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Response of the medial temporal lobe network in amnestic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance

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ABSTRACT

Studies of individuals with amnestic mild cognitive impairment (aMCI) have detected hyperactivity in the hippocampus during task-related functional magnetic resonance imaging (fMRI). Such elevated activation has been localized to the hippocampal dentate gyrus/CA3 (DG/CA3) during performance of a task designed to detect the computational contributions of those hippocampal circuits to episodic memory. The current investigation was conducted to test the hypothesis that greater hippocampal activation in aMCI represents a dysfunctional shift in the normal computational balance of the DG/CA3 regions, augmenting CA3-driven pattern completion at the expense of pattern separation mediated by the dentate gyrus. We tested this hypothesis using an intervention based on animal research demonstrating a beneficial effect on cognition by reducing excess hippocampal neural activity with low doses of the atypical anti-epileptic levetiracetam. In a within-subject design we assessed the effects of levetiracetam in three cohorts of aMCI participants, each receiving a different dose of levetiracetam. Elevated activation in the DG/CA3 region, together with impaired task performance, was detected in each aMCI cohort relative to an aged control group. We observed significant improvement in memory task performance under drug treatment relative to placebo in the aMCI cohorts at the 62.5 and 125 mg BID doses of levetiracetam. Drug treatment in those cohorts increased accuracy dependent on pattern separation processes and reduced errors attributable to an over-riding effect of pattern completion while normalizing fMRI activation in the DG/CA3 and entorhinal cortex. Similar to findings in animal studies, higher dosing at 250 mg BID had no significant benefit on either task performance or fMRI activation. Consistent with predictions based on the computational functions of the DG/CA3 elucidated in basic animal research, these data support a dysfunctional encoding mechanism detected by fMRI in individuals with aMCI and therapeutic intervention using fMRI to detect target engagement in response to treatment.

1. Introduction

A longstanding computational theory attributes successful memory to a balance between two complementary functions mediated by the hippocampal dentate gyrus and CA3 regions, which receive input from layer II neurons of the entorhinal cortex. The model proposes that pattern separation, a function ascribed to the granule cells of the dentate gyrus, reduces mnemonic interference by encoding distinctive representations for similar input patterns, while pattern completion refers to the recovery of a prior representation from partial or degraded input, a function ascribed to the extensive recurrent collaterals of CA3 neurons (McClelland et al., 1995; Norman and O'Reilly, 2003; O'Reilly and McClelland, 1994; Treves and Rolls, 1994); for a review see Yassa and Stark (2011). It has been proposed that such competing, yet complementary processes would minimize interference while maximizing storage capacity for episodic memories. Empirical evidence consistent with this model is supported by studies of the encoding properties of neurons in these brain regions in laboratory animals (Alme et al., 2014; Lee et al., 2004; Leutgeb et al., 2004; Neunuebel and Knierim, 2014). High-resolution functional magnetic resonance imaging (fMRI) has also demonstrated alterations in fMRI activation in the DG/CA3 regions consistent with such computational functions in the human brain (Bakker et al., 2008; Yassa et al., 2010, 2011a).

In elderly human subjects (compared to young adults) and in patients with aMCI (compared to age-matched controls), increased fMRI

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BOLD activation was localized to the DG/CA3 region (Yassa et al., 2010, 2011a), using a three-judgment memory task designed to tax pattern separation. In both cases, increased activity was correlated with worse memory performance. Moreover, this condition was associated with reduced pattern separation and a shift to errors indicative of pattern completion. Based on these findings, we conducted a randomized controlled trial (RCT) of the functional significance of excess fMRI activation and its contribution to cognitive impairment in aMCI subjects, using levetiracetam, an atypical anti-epileptic. We demonstrated that reduction of DG/CA3 BOLD overactivity, resulting from levetiracetam treatment, improved performance of the aMCI subjects on the 3-judgment memory scanning task (Bakker et al., 2012). The full RCT enrolled three cohorts of aMCI patients who were treated with levetiracetam in a range of low doses and evaluated on the 3-judgment memory task designed to assess pattern separation/completion processes. Here we report the findings from the full dose-finding study. The study focused on the network components most affected in the animal models, particularly subregions of the hippocampal formation and the entorhinal cortex. Consistent with those models, we reliably observed elevated fMRI BOLD activation localized to the DG/CA3 subregion of the hippocampal formation, together with a consistent profile in memory performance showing a shift in bias away from pattern separation in favor of pattern completion across aMCI cohorts. At doses of levetiracetam that improved memory performance in the scanning task, drug treatment also normalized fMRI activation in both the entorhinal cortex and DG/CA3 region, reducing DG/CA3 fMRI activity and boosting decreased fMRI activation in the entorhinal cortex (EC). Those findings are consistent with the close coupling across animal and human data in aging and prodromal Alzheimer's disease, with growing interest in the role of neural hyperactivity as a potential therapeutic target to restore the network properties of circuits that are among the earliest affected in Alzheimer's disease (Stargardt et al., 2015).

2. Methods

2.1. Study design

The design for this study is schematically shown in Fig. 1. The entire RCT protocol consisted of 4 study visits over an 8-week period. Each cohort of aMCI participants was randomized, double-blind, in a within-subject crossover design, with the order of treatment on drug and placebo counterbalanced within each cohort. Age-matched controls were treated single-blind on placebo as further described in the procedures that follow.

2.2. Participants and clinical characterization

During the baseline visit all participants completed the dementia rating scale (CDR: Morris, 1993), and underwent medical, psychiatric, neurological and neuropsychological evaluations, which included the Mini Mental Status Exam (Folstein et al., 1975), the Buschke Selective Reminding Test (Buschke and Fuld, 1974), the Verbal Paired Associated subtest of the Wechsler Memory Scale (Wechsler, 1987) and the Benton Visual Retention Test (Benton, 1974). All aMCI participants had a global CDR score of 0.5 with a sum of boxes score not exceeding 2.5 and met criteria for aMCI proposed by Petersen (Petersen, 2004), which includes impaired memory function on testing and no decline in basic activities of daily living. All control subjects had a global CDR score of 0. None of the aMCI participants or age-matched control subjects met criteria for dementia. Other exclusion criteria included major neurological and psychiatric disorders, head trauma with loss of consciousness, history of substance abuse or dependency, and general contraindications to having an MRI examination (e.g. cardiac pacemaker, aneurysm coils and claustrophobia) or taking the study medication (e.g. known sensitivity or allergies, or severe renal impairment). Participants taking anti-epileptic medications were excluded from participation in the study but use of other neuroactive medications was permitted if the participant was stable on the medication for at least 12 weeks and if the treatment regimen was not altered for the duration of the study. The study protocol was approved by the Institutional Review Board of the Johns Hopkins Medical Institutions. All participants provided written informed consent and were paid for their participation in the study.

At the baseline evaluation sixty-nine participants with aMCI and 24 age-matched controls met criteria for enrollment. Complete data from 54 participants with aMCI and 17 control participants were included in the analysis. Nine aMCI participants and 6 control participants did not complete the study protocol. Data from an additional 6 aMCI participants and 1 control participant were excluded before analysis due to excessive motion or in-scanner task performance that was inadequate for analysis of the fMRI data.

2.3. Study procedures

All participants completed the same study procedures with fMRI study visits after each of two treatment phases, separated by a washout period of 4 weeks as shown in Fig. 1. Control subjects were given placebo during both treatment phases (single-blind) while participants with aMCI were given placebo during one treatment phase and drug during the other treatment phase, with the order of treatment counterbalanced (randomized, double-blind). A first cohort of aMCI participants received treatment with 125 mg BID of levetiracetam (Keppra, UCB Laboratories), as was previously reported (Bakker et al., 2012). Based on those initial findings and earlier preclinical data in animals (Koh et al., 2010), two additional doses were selected for two subsequent cohorts of aMCI participants, receiving treatment with 62.5 mg BID and 250 mg BID of levetiracetam, respectively. All study treatments (drug and placebo)

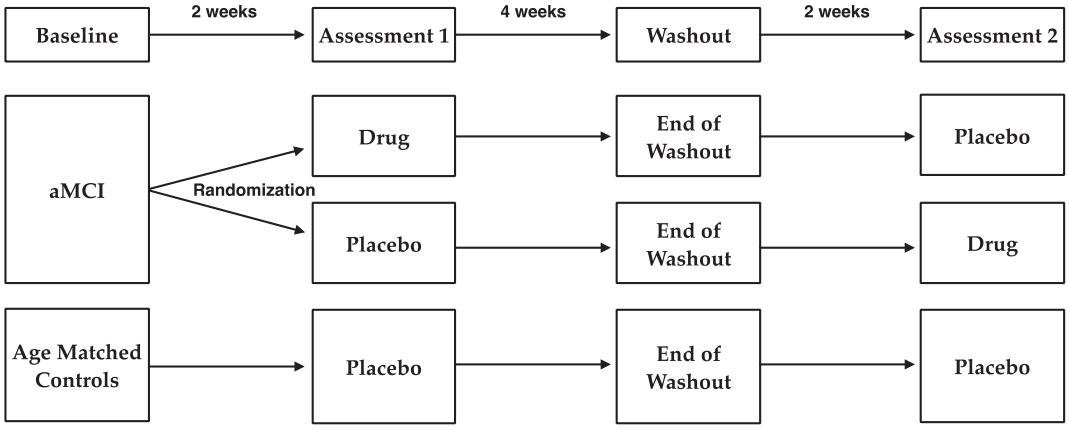

Fig. 1. Schematic of the study design.