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Task-evoked fMRI changes in attention networks are associated with preclinical Alzheimer's disease biomarkers

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ABSTRACT

There is a growing emphasis on examining preclinical levels of Alzheimer's disease (AD)–related pathology in the absence of cognitive impairment. Previous work examining biomarkers has focused almost exclusively on memory, although there is mounting evidence that attention also declines early in disease progression. In the current experiment, 2 attentional control tasks were used to examine alterations in task-evoked functional magnetic resonance imaging data related to biomarkers of AD pathology. Seventy-one cognitively normal individuals (females = 44, mean age = 63.5 years) performed 2 attention-demanding cognitive tasks in a design that modeled both trial- and task-level functional magnetic resonance imaging changes. Biomarkers included amyloid β_{42}, tau, and phosphorylated tau measured from cerebrospinal fluid and positron emission tomography measures of amyloid deposition. Both tasks elicited widespread patterns of activation and deactivation associated with large task-level manipulations of attention. Importantly, results from both tasks indicated that higher levels of tau and phosphorylated tau pathologies were associated with block-level overactivations of attentional control areas. This suggests early alteration in attentional control with rising levels of AD pathology.

1. Introduction

Alzheimer's disease (AD) is not a static disorder; there is accumulating evidence that pathologic processes begin up to 20 years before symptomatic stages (Bateman et al., 2012; Benzinger et al., 2013; Jack et al., 2013). Elevated amyloid β (Aβ) deposition in the brain is linked to a rise in hyperphosphorylated forms of tau in neuropil threads and neurofibrillary tangles (Hardy and Higgins, 1992). Aggregated tau leads to neuronal dysfunction and death that manifest in vivo as hypometabolism, atrophy, functional abnormalities, and progressive cognitive impairment (Bateman et al., 2012; Jack et al., 2013). The early detection of structural or functional changes in the absence of significant cognitive impairment provides candidate biomarkers and therapeutic targets.

In previous work in the literature, at-risk populations have been identified using genetic markers, such as the ε4 allele of the apolipoprotein E (*APOE*) gene, or high levels of amyloid deposition as evidenced by positron emission tomography (PET). Most functional magnetic resonance imaging (fMRI) studies examining such populations have used variations of memory encoding tasks (Bondi et al., 2005; Bookheimer et al., 2000; Dennis et al., 2010; Filbey et al., 2010; Han et al., 2007; Mormino et al., 2012; Trivedi et al., 2006). Although failing episodic memory is a hallmark of AD, the disorder is also characterized by attentional impairments (Balota and Faust, 2001; Bäckman et al., 2005; Perry and Hodges, 1999). Attentional control discriminates healthy individuals from those with dementia (Bäckman et al., 2005; Hutchison et al., 2010), predicts progression to dementia in a healthy sample (Balota et al., 2010), and from mild to more severe cognitive impairment (Albert et al., 2001; Sarazin et al., 2007). Early memory deficits in AD may in

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part be because of an inability to properly allocate attention, rather than pure declines of memory subsystems (Balota and Faust, 2001; Hutchison et al., 2010). The putative relationship between attention and memory is well established in the literature (e.g., Craik and Lockhart, 1972; Jacoby, 1991).

Cholinesterase inhibitors that are used to treat early symptoms of AD prevent the breakdown of acetylcholine (Birks, 2006; Kaduszkiewicz et al., 2005), which is a neurotransmitter heavily implicated in attentional control (Himmelheber et al., 2000; Sahakian et al., 1989; Sarter and Bruno, 1997). The basal forebrain cholinergic system projects to higher cortical areas including anterior cingulate, frontal, and parietal cortices (Selden et al., 1998). These 3 regions have been repeatedly implicated in neuroimaging studies of attention (Corbetta and Shulman, 2002; Coull and Nobre, 1998; Pardo et al., 1991; Wager et al., 2004). If attentional control is altered in preclinical AD, functional activity in these regions should be sensitive to rising levels of AD pathology.

To better understand the effects of increasing levels of AD pathology in clinically normal populations, we used 2 well-studied task-evoked fMRI paradigms (animacy judgments and Stroop) to examine cognitively normal adults with varying levels of pathology. Sustained attention was manipulated through the alteration between short rest blocks and long task blocks. An event-related design within each block allowed for the examination of trial-specific effects. Biomarkers were quantified using ^{11}[C]Pittsburgh Compound B (PiB)-PET and cerebrospinal fluid (CSF) assays. Focusing on the attentional control, and including CSF biomarkers, in a task-evoked design provides a novel approach to examine the early influence of AD pathology.

2. Methods

2.1. Study population

Participants were part of the Adult Children Study at the Knight Alzheimer's Disease Research Center at Washington University in St Louis. The Adult Children Study is an ongoing project designed to look at cognitively normal individuals with an elevated risk of developing AD. Participants underwent a clinical assessment, neuropsychological assessment, PiB-PET imaging, lumbar puncture (LP), structural MRI, and a functional MRI session. Participants were right handed and cognitively normal (Clinical Dementia Rating [CDR] = 0) (Morris, 1993). An initial sample of 92 participants was screened down to 79 by excluding individuals with neurologic damage (e.g., stroke and traumatic brain injury, $n = 5$), a lag between biomarker and MR acquisition ($n = 5$) >3 standard deviation from the initial group mean, or a biomarker values ($n = 3$) >3 standard deviation from the initial group mean. After screening for motion and abnormal behavior (see details subsequently), the final cohort consisted of 71 individuals. In this final group, the mean lag between functional MRI and biomarker assessment was 39 (median, 0; range, 0–415) days for PET and 473 (median, 161; range, 1–2227) days for LPs. Population demographics are presented in Table 1.

2.2. CSF samples

CSF (20–30 mL) was collected by LP after overnight fasting (Fagan et al., 2006). Total tau, phosphorylated tau 181 ($ptau_{181}$), and $A\beta_{42}$ were measured using enzyme-linked immunosorbent assay (ELISA) (INNOTEST; Fujirebio, formerly Innogenetics, Ghent, Belgium). The cohort had a mean $A\beta_{42}$ of 770.4 (median, 779.0; range, 285.3–1360.5) pg/mL, mean tau of 250.4 (median, 225.7; range, 100–588.3) pg/mL, and mean $ptau_{181}$ of 53.5 (median, 48.5; range, 24.8–127.2) pg/mL. For descriptive purposes, the percent of the population that would be deemed biomarker positive using previous published cutoffs of <459 pg/mL for $A\beta_{42}$, 339 pg/mL for tau, and >67 pg/mL for ptau (Vos et al., 2013) is presented in Table 1. Because the distribution of biomarker values had both high levels of skewness and kurtosis, all analyses of CSF values were log transformed to provide a more normal distribution.

Table 1
Demographics of the study cohort

Demographics	Mean	Median	Range	Abnormal (%)
Age (y)	63.5	63	49–78	
Education (y)	15.5	16	12–20	
MMSE	29.5	30	26–30	
$A\beta_{42}$ (pg/mL)	770.4	779.0	285.3–1360.5	15.5
Tau (pg/mL)	250.4	225.7	100.0–588.3	21.1
$Ptau_{181}$ (pg/mL)	53.5	48.5	24.8–127.2	16.9
CSF lag (d)	474	161	1–2227	
MCBP	0.29	0.13	0.02–1.32	25.4
PET lag (d)	39	0	0–415	

$n = 71$, female = 44 (62%), *APOE* $\varepsilon4 = 22$ (31%).
Key: Aβ, amyloid β; CSF, cerebrospinal fluid; lag, days between magnetic resonance imaging and biomarker assessment; MCBP, ^{11}[C]Pittsburgh Compound B mean cortical binding potential; MMSE, Mini Mental State Examination; PET, positron emission tomography; ptau, phosphorylated tau.

2.3. PET imaging

Methods have been described in detail elsewhere (Su et al., 2013). Participants underwent a 60-minute dynamic scan with PiB. In each region, a tissue mask (gray, white, and CSF) was generated based on the FreeSurfer segmentation (Fischl, 2004) (http://freesurfer.net/). A CSF dilution factor was calculated for each region, and the raw time-activity curve for that region was corrected by this dilution factor before its binding potential was calculated. From the dynamic scan, binding potentials were calculated using Logan graphical analysis and a cerebellar reference region. An average across both left and right lateral orbitofrontal, inferior parietal, precuneus, rostral middle frontal, superior frontal, superior temporal, and middle temporal regions derived from FreeSurfer was used to create a mean cortical binding potential (MCBP), with a mean value of 0.29 (median, 0.13; range, 0.02–1.32). Using a previously published approach using a receiver-operator curve (Vos et al., 2013), amyloid positivity was determined by comparing a large population ($n = 212$) of cognitive normal individuals against a population of mildly demented (CDR = 0.5, $n = 140$) with a confirmed diagnosis of dementia of the Alzheimer type. Using this approach, positivity was determined as an MCBP >0.23. For descriptive purposes, the percent of the population that would be deemed biomarker positive is presented in Table 1. As with the CSF biomarkers, analyses values were log transformed to yield a more normal distribution.

2.4. Task designs

The task design is depicted in Fig. 1. Participants had brief practice with the tasks immediately before scanning. In the scanner, participants performed 2 runs of an animacy judgment task followed by 2 runs of a Stroop task (Stroop, 1935). The 4 runs took a total of 39 minutes and 52 seconds. Both tasks were constructed with similar properties. During each run, tasks alternated between 30 seconds of rest and longer task blocks (114 seconds in the animacy task and 110 seconds in the Stroop task). During rest intervals, participants saw a red fixation cross; during task blocks, stimuli were presented above a white fixation cross. Within each run, there were 5 rest and 4 task blocks. Each task block consisted of 24 trials equally distributed across trial