Insight into Disrupted Spatial Patterns of Human Connectome in Alzheimer’s Disease via Subgraph Mining

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ABSTRACT

Alzheimer’s disease (AD) is the most common cause of age-related dementia, which prominently affects the human connectome. In this paper, the authors focus on the question how they can identify disrupted spatial patterns of the human connectome in AD based on a data mining framework. Using diffusion tractography, the human connectomes for each individual subject were constructed based on two diffusion derived attributes: fiber density and fractional anisotropy, to represent the structural brain connectivity patterns. After frequent subgraph mining, the abnormal score was finally defined to identify disrupted subgraph patterns in patients. Experiments demonstrated that our data-driven approach, for the first time, allows identifying selective spatial pattern changes of the human connectome in AD that perfectly matched grey matter changes of the disease. Their findings also bring new insights into how AD propagates and disrupts the regional integrity of large-scale structural brain networks in a fiber connectivity-based way.

Keywords: Alzheimer’s Disease, Diffusion Tensor Image, Frequent Subgraph, Graph Mining, Human Connectome

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1. INTRODUCTION

Unraveling the structural connectivity in the human brain (i.e. the human connectome (Sporns, Tononi, & Kötter, 2005) is challenging for neuroscientists for over a century. Brain’s wiring captures the basic feature of nervous system organization and is fundamental to understand the brain’s functions, which depend critically on the integration of regionally remote neural activity. In recent years, the advances of imaging technologies have provided a promising avenue of exploring structural brain connectivity in-vivo. The study of the human connectome has therefore attracted huge attention, especially for the research on various pathologies related to white matter changes such as Alzheimer’s disease (Damoiseaux et al., 2009), Schizophrenia (Park et al., 2004), and Multiple Sclerosis (Hesseltine et al., 2006). Discovering the disrupted wiring of the brain is essential for a better understanding of the pathophysiology of these diseases, finally to target potential treatments more specifically. Thereby a critical question is how to map aberrant brain connectivity spatially as specific as possible in these diseases. In this study, we aim to answer this question in patients with Alzheimer’s disease based on a data mining framework.

Alzheimer’s disease (AD), a neurodegenerative disease characterized by increasing cognitive and behavioral deficits (Blennow, de Leon, & Zetterberg, 2006), is neuropathologically defined by amyloid plaques, neurofibrillary tangles and the loss of neurons (i.e. atrophy), with changes starting regionally and spreading out gradually across brain’s grey matter (Braak & Braak, 1991; Thal, Rüb, Orantes, & Braak, 2002). Meanwhile, post-mortem histological and in-vivo imaging studies demonstrated wide-spread alterations of patients’ white matter, involving frontal, occipital, and temporal lobes (Englund 1998; Chua, Wen, Slavin, & Sachdev, 2008) and selected tracts such as the corpus callosum or cingulum (Rose et al., 2000). By far, AD is the most common cause of age-related dementia. Other causes are vascular diseases such as stroke or neurodegenerative diseases such as Lewy body disease or frontotemporal lobe degeneration. Due to the “aging society”, more and more people are diagnosed with dementia. According to the World Alzheimer Report in 2011 (http://www.alz.co.uk/research/world-report), about 36 million people worldwide are living with dementia, with numbers doubling every 20 years to 66 million by 2030, and 115 million by 2050. The worldwide costs of dementia (US$604 billion in 2010) amount to more than 1% of global GDP. Therefore, there is a strong interest in expanding our knowledge of diseases causing dementia, especially for AD. Recent findings demonstrated the selective disruption of large-scale brain functional networks. However, the aberrant patterns in structural brain networks in AD are still poorly understood.

Diffusion weighted magnetic resonance imaging (DWI) is a technique that can be used to explore white matter microstructure in-vivo, using water diffusion properties as a probe (Johansen-Berg & Rushworth, 2009). The DWI signal is sensitive for the diffusion of water molecules that it is along the direction of axons and restricted in the direction perpendicular to them. During DWI, multiple brain images are acquired where each is sensitive for a distinct direction. At each voxel, measured data are fitted to a mathematical diffusion tensor model describing diffusion as an ellipsoid or tensor. Both local properties of water diffusion (such as fractional anisotropy (FA) or mean diffusivity (MD) can be derived from the voxel-wise diffusion tensor (Mori, 2007). However, after diffusion tensor calculation, we obtain the diffusion-derived FA or MD maps which include millions of FA or MD values to capture the white matter microstructure. The remaining problem in clinical research is how we can make the information of millions of voxels to utilizable knowledge. Particularly, how to find the disrupted structural connectivity in AD relying on these vast amounts of data? To date, the most common used approaches to study AD by neuroimaging is called statistical parametric mapping (SPM), which investigates the change of each voxel independently, i.e. a
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