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Diminished neural network dynamics in amnestic mild cognitive impairment

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ABSTRACT

Mild cognitive impairment (MCI) is widely regarded as an intermediate stage between typical aging and dementia, with nearly 50% of patients with amnestic MCI (aMCI) converting to Alzheimer's dementia (AD) within 30 months of follow-up (Fischer et al., 2007). The growing literature using resting-state functional magnetic resonance imaging reveals both increased and decreased connectivity in individuals with MCI and connectivity loss between the anterior and posterior components of the default mode network (DMN) throughout the course of the disease progression (Hillary et al., 2015; Sheline & Raichle, 2013; Tijms et al., 2013). In this paper, we use dynamic connectivity modeling and graph theory to identify unique brain “states,” or temporal patterns of connectivity across distributed networks, to distinguish individuals with aMCI from healthy older adults (HOAs). We enrolled 44 individuals diagnosed with aMCI and 33 HOAs of comparable age and education. Our results indicated that individuals with aMCI spent significantly more time in one state in particular, whereas neural network analysis in the HOA sample revealed approximately equivalent representation across four distinct states. Among individuals with aMCI, spending a higher proportion of time in the dominant state relative to a state where participants exhibited high cost (a measure combining connectivity and distance), predicted better language performance and less perseveration. This is the first report to examine neural network dynamics in individuals with aMCI.

1. Background

Mild cognitive impairment (MCI) is widely regarded as an intermediate stage between typical aging and dementia, with about 30% of MCI patients converting to Alzheimer's dementia (AD) and nearly 50% of individuals with amnestic MCI (aMCI) converting to AD within a 30-month follow-up period (Fischer et al., 2007). Patients with aMCI are characterized by impairments in learning and memory, though additional cognitive deficits are often evident depending on when an individual presents clinically (Albert et al., 2011).

Resting-state functional magnetic resonance imaging (rs-fMRI) examines coherent oscillations of low frequency fluctuations in the blood oxygen level-dependent (BOLD) signal, thereby allowing for the identification of sets of regions whose activity is correlated when an individual is not engaging in any particular task (Biswal et al., 1995; Gusnard and Raichle, 2001). Using this method, there is now a large literature demonstrating a gradual loss of connectivity between anterior and posterior brain regions in AD, but this disconnection may be preceded by a mix of increased and decreased connectivity in individuals with MCI (Badhwar et al., 2017; Hillary et al., 2015; Sheline and Raichle, 2013; Tijms et al., 2013). Specifically, early disease states may result in hyperconnectivity in areas of the default mode network (DMN) (Hillary et al., 2015), a group of brain regions including the posterior cingulate cortex and the ventromedial prefrontal cortex that is believed to be involved in self-referential thought and memory processing (Raichle et al., 2001; Raichle, 2015). Other disruptions in connectivity

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Table 1
Demographics.

	Age (years)	Education (years)	Gender	Race
aMCI (n = 43)	71.77 ± 7.23 (55–88)	16.12 ± 2.75	21 F, 22 M	24 W, 16 B, 3 L
HOA (n = 33)	69.52 ± 7.73 (59–86)	16.61 ± 1.94	29 F, 4 M	23 W, 10 B

Data are expressed as mean ± standard deviation (range). No significant between-group differences in age (p = 0.186) and education (p = 0.468) were found (two-tailed). One individual's gender was not reported. W = white, B = black, L = latinx. This table represents demographics for the aMCI group excluding the individual who was excluded due to excessive movement.

within the hippocampus (Jones et al., 2016), posterior cingulate cortex (Brier et al., 2012), and medial temporal lobes (Dickerson and Sperling, 2008) have been associated with reduced memory performance. Furthermore, hubs in the cognitive control (CC) network, which includes the anterior cingulate cortex, dorsolateral prefrontal cortex, and posterior parietal cortex (Cole and Schneider, 2007), have shown increases in connectivity in individuals with AD when compared to healthy controls (Agosta et al., 2012; Hillary et al., 2015). Disease onset therefore presents as hyperconnectivity that degrades as the disease develops, cascading from posterior to anterior connectivity degradation (Damoiseaux et al., 2012; Hillary and Grafman, 2017; Jones et al., 2016).

In order to characterize distributed neural networks, investigators have combined rs-fMRI methods with graph theory, an applied mathematical approach permitting analysis of all possible connections across the network (Bassett and Bullmore, 2006). Recent application of graph theory methods in the study of aMCI has revealed an overall decrease in connectivity, which is commonly observed as an overall increase of average path length, or a decrease in the global efficiency of the network (Wang et al., 2013). Wang and colleagues also observed that participants with aMCI exhibited decreased modularity, a community structure metric characterized by groups of nodes densely linked among themselves and more sparsely linked to nodes outside the local grouping. Two related dimensions of network functioning may be affected in aMCI. First, there is a nonlinear trend in connectivity change, with enhanced connectivity early on in the disease giving way to connectivity loss based upon the degree of cortical atrophy (de Haan et al., 2009). Second, information processing via network hubs declines as connectivity is lost and modularity, or "community structure," degrades (for review see Hillary and Grafman, 2017).

To date, network studies in MCI, including those using graph theory, have investigated neural networks by quantifying the relationship (e.g., a single correlation coefficient) between any two nodes for the entire data collection period. This method assumes temporal and spatial stationarity in the relationship between network nodes over the course of the time series. New approaches such as dynamic connectivity, which have been applied to other clinical populations such as mild traumatic brain injury (TBI) (Mayer et al., 2015) and schizophrenia (Braun et al., 2016; Rashid et al., 2014), allow for increased sensitivity to subtle temporal variations that can be missed when correlating two time series. A relatively new method examining dynamic functional connectivity works by identifying brain states that neural networks transition through during resting state in the absence of any externally imposed task. In this paper, we examine dynamic functional connectivity by studying smaller windows of time to gain access to these brain states. We seek to understand the different resting-state profiles of individuals with aMCI compared to healthy older adults (HOAs), with a focus on network dynamics and flexibility as neural systems move between distinct connectivity states. To our knowledge, no other study has examined dynamic connectivity in individuals with aMCI.

1.1. Study goals and hypotheses

The goal of this paper is to compare dynamic functional connectivity brain states during rest between individuals with aMCI and HOAs. We focus on proportion of time spent in distinct brain states as well as transitions between distinct states based upon a dynamic functional connectivity analysis.

Overall, we hypothesized that compared to HOAs, individuals with aMCI will show network dynamics marked by fewer transitions between states and state attendance that is concentrated more heavily on one state instead of spread out across many. This hypothesis is based on previous literature demonstrating that diminished network variability has been observed after traumatic brain injury (TBI) (Nenadovic et al., 2008) where there exists challenges to neural network resources. Second, we predicted that hub regions within the DMN and CC network would function as "drivers" for the proportion of time spent in the most common state in the aMCI sample. Finally, given the above noted evidence of a posterior to anterior loss of long-distance connectivity in MCI, we predicted that diminished connectivity in posterior hubs in the aMCI sample would predict cognitive deficit (Brier et al., 2012; Dennis and Thompson, 2014; Li et al., 2013; Sorg et al., 2007).

2. Materials and methods

2.1. Procedure

Subjects included 44 individuals diagnosed with aMCI and 33 HOAs of comparable age and education (Table 1). Subjects with aMCI were recruited from the Atlanta Veterans Affairs Medical Center (VAMC) as well as the Emory University Alzheimer's Disease Research Center (ADRC). Those with aMCI were diagnosed according to the Petersen criteria (Petersen, 2004) via consensus conferences that included neurologists, geriatricians, neuropsychologists, and other clinical staff, who took into account laboratory results, neuroimaging, neuropsychological, and other test results as available. HOA participants were recruited from the Emory ADRC as well as the general Atlanta metropolitan area. These participants were determined to have normal cognition using the same consensus approach. General exclusion criteria included any other neurologic injury or disease, psychiatric disorders, and current or past alcohol or drug abuse or dependence. All of the data were collected at Emory University, and all participants gave written, informed consent. The study was approved by the Institutional Review Board of Emory University and the Research and Development Committee of the Atlanta VAMC.

2.2. Behavioral data

Given the time lag that can occur between diagnosis and study enrollment, all participants completed a standard neuropsychological protocol, described below, at the time of study enrollment. This ensured that patients with aMCI did not convert to AD or revert to normal and that HOAs were still cognitively intact. This protocol included the Mini-Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Wechsler Test of Adult Reading (WTAR), the Trail Making Tests A and B (Trails-A and Trails-B), and the Emory Version of the Wisconsin Card Sorting Test (EWCST). Table 2 reports means and standard deviations of neuropsychological test results for both groups, providing a good clinical indicator of disease severity in this cohort. In order to minimize