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

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**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.
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## 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 memory 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

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[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