0.03)	0.21 (0.05)	1.70	.10

Table 3.

MCI group parameter values used in, and the results of, the simulation study to determine individual parameter contributions to group differences in accuracy rate. Each column label indicates the main parameters of interest (S = sensitivity, A = accumulation speed, C = caution) that were “normalized” in each simulation condition by setting the MCI group’s average value to the average value of the HOA group. The “none” column indicates the simulation in which no MCI group parameters were normalized. In the S+A+C column, all parameter values were normalized, and the values reported therefore perfectly correspond to the average values of the HOA group. For clarity, the values of the raw LBA parameters (*b.1*, *b.2*, *b.3*, *vc*, *ve*, *sve*) that were used in each simulation for the MCI group are displayed along with the values of the main summary parameters of interest. The predicted between-group difference in accuracy rates (Acc. Diff.) and the percentage of the empirical between-group difference in accuracy rates (.11) that the predicted accuracy rates account for (% Acc. Diff.) are the primary outcome measures. These percentages can be greater than 100% if the model predicted a larger group difference than is present in the empirical data.

	None	C	A	S	A+C	S+C	S+A	S+A+C
<i>b.1</i>	1.43	1.11	1.43	1.43	1.11	1.11	1.43	1.11
<i>b.2</i>	1.25	1.11	1.25	1.25	1.11	1.11	1.25	1.11
<i>b.3</i>	1.78	1.32	1.78	1.78	1.32	1.32	1.78	1.32
<i>vc</i>	1.71	1.71	1.46	1.78	1.46	1.78	1.51	1.51
<i>ve</i>	1.52	1.52	1.27	1.47	1.27	1.47	1.20	1.20
<i>sve</i>	0.81	0.81	0.81	0.42	0.81	0.42	0.42	0.42
<i>Sensitivity</i>	0.21	0.21	0.21	0.40	0.21	0.40	0.40	0.40
<i>Accu. Speed</i>	1.62	1.62	1.36	1.62	1.36	1.62	1.36	1.36
<i>Caution</i>	1.49	1.18	1.49	1.49	1.18	1.18	1.49	1.18
Ace. Diff.	0.12	0.12	0.12	0.05	0.12	0.05	0.02	0.03
% Ace. Diff.	109%	109%	109%	45%	109%	45%	18%	27%

Table 4.

Peak voxel coordinates (Talairach) and *t*-values for significant clusters found in the whole-brain fMRI analysis for the Novel/Repeated by Group interaction contrast (HOA Novel/Repeated > MCI Novel/Repeated). The region labeled with an asterisk (*) was a large cluster (see Figure 3, top left panel) that spanned the anterior cingulate cortex and pre-supplemental motor area (pre-SMA).

Region	X	y	Z	t-value
R. lateral occipital cortex	34	-76	-16	5.05
R. medial frontal gyms	34	-3	55	3.88
R. caudate	12	-1	14	4.09
L. globidus pallidus	-17	6	-1	4.47
L. posterior cingulate	-3	-36	23	4.35
L. rostral prefrontal cortex	-24	60	14	4.70
Anterior cingulate/pre-SMA*	-4	25	24	4.92
L. anterior insula	-29	12	-2	3.67
R. parieto-occipital fissure	-8	-73	23	4.14