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Hierarchical subcortical sub-regional shape network analysis in Alzheimer's disease

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Abstract—In this paper, by utilizing surface diffeomorphic deformations, we constructed and analyzed subcortical shape morphometric networks in 210 healthy control (HC) subjects and 175 subjects with Alzheimer's disease (AD), aiming to identify AD-induced abnormalities in the subcortical shape network. We quantitatively analyzed pertinent network attributes of the entire network and each node. Further to this, hierarchical analyses were performed; group comparisons were conducted at the structure level first and then the sub-region level. The bilateral amygdalae, hippocampi, as well as the thalamus were all divided into multiple functionally distinct sub-regions. From the structure level analysis, we found significant HC-vs-AD group differences in the average local efficiency and average global efficiency. In addition, the local nodal efficiencies between the right thalamus and all three of the right hippocampus, right amygdala, and left thalamus, as well as that between the left amygdala and left hippocampus, decreased significantly in AD. According to the sub-regional network analyses, we observed significant AD-induced local efficiency decreases between different sub-regions within the right hippocampus itself and between the subiculum of the right hippocampus and the sub-region of the right thalamus connecting to the temporal lobe, indicating a degradation of circuit between the hippocampus, thalamus, and temporal lobe. Statistical comparisons were performed using 40,000 non-parametric permutation tests, with false discovery rate correction employed for multiple comparison correction.

Key words: brain morphology network, subcortical structures, shape network, sub-region, surface deformation, Alzheimer's disease.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative brain disorder, with memory problems being one of its earliest symptoms (Bayles, 1991). AD is characterized by neuropathological changes such as increased neurofibrillary tangles and brain atrophy (Serranopozo et al., 2011).

During the past decade, modern magnetic resonance imaging (MRI, including structural MRI (sMRI), functional MRI (fMRI), and diffusion MRI (dMRI)) and neurophysiological (e.g. electroencephalograph and magnetoencephalography) techniques have provided efficient, feasible, and non-invasive ways to investigate the neuropathological changes of AD *in vivo*. Relying on these techniques, a large number of studies have been conducted with a focus on structural and functional brain abnormalities in AD. Such abnormalities have been detected in various brain regions of interest (ROIs). For example, from task-based fMRI, decreased functional activations were detected in the hippocampus and the parahippocampal gyrus in AD when compared to control volunteers (Rombouts et al., 2000). Abnormal functional activation patterns were also observed in the prefrontal cortex and parietal cortex in AD patients (Sperling et al., 2010). From sMRI studies, a decrease in the gray matter (GM) density was found, with the largest decrease occurring in the hippocampus and amygdala complex (Frisoni

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Abbreviations: AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDR-SB, clinical dementia rating scale sum of boxes; dMRI, diffusion Magnetic Resonance Imaging; FDR, false discovery rate; fMRI, functional Magnetic Resonance Imaging; GM, gray matter; HC, healthy control; LDDMM, large deformation diffeomorphic metric mapping; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; PCC, partial correlation coefficient; ROIs, regions of interest; sMRI, structural Magnetic Resonance Imaging.

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et al., 2002). GM volume reductions in the temporal lobe have also been reported (Busatto et al., 2003).

Recently, graph theory-based MRI analysis has seen a considerable growth in popularity and the notion of "connection" has been proposed to describe the human brain's correlation patterns across ROIs in terms of functional and structural signals (Sporns et al., 2005; Stam and Reijneveld, 2007). Abnormalities in both functional and structural connectivity patterns have been implicated in AD. In fMRI, or specifically resting-state fMRI studies, disruptions to the organization of brain functional networks have been detected in AD, such as a loss of the small-worldness property (Supekar et al., 2008; Sanz-Arigita et al., 2010; Zhao et al., 2012) and a redistribution of brain hub regions (Yao et al., 2010). By investigating structural networks constructed from correlations between every two cortical ROIs in terms of thickness, researchers found AD-induced abnormalities in certain network metrics including the average characteristic path length and the average clustering coefficient (He et al., 2008; Li et al., 2012). Such structural networks have also been constructed using GM volumes, in which an increase in the average clustering coefficient and a boost in the average characteristic path length were detected in AD (Yao et al., 2010). In dMRI-based white matter network analyses, topological changes of the human brain were also identified in AD patients (Lo et al., 2010). Collectively, it has been suggested that disconnection is a plausible explanation for certain cognitive deficits observed in AD (Delbeuck et al., 2003).

In terms of the target areas, most existing graph theory-based brain network studies have focused on AD connectivity abnormalities at a relatively global level, such as the whole-brain level (Seo et al., 2013) and the cortex level (He et al., 2008). There has been much less research devoted to understanding the AD-induced network abnormalities at the subcortical structural level, especially at a sub-region level, even though numerous studies have reported subcortical abnormalities in AD from various aspects. As one of the earliest studies, De Lacoste and White found that the very first symptom in AD was damage to the connection between the hippocampus and the neocortex (De Lacoste and White, 1993). Hippocampal atrophy was also found to be an early symptom in AD (Price et al., 1991; Atiya et al., 2003). Similarly, volumetric alterations of other subcortical and ventricular structures have also been found in previous AD studies, such as ventricle enlargement (Ridha et al., 2008), putamen and thalamus volume reduction (De Jong et al., 2008), as well as caudate volume reduction (Madsen et al., 2010).

In our own previous subcortical and ventricular shape analyses, we observed prominent region-specific expansions in the ventricles alongside atrophies in the hippocampus and amygdala in AD when compared to healthy control (HC). These shape analyses also led to a discovery of sub-region-specific atrophies of the hippocampus and amygdala; the hippocampal atrophy mainly occurred on CA1 and the amygdalar atrophy mainly occurred on the basolateral complex (Tang et al., 2014). Similar sub-regional abnormality patterns were also detected in a second AD dataset, suggesting the robustness of those findings (Tang et al., 2015).

However, to the best of our knowledge, no previous study has ever investigated the topological architecture of either subcortical or related sub-regional morphological networks in AD. Vertex-based shape characteristics provide an effective approach for looking at a structure's morphometrics at either a coarse level (structure level) or a fine level (sub-region or even vertex level) (Tang et al., 2014). This is essentially the key motivation and contribution of this work, in which subcortical and related sub-regional networks were constructed and analyzed based on shape characteristics. Instead of using the cortical thickness or the GM volume, we used a shape deformation-based quantity representing the localized surface areas to construct our morphological networks. Surface area is a very important morphological characteristic for a 2D anatomical manifold (surface), similar to length for a 1D manifold (curve) and volumetric size for a 3D manifold (ROI segmentation). In the shape deformation setting, the localized surface area around a vertex can be reflected by the shape deformation degree with respect to a common template shape; for example, outward deformation (expansion) indicates a larger surface area in the target shape relative to the template whereas inward deformation (compression) indicates a smaller surface area in the target relative to the template. With a fixed template shape, the localized surface areas of different target shapes can be quantified using the deformation patterns and are indexed in a common template shape space.

Brain warping techniques such as the large deformation diffeomorphic metric mapping (LDDMM) have been applied to deforming shapes so as to quantify surface area morphometrics (Csernansky et al., 2000, 2002, 2005; Thompson et al., 2004; Wang et al., 2011). In previous studies, LDDMM has been applied to subcortical shape analysis (Miller et al., 2012; Tang et al., 2014) as well as subcortical sub-regional shape analysis (Qiu and Miller, 2008; Qiu et al., 2009; Tang et al., 2014, 2016) in terms of AD-induced morphometric abnormalities. However, up to now, LDDMM has not been applied to subcortical shape network nor subcortical sub-regional shape network analyses, which will be the key theme of this study. LDDMM is capable of transferring the sub-region definitions between coordinate systems, ensuring a sub-division of a structure of interest (e.g. the left hippocampus) in a study-specific template space. In this manner, we can conduct sub-regional subcortical shape network analyses in the common template space as well.

In this work, we performed subcortical shape network analysis in a coarse-to-fine fashion using a large dataset consisting of 210 AD patients and 175 HC subjects. We first analyzed the subcortical shape network at the structure level and identified the structures whose local network properties had been found to be affected by AD. After that, we proceeded further to analyze the sub-regional shape networks for those previously identified structures, such as the shape network constructed by sub-regions of the right hippocampus and the right

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