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Functional Magnetic Resonance Imaging of Semantic Memory as a Presymptomatic Biomarker of Alzheimer's Disease Risk

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Abstract

Extensive research efforts have been directed toward strategies for predicting risk of developing Alzheimer's disease (AD) prior to the appearance of observable symptoms. Existing approaches for early detection of AD vary in terms of their efficacy, invasiveness, and ease of implementation. Several non-invasive magnetic resonance imaging strategies have been developed for predicting decline in cognitively healthy older adults. This review will survey a number of studies, beginning with the development of a famous name discrimination task used to identify neural regions that participate in semantic memory retrieval and to test predictions of several key theories of the role of the hippocampus in memory. This task has revealed medial temporal and neocortical contributions to recent and remote memory retrieval, and it has been used to demonstrate compensatory neural recruitment in older adults, apolipoprotein E ε4 carriers, and amnestic mild cognitive impairment patients. Recently, we have also found that the famous name discrimination task provides predictive value for forecasting episodic memory decline among asymptomatic older adults. Other studies investigating the predictive value of semantic memory tasks will also be presented. We suggest several advantages associated with the use of semantic processing tasks, particularly those based on person identification, in comparison to episodic memory tasks to study AD risk. Future directions for research and potential clinical uses of semantic memory paradigms are also discussed.

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Keywords

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1. Introduction

1.1 Alzheimer's disease and prediction

Alzheimer's disease (AD) is a worldwide health concern. It has been projected that by the year 2050, over 100 million people worldwide will be diagnosed with AD [1], including between 8 and 13 million individuals in the United States [2]. Currently, there are no effective treatments for persons with AD. However, several promising strategies have been identified that may delay or even prevent the progression of AD [3]. Various lifestyle factors, such as dietary modifications [4] and participation in physical [5], social [6, 7], and cognitively stimulating activities [8, 9], have been associated with a decreased risk for developing AD. It is known that AD-related neuropathology begins to accumulate decades prior to the onset of cognitive symptoms [10, 11]. Thus, implementation of an intervention well before the onset of observable symptoms, such as episodic memory loss, could provide the greatest opportunity to slow or minimize damage due to the disease, particularly if they are targeted toward individuals with the greatest risk of developing AD.

In order to identify those individuals who are at the highest likelihood of developing the disease, considerable research efforts have been directed toward identifying specific risk factors and biomarkers of the disease. Two well-established risk factors for late-onset, non-sporadic AD are a history of dementia in a first-degree relative [12] and possession of one or more apolipoprotein (APOE) ε4 alleles [13–15]. However, these factors alone are far from perfect in predicting who will develop the disease, and a number of studies have recently started to identify preclinical biomarkers [16]. Cerebrospinal fluid (CSF) indices of isoprostane [17–19], total tau and phosphorylated tau [20–22], and amyloid-β 1–42 ($A\beta_{42}$) [17, 23–25] levels have been successful in predicting conversion from mild cognitive impairment (MCI) to AD. Additionally, neuroimaging methods have been used to predict conversion from MCI to AD, including structural magnetic resonance imaging (sMRI) of hippocampal volume [26–28], hippocampal rate of atrophy [29–31], and entorhinal cortex [31–34] volume, electroencephalography (EEG) [35, 36], and positron emission tomography (PET) using measurement of regional glucose metabolism [37–39] and amyloid imaging [40–42].

While a number of studies have been successful in predicting conversion from MCI to AD, predicting cognitive decline or onset of dementia in cognitively healthy older adults presents a greater challenge. Longitudinal follow-up intervals need to be conducted over a sufficiently long time frame to observe a clinically significant amount of cognitive decline. Because participants are by definition cognitively intact, determination of whether performance change over time is a reflection of test unreliability, practice effects, or age-appropriate cognitive change can be difficult. Furthermore, clinical samples need to be large in order to detect an adequate number of participants who actually do show cognitive decline. Given the expense of neuroimaging methods, it is often difficult to dedicate the resources necessary to studies of this magnitude. Hence, most longitudinal neuroimaging studies to date have attempted to predict conversion of MCI to AD. However, for interventions to be maximally effective in altering the disease course of AD, earlier identification of AD risk is essential. Advanced neuroimaging methodologies have considerable potential to function as biomarkers of risk. Therefore, longitudinal

neuroimaging studies focusing on prediction of cognitive decline in cognitively intact older adults are needed to further evaluate and implement this potential.

1.2 Functional magnetic resonance imaging of risk and prognosis

Functional magnetic resonance imaging (fMRI) has considerable promise as an effective preclinical biomarker of AD. Because task-activated fMRI relies on the capability to carry out specific cognitive tasks, it is sensitive to the dynamic functional integrity of the brain. Therefore, fMRI may be able to reveal early abnormalities in brain function that could reflect the initial stages of AD neuropathology. Indeed, analysis of the task-activated blood-oxygen-level-dependent (BOLD) signal has yielded successful prediction of conversion from MCI to AD [43–45]. A limited number of studies have also used fMRI to predict subsequent cognitive decline in cognitively intact older adults [46–50]. Having a genetic predisposition to develop AD has been demonstrated to influence the BOLD signal in asymptomatic older adults [51–53]. Similar risk-related alterations of the BOLD signal have been observed throughout adulthood [54–58], suggesting that factors including the APOE ε4 allele and a family history of AD influence brain functioning across the lifespan. Given these factors, fMRI biomarkers may allow for more accurate prediction of cognitive decline over sMRI, family history, and APOE genotype information alone [48].

1.3 Overview

In this review, we will present a summary of work from cross-sectional and longitudinal studies investigating imaging strategies for early detection of cognitive decline. Our collaborative research group has focused on identification of the neural correlates of semantic memory to investigate early prediction of cognitive decline. Using person-identity memory as a foundation, we evaluated face and name discrimination and subsequently developed a famous name discrimination task. fMRI activation associated with this task has successfully differentiated younger control participants from cognitively intact older adults [59], healthy older APOE ε4 carriers from non-carriers [52], and persons with amnestic MCI from older healthy and at-risk controls [60]. The task has also assisted in contrasting theories of age-related neural network change [59, 61, 62], to evaluate hypotheses regarding the relative roles of the neocortex and the medial temporal lobe in the retrieval of recent and remote semantic memories, and to investigate the nature of temporally graded remote memory retrieval [61, 62]. Recently, we have developed a prediction model to assist in identifying cognitively intact older adults who were at the greatest risk of cognitive decline [48], and we evaluated the effects of self-reported physical activity on alteration of semantic memory activation in healthy older adults [63] and MCI patients [64].

Our results, in addition to research findings from several other laboratories, suggest that fMRI during semantic processing tasks may provide advantages over episodic memory tasks in the assessment of risk for AD and prognosis for future cognitive decline. The present work will review research conducted by our lab and others on the functional correlates of semantic memory with regard to aging, AD risk, cognitive decline, and MCI. Future directions for research and the viability of fMRI in a clinical setting will also be discussed.

2. Semantic Memory Task Development, Results and Implications for Memory Theories

2.1 Episodic v. semantic memory in AD biomarker research

A number of fMRI studies engage participants in various tasks involving aspects of memory functioning. Two general categories of memory performance are frequently assessed – episodic memory (e.g. discriminating between previously learned and novel stimuli) and semantic (recall of general facts and knowledge about the world that is not contextually

specific, e.g. making a categorical or attributional judgment to a presented item). Given that episodic memory impairment is a hallmark of AD [65], most fMRI studies of AD risk have used episodic memory tasks [53]. However, the use of episodic memory tasks in fMRI studies that focus on prediction of MCI, AD, and risk factors for these conditions may present challenges. Episodic memory impairment is typically observed not only in association with symptom onset of MCI or AD [66–70], but declines in episodic memory performance are also observed in normal aging [71]. Therefore, disparities in task performance between participants and groups may confound results. Discrepancies in the BOLD signal between participants during episodic memory tasks may therefore be a product of neuropathology or age-related differences in task performance (or both). However, for the purposes of fMRI biomarker research, the question of interest focuses primarily on the extent to which neuropathology influences the brain's hemodynamic response during cognitive processing; imaging is not necessary to assess age-related memory performance differences. Furthermore, episodic memory tasks may also be inherently more difficult than semantic memory tasks, and individuals who are in the preliminary stages of cognitive decline may exert greater effort and may paradoxically display a greater BOLD signal [72] due to the increased cognitive challenge. Indeed, in longitudinal studies utilizing episodic memory tasks, participants who display a greater extent of activation are typically at the greatest risk of subsequent cognitive decline [46, 49, 50].

The use of semantic memory tasks during fMRI may provide several advantages over episodic tasks. Semantic memory tasks involve immediate, context-independent familiarity with previously learned information, and they are typically easier and less frustrating for older participants to complete than episodic tasks. Unlike episodic memory skills, semantic memory abilities remain relatively intact with normal aging [71] but are commonly affected during AD [73–75]. In studies of risk, between-group discrepancies in task performance are not frequently observed, because all participants can perform with a high degree of accuracy [48, 52]. Contrary to the results from longitudinal episodic memory studies [46, 49, 50], participants who exhibit *lower* activation during semantic tasks appear to be at the greatest risk of future cognitive decline [47, 48]. Furthermore, regions that are typically activated during semantic memory retrieval overlap with those associated with the default mode network [76] as well as with regions that are the most susceptible to neuropathological changes associated with AD [77]. Thus, analysis of the BOLD signal during semantic memory processing has a number of advantages over episodic memory for discriminating between healthy aging and disease-related changes and risk.

Several semantic processing tasks have been utilized in functional imaging studies. The most common contrasts [76] include semantic versus phonological word judgments (e.g. [78, 79]), discriminating between words and pseudowords (e.g. [80, 81]), high versus low meaningfulness judgments (e.g. related and unrelated word pairs, [82, 83]), and comparing members of specific categories (e.g. concrete or abstract words, [84, 85]). Considerable research has also been dedicated to tasks involving person identity, such as the recognition of famous and unfamiliar names or faces [86–92], which reflects a semantic meaningfulness dimension (e.g., meaningful vs. non-meaningful) [76]. When contrasting the recognition of famous names with the correct rejection of unfamiliar names, activation has been observed in a variety of neocortical and medial temporal lobe (MTL) regions, including the hippocampus [61, 62]. Our research has focused on this paradigm to investigate the neural correlates of person identity and memories of different ages, and how these processes may be affected by aging and risk for AD. In the following sections, we describe the development and preliminary usage of our famous and unfamiliar name stimuli.

2.2 Episodic and semantic memory networks during face recognition

The first study of the long-term, semantic memory network by our group [93] involved the use of fMRI during familiarity judgments of famous and recently learned faces. Our initial focus was to contrast the neural correlates of semantic and episodic memory with regard to person identity. Participants were instructed to learn and remember novel, unfamiliar pictures of faces during an encoding phase. During a retrieval phase, participants were asked to determine whether a presented face was familiar or unfamiliar. Familiar faces were either previously seen during the encoding phase or were famous individuals, and unfamiliar faces were non-famous foils. The famous faces consisted of well-known entertainers, politicians, and sports figures from the previous 30 years. Thus, this paradigm allowed for direct comparison between the neural networks associated with two distinct retrieval memory systems: newly learned episodic memory (from the encoding phase) and long-term semantic memory (famous faces).

Compared to the correct rejection of unfamiliar faces, recognition of newly learned faces induced a left-lateralized cortical pattern of fMRI activation. Greater activation was observed for unfamiliar faces over newly learned faces in several bilateral frontal regions and the right fusiform gyrus. In contrast, recognition of famous faces activated an extensive bilateral network incorporating both *cortical and subcortical* regions, compared to newly learned and unfamiliar faces. Importantly, greater activation was observed in MTL structures, including the left hippocampus and right parahippocampal gyrus. Behavioral differences could not account for the discrepancy in neural recruitment between newly learned and famous faces. Thus, this low effort, high accuracy semantic processing task, which is usable in large segments of the population due to the high familiarity of the stimuli, activated an extensive bilateral network associated with the recognition of well-known individuals.

A critical question of interest is whether pictures of faces and written names of familiar individuals are processed in similar brain regions or whether the mental representation of this person-identity material may engage different brain regions. In addition, face stimuli tend to contain complex visual information, including affective valence (e.g., the individual is typically smiling), variations along an attractiveness continuum, and other visual details (e.g., hair style, presence of facial hair, clothing). Name stimuli tend to be more uniform in terms of the visual stimulus that is presented (i.e., letters). Therefore, name stimuli may have advantages over face stimuli in terms of reducing the complexity of the material presented to participants. The ability to present names of individuals who became famous in different eras also affords the opportunity to explore the brain's responses during activation of memories of different ages.

2.3 Development and pilot testing of famous names

We sought to identify the patterns of neural activity associated with the recognition of persons from different time periods to determine whether the brain exhibits a temporally graded pattern of regional recruitment in response to memories of different ages. To address these questions, we developed a list of famous and unfamiliar names that could be reliably categorized by older and younger individuals alike [62]. We identified entertainers, politicians, criminals, or athletes who achieved public prominence either between approximately 1990 and 2000 (Recent famous names) or between approximately 1950 and 1965 (Remote famous names). Unfamiliar names were randomly selected from a local phone book as a control condition. Following pilot testing with older and younger adults, we created a final list of 30 names in each of four categories. Unfamiliar names were selected for inclusion on the final list if they were correctly identified as non-famous by 90% of both older and younger participants. Recent famous names from the 1990's (e.g. George

Clooney, Colin Powell) were correctly identified as famous by at least 90% of both younger and older adults. Enduring famous names (individuals who achieved fame between 1950 and 1965 and are still well known today; e.g., John F. Kennedy, Marilyn Monroe) were also correctly identified as famous by at least 90% of both younger and older adults. Our fourth category, Remote famous names, consisted of individuals who achieved fame between 1950 and 1965 but who were correctly identified by at least 90% of older adults and by no more than 30% of younger participants. This latter stimulus category was designed to represent famous names that would be easily recognizable to older adults while being out of the public eye for several decades. Therefore, correct identification of these stimuli was thought to reflect retrieval of remote semantic material without being contaminated by recent updating. In this task, participants are required to categorize each name as famous or unfamiliar. Thus, the task is known as the famous name discrimination task (FNDT).

2.4 Famous name recognition of recent and remote memories

Our initial study using the FNDT investigated functional activity specifically in the hippocampal complex and parahippocampal gyrus (PHG) in response to Recent, Remote, and Unfamiliar names [62]. A goal of this study was to contrast predictions of two models of hippocampal functioning: Hippocampal Consolidation [94] and Multiple Trace Theory [95]. According to the Hippocampal Consolidation model, the hippocampus guides the formation of memory representations in the neocortex and serves only a time-limited role in memory retrieval. In contrast, Multiple Trace Theory posits that successful memory retrieval relies on the interaction between the hippocampus and neocortex, and the hippocampus is involved as long as the memory is available. Analysis of memories of different ages, such as the recognition of famous names from Recent and Remote time periods, presents the opportunity to test these competing theories. The Hippocampal Consolidation model would predict that hippocampal activation would be observed for Recent but not Remote names, and Multiple Trace Theory predicts that hippocampal activation would be seen in response to names from both time epochs.

Cognitively intact older adults completed the FNDT during event-related task-activated fMRI. Bilateral activation was observed in both the hippocampus and PHG during both Recent and Remote name recognition compared to Unfamiliar names, substantiating the participation of MTL structures during long-term recognition memory. However, a temporally graded retrieval pattern was observed in the right MTL, but not in the left MTL. That is, greater activation in both the right hippocampus and PHG was observed during recognition of Recent famous names relative to Remote famous names. No significant activation differences between Recent and Remote famous names were observed in the left MTL (Figure 1).

A subsequent report [61] utilizing the same imaging dataset examined patterns of *neocortical* activation associated with the recognition of Recent and Remote famous names. Both Recent and Remote names recruited an extensive bilateral pattern of cortical regions compared to Unfamiliar names, including regions in the frontal, temporal and parietal lobes. A temporally graded retrieval pattern was also observed in posterior cingulate cortex (PCC), with greater activation during Recent compared to Remote name recognition (Figure 2). The PCC has extensive connections to frontal cortex [96] as well as to the MTL [97–99], and it appears to play a major role in the neural circuitry involved in both episodic [100] and semantic [76] memory retrieval. Additionally, a number of studies have demonstrated hypometabolism, hypoperfusion, or decreased activation in the PCC in individuals with MCI [38, 101] or AD [102–104].

The findings of these two studies [61, 62] have implications regarding the relative contributions of MTL and cortical regions during memory retrieval. The MTL activation

associated with famous name recognition memory [62] primarily supported the Multiple Trace Theory [95] of hippocampal functioning, because greater hippocampal complex activity was observed during correct identification of both Recent and Remote famous names relative to the rejection of Unfamiliar names. However, evidence of temporally graded memory retrieval observed in the right MTL and PCC also provided some support for the Hippocampal Consolidation theory [94]. Because Remote famous names elicited less hippocampal activation than Recent names, this pattern suggests that older memories may be predominantly stored in neocortical rather than in hippocampal regions. A similar pattern of temporally graded activity in the MTL during famous *face* recognition has also been reported, with greater activation in response to recently learned faces being observed in the right entorhinal cortex [91]. However, evidence supporting the presence of a temporal gradient in the hippocampus during famous face recognition has been mixed, with one study observing no difference between recent and remote faces [89] and another showing greater activation in response to recent faces in right hippocampus only [91]. Despite these mixed findings associated with the temporal gradient, identification of famous faces and names appears to reliably engage both hippocampal and neocortical regions. Differences across studies in the definitions of recent and remote time epochs and the nature of the stimuli themselves (e.g. visual characteristics of face stimuli) could possibly account for the variability in findings. Robust evidence supporting evidence of hippocampal consolidation model has been demonstrated using episodic recognition of newly-learned photographs over a 3-month interval [105].

2.5 Face vs. name recognition

Differences in the activation pattern between famous names and famous faces noted across the studies described above prompted us to investigate whether there are common and/or unique neural network components subserving famous face and name recognition [106]. Using the stimuli described earlier [59, 93], young adult participants viewed famous and unfamiliar faces and names during task-activated fMRI. Although recognition performance exceeded 90% for all stimulus types, accuracy was significantly better for names than for faces. Collapsed across famous and unfamiliar stimuli, each presentation modality activated distinct regions, most notably bilateral fusiform and lateral occipital regions for faces relative to names and diffuse left neocortical regions for names relative to faces. However, when collapsed across stimulus type, there was a distinct pattern of overlapping neural activation for famous compared to unfamiliar stimuli. This “fame network” consisted of bilateral hippocampal regions in addition to regions in the left frontal, insular, temporal, and parietal lobes, and posterior cingulate. The presence of common regions between both famous face and name recognition suggests that these areas are involved with person identity semantic memory, regardless of presentation modality. The preceding studies were helpful in validating the FNDT for use in studying semantic memory processes associated with person-identity information and enabled us to investigate aspects of the cognitive neuroscience associated with fame recognition. The following sections will discuss the use of the FNDT and semantic memory activity in the study of normal and pathological aging.

3. Integrity of semantic processing as a biomarker

3.1 Age-related differences in semantic processing

Previous neuroimaging research has demonstrated that compared to younger adults, older adults typically display a more widespread pattern of fMRI activation with reduced hemispheric asymmetry [107, 108]. A potential explanation for these findings is that increased activation represents compensatory recruitment of additional resources to achieve equivalent cognitive performance, despite declining brain function. An alternative but not mutually exclusive hypothesis suggests that the specialization of neural regions decreases

with age, resulting in dedifferentiated, more diffuse patterns of activation. Using the FNDT, we have observed similar compensatory patterns of increased fMRI activity during semantic memory retrieval in older compared to younger adults [59].

Younger and older adult participants completed the FNDT during fMRI. In 15 out of 20 neocortical and MTL regions (including the right hippocampus), older adults exhibited a greater magnitude and spatial extent of activation than younger adults. Younger adults did not demonstrate greater activation than older participants in any region. The difference between groups was particularly large for Recent names, with greater activation observed for older adults in all 15 regions, whereas greater activation for Enduring names was observed in 7 out of the 15 regions. The selectively greater activation observed in older compared to younger adults provides evidence for compensatory recruitment during semantic memory retrieval, even though task accuracy was comparable to younger adults.

These findings stand somewhat in contrast to other studies of semantic processing and aging. One study [109] observed *reduced* activation in older compared to younger participants during a semantic word judgment task (concrete vs. abstract) in left prefrontal cortex, and older participants did not recruit additional regions compared to younger adults. Another study [110] reported that younger and older adults recruited mainly overlapping regions of neocortex during semantic word encoding (living vs. non-living), but a greater magnitude of activation in younger adults was observed in the left hippocampus. The authors of these studies argue that frontal and MTL regions subserving semantic encoding may be functionally deficient in older adults. Although compensatory recruitment was not observed in these studies, the hypothesized functional deficiencies may help to explain why additional regions appear to have been recruited in other fMRI studies assessing episodic memory [107] or the FNDT [59].

3.2 Evidence for compensatory recruitment associated with risk for AD

According to the Scaffolding Theory of Aging and Cognition (STAC; [108]), the recruitment of additional neural circuitry during task performance occurs to support structures with declining functional integrity. This additional recruitment may reflect an essential component of healthy, adaptive cognitive aging. For example, a study using PET [111] observed greater hemispheric asymmetry during an episodic memory task in older adults who performed well compared to those who did poorly on the task, suggesting that “scaffolding” is beneficial for maintaining late-life cognition. Another study [112] observed that increased prefrontal activity in AD patients was correlated with better performance on both episodic and semantic memory tasks. Such scaffolding may occur across the lifespan, although in older individuals this adaptation may be more common and necessary due to the accumulated deterioration of neural circuitry. The additional recruitment in response to task demands is reflected by increased regional brain activation.

Scaffolding has been observed in those at the greatest risk for late-life degenerative conditions, such as AD, prior to the onset of clinical symptoms. For example, one study [51] observed greater magnitude and spatial extent of activation during an episodic picture encoding task in older adults who were carriers of the APOE ε 4 allele compared to non-carriers, even though all participants were non-demented and had normal memory functioning. A similar compensatory response was observed in right hemisphere regions of older, non-demented APOE ε 4 carriers during a verbal episodic encoding task compared to non-carriers [113]. This risk-related scaffolding pattern has been observed to occur throughout middle age and late-life. In a cross-sectional study [56], right hippocampal activation during episodic encoding decreased with age in low risk participants (APOE ε 4 non-carriers without a first-degree family history of dementia). However, right hippocampal activation *increased* with age in APOE ε 4 carriers and those with a family history of

dementia, with the greatest increases observed in persons with both risk factors. Furthermore, greater bilateral hippocampal activation has been observed in young adult APOE ε 4 carriers compared to non-carriers during episodic picture encoding [57].

Not all studies examining the effects of the APOE ε 4 allele have observed increased recruitment. Some studies have observed a reduced signal in APOE ε 4 carriers [114, 115], whereas other studies reported no differences between groups [116, 117]. The nature of the effects may vary with the choice of task, stimuli, or region studied [53]. However, these studies of altered patterns of activation associated with risk factors for dementia are consistent with evidence that AD pathology may accumulate over decades prior to clinical onset [10, 11]. According to STAC, the compensatory recruitment pattern would imply that possession of these risk factors is associated with declining functional integrity despite equivalent task performance.

Limited research has examined the effects of risk on functional activation during semantic memory processing. One study [118] reported decreased activity in APOE ε 4 carriers compared to non-carriers during a word categorization paradigm relative to a baseline passive fixation condition, in regions in the anterior cingulate and left parietal lobe. However, a follow-up report from the same dataset [119] indicated that APOE ε4 carriers had reduced deactivation from baseline due to abnormalities in the default mode (or "resting state") network. Thus, the interpretation of the previous study [118] is tempered by the choice of passive fixation as a comparison condition. Using the FNDT, which uses active identification of unfamiliar names as a comparison condition for active recognition of famous names, we observed evidence of compensatory recruitment in asymptomatic older adults at-risk for AD during semantic memory processing [52].

Cognitively intact older adults were divided into three groups based on genetic risk for AD: APOE ε 4 carriers with a family history of dementia in a first degree relative (FH+ε4), APOE ε 4 non-carriers with a family history of dementia (FH), and control participants with neither risk factor (CON). During the FNDT, both at-risk groups demonstrated nearly completely independent regions of activation from the control group. Moreover, the control group displayed predominantly greater activation during the presentation of unfamiliar names, whereas the at-risk groups had a greater response to famous names. Overall, the FH +ε 4 had a greater volume of activation in response to famous relative to unfamiliar names than the FH group (Figure 3). The results of this study are consistent with the aforementioned studies that demonstrated the impact of risk factors for AD on the BOLD signal prior to the onset of cognitive symptoms. The additional neural recruitment observed during semantic memory retrieval in those at genetic risk for AD provides evidence supporting STAC and the declining integrity of neural resources in these individuals. Moreover, the impact of risk factors appeared to be additive, with the greatest functional recruitment being observed in individuals with both risk factors. These results could not be explained by differences in task performance or effort, as all groups exhibited equivalent accuracy and reaction times. Importantly, the striking differences in brain activation maps between persons with and without risk factors for AD highlighted the potential use of the FNDT as a method for assessing presymptomatic dementia risk. However, limitations of this and other studies of risk include that they are cross-sectional, and the altered activation patterns are not necessarily evidence of increased risk. Longitudinal studies are necessary to determine the predictive utility of fMRI (discussed in section *3.4*).

3.3 Altered activation in MCI patients

In addition to revealing early abnormalities in patterns of activation that may reflect AD risk in cognitively intact older adults, altered semantic memory processing has been reported in individuals with MCI. A diagnosis of MCI typically precedes AD, although not all cases

will progress to dementia [120]. MCI is characterized by deficits in both episodic and semantic memory systems[121, 122]. Several previous fMRI studies have observed differences in the BOLD signal associated with episodic memory processing between MCI patients and age-matched controls [123–127]. However, it should be noted that these studies used generally effortful episodic memory tasks, and in one study [127], MCI patients performed significantly worse than controls. While this discrepancy in performance was not universally observed in the aforementioned studies, it is nonetheless difficult to interpret between-group fMRI data when differences in motivation and cognitive performance are potential confounds [128]. The use of a low effort, high accuracy task provides advantages for the examination of MCI-related alterations to the BOLD signal, because all subjects can perform at high levels. One previous study [129] utilized a lexical decision task that MCI patients were able to perform with comparable accuracy relative to controls. The results revealed a differential pattern of activation between groups, including *hyper*activation in bilateral anterior cingulate cortex and *hypo*activation in bilateral fusiform and left occipitotemporal and inferior frontal regions in MCI patients relative to controls. Furthermore, there was no evidence of atrophy in these regions in the MCI patients. Another study [130] investigated fMRI activation during a semantic word association task and observed equivalent performance between MCI patients and controls. Compared to a size discrimination control condition, MCI patients displayed hypoactivation relative to controls in the posterior third of the lower bank of the superior temporal sulcus. The results of these studies suggest that patterns of fMRI activation can reliably identify abnormal functioning in neocortical regions and can be used to distinguish between MCI patients and cognitively intact older adults, even when task performance is comparable.

We demonstrated evidence of compensatory recruitment during semantic memory retrieval in MCI patients using the FNDT [60]. Older adults with MCI (according to Petersen criteria [131]) and cognitively intact controls with or without the APOE ε 4 allele (“high-risk” and “low-risk” groups, respectively) served as study participants. Importantly, the three groups did not differ on task performance. Consistent with our previous work [52], high-risk controls displayed greater activation than low-risk controls for famous relative to unfamiliar names in several MTL and neocortical regions. Interestingly, MCI patients displayed a similar compensatory response, with a greater extent and magnitude of activation across a number of brain regions compared to both high- and low-risk controls.

This study [60] demonstrated evidence for compensatory recruitment and/or scaffolding, which may reflect compensation for functional deficits in the neural networks subserving semantic memory in MCI patients. Importantly, these differences were observed when task performance was equivalent between groups. While semantic memory impairment is commonly associated with MCI [121, 122], our participants were still able to perform this relatively simple task at a high level of accuracy. Thus, activation associated with semantic processing of person-identity information can be used to identify abnormal patterns of activation in older individuals who have experienced cognitive impairment. Subsequent research from our group has focused on evaluating the FNDT for use as a *predictor* of cognitive decline in asymptomatic older adults.

3.4 Longitudinal prediction of cognitive decline

A limited number of longitudinal studies (see section *1.1*) have attempted to use patterns of fMRI activation to predict cognitive decline in cognitively intact older adults [46, 47, 49, 50]. In many of these studies, *greater* activation in left [46] or right [49] hemispheric regions or hippocampus [50] at baseline was indicative of an increased risk for subsequent decline. Other longitudinal studies [43, 44] have examined the value of task-activated fMRI for the prediction of the conversion from MCI to AD. In these studies, greater activation was again associated with a poorer prognosis, either when observed in the hippocampus during

episodic encoding [43] or in parietal regions during an angle discrimination task [44]. We recently reported contrasting findings from a longitudinal prediction study utilizing a *semantic* processing task [48].

Cognitively intact older adults were compared on neuropsychological testing, sMRI, and the FNDT during fMRI at baseline versus at 18-month follow-up. Participants were recruited from newspaper advertisements, and half were selected on the basis of a family history of dementia in a first-degree relative. Thus, our sample was enriched with a greater proportion of APOE ε4 carriers than in the general population, as this allele is more common in individuals with a family history of dementia [54, 132]. At follow-up, 34.6% of participants exhibited cognitive decline, defined as a performance deficit of at least one SD compared to the predicted value on one or more of three neuropsychological outcome measures (Mattis Dementia Rating Scale-2 [133–135], Rey Auditory Verbal Learning Test (AVLT) Sum of Trials 1–5 and AVLT Delayed Recall [136]). Given the relatively brief follow-up period, the purpose of this study was not to predict cognitive impairment or MCI status (only 7.4% of declining participants met Petersen criteria for MCI [131] after 18 months), but rather to predict a one SD or greater decline in performance that may represent the early phases of MCI or dementia. Although it is possible that other factors may have accounted for decline in some participants, the majority of participants who declined by one SD at follow-up continued to exhibit decline at five-year follow-up (unpublished data).

Stable and declining participants had equivalent FNDT performance at baseline. Notably, participants with greater fMRI activation at baseline were *less* likely to have exhibited cognitive decline at follow-up. Logistic regression analyses demonstrated that *lower* activation during the FNDT in cortical and hippocampal regions, *smaller* bilateral hippocampal volume (as determined by manually-traced sMRI), and presence of the APOE ε 4 allele were each independently associated with a *greater* risk of cognitive decline at 18-month follow-up (Figure 4). Thus, baseline semantic memory activation provided predictive information regarding future cognitive decline above and beyond genetic risk and hippocampal atrophy. Even though the reduced hippocampal activation in the declining group may have been due to atrophy, the activation still functioned as an independent predictor of decline. Consistent with our cross-sectional studies [52, 60], carriers of the APOE ε 4 allele displayed greater activation in response to famous relative to unfamiliar names at baseline than non-carriers. However, for both APOE ε 4 carriers and non-carriers, *greater* BOLD signal activation was associated with a *reduced* probability of decline.

These results appear to contradict previous longitudinal studies that used fMRI to predict cognitive decline [46, 50], where greater baseline activation was associated with a poorer prognosis. However, an important difference in our study was the use of a low effort, high accuracy semantic memory paradigm, as opposed to an episodic memory task. Our results are consistent with another longitudinal study that observed that greater activation in a left parietal region during semantic word classification was associated with a reduced incidence of future cognitive decline [47]. Because episodic tasks are cognitively demanding, greater activation in declining participants could reflect the additional cognitive effort necessary to complete the tasks. This additional exertion could be the product of declining functional integrity in neural resources, hence the greater probability of subsequent cognitive decline. In contrast, greater fMRI activation during semantic processing tasks could represent a healthy, adaptive response to combat declining neural resources that is protective against future degeneration, consistent with STAC [108].

Recently, we reported advantages of semantic processing tasks over episodic memory tasks for the prediction of cognitive decline [137], which may have important implications for the use of fMRI as a clinical biomarker for cognitive decline and dementia. The participants

from our longitudinal study [48] completed an episodic memory task at baseline after the semantic task, during which they were required to discriminate between names presented during the semantic trial and novel famous and unfamiliar names. Accuracy was equivalent between cognitively stable and declining participants for all stimulus conditions, although accuracy was much poorer for the episodic task.

A principal components analysis revealed a network of subcortical, parietal/temporal, and frontal activation associated with identification of previously seen relative to novel names. Logistic regression analyses revealed that only increased subcortical activation (including bilateral caudate and thalamus) was associated with a higher predicted probability of decline. However, the predictive utility of the episodic memory-induced fMRI regional activation components was inferior to the regional activation induced by the FNDT. The semantic task's enhanced sensitivity to probability of future decline may be due in part to the overlap between the semantic memory and default mode networks [76].

In a recent meta-analysis of fMRI studies using semantic processing tasks [76], a left-lateralized network was identified as being crucial to semantic retrieval. This network included seven regions – posterior inferior parietal lobe, middle temporal gyrus, fusiform and parahippocampal gyri, dorsomedial prefrontal cortex, inferior frontal gyrus, ventromedial prefrontal cortex, and posterior cingulate gyrus. We have observed activation in all of these regions when contrasting famous relative to unfamiliar name recognition with the FNDT [61]. Additionally, this meta-analysis suggested that these regions appear to overlap with areas commonly associated with the default mode, or "resting state" network [76]. This network typically displays deactivation during task engagement in healthy controls, and reduced task-activated inhibition of the default mode network has been observed in older compared to younger adults [138], as well as in MCI and AD patients compared to age-matched controls [138, 139]. Furthermore, reductions in default mode deactivation have been observed in asymptomatic APOE ε 4 carriers compared to non-carriers [57] and have been associated with an increased risk for the conversion from MCI to AD [45]. One group [77] noted that regions commonly associated with the default mode network parallel the regional distribution of amyloid-beta plaques that are common in the early phases of AD, and they postulated that the continuous activity of these regions throughout life may increase the susceptibility to this late-life pathology. This "Metabolism Hypothesis" would imply that overuse of these regions confers a greater risk for AD pathology. Given the overlap between the semantic memory and default mode networks [76], this assertion may help to explain why semantic memory tasks are sensitive to AD risk and likelihood of cognitive decline.

3.5 Associations with physical activity

Our review of the literature suggests that task-activated fMRI provides predictive information concerning cognitive decline in asymptomatic older adults. Various other biomarkers [16] and lifestyle behaviors [3] have been identified as risk factors for cognitive decline and AD. Thus, the most effective combination for prediction models may consist of fMRI combined with other variables. One area of research has investigated the influence of physical activity (PA), which has been identified as a possible protective factor involved in maintaining late-life cognitive functioning [5]. Although the specific neural mechanisms by which PA might confer resistance to decline are still largely unknown, some candidates have emerged. Exercise interventions (such as wheel running) in rodents increase levels of brain-derived neurotrophic factor (BDNF), which, in turn, promotes synaptogenesis, neurogenesis, and plasticity [140–144].

Recently, PA has been demonstrated to increase brain tissue volume in older humans, potentially as a result of exercise-mediated neurogenesis [145]. Physically inactive elderly

adults were randomly assigned to aerobic exercise (walking) or stretching (control) conditions. At six-month and one-year follow-up, bilateral hippocampal volume as measured by sMRI increased in the aerobic exercise group, whereas hippocampal volume decreased in the stretching group. The greatest differences were observed in bilateral anterior hippocampus, which contains the dentate gyrus, a site of adult neurogenesis [140]. Moreover, elevations in serum BDNF compared to baseline were associated with greater volume increases in bilateral anterior hippocampus, substantiating the role of neurogenesis as a potential mechanism by which PA may delay AD-related neuropathology and hippocampal atrophy. Additionally, the aerobic exercise group displayed an improvement in spatial memory abilities compared to control participants.

We recently observed fMRI evidence of the protective effects of PA on brain functioning [63]. Using a previously validated measure of PA for older adults (the Stanford Brief Activities Survey; [146, 147]), we separated cognitively intact older adults into four groups: Low Risk/Low PA, Low Risk/High PA, High Risk/Low PA, and High Risk/High PA. Risk was defined as the presence or absence of the APOE ε 4 allele. Consistent with our previous research [48, 52, 60], High Risk participants displayed a greater extent and magnitude of activation compared to Low Risk individuals during the FNDT. Interestingly, High PA participants displayed greater semantic memory activation than Low PA in several frontal and temporal regions. Furthermore, an interaction between risk and PA indicated that the elevated activation associated with engagement in PA was greater for High Risk than Low Risk participants. Interaction effects (defined as a familywise error threshold of $p < .01$) were observed in predominately left hemisphere neocortical regions (Figure 5). Combined with our previous longitudinal study [48], these findings imply that High PA participants may be at reduced risk for cognitive decline, with the beneficial effects of PA being potentiated in those at genetic risk for dementia.

A follow-up study [148] supported the prognostic implications of the relationship between PA and the BOLD signal. PA was added as a variable to the 18-month prediction models developed from the participants from our longitudinal study [48]. In a model including hippocampal activation, APOE ε 4 allele status, PA, and the interaction between APOE and PA, PA alone was not a significant predictor of cognitive decline, but the interaction effect was significant. This result indicated that PA can provide information regarding prognosis for cognitive decline beyond genetic and fMRI variables alone. Analysis of the simple effects revealed that the protective effects of PA in reducing the probability of cognitive decline were limited to APOE ε 4 carriers, in concordance with the results of our previous study [63]. Moreover, in APOE ε 4 carriers, the effects of PA were non-significant in participants with below average (in our sample) hippocampal volume or semantic memory activation, suggesting that PA may be more beneficial for older adults with strong hippocampal integrity. Thus, information concerning leisure engagement in PA may enhance prediction of cognitive decline over fMRI, sMRI, and genetic variables alone, and optimal prediction may include the assessment of several factors.

The enhanced protective effects of PA for APOE ε 4 carriers compared to non-carriers have been reported in other studies as well [149–151], although one notable study found the opposite interaction. In that longitudinal study, greater engagement in PA was associated with a reduced risk for dementia in APOE ε 4 *non*-carriers only [152]. Further research is necessary to determine the exact nature of this interaction, but at present, our results suggest that the potential of PA as a late-life intervention to delay or prevent cognitive decline may be limited (or at least maximally beneficial) to those at genetic risk for AD.

A recent report by our group also suggests that PA may be protective against further cognitive decline in amnestic MCI patients [64]. Nine Low PA and nine High PA MCI

patients, matched on demographic variables, completed the FNDT. Greater activation for famous relative to unfamiliar names was observed in High PA compared to Low PA participants in the left caudate nucleus. Reductions in caudate volume have been associated with MCI and an increased risk for conversion to AD [153, 154]. These results suggest that PA may assist in preserving caudate integrity and may reduce the risk of conversion to AD, even though no group differences were observed in caudate volume in our sample. A longitudinal follow-up is necessary to assess the validity of this postulation. A limitation of this study and the other PA studies by our group [63, 148] is that our measure of PA [146, 147] is based on self-report, and the studies are purely observational in nature. Controlled intervention studies are necessary to validate the protective value of PA for the late-life maintenance of cognitive functioning.

4. Summary and future directions

4.1 Semantic memory probes as a clinical biomarker

The use of a low effort, high accuracy task that recruits a semantic memory network during task-activated fMRI may be beneficial for studying healthy and degenerative aging processes. The FNDT can be used to study activation attributable to memories of different ages and can reveal the involvement of MTL structures during memory retrieval of recent and remote material. Semantic processing paradigms have also successfully demonstrated evidence of compensatory recruitment and/or cognitive scaffolding in older compared to younger adults [59], amnestic MCI patients [60], and those at the greatest risk for AD [52]. Eighteen-month follow-up suggests that *greater* functional activation during the FNDT in cortical and hippocampal brain regions is associated with a *reduced* probability of cognitive decline [48]. This finding suggests that cognitive scaffolding [108] may be a protective adaptation to combat the declining functional integrity of neural resources that occurs with normal and pathological aging. There are also indications from this work that fMRI activation during semantic processing tasks may be advantageous over episodic memory paradigms for identifying individuals who are at the greatest risk of cognitive decline [137]. The most effective model for prediction of cognitive decline consisted of fMRI activation during semantic memory processing in cortical and hippocampal regions and APOE allele status [48]. Reduced baseline hippocampal volume was also related to cognitive decline in a separate model. Last, we reported that engagement in PA was associated with greater task-induced fMRI semantic memory activation [63], which may confer resistance to cognitive decline. However, these benefits may be limited to or enhanced in APOE ε 4 carriers [148]. PA was also associated with greater functional activity in the left caudate in MCI patients [64], which may indicate preservation of caudate functioning and possibly a reduced risk for conversion from MCI to AD.. These studies, combined with research from other groups, suggest that the use of semantic processing tasks during fMRI may be a promising presymptomatic biomarker of future cognitive decline. Optimal use of such a task may require integration with other relevant variables, such as sMRI measures, APOE genotyping, assessment of habitual or lifetime PA, or other biomarkers of AD [16].

4.2 Future longitudinal prediction

The prediction models derived from our longitudinal cohort [48, 148] were based on baseline and 18-month follow-up neuropsychological assessments. This timeframe may be somewhat brief for detecting clinically significant cognitive impairment; indeed, only two of our declining participants met Petersen criteria for MCI [131]. We are now completing neuropsychological follow-up for our original participants five years after baseline. Analysis of these longer-term data will enable us to develop more powerful models using baseline task-activated fMRI to predict cognitive decline more accurately. The utilization of three time points will also permit the development of prediction models for assessing multiple

trajectories of cognitive decline. For example, if a participant was cognitively stable at 18-month follow-up but demonstrated decline after five years, is this pattern detectable at baseline? Likewise, if a participant declines from baseline to 18 months but does not decline further at five years, can this pattern be predicted from baseline data? Additional follow-up intervals may eventually permit further refinement of a prediction model of the risk for AD in cognitively intact, asymptomatic older adults using fMRI activation during semantic memory processing tasks.

Other variables associated with the risk for developing AD can be added to our sMRI, fMRI, and genotype models to further optimize prediction. Thus, we can determine whether our identified predictors contain independent or overlapping information pertaining to risk for cognitive decline. Recently, we reported that self-report measures of PA (but not self-reported participation in cognitively stimulating activities) can enhance prediction of cognitive decline [148]. An upcoming project involves the addition of blood plasma levels of homocysteine, folate, and vitamin B12 to our prediction model. All three measures have been implicated in risk for developing dementia [155, 156].

4.3 Issues with the clinical adaptation of fMRI for the assessment of risk

We have proposed that fMRI in conjunction with other markers of AD risk may be a valuable model for preclinical prediction of future cognitive decline. However, several methodological issues associated with fMRI may limit its clinical utility. First and foremost, between-site standardization may be the largest hindrance preventing the development of normative data for widespread usage [157]. It has been demonstrated that when an individual is scanned with the same paradigm at multiple sites, there is substantial fluctuation in the spatial extent of the obtained BOLD signal [158]. Factors that contribute to this variability include magnet manufacturer, the method for sampling image information, the software used to construct the image, the type of paradigm used, and perhaps most importantly, magnet strength [157]. High field strength (i.e. 3.0 Tesla or greater) appears to yield the best between-site reproducibility [158].

Furthermore, the image processing time necessary for functional data can contribute to additional expense. Given that the maximally effective prediction model would include other relevant (and perhaps costly) variables such as APOE genotyping, blood serum measurements, and sMRI volumetrics, the total price tag of such a procedure may limit accessibility. Patient motivation in the scanner may also be a relevant factor that can influence the BOLD signal and/or behavioral performance and reduce within-subject reliability. The presence of medical conditions such as hypertension, diabetes, or hyperlipidemia (as well as medications associated with these conditions) may also influence activation patterns and further complicate the establishment of usable norms [157, 159]. Dietary intake of common substances such as caffeine [160–162] and nicotine [163–165], or the presence of psychological comorbidities such as depression [166, 167], anxiety disorders [168–170], or psychosis [171, 172] also need to be accounted for when interpreting fMRI data. Thus, while research studies have been successful in demonstrating fMRI's ability to assist in the prediction of cognitive decline, the adaptation to clinical settings may require rigorous standardization.

4.4 Conclusion

Targeted intervention towards those at greatest risk is currently the most promising strategy for anticipating and minimizing the burden of AD. Great advances have been made in identifying lifestyle behaviors, biological measurements, and neuroimaging biomarkers that are associated with risk for dementia. Task-activated fMRI during semantic memory processing may be a promising biomarker of future cognitive decline. The FNDT can be

completed even by individuals with MCI, and task performance generally remains high [60]. Semantic memory processing tasks, in conjunction with other risk factors or biomarkers, may provide a sensitive and comprehensive estimate of an individual's risk for late-life cognitive decline and dementia. Further longitudinal research will produce additional preclinical prediction strategies that can make the most effective use of emerging intervention strategies for AD.

Highlights

1. Person identity presents an opportunity to study semantic memories of different ages
2. Semantic processing tasks may function as an fMRI biomarker for cognitive decline
3. Semantic tasks present advantages over episodic tasks for studying aging and AD risk
4. Optimal prediction of risk may include a combination of variables

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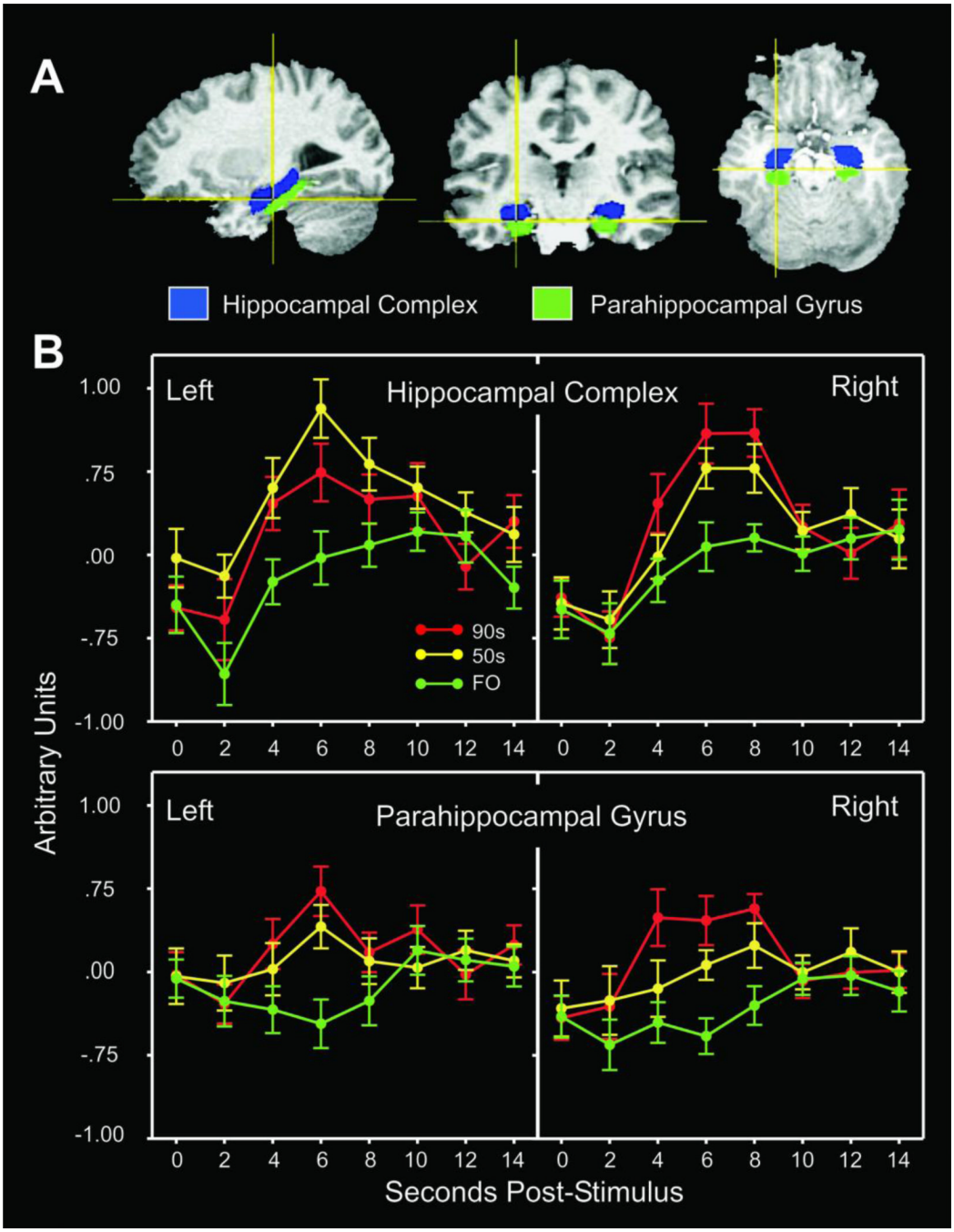

Figure 1.
From reference [62]. Temporally graded MTL activation during the FNDT. (A) Anatomical maps of MTL structures for a typical cognitively intact older participant. (B) Hemodynamic response functions for recent (90s) and remote (50s) famous names and foils (FO). Note the temporal gradient present in the right MTL structures. Area under the curve (AUC) analyses between four and eight seconds post stimulus onset revealed greater activation for recent compared to remote famous names in both the right hippocampal complex and parahippocampal gyrus. Error bars reflect the standard error of the mean. Figure reproduced with permission.

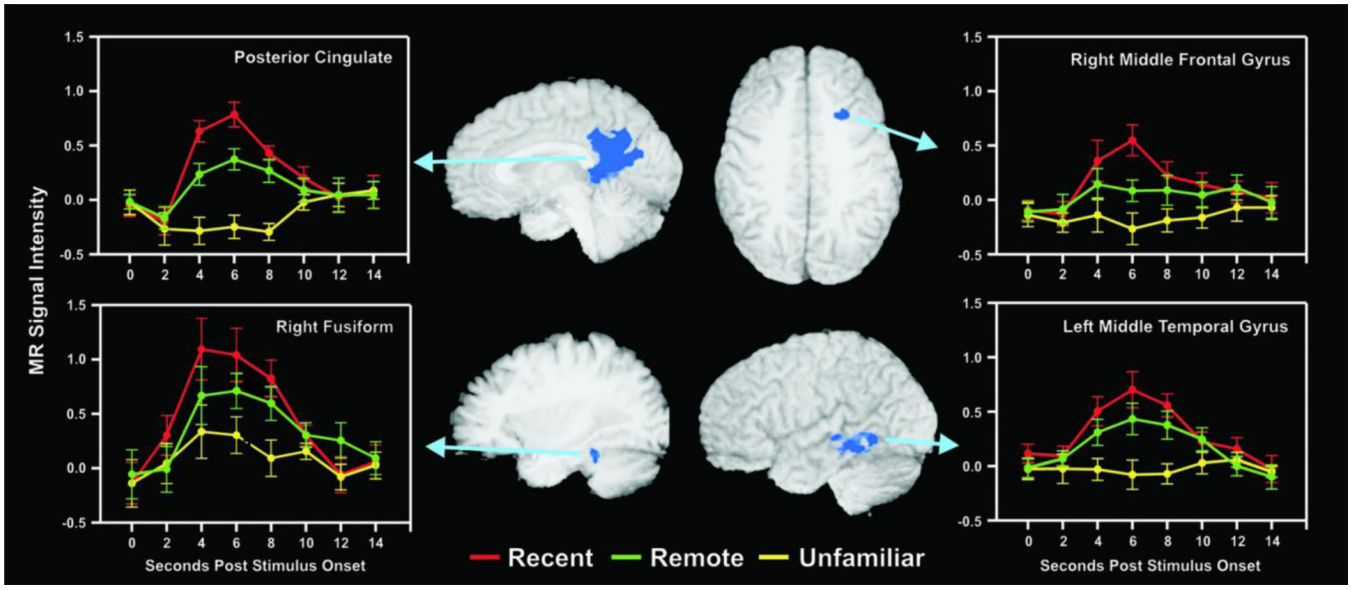

Figure 2.

From reference [61]. Temporally graded neocortical activation during the FNDT. Four regions that demonstrated evidence of a temporally graded response to names from different time epochs are depicted with anatomical localization and full time-course, group-averaged hemodynamic response functions (HRFs). Significant time epoch differences were identified using estimates of the hemodynamic response (AUC for 4–8 sec poststimulus). Error bars reflect the standard error of measurement at each time point. Figure reproduced with permission.

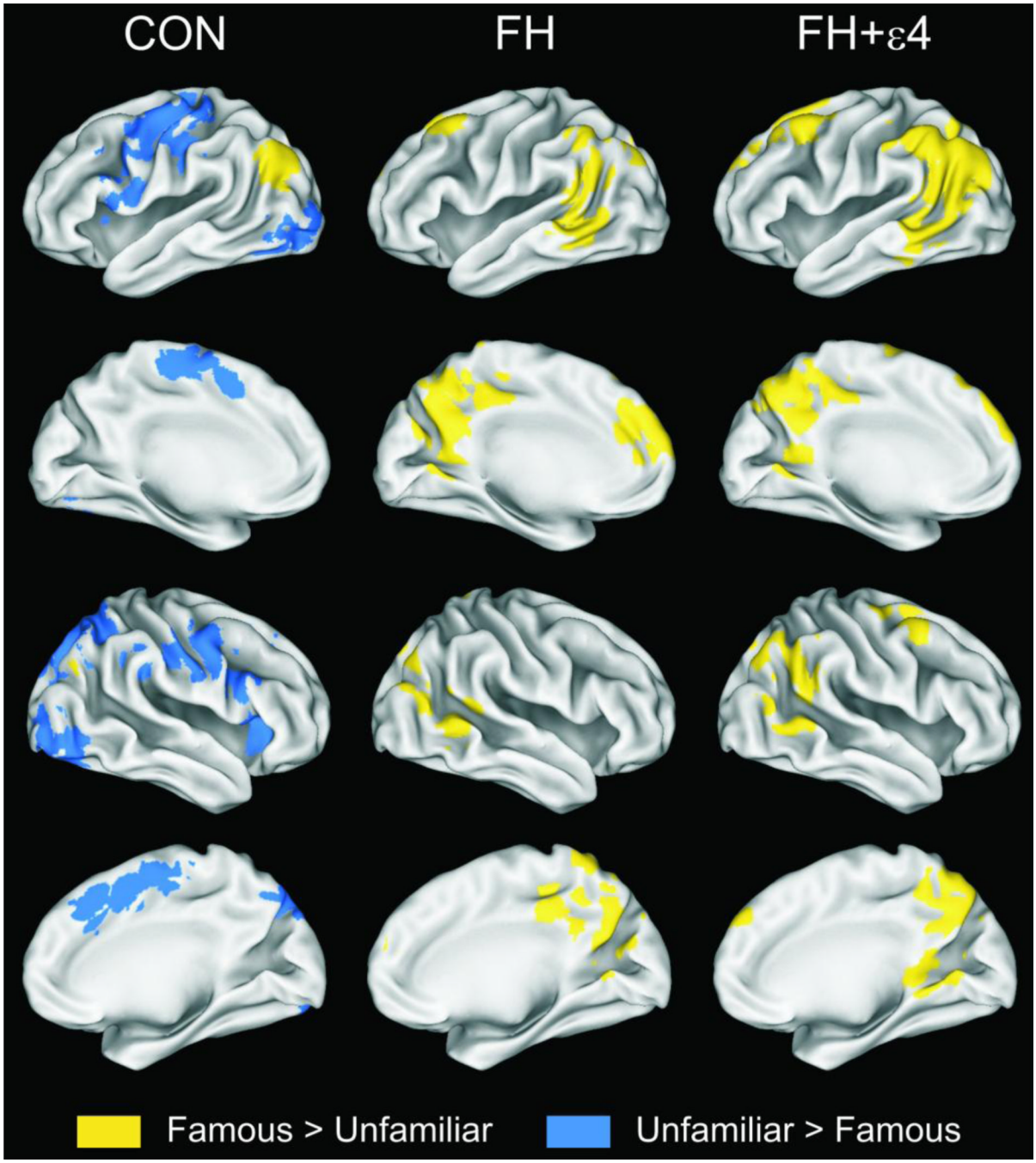

Figure 3.
From reference [52]. Effects of risk factors for AD on the functional memory recruitment during famous compared to unfamiliar names. Note the greater activation for unfamiliar names in control (CON) participants and the opposite patterns in the at-risk groups (FH and FH+ε4). Also note the dose-dependent effects of risk factors on recruitment, with the greatest activation observed in the FH+ε4 group. Figure reproduced with permission.

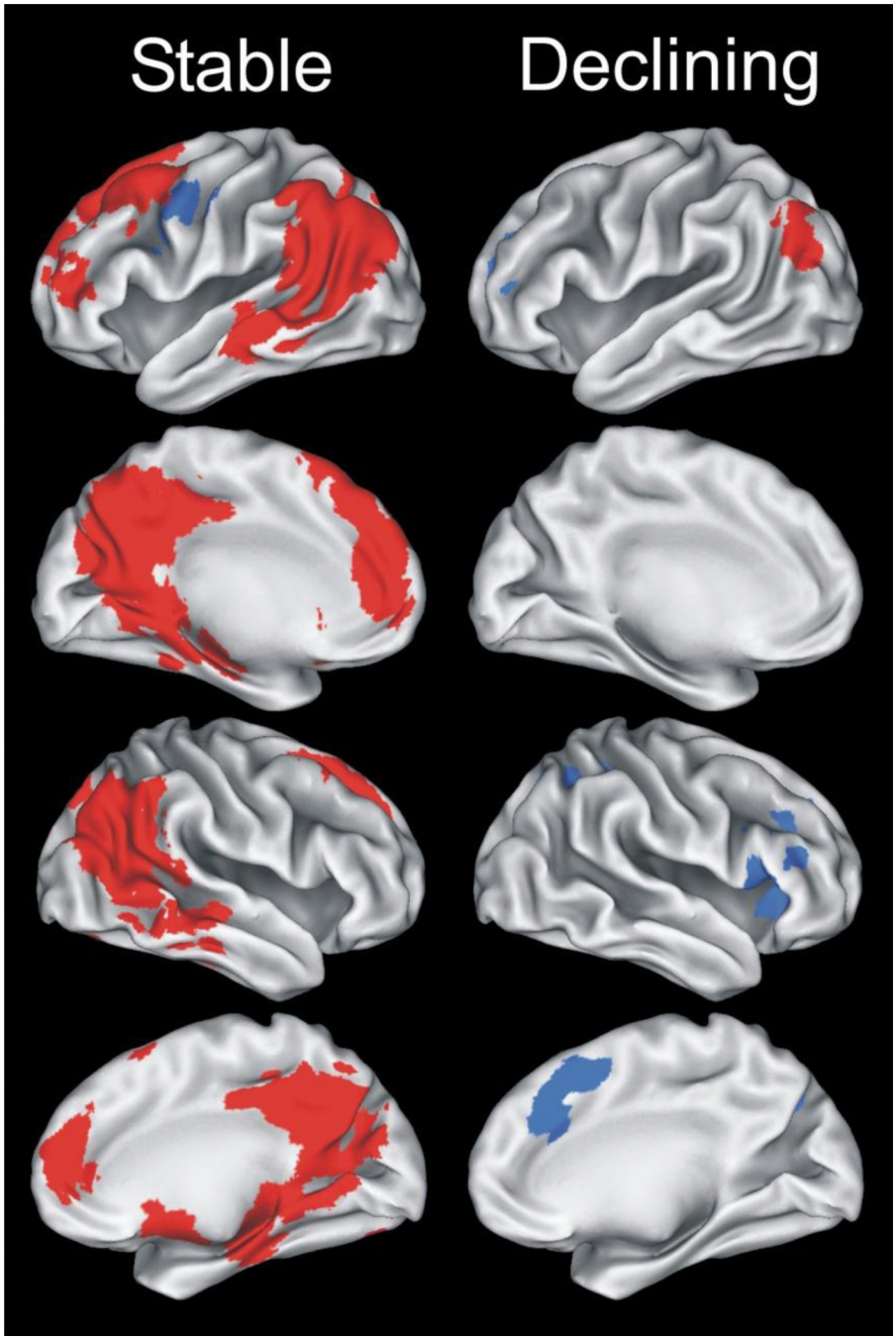

Figure 4.
From reference [48]. Baseline fMRI activation used in the prediction model of cognitive decline, highlighting group differences in activation derived from the comparison of the famous and unfamiliar names conditions: Famous > Unfamiliar is in red, Unfamiliar > Famous in blue. Note the greater spatial extent of activation in the Famous > Unfamiliar names comparison in the Stable compared to the Declining group. Figure reproduced with permission.

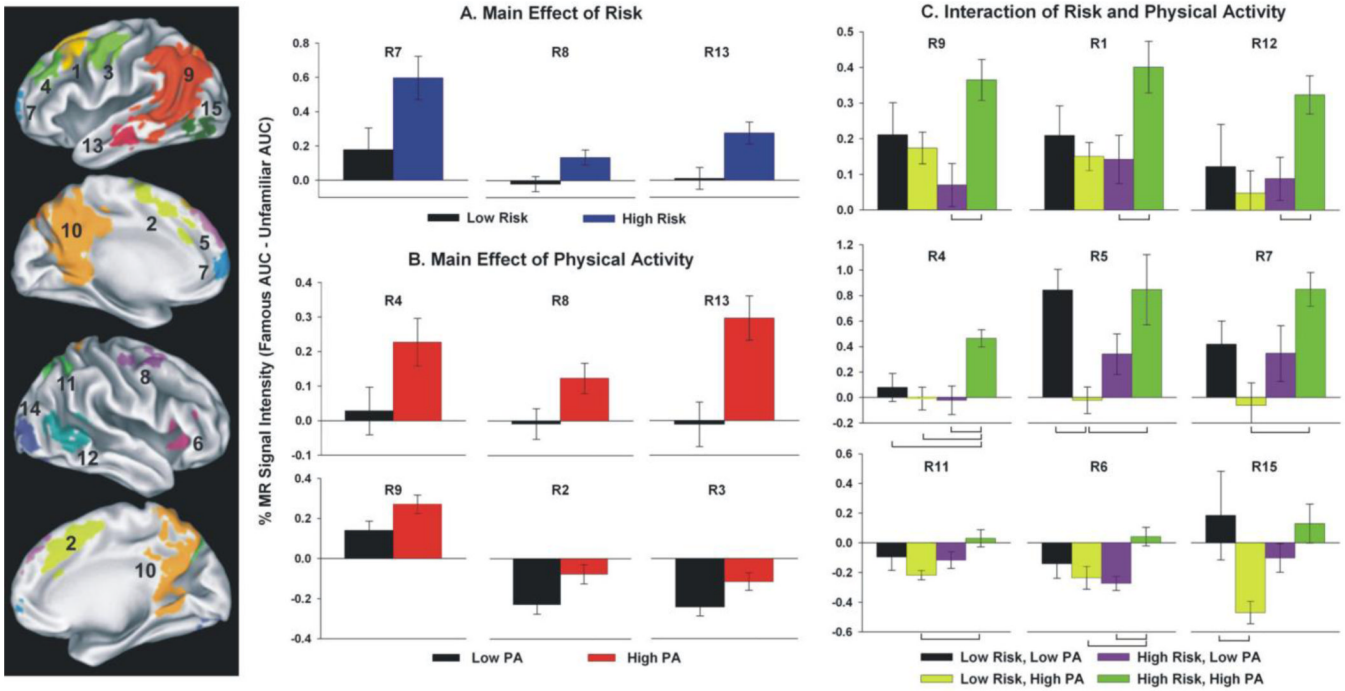

Figure 5.

From reference [63]. Effects of physical activity (PA) and risk for AD (APOE ε4 allele) on functional recruitment in cognitively intact older adults. 15 functional regions of interest are identified in the left panel with region numbers (R#). Bar graphs represent mean percent MR signal intensity change for Famous > Unfamiliar name contrasts, for the main effects of PA (panel A) and Risk (panel B) and the interaction effect of PA × Risk (panel C). Post-hoc group differences are indicated by brackets in panel C ($p < .001$). Error bars reflect the standard error of the mean. Figure reproduced with permission.