

# Phenotypic regional functional imaging patterns during memory encoding in mild cognitive impairment and Alzheimer's disease

Jeffrey N. Browndyke<sup>a,b,c,\*</sup>, Kelly Giovanello<sup>d</sup>, Jeffrey Petrella<sup>c</sup>, Kathleen Hayden<sup>a,b</sup>,  
Ornit Chiba-Falek<sup>a,e</sup>, Karen A. Tucker<sup>b</sup>, James R. Burke<sup>a,f</sup>, Kathleen A. Welsh-Bohmer<sup>a,b,f</sup>

<sup>a</sup>Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University, Durham, NC, USA

<sup>b</sup>Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

<sup>c</sup>Brain Imaging and Analysis Center, Duke University Medical Center, Durham, NC, USA

<sup>d</sup>Department of Psychology, Biomedical Research Imaging Center, University of North Carolina, Chapel Hill, NC, USA

<sup>e</sup>Institute for Genomic Science and Policy, Duke University, Durham, NC, USA

<sup>f</sup>Division of Neurology, Department of Medicine, Duke University Medical Center, Durham, NC, USA

## Abstract

**Background:** Reliable blood-oxygen-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) phenotypic biomarkers of Alzheimer's disease (AD) or mild cognitive impairment (MCI) are likely to emerge only from a systematic, quantitative, and aggregate examination of the functional neuroimaging research literature.

**Methods:** A series of random-effects activation likelihood estimation (ALE) meta-analyses were conducted on studies of episodic memory encoding operations in AD and MCI samples relative to normal controls. ALE analyses were based on a thorough literature search for all task-based functional neuroimaging studies in AD and MCI published up to January 2010. Analyses covered 16 fMRI studies, which yielded 144 distinct foci for ALE meta-analysis.

**Results:** ALE results indicated several regional task-based BOLD consistencies in MCI and AD patients relative to normal control subjects across the aggregate BOLD functional neuroimaging research literature. Patients with AD and those at significant risk (MCI) showed statistically significant consistent activation differences during episodic memory encoding in the medial temporal lobe, specifically parahippocampal gyrus, as well superior frontal gyrus, precuneus, and cuneus, relative to normal control subjects.

**Conclusions:** ALE consistencies broadly support the presence of frontal compensatory activity, medial temporal lobe activity alteration, and posterior midline "default mode" hyperactivation during episodic memory encoding attempts in the diseased or prospective predisease condition. Taken together, these robust commonalities may form the foundation for a task-based fMRI phenotype of memory encoding in AD.

© 2013 The Alzheimer's Association. All rights reserved.

## Keywords:

Alzheimer's disease; Mild cognitive impairment; fMRI; Episodic memory; Activation likelihood estimation; Meta-analysis

## 1. Introduction

Associated with the discovery of the blood-oxygen-level-dependent (BOLD) magnetic resonance effect, the past 2 decades are witness to an explosion in research regarding the functional neuroanatomical correlates of normal mem-

ory function. Less abundant, however, are functional imaging studies examining memory dysfunction in populations of patients such as those with Alzheimer's disease dementia (hereafter referred to as AD) and those at higher risk for AD (e.g., mild cognitive impairment; MCI [1,2]). To date, a modest, but growing, number of AD-related functional magnetic resonance imaging (fMRI) studies have been conducted tapping episodic memory [3–19], semantic memory [20–22], implicit memory [6,12], executive processes

\*Corresponding author. Tel.: 919-668-1586; Fax: 919-286-3406.

E-mail address: j.browndyke@duke.edu

[5,23,24], and visuospatial abilities [25,26]. Also, please refer to Albert et al, [27] and Lee et al, [28] for reviews on the general use of fMRI in MCI. Nevertheless, gleaning a firm consensus within any particular cognitive domain mentioned previously has proven difficult owing to study-wise differences in imaging methodologies, task paradigms, and subject characteristics.

Critically, such studywise differences have contributed to apparently contradictory results in the research literature. For example, possible medial temporal lobe (MTL) compensatory cortical activity during episodic encoding has been observed in some AD and MCI participant groups relative to control groups [18]; yet, subsequent researchers have found decreased MTL activation in similar cortical regions [29]. This discrepancy speaks less to a fundamental problem in our understanding of the fMRI correlates of AD and more to the variance in fMRI task methodologies and subject sample differences across studies. Although these methodological variances are practically unavoidable owing to the heterogeneity in study designs, there may be robust commonalities in task-related fMRI results that reveal spatially relevant patterns of brain activation and deactivation. These commonalities may then be thought of as task-related phenotypic brain activity patterns. This notion of functional imaging-related phenotypes, although relatively new to the field of age-related disease research, has been described by researchers within such fields involving disorders of thought [30,31], executive control [32–34], and neurodevelopment [35–37]. Establishing putative MCI-/AD-associated phenotypes through meta-analytic techniques, such as those used here, may eventually allow for more targeted intermediate phenotype (endophenotype) detection, facilitating genetic discovery and streamlining clinical trial subject selection.

The goal of the current analysis was to determine whether such phenotypes could be established by detectable and consistently robust fMRI patterns. To this end, we chose to focus on a cognitive domain tapped by the majority of AD and MCI fMRI studies to date. Episodic memory encoding, a central function of the declarative memory system [38], represents the cognitive process involved when an individual is attending to a specific set of novel, event-based, or item-based information for memory consolidation and storage for subsequent retrieval or recognition. Individuals diagnosed with AD and, to a lesser extent, MCI show notable changes in episodic memory abilities relative to cognitively normal peers (for a comprehensive review, see [39]). Deficits in episodic memory encoding and consolidation are thought to be the primary bases of memory impairment noted in AD and its associated incipient states [40–42]. The severity of deficits in encoding and consolidation tends to track closely with the burden of AD-related pathology in the MTL [43]. Thus, the MTL has been fairly well characterized as the primary regional neuroanatomical correlate of episodic memory dysfunction in AD. What is less clear is whether there are additional regions of dysfunction in AD

and whether consistent spatial patterns of memory-related brain dysfunction across studies may provide an fMRI BOLD phenotype of AD.

To address these questions, we exhaustively researched the available literature for pertinent task-based episodic memory fMRI studies and compared their patient versus normal control contrast differences using a set of activation likelihood estimation (ALE 2.0; [44]) analyses. ALE is a permutation-based meta-analytic imaging approach for interrogating the likelihood of brain activation pattern overlap from a group of similar functional imaging study contrasts, and, with the advent of newer iterations of the ALE procedure [45], statistically significant regional ALE consistencies may be broadly generalized to populations of interest (i.e., random-effects data analysis). Any statistically significant spatial patterns to arise from our ALE meta-analyses are hypothesized to reflect aggregate empirical support for brain regions associated with episodic memory encoding attempts in MCI and AD patients relative to normal control subjects, thereby providing an example of a consistent and robust phenotype of task-based BOLD activity in MCI and AD.

In summary, the current analysis extends previous research by using a random-effects, coordinate-based, and spatial ALE analysis, providing a rigorous, conservative empirical examination of common regions of fMRI/BOLD activation in MCI and AD patients relative to normal elderly control subjects.

## 2. Methods

An initially broad and thorough literature search was conducted, focusing on studies that used functional neuroimaging in MCI and AD participant groups. The literature search was conducted on the MEDLINE/PubMed databases using the following National Library of Medicine MeSH term algorithm: [(Magnetic Resonance Imaging OR positron emission tomography) AND (Alzheimer Disease OR Amnesia OR Cognition Disorders) AND (Humans) AND (middle age OR aged OR (aged, 80 and over))]. This search was confined to articles published between January 1, 1980 and December 31, 2009, which yielded 2719 unique research or review manuscripts. From these research articles, we examined and considered only those that had group-related task contrasts tapping aspects of declarative memory in AD and MCI patient samples relative to normal elderly participants, which significantly narrowed the original pool to 81 studies. Divided by imaging modality, 62 of these studies were conducted using fMRI, and the remaining 19 used positron emission tomography (PET) during performance of a cognitive task paradigm. For the current meta-analyses, only articles that reported fMRI contrasts of task components involving episodic memory encoding (i.e., face-name encoding, novel vs familiar encoding, and others) were considered for analysis, yielding a total of 38 studies published between 2003 and 2009. For entry into the planned

ALE meta-analyses [44,45], a procedure successfully implemented in several recent functional imaging reviews of episodic memory function [46–48], it was also necessary that studies referenced significant groupwise contrast results in a standardized neuroanatomical spatial coordinate system, either Talairach or Montreal Neurological Institute (MNI) space. Ten studies from the pool of 38 were excluded owing to lack of reported brain atlas coordinates. Studies were also excluded if subjects were healthy but only genetically at risk for AD (e.g., apolipoprotein E  $\epsilon$ 4) and did not evince cognitive symptoms (seven studies), or if the studies primarily involved pharmacological fMRI effects, without baseline comparisons of MCI or AD patients (five studies). A final set of 16 studies remained with a publication date range from 2003 to 2009 (Table 1).

One hundred and forty-four distinct spatial foci from 30 different groupwise episodic memory encoding contrasts served as the primary data for the planned series of ALE meta-analyses [44]. Four separate ALE analyses were conducted to interrogate the directionality of episodic memory encoding activity differences in MCI and AD patients relative to control subjects. AD-related ALE analyses examined contrast foci associated with greater encoding-related activation in AD patients relative to elderly control subjects (8 contrasts, 42 foci) and reduced activation in AD patients relative to control subjects (10 contrasts, 52 foci), whereas MCI analyses examined contrast foci associated with greater activation in MCI participants relative to elderly control subjects (4 contrasts, 22 foci) and less activation in MCI than control subjects (8 contrasts, 28 foci). Group comparisons and task paradigms with corresponding foci are presented in Table 1.

Task paradigms with episodic memory encoding components varied somewhat across the included studies. Of the 16 studies analyzed, 8 different types of paradigms were represented (the “fMRI Task Paradigm” column in Table 1 denotes the task type used to obtain groupwise comparison of episodic memory encoding activity). One particularly prevalent paradigm among the studies identified is a face/name paired-associate learning task adapted from Sperling et al [53]. In this task, participants are shown blocks of stimuli in which a novel or familiar face is paired with a name. In a later run, participants are again shown the stimuli and asked whether the correct name is matched with the correct face. In some of the studies, participants were asked to give an initial subjective determination of whether the name “fit” the face. Other studies (Table 1, numbers 4 and 12) did not use a name component but simply presented unfamiliar faces and asked participants to encode them for later recall during a subsequent recognition task [8,17]. Other variants of discrimination between novel and repeated stimuli were represented in the selected studies. Golby et al asked participants to remember whether they had previously viewed a particular visual scene [6], whereas Kircher et al used verbal, rather than visual, stimuli and instructed partic-

ipants to encode words that would be recalled in a subsequent memory test [11].

In addition to task variation, the studies included in the current ALE analyses differed in their classification methods for MCI or AD. All AD patients from the included studies were classified as having probable AD of mild to mild-to-moderate severity based on National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association diagnostic criteria [54]. Most studies relied on Clinical Dementia Rating scale (CDR; [55]) and the Mini-Mental State Examination (MMSE; [56]) scores as the primary measures of functional and cognitive decline, respectively. Although these measures were not the sole criteria for diagnostic classification, they provide a general indication of the extent of cognitive impairment among the participants in the included studies. AD patients in the included studies had mean MMSE scores ranging from 20.8 to 26.33, whereas the range of mean MMSE scores among the MCI participants was characteristically higher (i.e., 25.3–28.4; see Table 1). CDR totals were consistent with suggested guidelines for functional impairments suggestive of AD or MCI (i.e., AD  $\geq 1$ , MCI = 0.5). In addition to the MMSE and CDR, MCI participants from the included studies were further classified based on cognitive assessments, the results of which suggested comparative mild weaknesses in memory performance and possibly another cognitive domain in line with established MCI classification criteria [57].

To allow for direct comparison of brain spatial coordinates across studies, transformations were required to bring all contrast foci to a common atlas space. Spatial coordinates reported by the included studies in MNI space were transformed to Talairach atlas space [58] using the Lancaster “icbm2tal” transform [59]. Specialized versions of the Lancaster transform were used to account for spatial transformation differences among the various imaging analysis platforms (e.g. icbm\_spm2tal). Coordinates that had already undergone the Brett transform [60] from MNI to Talairach space before publication were treated differently. Brett transform Talairach foci coordinates were converted back to MNI atlas space using a reverse transform algorithm, after which these coordinates were then returned to Talairach space using the aforementioned Lancaster transform [59]. After all study coordinates were transformed similarly to common Talairach space, the four ALE meta-analyses were performed [44].

ALE analyses were conducted for each directional contrast (AD/MCI > control and AD/MCI < control) by modeling each reported study foci as a three-dimensional Gaussian function smoothed with a 12-mm full width at half maximum kernel [61] to allow enough spatial overlap among foci for statistical comparison. Statistical significance was evaluated using the standard ALE permutation procedure with a minimum of 5000 permutations per solution. ALE analyses were corrected for multiple comparisons using a false discovery rate procedure (FDR; [44,62]) and thresholded for cluster

Table 1

Reported fMRI studies with episodic memory encoding group contrasts involving AD patients or MCI persons relative to elderly control subjects

Functional imaging study	Participants						fMRI task paradigm	Encoding contrast	Group comparison	Number of foci
	AD		MCI		Controls					
	n	MMSE (SD)	n	MMSE (SD)	n	MMSE (SD)				
Celone et al [3]	–	–	15	29.3 (0.9)	15	29.5 (0.5)	Face/name paired-associate learning task	Encoding component (ICA data)	MCI > controls*	4
Golby et al [6]	7 <sup>†</sup>	20.8 (2.0)	–	–	7	29.4 (0.5)	Novel versus repeated scenes task	Novel > repeated stimuli	AD < controls	7
Gould et al [7]	12 <sup>†</sup>	26.3 (2.1)	–	–	12	29.1 (0.9)	Visuospatial paired-associate learning for subsequent recognition task	Encoding > baseline	AD > controls	6
								Encoding > baseline	AD < controls	5
								Remembered > forgotten	AD > controls	2
								Remembered > forgotten	AD < controls	3
Hamalainen et al [49]	15 <sup>†</sup>	21.7 (3.7)	14	25.6 (3.1)	21	27.7 (2.0)	Visual object encoding for subsequent recognition task	Encoding > baseline	MCI < controls	1
								Encoding > baseline	MCI > controls	13
								Encoding > baseline	AD < controls	5
								Encoding > baseline	AD > controls	2
Johnson et al [10]	–	–	14 <sup>†</sup>	28.6 (1.5)	14	29.4 (0.8)	Novel versus familiar line-drawings task	Novel > repeated stimuli	MCI < controls	4
Johnson et al [9]	–	–	9	26.2 (3.1)	12	29.5 (1.0)	Spatial location encoding/learning task	Encoding > baseline	MCI < controls	1
Kircher et al [11]	–	–	21	26.6 (1.4)	29	28.8 (1.2)	Visual encoding of printed words for subsequent recognition task	Remembered > forgotten	MCI > controls	4
Machulda et al [50]	–	–	19	–	29	–	Visual scene encoding for subsequent recognition task	Encoding > baseline	MCI < controls	7
Pariante et al [13]	12	25.1 (1.8)	–	–	17	29.0 (1.0)	Face/name paired-associate learning for subsequent recognition task	Remembered > forgotten	AD < controls	2
Peters et al [51]	16 <sup>†</sup>	23.4 (1.7)	–	–	16	–	Auditory encoding of words for subsequent recognition task	Remembered > forgotten	AD > controls	4
								Encoding > baseline	AD < controls	5
Petrella et al [14]	–	–	20	26.7 (1.5)	20	28.4 (1.4)	Face/name paired-associate learning task	Novel > repeated stimuli	MCI < controls	5
Petrella et al [52]	13	24.6 (2.4)	–	–	28	28.2 (1.4)	Face/name paired-associate learning task	Novel > repeated stimuli	AD < controls	8
									AD > controls	10
Remy et al [16]	8 <sup>†</sup>	21.2 (6.4)	–	–	11	29.4 (0.5)	Visual encoding of printed words for subsequent recognition task	Encoding > baseline	AD < controls	12
								Encoding > baseline	AD > controls	3
Sperling et al [18]	7	22.6 (2.2)	–	–	10	–	Face/name paired-associate learning task	Encoding > baseline	AD < controls	4
								Novel > repeated stimuli	AD < controls	1
								Encoding > baseline	AD > controls	6
								Novel > repeated stimuli	AD > controls	9
Trivedi et al [19]	–	–	16	26.3 (2.3)	23	28.8 (1.2)	Visual object encoding for subsequent recognition task	Encoding > baseline	MCI < controls	6
								Remembered > forgotten	MCI < controls	2
								Remembered > forgotten	MCI > controls	1

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; fMRI, functional magnetic resonance imaging; ICA, independent components analysis.

\*MCI subtype characterized by low Clinical Dementia Rating-Sum of Boxes score (e.g., 1.1 ± 0.4).

<sup>†</sup>Portion of participants noted as being on acetylcholinesterase inhibitors at the time of neuroimaging.

size to conservatively control for type I error. To exceed established analysis thresholds, ALE analysis clusters were required to be statistically significant at FDR  $q < .05$  with a minimum volume of  $100 \text{ mm}^3$ , and to be considered “phenotypic,” ALE analysis clusters were required to have contributing spatial coordinates from a minimum of at least two independent studies from Table 1. The resulting ALE coordinates for clusters surviving these analysis thresholds were then reconverted back to MNI atlas space using the Lancaster transform [59]. Additionally, for visualization purposes, the resulting ALE image maps were warped from Talairach atlas space to MNI space (Fig. 1 and Supplemental Figs. 1–4) using SPM8 (Wellcome Institute, London, UK) nonlinear warp transformation.

### 3. Results

Peak MNI coordinates, Brodmann areas (BA), and cluster sizes for significant ALE regional commonalities are summarized in Table 2. The ALE values noted in Table 2 are the maximum activation likelihood estimates for individual statistically significant clusters. All ALE values are significant based on a FDR of  $q < .05$ ;  $k \geq 100 \text{ mm}^3$ .

Thresholded ALE spatial maps for regions of common difference between AD or MCI patients and control subjects during episodic memory encoding are presented in Fig. 1. Brain regions where encoding-related activation tends to be greater in MCI individuals relative to elderly control subjects are shown in red, whereas regions where relative activation was greater in control subjects than in MCI patients are denoted in green (Fig. 1, Section A). A single common cluster in the right anterior parahippocampal gyrus ( $\sim$ BA 35 region;  $25x, -15y, -14z$ ) survived ALE analysis of study contrasts where activity was greater in MCI relative to control participants. Conversely, two regions survived ALE statistical thresholding where activity was less in MCI patients relative to control subjects. One such focus was in the right anterior parahippocampal gyrus, similar to the MCI > control ALE results, although more posterior along the hippocampal axis ( $\sim$ BA 28 region;  $27x, -27y, -11z$ ), and the other focus in the left inferior frontal gyrus region (BA 9;  $-46x, 11y, 31z$ ).

Significant common spatial foci for task-based episodic memory BOLD activation/deactivation in AD patients relative to control subjects are shown in Fig. 1 (Section B). Blue regions indicate areas of greater activation in AD patients, whereas yellow foci indicate greater activation in control subjects. Robust ALE regions in AD patients relative to control subjects were in the bilateral posterior midline (i.e., right precuneus [BA 31;  $10x, -66y, 29z$ ], left precuneus [BA 31;  $-11x, -64y, 33z$ ], and left cuneus [BA 18;  $-16x, -72y, 18z$ ]), right superior temporal gyrus (BA 41;  $53x, -30y, 4z$ ), and left superior frontal gyrus (BA 6/8;  $-24x, 40y, 43z$ ). Control, relative to AD, regions were in the anterior cerebellum ( $5x, -48y, -31z$ ), right anterior parahippocampal gyrus ( $\sim$ BA 28;  $18x, -17y, -23z$ ), and right lingual gyrus (BA 19;  $32x, -75y, 2z$ ).

Other smaller ALE analysis clusters are revealed when analyses are run with less conservative statistical and extent thresholds, but the regional commonalities reported previously reflect the most robust findings across studies lending support to common phenotypic fMRI activation pattern associated with AD (and to a lesser extent, MCI). Therefore, the reported results reflect conservative estimates of commonly observed phenotypic differences in the functional neuroanatomical substrates governing episodic encoding between MCI or AD subjects and normal elderly control subjects. Broadly, MCI and AD subjects both show a marked decrease in BOLD activation during episodic memory encoding in the right anterior parahippocampal region ( $\sim$ BA 28), whereas encoding-related BOLD patterns differentiate between patient and control subjects in terms of the relative activation of other MTL structures, dorsolateral prefrontal cortex, and posterior midline regions during episodic memory encoding.

Supplemental Figs. 1–4 illustrate the spatial positions of foci maxima for the various episodic memory-related task contrasts that contributed to the composite ALE findings given in Fig. 1 (Sections A and B). Supplemental Fig. 1 shows the spatial locations of increased BOLD activity contrast maxima for elder control subjects relative to MCI patients. Red coordinates indicate areas where encoding certain stimuli (objects, scenes, spatial locations, or faces) elicited a significant increase in BOLD activity from baseline, whereas blue foci indicate increased activation for novel versus repeated stimuli and green foci show areas of increased activation for successful memory encoding in normal subjects relative to MCI patients. Conversely, Supplemental Fig. 2 reveals the spatial locations for increased activation in MCI patients versus normal control subjects during simple encoding greater than baseline contrasts (red) and remembered versus forgotten (i.e., successful memory encoding) task paradigms (green). Supplemental Figs. 3 and 4 illustrate similar contrast differences by episodic memory task type between AD patients and normal control subjects.

### 4. Discussion

Numerous functional imaging investigations examining the neural substrates underlying AD-related memory decline have yielded a substantial body of literature on the subject; however, the diversity across experimental paradigms has made it difficult to draw consistent inferences from these findings [27,28]. By amassing results of studies focused on a single component of memory (episodic encoding) and performing a series of ALE meta-analyses on the available fMRI data, it is possible to spatially illustrate statistically significant concordant findings. The results of these aggregate analyses highlight consistent functional neuroanatomical regions important to episodic memory dysfunction in individuals with AD and those at significant risk (MCI). They also model an empiric approach capable of consolidating the results of multiple

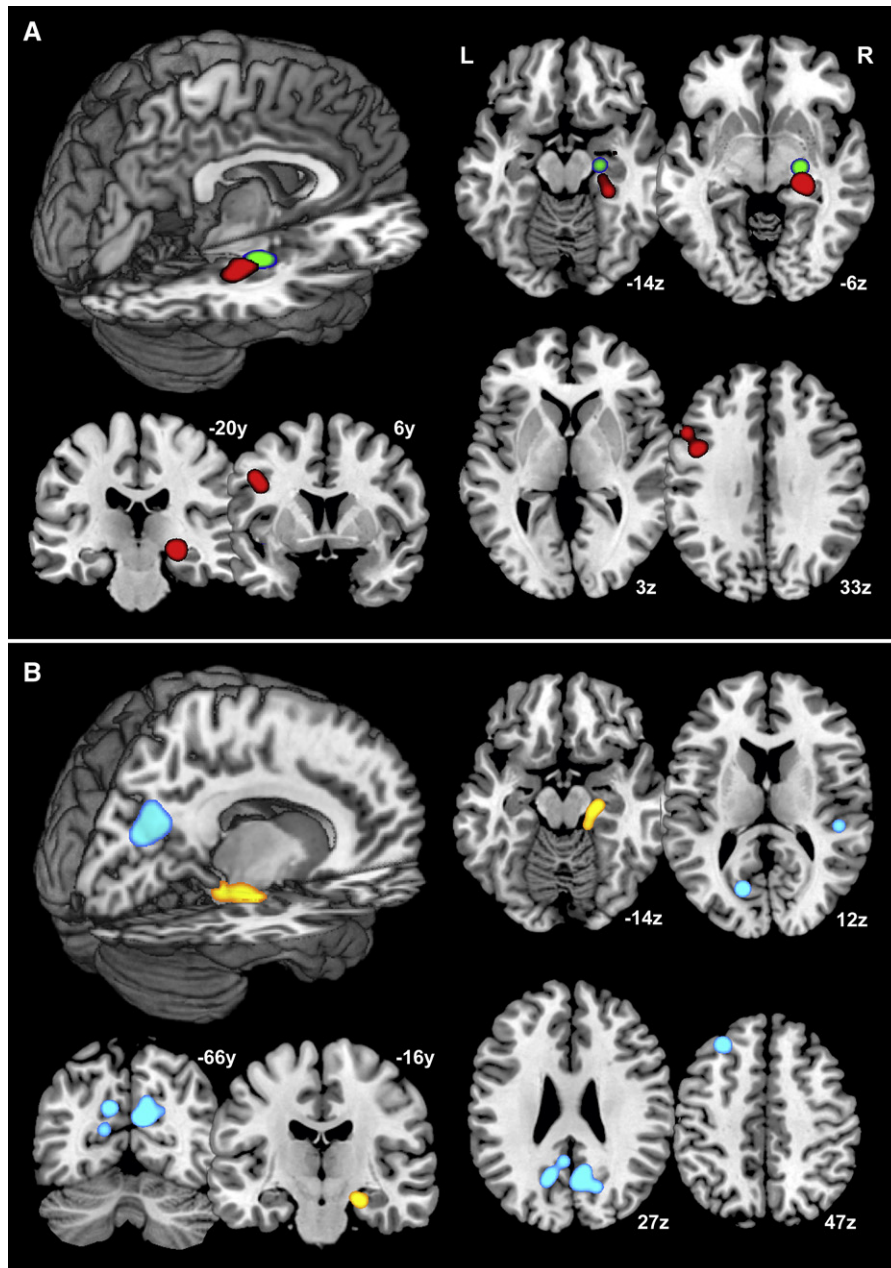


Fig. 1. Common regional blood-oxygen-level-dependent activation differences during episodic memory encoding in mild cognitive impairment (MCI) or Alzheimer's disease (AD) persons relative to normal elderly control subjects. (A) MCI relative to normal control subjects. Activation likelihood estimation (ALE) meta-analysis of 12 experimental contrasts (50 foci) with a statistical significance threshold of false discovery rate  $q < .05$ ,  $k_{\text{extent}} \geq 100 \text{ mm}^3$ , and requirement of contributing coordinates from at minimum of two independent studies from Table 1. Red foci = MCI < control; Green foci = MCI > control. (B) AD relative to normal control subjects. ALE meta-analysis of 18 experimental contrasts (94 foci) with a statistical significance threshold of false discovery rate  $q < .05$ ,  $k_{\text{extent}} \geq 100 \text{ mm}^3$ , and requirement of contributing coordinates from at least two independent studies from Table 1. Yellow foci = AD < control; Blue foci = AD > control. Neurological representation slices in plane with statistically significant ALE foci, visualized on a single-subject, ICBM Montreal Neurological Institute atlas space brain (MNI; [63]).

studies across a variety of institutions, scanner types, and patient samples.

The anterior parahippocampal gyrus, at approximately the BA 28 region (entorhinal cortex), demonstrated consistently decreased activation in both AD and MCI patients versus control subjects across the studies used in the current ALE analyses. Such results are in line with volumetric

studies documenting decreased entorhinal volume in MCI and AD groups. For example, Du et al [65] reported that entorhinal cortex and hippocampal volumes were significantly reduced in MCI (entorhinal cortex 13%, hippocampus 11%) and AD (entorhinal cortex 39%, hippocampus 27%) patients compared with normal control subjects. Furthermore, AD showed greater volume losses in the

Table 2  
ALE meta-analysis results for reported episodic memory encoding contrasts between MCI and AD persons and normal elderly control subjects

ALE group contrasts	Location (BA)*	Local extrema <sup>†</sup>			Cluster volume (mm <sup>3</sup> )	ALE value (×10 <sup>-3</sup> )
		x	y	z		
MCI > controls						
Right hemisphere	Anterior parahippocampal gyrus (~BA 35)	25	-15	-14	456	2.12
MCI < controls						
Right hemisphere	Anterior parahippocampal gyrus (~BA 28)	27	-27	-11	1040	2.13
Left hemisphere	Inferior frontal gyrus (BA 9)	-46	11	31	296	1.34
AD > controls						
Right hemisphere	Precuneus (BA 31)	10	-66	29	1720	1.15
	Superior temporal gyrus (BA 41)	53	-30	4	328	1.49
Left hemisphere	Cuneus (BA 18)	-16	-72	18	440	1.93
	Superior frontal gyrus (BA 6/8)	-24	40	43	424	1.81
	Precuneus (BA 31)	-11	-64	33	392	1.62
AD < controls						
Right hemisphere	Cerebellum, anterior lobe	5	-48	-31	392	1.70
	Anterior parahippocampal gyrus (~BA 28)	18	-17	-23	360	1.39
	Lingual gyrus (BA 19)	32	-75	2	152	1.17

Abbreviations: ALE, activation likelihood estimation; BA, Brodmann area.

NOTE. ALE analyses of MCI relative to normal control subjects (12 experimental contrasts [50 foci]) and AD relative to normal control subjects (18 experimental contrasts [95 foci]) with statistical significance threshold of false discovery rate  $q < .05$ ,  $k_{\text{extent}} \geq 100 \text{ mm}^3$ , and requirement of contributing coordinates from at least two independent studies from Table 1.

\*BA assignments based on 3-mm search radius of the Talairach Daemon database [64] using MNI-to-Talairach-transformed (Lancaster transform; [59]) cluster local extrema coordinates.

<sup>†</sup>Cluster local extrema coordinates provided in MNI [63] atlas space.

entorhinal cortex than in the hippocampus. Taken together, these findings suggest that volumetric and functional reductions in anterior parahippocampal cortex (~BA 28) play an important role in the episodic encoding impairments observed in MCI and AD groups. Of note, none of the considered studies accounted for the possible effects of atrophy on activation in the MTL [66,67]; therefore, it is not possible to disentangle these two effects on the basis of our results.

Another region along the anterior parahippocampal gyrus, approximately in BA 35 (perirhinal cortex), demonstrated greater activity in MCI than control individuals. Although there have been extensive discussions about the role of the perirhinal cortex in episodic memory (see [68] for recent review), one prominent view is that perirhinal activity is associated with processing episodic familiarity signals [69]. Studies in healthy young individuals have documented enhanced perirhinal activity during encoding [70] and retrieval [71] of “unitized” information (e.g., a background color of a studied word or features of a face), leading to the proposal that perirhinal cortex may encode feature-fused item representations that can support later source judgments on the basis of stimulus familiarity [70,72,73]. However, overreliance on stimulus familiarity during encoding can lead to high levels of memory errors, and under such conditions, significantly greater activity during false than during accurate retrieval has been reported in the perirhinal cortex in older adults [74]. Such findings suggest that the anterior parahippocampal activity (at approximately BA 35) observed in the current analysis may reflect an increase or overreliance on familiarity-based processing

during episodic encoding in MCI, not necessarily beneficial to successful memory.

Another strong ALE finding was apparent in the comparison of study contrasts involving greater activity in AD patients relative to control subjects. Precuneus and cuneus activation is particularly robust across contrasts of this type, and these regions are known to be part of a “default network” associated with intrinsic baseline activity in the brain, and physiologically normal deactivation during a wide variety of tasks, including memory encoding [75]. The consistent observation of greater activation in these regions in AD patients compared with control subjects reinforces an aberration in the ability to effectively redistribute cognitive resources during memory tasks, perhaps indicating a functional breakdown in precuneus/cuneus connectivity in AD/MCI patients. A distinct pattern of abnormally high activity in the default network has been consistently found in AD and MCI patients when compared with healthy control subjects [52]. In fact, this finding is often consistent enough as to be able to discriminate AD patients from healthy control subjects based on default network activation, with a sensitivity of 85% [76]. Thus, our findings support a similarly strong phenotypic dysfunction of cuneus/precuneus BOLD activation during memory task performance in AD patients, which is consistent with recent findings that strong posterior midline activation during memory task performance is a negative predictor of memory encoding success [77].

Increased activation in left superior frontal gyrus for both MCI and AD patients versus normal control subjects, an area known to be important in memory encoding and retrieval, suggests that both patient types tend to engage in their

respective memory tasks. Prefrontal lobe activation is observed in AD patients relative to control subjects, but the activation locus tends to be smaller and more superior to the MCI aggregate ALE result locus. This general reduction in prefrontal lobe activation for AD versus control groups may suggest some variability in task attention between AD versus control groups.

Our analyses also reveal a robust increase in prefrontal activity during encoding tasks for both AD and MCI patients versus control subjects. This finding points to the prefrontal cortex (PFC) as a possible compensatory mechanism for patients with lower-than-normal activity in traditional memory networks (i.e., entorhinal cortex). For example, a shift from medial temporal- to frontal-based processing has been documented previously in healthy older adults during episodic encoding [78] and episodic retrieval [79]. In those studies, significant correlations were obtained between decreased MTL activity and increased prefrontal activity during accurate performance, and the results are interpreted to reflect compensatory processes whereby prefrontal regions are recruited to counteract neurocognitive decline in the context of deficient MTL memory system function. The current findings indicate that a similar shift from MTL to prefrontal regions occurs in populations with frank episodic encoding impairments.

Schwindt and Black [47] conducted a similar quantitative ALE meta-analysis of fMRI studies involving episodic memory dysfunction. In alignment with our results, they confirmed a decrease in MTL activity during episodic memory tasks in AD patients. Their general results for areas of increased activity in AD patients matched our results as well, including activation in the prefrontal cortex, parietal lobe, cuneus, and superior temporal gyrus. However, there are several factors that differentiate our results. For example, their study focused on results from AD patients only, excluding findings from subjects with milder forms of cognitive impairment likely reflecting prodromal AD. In contrast, the present study provides a basis for examining the regional consistency of task-related BOLD activity along a spectrum of cognitive disorder from normal control subjects to MCI patients to AD patients. Additionally, our analysis included only those studies that reported data for both cognitively impaired patients and healthy control subjects, allowing us to isolate patterns of common difference and reducing the heterogeneity of these patterns. Conversely, Schwindt and Black included some studies with data of AD patients only (without a control comparison). Their study also included PET data in the meta-analysis. However, because there tends to be variability between fMRI and PET results, we elected not to include PET studies to elucidate more refined activity patterns specific to task-related BOLD. Additionally, in contrast to the Schwindt and Black analyses, we opted not to include fMRI BOLD studies in our analyses that primarily involved pharmacological interventions for AD. A few of the studies included in our analyses noted pharmacological treatment of AD patients, which are noted in Table 2, but

these treatments were not the focus of the included studies and were limited to standard acetylcholinesterase inhibition approaches. Methodologically, an important distinguishing factor of the present study is its implementation of the ALE meta-analysis technique amenable to random-effects inference of the results. Previous ALE analyses (including the one conducted by Schwindt and Black) used a fixed-effects ALE analysis that tested for above-chance clustering between foci. However, the current results assessed for random-effects clustering between experiments; thus, our results may be more generalized to the population of task-based BOLD studies of MCI and AD.

To be considered “phenotypic,” ALE analysis clusters were required to have contributing spatial coordinates from a minimum of at least two independent studies from Table 1. However, significant regions actually reflect a much greater contribution from multiple independent studies. For example, in the comparison of activity greater for AD participants than for control participants, contributing spatial coordinates from right precuneus (BA 31) were observed in four of the studies (i.e., Gould et al, [7]; Pariente et al, [13]; Petrella et al, [52]; and Sperling et al, [18]), reflecting the same observation from independent research groups and distinct patient samples. Similarly, the reduced activity during episodic memory encoding in the right anterior parahippocampal gyrus of MCI participants relative to control subjects (~BA 28) was also detected in four independent studies [8–10,19]. It should be noted, however, that the notion of task-based fMRI phenotypes for episodic memory encoding applies only to each patient group separately. The relationship between MCI, dementia, and AD has yet to be fully elucidated, and often, depending on the diagnostic criteria selected, MCI may or may not reflect incipient AD. Therefore, any significant ALE regions from the analyses represent contrasts between AD or MCI patients and elder control subjects, not a direct contrast between AD and MCI patients. A potential source of bias in our ALE results is the use of varied paradigms to investigate episodic encoding. A majority of the studies included for analyses used visual memory paradigms, which likely accounts for the greater emphasis of right hemispheric common differences, particularly those noted in the MTL region. The face-name associative encoding task developed by Sperling et al [53] was particularly well represented, whereas remaining studies tended to use verbal encoding tasks involving recall of word lists. Although we grouped visual and verbal studies together in the ALE analysis, the results are heavily weighted toward visual episodic encoding (hence the consistent right MTL activation foci in both patient groups).

Our analysis of the episodic encoding component of memory using ALE gives us an interesting new perspective on possible MCI and AD task-based BOLD phenotypes. More specifically, our analysis suggests a robust imaging phenotype in AD and MCI confined to the MTL, specifically the parahippocampal gyrus, as well as superior frontal gyrus, precuneus, and cuneus. The locality of these consistent

task-based fMRI signatures appears to support current research about the effect of AD pathogenesis on functional network connectivity. For example, Sperling and Dickerson postulate that the initial hyperactivity observed in the MTL during episodic encoding in MCI may be secondary to this region becoming progressively more functionally “disconnected” from the rest of the Papez circuit and posterior cingulate gyrus (PCG) region [80]. This general pattern of episodic memory functional network disruption appears to fit with the current ALE analyses results—when MTL functioning begins to fail secondary to AD neuropathological changes, patients may rely more on self-referential information search (i.e., PCG activity) during memory encoding and retrieval attempts [81]. Consistent findings of coincident prefrontal cortex (PFC) activity in AD patients during memory task performance indicate that the PCG activity is not likely to just be a by-product of their not trying during the task.

More research is needed particularly in early prodromal AD to better understand the extent to which the current findings in MCI reflect early AD traits, but the consistent robustness of ALE activation commonalities in the MTL and PCG certainly highlights these regions as being central to any future functional neuroimaging studies of AD pathogenesis.

## Acknowledgments

The authors thank Steven Prince, Nina Borges, Katherine Rief, and Colby Keistler for their assistance in literature search, ALE analyses, and document retrieval and edits. J.N.B. also thanks Drs. David Brizel, Frank Dunphy, Ramon Esclamado, and Richard Scher for providing their expertise and care, which made his work existentially possible. This research was supported, in part, by National Institutes of Health/National Institute on Aging grants P30-AG028377 (K.A.W.B.), R01-AG019728 (J.P.), and L30-AG029001 (J.N.B.).

## References

- [1] Morris JC. Mild cognitive impairment and preclinical Alzheimer's disease. *Geriatrics* 2005;(Suppl):9–14.
- [2] Petersen RC, Negash S. Mild cognitive impairment: an overview. *CNS Spectr* 2008;13:45–53.
- [3] Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, et al. Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. *J Neurosci* 2006;26:10222–31.
- [4] Drzezga A. Concept of functional imaging of memory decline in Alzheimer's disease. *Methods* 2008;44:304–14.
- [5] Elgh E, Larsson A, Eriksson S, Nyberg L. Altered prefrontal brain activity in persons at risk for Alzheimer's disease: an fMRI study. *Int Psychogeriatr* 2003;15:121–33.
- [6] Golby A, Silverberg G, Race E, Gabrieli S, O'Shea J, Knierim K, et al. Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. *Brain* 2005;128(Pt 4):773–87.
- [7] Gould RL, Brown RG, Owen AM, Bullmore ET, Williams SC, Howard RJ. Functional neuroanatomy of successful paired associate learning in Alzheimer's disease. *Am J Psychiatry* 2005;162:2049–60.
- [8] Johnson SC, Baxter LC, Susskind-Wilder L, Connor DJ, Sabbagh MN, Caselli RJ. Hippocampal adaptation to face repetition in healthy elderly and mild cognitive impairment. *Neuropsychologia* 2004;42:980–9.
- [9] Johnson SC, Schmitz TW, Asthana S, Gluck MA, Myers C. Associative learning over trials activates the hippocampus in healthy elderly but not mild cognitive impairment. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2008;15:129–45.
- [10] Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, et al. Activation of brain regions vulnerable to Alzheimer's disease: the effect of mild cognitive impairment. *Neurobiol Aging* 2006;27:1604–12.
- [11] Kircher TT, Weis S, Freymann K, Erb M, Jessen F, Grodd W, et al. Hippocampal activation in patients with mild cognitive impairment is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry* 2007;78:812–8.
- [12] Koenig P, Smith EE, Troiani V, Anderson C, Moore P, Grossman M. Medial temporal lobe involvement in an implicit memory task: evidence of collaborating implicit and explicit memory systems from fMRI and Alzheimer's disease. *Cereb Cortex* 2008;18:2831–43.
- [13] Pariente J, Cole S, Henson R, Clare L, Kennedy A, Rossor M, et al. Alzheimer's patients engage an alternative network during a memory task. *Ann Neurol* 2005;58:870–9.
- [14] Petrella JR, Krishnan S, Slavin MJ, Tran TT, Murty L, Doraiswamy PM. Mild cognitive impairment: evaluation with 4-T functional MR imaging. *Radiology* 2006;240:177–86.
- [15] Pihlajamaki M, DePeau KM, Blacker D, Sperling RA. Impaired medial temporal repetition suppression is related to failure of parietal deactivation in Alzheimer disease. *Am J Geriatr Psychiatry* 2008;16:283–92.
- [16] Remy F, Mirrashed F, Campbell B, Richter W. Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study. *Neuroimage* 2005;25:253–66.
- [17] Rombouts SA, Barkhof F, Goekoop R, Stam CJ, Scheltens P. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. *Hum Brain Mapp* 2005;26:231–9.
- [18] Sperling RA, Bates JF, Chua EF, Cocchiarella AJ, Rentz DM, Rosen BR, et al. fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2003;74:44–50.
- [19] Trivedi MA, Murphy CM, Goetz C, Shah RC, Gabrieli JD, Whitfield-Gabrieli S, et al. fMRI activation changes during successful episodic memory encoding and recognition in amnesic mild cognitive impairment relative to cognitively healthy older adults. *Dement Geriatr Cogn Disord* 2008;26:123–37.
- [20] Grossman M, Koenig P, Glosser G, DeVita C, Moore P, Rhee J, et al. Neural basis for semantic memory difficulty in Alzheimer's disease: an fMRI study. *Brain* 2003;126(Pt 2):292–311.
- [21] Saykin AJ, Flashman LA, Frutiger SA, Johnson SC, Mamourian AC, Moritz CH, et al. Neuroanatomic substrates of semantic memory impairment in Alzheimer's disease: patterns of functional MRI activation. *J Int Neuropsychol Soc* 1999;5:377–92.
- [22] Woodard JL, Seidenberg M, Nielson KA, Antuono P, Guidotti L, Durgerian S, et al. Semantic memory activation in amnesic mild cognitive impairment. *Brain* 2009;132(Pt 8):2068–78.
- [23] Lim HK, Juh R, Pae CU, Lee BT, Yoo SS, Ryu SH, et al. Altered verbal working memory process in patients with Alzheimer's disease: an fMRI investigation. *Neuropsychobiology* 2008;57:181–7.
- [24] Yetkin FZ, Rosenberg RN, Weiner MF, Purdy PD, Cullum CM. fMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. *Eur Radiol* 2006;16:193–206.
- [25] Prvulovic D, Hubl D, Sack AT, Melillo L, Maurer K, Frolich L, et al. Functional imaging of visuospatial processing in Alzheimer's disease. *Neuroimage* 2002;17:1403–14.
- [26] Thiyagesh SN, Farrow TF, Parks RW, Accosta-Mesa H, Young C, Wilkinson ID, et al. The neural basis of visuospatial perception in Alzheimer's disease and healthy elderly comparison subjects: an fMRI study. *Psychiatry Res* 2009;172:109–16.

- [27] Albert MS. Detection of very early Alzheimer disease through neuro-imaging. *Alzheimer Dis Assoc Disord* 2003;17(Suppl 2):S63–5.
- [28] Lee BC, Mintun M, Buckner RL, Morris JC. Imaging of Alzheimer's disease. *J Neuroimaging* 2003;13:199–214.
- [29] Prince SE, Woo S, Doraiswamy PM, Petrella JR. Functional MRI in the early diagnosis of Alzheimer's disease: is it time to refocus? *Expert Rev Neurother* 2008;8:169–75.
- [30] Callicott JH, Egan MF, Mattay VS, Bertolino A, Bone AD, Verchinski B, et al. Abnormal fMRI response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. *Am J Psychiatry* 2003;160:709–19.
- [31] Callicott JH, Weinberger DR. Brain imaging as an approach to phenotype characterization for genetic studies of schizophrenia. *Methods Mol Med* 2003;77:227–47.
- [32] Dillon DG, Bogdan R, Fagermess J, Holmes AJ, Perlis RH, Pizzagalli DA. Variation in TREK1 gene linked to depression-resistant phenotype is associated with potentiated neural responses to rewards in humans. *Hum Brain Mapp* 2010;31:210–1.
- [33] Greene CM, Braet W, Johnson KA, Bellgrove MA. Imaging the genetics of executive function. *Biol Psychol* 2008;79:30–42.
- [34] Kalin NH, Shelton SE, Fox AS, Rogers J, Oakes TR, Davidson RJ. The serotonin transporter genotype is associated with intermediate brain phenotypes that depend on the context of eliciting stressor. *Mol Psychiatry* 2008;13:1021–7.
- [35] Chiu PH, Kayali MA, Kishida KT, Tomlin D, Klinger LG, Klinger MR, et al. Self responses along cingulate cortex reveal quantitative neural phenotype for high-functioning autism. *Neuron* 2008;57:463–73.
- [36] Kates WR, Krauss BR, Abdulsabur N, Colgan D, Antshel KM, Higgins AM, et al. The neural correlates of non-spatial working memory in velocardiofacial syndrome (22q11.2 deletion syndrome). *Neuropsychologia* 2007;45:2863–73.
- [37] Meyer-Lindenberg A, Kohn P, Mervis CB, Kippenhan JS, Olsen RK, Morris CA, et al. Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. *Neuron* 2004;43:623–31.
- [38] Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci USA* 1996;93:13515–22.
- [39] Carlesimo GA, Oscar-Berman M. Memory deficits in Alzheimer's patients: a comprehensive review. *Neuropsychol Rev* 1992;3:119–69.
- [40] Cullum CM, Filley CM, Kozora E. Episodic memory function in advanced aging and early Alzheimer's disease. *J Int Neuropsychol Soc* 1995;1:100–3.
- [41] Grosse DA, Gilley DW, Wilson RS. Episodic and semantic memory in early versus late onset Alzheimer's disease. *Brain Lang* 1991;41:531–7.
- [42] Hamilton JM, Salmon DP, Galasko D, Delis DC, Hansen LA, Masliah E, et al. A comparison of episodic memory deficits in neuropathologically-confirmed Dementia with Lewy bodies and Alzheimer's disease. *J Int Neuropsychol Soc* 2004;10:689–97.
- [43] Grober E, Dickson D, Sliwinski MJ, Buschke H, Katz M, Crystal H, et al. Memory and mental status correlates of modified Braak staging. *Neurobiol Aging* 1999;20:573–9.
- [44] Laird AR, Fox PM, Price CJ, Glahn DC, Uecker AM, Lancaster JL, et al. ALE meta-analysis: controlling the false discovery rate and performing statistical contrasts. *Hum Brain Mapp* 2005;25:155–64.
- [45] Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT. Coordinate-based activation likelihood estimation meta-analysis of neuro-imaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Hum Brain Mapp* 2009;30:2907–26.
- [46] Ragland JD, Laird AR, Ranganath C, Blumenfeld RS, Gonzales SM, Glahn DC. Prefrontal activation deficits during episodic memory in schizophrenia. *Am J Psychiatry* 2009;166:863–74.
- [47] Schwindt GC, Black SE. Functional imaging studies of episodic memory in Alzheimer's disease: a quantitative meta-analysis. *Neuroimage* 2009;45:181–90.
- [48] Spaniol J, Davidson PS, Kim AS, Han H, Moscovitch M, Grady CL. Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia* 2009;47:1765–79.
- [49] Hamalainen A, Pihlajamaki M, Tanila H, Hanninen T, Niskanen E, Tervo S, et al. Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiol Aging* 2007;28:1889–903.
- [50] Machulda MM, Senjem ML, Weigand SD, Smith GE, Ivnik RJ, Boeve BF, et al. Functional magnetic resonance imaging changes in amnesic and nonamnesic mild cognitive impairment during encoding and recognition tasks. *J Int Neuropsychol Soc* 2009;15:372–82.
- [51] Peters F, Collette F, Degueldre C, Sterpenich V, Majerus S, Salmon E. The neural correlates of verbal short-term memory in Alzheimer's disease: an fMRI study. *Brain* 2009;132(Pt 7):1833–46.
- [52] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
- [53] Sperling RA, Bates JF, Cocchiarella AJ, Schacter DL, Rosen BR, Albert MS, et al. Encoding novel face-name associations: a functional MRI study. *Hum Brain Mapp* 2001;14:129–39.
- [54] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34:939–44.
- [55] Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993;43:2412–4.
- [56] Petrella JR, Wang L, Krishnan S, Slavin MJ, Prince SE, Tran TT, et al. Cortical deactivation in mild cognitive impairment: high-field-strength functional MR imaging. *Radiology* 2007;245:224–35.
- [57] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
- [58] Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. New York, NY: Thieme Medical Publishers; 1988.
- [59] Lancaster JL, Tordesillas-Gutiérrez D, Martínez M, Salinas F, Evans A, Zilles K, et al. Bias between MNI and Talairach coordinates analyzed using the ICBM-152 brain template. *Hum Brain Mapp* 2007;28:1194–205.
- [60] Brett M. The MNI brain and the Talairach atlas, Cambridge Imagers, 1999. Available at: <http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>.
- [61] Turkeltaub PE, Eden GF, Jones KM, Zeffiro TA. Meta-analysis of the functional neuroanatomy of single-word reading: method and validation. *Neuroimage* 2002;16(3 Pt 1):765–80.
- [62] Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 2002;15:870–8.
- [63] Evans AC, Collins DL, Mills SR, Brown ED, Kelly RL, Peters TM. 3D statistical neuroanatomical models from 305 MRI volumes. IEEE Nuclear Science Symposium and Medical Imaging Conference; 1993. p. 1813–7.
- [64] Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al. Automated Talairach atlas labels for functional brain mapping. *Hum Brain Mapp* 2000;10:120–31.
- [65] Du AT, Schuff N, Amend D, Laakso MP, Hsu YY, Jagust WJ, et al. Magnetic resonance imaging of the entorhinal cortex and hippocampus in mild cognitive impairment and Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2001;71:441–7.
- [66] Krishnan S, Slavin MJ, Tran TT, Doraiswamy PM, Petrella JR. Accuracy of spatial normalization of the hippocampus: implications for fMRI research in memory disorders. *Neuroimage* 2006;31:560–71.
- [67] Sandstrom CK, Krishnan S, Slavin MJ, Tran TT, Doraiswamy PM, Petrella JR. Hippocampal atrophy confounds template-based functional MR imaging measures of hippocampal activation in patients with mild cognitive impairment. *Am J Neuroradiol* 2006;27:1622–7.

- [68] Diana RA, Yonelinas AP, Ranganath C. Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends Cogn Sci* 2007;11:379–86.
- [69] Daselaar SM, Fleck MS, Cabeza R. Triple dissociation in the medial temporal lobes: recollection, familiarity, and novelty. *J Neurophysiol* 2006;96:1902–11.
- [70] Haskins AL, Yonelinas AP, Quamme JR, Ranganath C. Perirhinal cortex supports encoding and familiarity-based recognition of novel associations. *Neuron* 2008;59:554–60.
- [71] Ford JH, Verfaellie M, Giovanello KS. Neural correlates of familiarity-based associative retrieval. *Neuropsychologia* 2010;48:3019–25.
- [72] Diana RA, Yonelinas AP, Ranganath C. The effects of unitization on familiarity-based source memory: testing a behavioral prediction derived from neuroimaging data. *J Exp Psychol Learn Mem Cogn* 2008;34:730–40.
- [73] Staresina BP, Davachi L. Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *J Cogn Neurosci* 2008;20:1478–89.
- [74] Giovanello KS, Kensinger EA, Wong AT, Schacter DL. Age-related neural changes during memory conjunction errors. *J Cogn Neurosci* 2010;22:1348–61.
- [75] Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. *Neuroimage* 2007;37:1083–90. discussion 1097–9.
- [76] Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci USA* 2004;101:4637–42.
- [77] Daselaar SM, Prince SE, Dennis NA, Hayes SM, Kim H, Cabeza R. Posterior midline and ventral parietal activity is associated with retrieval success and encoding failure. *Front Hum Neurosci* 2009;3:13.
- [78] Gutches AH, Welsh RC, Hedden T, Bangert A, Minear M, Liu LL, et al. Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *J Cogn Neurosci* 2005;17:84–96.
- [79] Grady CL, McIntosh AR, Craik FI. Task-related activity in prefrontal cortex and its relation to recognition memory performance in young and old adults. *Neuropsychologia* 2005;43:1466–81.
- [80] Dickerson BC, Sperling RA. Large-scale functional brain network abnormalities in Alzheimer's disease: insights from functional neuroimaging. *Behav Neurol* 2009;21:63–75.
- [81] Bai F, Shi Y, Yuan Y, Wang Y, Yue C, Teng Y, et al. Altered self-referential network in resting-state amnesic type mild cognitive impairment. *Cortex* 2012;48:604–13.

# Did you know?

The screenshot displays the website for *Alzheimer's & Dementia*, The Journal of the Alzheimer's Association. The page includes a search bar at the top, a navigation menu on the left with options like 'JOURNAL HOME', 'CURRENT ISSUE', and 'ARTICLES IN PRESS', and a main content area featuring 'Current Issue' information (November 2009 | Vol. 5, No. 6) and 'Featured Articles' such as 'Cognitive performance and informant reports in the diagnosis of cognitive impairment and dementia in African Americans and whites'. A 'Now Included on MEDLINE' badge is also visible. At the bottom, there are sections for 'JOURNAL ACCESS', 'FEATURES', and 'ABOUT THE ALZHEIMER'S ASSOCIATION'.

You can access back issues of **Alzheimer's & Dementia** online.

[www.alzheimersanddementia.org](http://www.alzheimersanddementia.org)