Cholinergic enhancement of frontal lobe activity in mild cognitive impairment

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Summary
Cholinesterase inhibitors positively affect cognition in Alzheimer’s disease (AD) and other conditions, but no controlled functional MRI studies have examined where their effects occur in the brain. We examined the effects of donepezil hydrochloride (Aricept) on cognition and brain activity in patients with amnestic mild cognitive impairment (MCI), a diagnosis associated with a high risk of developing AD. Nine older adults with MCI were compared with nine healthy, demographically matched controls. At baseline, patients showed reduced activation of frontoparietal regions relative to controls during a working memory task. After stabilization on donepezil (5.7 ± 1.7 weeks at 10 mg) patients showed increased frontal activity relative to unmedicated controls, which was positively correlated with improvement in task performance (r = 0.49, P = 0.05) as well as baseline hippocampal volume (r = 0.62, P < 0.05). The patients’ overall cognitive function was stable or improved throughout the study. Short-term treatment with a cholinesterase inhibitor appears to enhance the activity of frontal circuitry in patients with MCI, and this increase appears to be related to improved cognition and to baseline integrity of the hippocampus. These relationships have implications for understanding the mechanisms by which cognition-enhancing medications exert their effects on brain function and for the use of functional MRI in early detection and treatment monitoring of AD and MCI.

Keywords: mild cognitive impairment; Alzheimer’s disease; cholinesterase inhibitor; functional MRI; hippocampal volume

Abbreviations: AChE = acetylcholinesterase; AD = Alzheimer’s disease; CVLT = California Verbal Learning Test; fMRI = functional MRI; MCI = mild cognitive impairment; WM = working memory

Introduction
Developing effective treatments for Alzheimer’s disease (AD) and related dementias is crucial both for those directly affected and for society in general, given the growing proportion of the population composed of older adults (World Health Organization, 2001). Numerous treatment strategies are under investigation and significant advances have been made in early detection and diagnosis (Doody et al., 2001; Knopman et al., 2001; Petersen et al., 2001). Mild cognitive impairment (MCI) is characterized in its typical amnestic form by isolated memory impairment and memory complaints in the context of otherwise normal cognition and normal daily functioning (Petersen, 2000; Petersen et al., 1999). Patients with MCI show atrophy of the hippocampus and other medial temporal lobe structures that are important for the formation of new memories similar to, though less pronounced than, the structural brain changes seen in AD (Jack et al., 2000; Du et al., 2001; Chetelat et al., 2002; Saykin et al., 2003a; Wolf et al., 2003; Zakzanis et al., 2003).

Approximately half of patients diagnosed with MCI develop AD or another dementia within 5 years (Petersen, 2000; Petersen et al., 1999).

Currently approved treatments for AD focus on increasing the availability of acetylcholine, a neurotransmitter linked to memory systems function (for review see Gauthier, 2002). Cholinergic or other therapies may be effective in treating MCI, perhaps delaying or eventually even preventing the development of dementia (National Institutes of Health, 1999; Allain et al., 2002). However, the mechanisms by which cholinergic treatments affect brain function are not fully understood. At the cellular/molecular level, rat experi-
ments with two cholinesterase inhibitors (donepezil and galantamine) demonstrated cholinergic modulation of synaptic plasticity and an increase in nicotinic receptors in the hippocampus and frontal neocortex (Barnes et al., 2000). Initially developed to target the cholinergic system and recent memory and learning, these medications have also been found to affect other neurotransmitter systems and other cognitive functions, such as attention and working memory (Levin and Simon, 1998; Svensson and Giacobini, 2000; Soreq and Seidman, 2001; McAllister et al., 2004).

Relatively little is known about the mechanism of action of acetylcholinesterase (AChE) inhibitors at the brain systems level. Single doses of cholinesterase inhibitors have been shown to normalize quantitative electroencephalographic patterns in patients with AD (Lanctot et al., 2003). PET and single-photon emission computed tomography (SPECT) studies have shown preserved or increased cerebral blood flow in AD patients treated with cholinesterase inhibitors (Matsuda, 2001; Mega et al., 2001; Nakano et al., 2001; Nobili et al., 2002a, b; Vennerica et al., 2002). PET studies have also shown inhibition of AChE activity in vivo in AD patients treated with AChE inhibitors (Kuhl et al., 1999, 2000; Shinotoh et al., 2001) and one study showed a regionally specific effect in the frontal cortex (Kaasinen et al., 2002). Additionally, one functional MRI (fMRI) study showed enhanced frontal activation during a working memory task in five AD patients after a single dose of rivastigmine (Rombouts et al., 2002). This study also found increased activation of the fusiform gyrus during a face-memory task in seven AD patients after rivastigmine. Because this study did not include control subjects, it was not possible to determine whether this represented an effect of the medication or another factor. Although there are preliminary indications that AChE inhibitors influence cognition at least partly by upregulating frontal systems functioning (for review see Thiel, 2003), the fact that cholinergic projections are widespread and interact with other neurotransmitter systems suggests that a more global alteration in brain activity is also possible (Levin and Simon, 1998). Furthermore, there may be task-specific regional changes.

Although no controlled fMRI studies of treatment effects have been published in MCI or AD to date, fMRI is useful for examining brain function in these patients. Overall, fMRI studies have demonstrated altered patterns of brain activity associated with memory in patients with AD or at risk of AD. These alterations include both increases and decreases in activity relative to healthy controls, depending on the stage of disease and memory system being investigated (for review see Saykin and Wishart, 2003). Evidence of increased or spatially expanded activation in AD and other patient groups has been interpreted as compensatory. Genetically at-risk individuals with no current neurological symptoms also show this pattern (Booher et al., 2000; Smith et al., 2002). The extent to which AD patients can activate additional tissue for task completion has been related to the degree of regional cortical integrity, suggesting that compensatory activation may require a certain level of preservation of brain structure (Johnson et al., 2000).

We conducted a controlled fMRI study of working memory (WM) in MCI patients before and after treatment with the cholinesterase inhibitor donepezil hydrochloride (Aricept®) to determine how an AChE inhibitor affects brain activity in older adults at risk of AD. WM, the ability to hold information in memory while performing another mental operation (Baddeley, 1995, 1998), is impaired in AD (Belleville et al., 1996). Healthy adults usually show prominent activity in bilateral frontal and parietal regions, as well as the cingulate cortex, cerebellum and other areas, when performing WM tasks (Cabeza and Nyberg, 2000). We hypothesized that patients with MCI would show altered patterns of brain activity for WM at baseline. We also predicted that treatment with an AChE inhibitor would help to normalize activation patterns in the patient group.

Methods
Participants were nine consecutive older adults with MCI who met the study criteria and nine healthy older adults with no cognitive complaints or deficits. Participants were recruited through the use of flyers, public lectures, newspaper advertisements and referrals from our medical centre’s General Internal Medicine, Community Health and Geropsychiatry Clinics. All of the controls indicated that they learned about the study through public lectures and advertisements, whereas all but one of the MCI patients were referred by their physicians. This MCI patient learned about the study from another participant.

Comprehensive screening, including medical chart review, standardized phone interview, geropsychiatric evaluation and background questionnaires (completed by participants and their collaterals), was used at baseline to ensure that no participant had a significant medical, psychiatric or neurological condition (other than MCI), a history of head trauma with loss of consciousness lasting more than 5 min, a current or past history of substance abuse or dependence, or factors contraindicating fMRI. Participants were also screened for medications that could affect cognition or the haemodynamic response in the scanner. All participants were naïve to AChE inhibitor treatment. Participants provided written informed consent according to the Declaration of Helsinki and the procedures were approved by the Dartmouth Medical School Committee for the Protection of Human Subjects.

All participants underwent a comprehensive neuropsychological evaluation to characterize their cognition. We analysed specific measures of verbal learning and executive functioning related to MCI and the fMRI task. We assessed verbal learning using the participants’ total word acquisition scores over five trials on the California Verbal Learning Test (CVLT and CVLT-II) (Delis et al., 1987; Delis, 2000), as well as executive functioning using the Number–Letter Switching Trials of the Trail-Making Test (Spren and Strauss, 1991; Reitan and Wolfson, 1993) and the Delis
Kaplan Executive Function System (Delis and Kaplan, 2001). Because we used different forms of the CVLT and Trail-Making Tests, all raw scores were converted to Z-scores using published standardized norms, so that the data could be compared directly across participants and time. Data from the self-report inventories and standardized telephone interview were used to characterize participants’ complaints about their cognition. The self-report inventories included the Squire Memory Self-Rating Questionnaire (Squire et al., 1979), an activities of daily living scale (Saykin et al., 1991), a 16-item self- and informant-rating questionnaire examining subjective cognitive decline adapted from Jorm and Jacomb (Jorm and Jacomb, 1989), the Geriatric Depression Scale (Yesavage et al., 1982) and the Dartmouth Telephone Screening Instrument for Cognitive Impairment (Rabin et al., 2004). Knowledgeable informants also completed the same scales. The cognitive complaint index shown in Table 1 was based on the percentage of all possible complaints endorsed by the participant across all inventories.

Diagnoses were made in a multidisciplinary consensus meeting applying criteria developed by Petersen and colleagues for amnestic MCI (Petersen et al., 1999; Petersen et al., 2001) and incorporating the Clinical Dementia Rating (CDR) according to published guidelines (Morris, 1993). Sources of information included results of a comprehensive neuropsychological evaluation (reviewed by two Board-certified neuropsychologists), a semi-structured interview and examination by a Board-certified geropsychiatrist, responses to self- and informant-report inventories, and brain MRI findings (read by a Board-certified neuroradiologist blinded to clinical status). No participant was clinically depressed, as determined by the participating geropsychiatrist. The diagnosis of MCI was made if the patient met the following criteria: (i) significant memory complaints; (ii) normal activities of daily living; (iii) normal general cognitive functioning; (iv) abnormal memory performance (at least 1.5 SD below the mean established for age-matched controls on standardized tests of memory); and (v) no dementia. Cutoff scores were adjusted on the basis of demographic variables (e.g. estimated superior baseline level of intelligence) (Petersen et al., 1999; Knopman et al., 2003). Because of this adjustment, memory scores for some patients with high baselines did not reach the −1.5 SD criterion relative to normative data as reflected in the group mean for CVLT memory (Table 1). However, all patients had significantly impaired memory (≥ 1.5 SD) relative to their baseline estimated from educational level and the American National Adult Reading Test (ANART; Gladsjo et al., 1999). Healthy controls showed no cognitive impairment and had no significant cognitive complaints. There were no significant group differences in demographics (Table 1). Because the group difference in sex distribution approached significance, all fMRI analyses were repeated with sex as a covariate, with no difference in the overall pattern of results. All participants had normal haemoglobin and hematocrit levels, and there were no group differences in these variables (Table 1).

Table 1  Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 9)</th>
<th>MCI (n = 9)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>70.0 (4.7)</td>
<td>69.9 (5.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Education (years)</td>
<td>16.7 (3.0)</td>
<td>17.1 (3.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>ANART&lt;sup&gt;a&lt;/sup&gt;</td>
<td>122.0 (6.0)</td>
<td>121.9 (4.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sex (M, F)</td>
<td>3, 6</td>
<td>6, 3</td>
<td>n.s.</td>
</tr>
<tr>
<td>ApoE&lt;sup&gt;e&lt;/sup&gt;4 allele present&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3</td>
<td>6</td>
<td>n.s.</td>
</tr>
<tr>
<td>CVLT total 1–5 (Z score)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.26 (0.62)</td>
<td>−1.0 (0.71)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Cognitive complaints (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>11.3 (5.9)</td>
<td>47.3 (20.8)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>14.6 (1.2)</td>
<td>14.9 (0.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>42.9 (2.8)</td>
<td>42.9 (1.6)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Data are mean (SD). <sup>a</sup>ANART = American National Adult Reading Test; <sup>b</sup>number of people with an ApoE<sup>e</sup>4 allele (no participant had two ApoE<sup>e</sup>4 alleles); <sup>c</sup>California Verbal Learning Test, standardized Z scores for total correct, Trials 1–5; <sup>d</sup>percentage of all possible cognitive complaints across multiple scales (range 0–100%). See text for a description of the scales and methods used to derive this index.

Following the complete diagnostic work-up, the geropsychiatrist reviewed the findings with the participants, and patients with MCI were provided with information on treatment options. All patients elected to start treatment with donepezil. The standard dosing plan began with 5 mg and increased to 10 mg after 4 weeks. In one case, dose escalation proceeded more slowly to help minimize side-effects. Side-effects included gastrointestinal symptoms in four patients, sleep disturbance in three, and leg cramps in two. There were no unexpected or serious side-effects. Patients were re-scanned after an average of 10.78 (± 1.99) weeks on medication, including an average of 5.67 (± 1.66) weeks at the level of 10 mg.

MRI data acquisition and analysis

Scanning was completed on a GE Signa 1.5 Tesla Horizon LX scanner with echo speed gradients using a standard head RF coil. fMRI parameters were TR 2500 ms, TE 40 ms, FOV 24 cm, NEX 1, yielding 29 contiguous 5 mm sagittal slices in a 64 × 64 matrix with an in-plane resolution of 3.75 mm<sup>2</sup>. An auditory n-back task adapted from prior research in our laboratory and others (Jonides et al., 1997; McAllister et al., 1999) was used to probe working memory. There were three conditions: 0-, 1- and 2-back, presented in a blocked design. In each condition, participants heard a string of consonants (except L, W and Y) presented at a rate of one every 3 s. In the 0-back condition, the match is a prespecified target letter, as shown in Fig. 1. This condition controls for simple target vigilance without making significant demands on working memory. In the 1-back condition, a match occurs when the letter presented is identical to the preceding one. In the 2-back condition, a match occurs when the letter presented is identical to the letter two positions back in the list. The 1- and 2-back conditions make increasing working memory demands. Upon hearing a correct target, participants pressed a key on an MR-compatible response device with their right thumb. Upon hearing a non-target letter, participants pressed an adjacent key on the response device with their right index finger. Response accuracy
and reaction times were recorded. The scanning run lasted 370 s, and each n-back condition (0-, 1-, 2-back) was presented three times in pseudorandom order. Epochs (condition blocks) were 27 s in duration, each preceded by the specific instructions (e.g. ‘the match is j, remember j’ or ‘the match is 1 back, any two of the same letters in a row’). The task included 21 matches (seven per condition) and the percentage of matching to total items was 23.6%.

Prior to the scan, participants rehearsed the tasks outside the scanner to ensure understanding of task demands. A visual aid was used to help clarify the instructions (Fig. 1). Given the mild level of cognitive impairment in this MCI sample, the extent of pretraining they required was little or no more than that required by the controls. All participants demonstrated comprehension of the task prior to entering the scanner. Instructions were repeated in full immediately prior to the beginning of the task and participants confirmed via intercom that they understood the requirements. MCI patients completed a post-scanning questionnaire to determine their levels of anxiety, fatigue and motivation during the procedure. Response choices for each question were ‘yes’, ‘no’ and ‘somewhat’. Data were available for eight of the nine patients in this study. Six indicated they were not nervous or tense while performing the task, one was anxious, and one was somewhat anxious. Five reported no fatigue while performing the task, one reported feeling tired, and two reported feeling somewhat tired. All reported that they were motivated to do their best.

Structural scanning included a T1-weighted sagittal scan used for anatomical reference (TR = 525, TE = 9, axial 5 mm slices), and a T2-weighted fast spin echo scan (TR = 3000, TE = 100, ETL = 13, axial 3 mm slices) reviewed by the study neuroradiologist (A.C.M.) to rule out lesions. Additionally, a 3D SPGR T1-weighted volumetric scan (TR = 24, TE = 8, flip angle = 40, NEX = 1, slice thickness = 1.5 mm, no gap, coronal) was acquired. The FOV was 24 cm for all scans. Total hippocampal volume (L + R), corrected for intracranial volume, was obtained by an image analyst (T.L.M.) blind to diagnosis. Intraclass correlation coefficient reliabilities for hippocampal volume measures following our standardized protocol were >0.9.

After ruling out artefact and excessive motion, fMRI data were preprocessed and analysed using standard procedures, as implemented in the Statistical Parametric Mapping package (SPM99; http://www.fil.ion.ucl.ac.uk/spm/). fMRI data were spatially realigned to remove any minor (subvoxel) motion-related signal change; normalized to the Montreal Neurological Institute standard atlas space using a 12-parameter affine approach followed by default non-linear warping using spatial basis functions; resampled to 2 mm³ isotropic voxels; and spatially smoothed to a full-width half-maximum of 10 mm. Next, statistical parametric mapping was carried out on a voxel-by-voxel basis using the general linear model in SPM99 (Friston et al., 1995), followed by implementation of random effects procedures, as developed by Holmes and Friston (1998). Random effects analyses involve deriving one contrast image per individual for each relevant paired contrast of the activation task, in this case the 2-back condition relative to the 0-back condition. These contrast images were further analysed using standard ANOVA (analysis of variance) and correlational procedures in SPM and Matlab. Additional statistical analyses were conducted using SPSS 11.5 and SAS/Stat 8.0.

**Results**

**Behavioural data**

Adjusted n-back accuracy scores were calculated to correct for false positive (FP) errors using the following formula: adjusted score = [(correct – (0.35 × FP))/7] × 100. Using this formula, if a participant made proportionately as many false positive errors as true positive responses, his or her score
would be 0. Because of a directional hypothesis that patients would show increased performance after treatment with donepezil, the analyses of behavioural data used one-tailed probability values. MCI patients’ accuracy on the 2-back condition was somewhat lower than that of controls at baseline, though the difference did not reach statistical significance \( t(16) = 1.4, P = 0.10 \). Analysis of change scores (Time 2 minus Time 1 adjusted accuracy scores) revealed improved performance in the patient group compared with controls after stabilization on donepezil \( t(14) = 2.0, P < 0.05; \) Fig. 2, Table 2). There were no significant effects of group or time on response latencies. Response data for the 2-back condition were missing for two controls at Time 2 because of technical difficulties. These participants were eliminated from the analysis of in-scanner behavioural data but not any other analyses. By definition, patients showed poorer verbal learning and memory than controls \( t(16) = 3.9, P < 0.0005; \) Table 1] and made more complaints about their cognition than controls at baseline \( t(16) = 5.0, P < 0.0005; \) Table 1]. There was no significant group difference in change in verbal memory performance over time (Table 2). While controls’ complaint index changed little from Time 1 to Time 2, patients showed a reduction in subjective cognitive concerns after stabilization on donepezil \( t(16) = 3.3, P < 0.005 \). On a measure of executive functioning (Trail-Making Test, Switching condition), patients performed more poorly than controls at Time 1 \( t(16) = 2.3, P < 0.05 \] and improved after stabilization on the medication \( t(16) = 1.8, P < 0.05; \) Fig. 3, Table 2).

**Neuroimaging data**
Controls showed bilateral activation of frontal and parietal cortex, among other regions, at Times 1 and 2 \( (P < 0.01, k = 3; \) k = cluster extent), as is typical for a working memory task. Patients showed reduced frontoparietal activation at baseline relative to controls \( (P < 0.01, k = 3) \). From Time 1 to Time 2, controls’ activation patterns changed little (Fig. 4A). In contrast, patients showed increased activity predominantly in the dorsolateral prefrontal cortex (Fig. 4B), as indicated by the group \( \times \) time interaction with a critical threshold \( (P_{uncorr}) \) of 0.001 and a minimum \( k \) of 3 contiguous active voxels (24 mm\(^3\)). Relative to controls, patients showed increased activity in the left superior frontal gyrus (Brodmann area 9; \( x, y, z = -24, 38, 42, z = 3.3, k = 51; \) \( P = 0.001 \). There were two additional small regions of group difference in signal change as a function of time (post- versus pre-medication): one was in the left occipital region \( (x, y, z = -32, -72, -6, z = 3.4, k = 6; \) \( P < 0.0005 \), patients showing a greater increase than controls as a function of treatment; and the second was in the left temporal lobe \( (x, y, z = -40, -14, -22, z = 3.19, k = 3; \) Table 2 Performance on clinical and behavioural tests

<table>
<thead>
<tr>
<th></th>
<th>Control ((n = 9))</th>
<th>MCI ((n = 9))</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
</tr>
<tr>
<td>Adjusted 2-back accuracy(^a)</td>
<td>69.1 (10.3)</td>
<td>69.2 (11.9)</td>
</tr>
<tr>
<td>CVLT (Z score)</td>
<td>0.26 (0.62)</td>
<td>0.43 (0.84)</td>
</tr>
<tr>
<td>Cognitive complaints (%)</td>
<td>11.3 (5.9)</td>
<td>13.9 (13.3)</td>
</tr>
<tr>
<td>Trails (Switching, Z score)</td>
<td>0.53 (0.36)</td>
<td>0.60 (0.35)</td>
</tr>
</tbody>
</table>

Data are mean (SD). \(^a\)Time 2 data for in-scanner n-back performance were unavailable for two controls who had otherwise complete data. Therefore, for this analysis only, there were seven controls and nine patients. CVLT = California Verbal Learning Test; Trails = Trail-Making Test.

![Fig. 3 Change in out-of-scanner executive task performance. Participants’ scores on the Number–Letter Switching condition of the Trail-Making Test were converted to Z scores based on demographically appropriate normative data. The change scores (shown in the figure) were obtained by subtracting Time 1 from Time 2 Z scores. Filled circles indicate MCI patients and open circles indicate healthy controls. Mean change for each group is indicated by a horizontal bar. Controls showed approximately the same level of performance in both sessions, whereas patients showed improved performance after stabilization on donepezil.](http://brain.oxfordjournals.org/)

![Table 2](http://brain.oxfordjournals.org/)

controls showing a greater increase in activity than patients. Results of the interaction analysis are shown in Fig. 5, which, for display purposes, is based on a \( P_{\text{crit}} \) of 0.01 and \( k = 3 \). Further correlational analysis of the interaction data at the global maxima in the left frontal lobe revealed that the extent of increase in activation in that cluster of voxels was positively related to the extent to which accuracy improved on the working memory task across subjects (2-back condition, \( r = 0.49, P = 0.05 \); Fig. 6). Increased activation in this region was also positively related to baseline hippocampal volume (\( r = 0.62, P < 0.05 \)) within the patient group.

**Discussion**

We believe this to be the first controlled fMRI study to demonstrate altered patterns of brain activity associated with WM in older adults with MCI, and the first to demonstrate that pharmacological enhancement of cholinergic availability in the brain helps normalize brain activity in these patients in a regionally specific manner. The data indicate that short-term treatment with an AChE inhibitor enhances the activity of frontal circuitry in patients with MCI, and that this regional increase in activity is related to improved cognition and to the baseline integrity of the hippocampus, a surrogate for severity of disease.
and open circles indicate healthy controls.

Fig. 6 Relationship between changes in brain activation and performance accuracy on the working memory task (Time 2 – Time 1; \( r = 0.49, P = 0.05 \)). Filled circles indicate MCI patients and open circles indicate healthy controls.

A potential limitation of our study warrants comment. Differential test–retest effects between patients and controls could have influenced the observed pattern of behavioural and imaging changes. MCI patients might have benefited more than controls from repetition of the task, which could have potentially accounted for improved task performance or differences in brain activation at post-test. We do not believe that this potential confound significantly biased the present results. Our inclusion of a control group of demographically matched healthy older adults tested at the same time intervals as the MCI group permitted a degree of control over practice effects, given the comparable age and overall baseline cognitive abilities between the groups. Of note, in neuro-psychological studies it is usually healthy controls that benefit more from familiarity or practice effects than patient groups. Better control of possible differential test–retest effects could be obtained in future research by including multiple baseline scans in patients or, ideally, by employing a randomized controlled trial design.

Little is known about how AChE inhibitors affect functional brain systems. The present fMRI data indicate a specific rather than global effect on brain activity. There are preliminary indications that AChE inhibitors exert regionally specific effects on frontal regions in some circumstances (Nordberg et al., 1998; Kaasinen et al., 2002; Nobili et al., 2002a), and our data support a role for the frontal lobe. Upregulation in frontal regions may result from the comparatively dense representation of cholinergic receptors and fibres in brainstem areas that project to this region (Mesulam, 2000), a drug-induced increase in frontal nicotinic receptors (Barnes et al., 2000) or from secondary upregulation of dopaminergic systems involving the frontal lobe. A preferential frontal response could also be related to the fact that the frontal cortex is relatively spared in MCI and in the early stages of AD compared with temporal and parietal regions (for review see Flashman et al., 2003) and therefore has greater structural integrity with which to support increased activation in response to pharmacological stimulation. There is evidence of cholinergic regulation of neurovascular coupling (Tsukada et al., 2000). It is unclear whether altered neurovascular coupling contributes to the regional specificity noted here. A combination of factors is most likely involved. The next step is to examine changes in brain activity with cholinergic enhancement using fMRI tasks that rely on different (though interrelated) brain circuitries, to determine whether the frontal lobe is preferentially affected or whether task-specific regional upregulation occurs, as the preliminary data from Rombouts and colleagues suggest (Rombouts et al., 2002). Effects specific to the frontal cortex may co-exist with task-specific effects. Overall, the data suggest an adaptive potential in the older human brain that can be influenced pharmacologically in a manner that may help delay or prevent development of AD in at-risk older adults.

We observed differences in response to medication within the MCI group. As shown in Fig. 6, approximately half of the patients showed improvement in both working memory performance and frontal lobe activation, whereas the others did not. This heterogeneity may reflect the fact that MCI represents a categorization imposed on an underlying continuum from normal cognitive ageing to Alzheimer’s disease. A heterogeneous treatment response within the MCI group may be related to variations in the degree of structural tissue integrity, genetic factors, or other variables. In this study we found that the extent to which frontal activity increased after stabilization on donepezil was directly related to hippocampal integrity, as indicated by volume. That is, patients with less severe hippocampal atrophy showed a greater increase in potentially compensatory frontal activation, a finding consistent with our observations for episodic memory patients in mild AD (Saykin et al., 2000). Since hippocampal atrophy is a good index of disease stage (Jack et al., 2000), these results suggest that early intervention may capitalize on the potential for compensatory changes in brain activity. Further cross-sectional and longitudinal research is needed to determine whether early intervention in patients at risk of AD uses different brain mechanisms from later intervention. This finding serves to underscore the importance of considering brain activation in the context of structural changes in imaging studies of dementia and other brain disorders. Additionally, genetic factors could play a role in predicting treatment response. The present study did not have sufficient power to examine the role of ApoE status in predicting signal change in MCI patients. Larger-scale studies are needed to determine if genetic markers can predict pharmacologically induced changes in brain activity.

DeKosky and colleagues reported normal to elevated levels of choline acetyltransferase in MCI and early AD (DeKosky et al., 2002). Only patients with end-stage AD showed decreased choline acetyltransferase. Although these findings require replication, they challenge a simple cholinergic
hypothesis of AD, and suggest that different neurotransmitter abnormalities may occur at different stages of the disease. Despite this challenge to the cholinergic model, the present study indicates that AChE inhibition helps normalize brain activity patterns and leads to related cognitive improvement in MCI. If the availability of acetylcholine is not the primary neurotransmitter abnormality at this stage of the disease, as suggested by DeKosky and colleagues’ data, the observed improvement in this study may result from cholinergic receptor changes (Barnes et al., 2000) or secondary effects on other neurotransmitter systems (Levin and Simon, 1998; Svensson and Giacobini, 2000). Further investigation of MCI at the level of neurotransmitter systems and brain functional circuitries should lead to improved treatment development.

Our findings have potential implications for the early detection and treatment of dementia. Cognitive fMRI testing may ultimately prove useful for detecting individuals at risk of dementia, tracking the disease over time and evaluating treatment effects. Correlation with comprehensive out-of-scanner memory, executive and other cognitive testing will help determine the generalizability of the effects. Functional MRI has an advantage over PET for repeat assessments because it is non-invasive. In addition, fMRI has a higher temporal and spatial resolution than PET. Research is needed to determine whether a signature pattern or patterns can be discerned using fMRI for memory and other cognitive functions in MCI or even earlier stages of AD (Bookheimer et al., 2003a; Saykin et al., 2003b). Intra-individual stability of activation patterns will need to be fully assessed for fMRI to be used effectively in disease tracking and the evaluation of treatments (Rosen et al., 2002). Preliminary evidence suggests that some patients who fail to respond to one AChE inhibitor may respond to another (Gauthier et al., 2002). Functional MRI could be developed to help match individual patients to optimal treatment modalities, i.e. using short-term pharmacological trials to determine which medication(s) normalize activation patterns most effectively. Large-scale studies of the efficacy of AChE inhibitors and other potential treatments are under way in MCI (Allain et al., 2002: National Institutes of Health, 1999), and fMRI research has the potential to improve both our understanding of the mechanism of action of these interventions and the clinical care of patients with MCI and AD.

Acknowledgements
The authors wish to thank Clifford Eskey MD PhD, Robert Ferranti, Alice Davison, Shreve Soule and colleagues in the DHMC MRI Center, and Margo Krasnoff MD and other members of the DHMC General Internal Medicine Clinic for their help with aspects of the study. The authors also wish to thank Leslie Baxter PhD, Cheryl Brown, Katherine Nutter-Upham, Heather Pixley, Thomas McAllister MD, Thomas Mellman MD and Jennifer Ramirez of the Department of Psychiatry, and James Ford PhD and Filia Makedon PhD of the Dartmouth Experimental Visualization Laboratory (DEVLAB), Department of Computer Science at Dartmouth College for their contributions. Preliminary results of this study were presented at the American Neuropsychiatric Association Meeting, February, 2004 in Bal Harbour, Florida, USA. This project was supported in part by funding from the NIA (R01 AG19771), Alzheimer’s Association (IIRG-99-1653 sponsored by the Hedco Foundation), Hitchcock Foundation, Ira DeCamp Foundation, NSF Information and Data Management Program (0083423), as well as an investigator-initiated pilot grant from Pfizer, Inc.

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