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Flexible modulation of network connectivity related to cognition in Alzheimer's disease

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ABSTRACT

Functional neuroimaging tools, such as fMRI methods, may elucidate the neural correlates of clinical, behavioral, and cognitive performance. Most functional imaging studies focus on regional task-related activity or resting state connectivity rather than how changes in functional connectivity across conditions and tasks are related to cognitive and behavioral performance. To investigate the promise of characterizing context-dependent connectivity–behavior relationships, this study applies the method of generalized psychophysiological interactions (gPPI) to assess the patterns of associative-memory-related fMRI hippocampal functional connectivity in Alzheimer's disease (AD) associated with performance on memory and other cognitively demanding neuropsychological tests and clinical measures. Twenty-four subjects with mild AD dementia (ages 54–82, nine females) participated in a face-name paired-associate encoding memory study. Generalized PPI analysis was used to estimate the connectivity between the hippocampus and the whole brain during encoding. The difference in hippocampal–whole brain connectivity between encoding novel and encoding repeated face–name pairs was used in multiple-regression analyses as an independent predictor for 10 behavioral, neuropsychological and clinical tests. The analysis revealed connectivity–behavior relationships that were distributed, dynamically overlapping, and task-specific within and across intrinsic networks; hippocampal–whole brain connectivity–behavior relationships were not isolated to single networks, but spanned multiple brain networks. Importantly, these spatially distributed performance patterns were unique for each measure. In general, out-of-network behavioral associations with encoding novel greater than repeated face–name pairs hippocampal-connectivity were observed in the default-mode network, while correlations with encoding repeated greater than novel face–name pairs hippocampal-connectivity were observed in the executive control network ($p < 0.05$, cluster corrected). Psychophysiological interactions revealed significantly more extensive and robust associations between paired-associate encoding task-dependent hippocampal–whole brain connectivity and performance on memory and behavioral/clinical measures than previously revealed by standard activity–behavior analysis. Compared to resting state and task-activation methods, gPPI analyses may be more sensitive to reveal additional complementary information regarding subtle within- and between-network relations. The patterns of robust correlations between hippocampal–whole brain connectivity and behavioral measures identified here suggest that there are 'coordinated states' in the brain; that the dynamic range of these states is related to behavior and cognition; and that these states can be observed and quantified, even in individuals with mild AD.

Introduction

The use of fMRI methods to reveal relationships between behavior and cognitive function, whether in cognitively normal individuals or in patients with cognitive impairments due to conditions such as Alzheimer's disease (AD), can be divided into three key areas: resting connectivity (Balthazar et al., 2014; Biswal et al., 1995; Damoiseaux et al., 2012; Fox et al., 2006; Kelly et al., 2008; Li et al., 2013; Sala-Llonch et al., 2012; Shehzad et al., 2014), evoked task-related activity (Atri et al., 2011; DeYoe et al., 1994; Diamond et al., 2007; Dolcos et al., 2013; Ewbank et al., 2009; Friston et al., 1995a, 1995b; McLaren

Abbreviations: AD, Alzheimer's disease; ADAS-Cog, AD Assessment Scale — Cognitive Subscale; CDR, clinical dementia rating; CDR-sb, CDR sum-of-boxes; FCSRT, Free and Cued Selective Reminding Test; FCR, post-scan forced-choice recognition; FR, post-scan free recall; GLMs, general linear models; gPPI, generalized psychophysiological interactions; MMSE, Mini-Mental State Examination; N > R PPI, connectivity difference between encoding novel face–name and repeated face–name pairs; NINCDS/ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; PPI, psychophysiological interactions; R > N PPI, connectivity difference between encoding repeated face–name and novel face–name pairs.

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et al., 2012b; Putcha et al., 2011; Simon et al., 2010; Wig et al., 2008), and more recently context-dependent connectivity (Chatham et al., 2014; Farr et al., 2012; Friston et al., 2003; McLaren et al., 2012a; Raz et al., 2014).

Context-dependent connectivity, or the connectivity during different task conditions, has the potential to reveal information about neural and synaptic function and response. Psychophysiological interactions (PPI), the form of context-dependent connectivity used in the present analysis, specifically investigates how one brain region increases or decreases its relationship with another brain region under different contexts (Cisler et al., 2014; Friston et al., 1997; O'Reilly et al., 2012). Generalized psychophysiological interactions (gPPI; McLaren et al., 2012a) assess how the connectivity changes for each task condition relative to the implicit baseline, usually fixation. This method has been shown to be more sensitive and accurate at estimating the pair-wise connectivity differences between conditions (e.g. novel > repeated) than the standard PPI implemented in SPM software (SPM5/8; Cisler et al., 2014; Gitelman et al., 2003; McLaren et al., 2012a). In the present study, in individuals with mild AD, it was hypothesized that increased accuracy of gPPI analyses may allow the detection of subtle differences in hippocampal seed–whole brain connectivity that are related to specific task-supported (context-dependent) cognitive processes.

Context-dependent connectivity approaches are varied and include PPI, dynamic causal modeling and beta-series correlations, but each should be tailored to the question at hand (Friston et al., 2003; Rissman et al., 2004). For example, while dynamic casual modeling has been shown to be more predictive of memory success than simple task activations (Gagnepain et al., 2011), it requires the analysis to be limited to only an a priori specified and small set of brain regions (Neufang et al., 2011; Rytsar et al., 2011). Yet, collectively, previous studies support that context-dependent connectivity has the potential to characterize neural correlates of synaptic, neuronal and/or neurovascular integrity as they relate to cognition and behavioral performance.

What remains unknown is whether patterns of context-dependent connectivity, using gPPI, during performance of specific fMRI memory paradigms can capture a representation of neural dysfunction that correlates with specific clinical, cognitive and behavioral impairments. The objective of this study was to determine, in individuals with mild AD dementia, the characteristics of context-dependent hippocampal–whole brain functional connectivity analysis using our fMRI associative memory encoding paradigm in conjunction with performance outside the scanner on clinical and behavioral measures (Diamond et al., 2007; McLaren et al., 2012b; Sperling et al., 2003a). More broadly, the question assessed is: are differences in hippocampal–whole brain connectivity between conditions related to behavior in AD? We hypothesized that hippocampal connectivity differences between encoding novel face–name pairs (N) and encoding repeated face–name pairs (R) (i.e. the N versus R PPI contrast) in memory performance-related network regions, including the default-mode network, will be associated with cognitive measures in our test battery that better assess episodic memory processes.

Materials and methods

Subjects

Twenty four right-handed, English-speaking subjects meeting National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD (McKhann et al., 1984), with Mini-Mental State Examination (MMSE, see Study procedure for details) scores between 16 and 24, and taking a stable-dose of donepezil (Aricept®) treatment 10 mg daily for at least 6 months were enrolled in the study. The subjects were first diagnosed clinically with AD dementia by a clinical neurologist and were subsequently evaluated at one of two university memory disorders units and given the diagnosis of probable AD by a cognitive neurologist; a diagnosis which was then reviewed and confirmed by the memory disorders unit's consensus committee. Demographics, clinical characteristics and test scores can be found in Table 1. Exclusion criteria included unstable psychiatric or medical illness, severe renal insufficiency, contraindication to MRI, and use of antipsychotic medication in the six months prior to screening. Subjects and caregivers provided informed consent according to the Declaration of Helsinki and with protocols approved by the Partners Healthcare Inc. Institutional Review Board.

Study procedure

All subjects first underwent clinical and neuropsychological testing, followed by fMRI, and finally behavioral testing outside the scanner. Neuropsychological and clinical measures included standard measures used in AD clinical trials such as the Mini-Mental State Examination (MMSE; Folstein et al., 1983), AD Assessment Scale — Cognitive Subscale (ADAS-Cog; Pena-Casanova, 1997), Free and Cued Selective Reminding Test (FCSRT; Grober et al., 2000), and Clinical Dementia Rating scale (CDR; Morris, 1993). The data presented here is the baseline data from a longitudinal pharmacological fMRI study in subjects with mild AD dementia. FMRI data from some subjects has been used in previous publications (Atri et al., 2011; Diamond et al., 2007; McLaren et al., 2012b).

MMSE

The MMSE is a standard instrument used to screen global cognitive function in the clinic and for inclusion in dementia clinical trials. Subjects are asked a number of questions that probe a range of cognitive processes including: orientation of time and place; verbal registration of three simple words; attention; delayed recall of the earlier presented words; language (naming; repetition; and following multi-step commands); and visuospatial function (copying of intersecting pentagons). It takes about 7–10 min to administer. A higher MMSE score indicates better cognitive performance and scores range from 0 to 30.

ADAS-Cog

The ADAS-Cog is a standard instrument utilized as a primary cognitive outcome measure in AD clinical trials and includes 11 cognitive subscales. In the present study, we focus on the subscales for Word Recall (ADAS-Cog Recall), Delayed Word Recall (ADAS-Cog Delayed Recall) and Word Recognition (ADAS-Cog Recognition) and on the total score (ADAS-Cog Total). In the word recall task, subjects read a list of 10 high-frequency nouns over three trials and are asked to recall as many

Table 1
Demographics and cognitive tests.

Demographics	
Age	71.63 (1.71)
Education	16.00 (0.57)
Gender (f/m)	9/15
Cognitive tests	
FR (% correct)	67.00 (3.05)
FCR (% correct)	68.75 (3.31)
FCSRT-Free Recall (# correct)	10.08 (1.72)
FCSRT-Total (# correct)	30.54 (2.78)
ADAS-Cog Total (# of errors)	26.15 (1.90)
ADAS-Cog Recall (# of errors)	5.94 (0.35)
ADAS-Cog Delayed Recall (# of errors)	8.33 (0.39)
ADAS-Cog Recognition (# of errors)	6.71 (0.66)
MMSE (# correct)	24.04 (0.58)
CDR-sb (score)	4.67 (0.50)

For FCSRT, MMSE and post-scan memory tests higher scores indicate better performance. For CDR-sb and ADAS-Cog lower scores represent better performance. Values are the mean and standard error.