European Neuropsychopharmacology (■■■■) ■, ■■■–■■■

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Aberrant development of the asymmetry between hemispheric brain white matter networks in autism spectrum disorder

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Received 27 June 2017; received in revised form 26 September 2017; accepted 22 November 2017

KEYWORDS
Autism;
Connectome;
Development;
Diffusion MRI;
Graph theory;
Lateralization

Abstract
Atypical brain asymmetry/lateralization has long been hypothesized for autism spectrum disorder (ASD), and this model has been repeatedly supported by various neuroimaging studies. Recently, hemispheric network topologies have been found to be asymmetric, thereby providing a new avenue for investigating brain asymmetries under various conditions. To date, however, how network topological asymmetries are altered in ASD remains largely unexplored. To clarify this, the present study included ASD individuals from the newly released Autism Brain Imaging Data Exchange II database (58 right-handed male ASD individuals aged 5 to 26 years and 70 age- and IQ-matched typically developing (TD) individuals). Diffusion and structural magnetic resonance imaging were used to construct hemispheric white matter networks, and graph-theory approaches were applied to quantify topological efficiencies for hemispheric networks. Statistical analyses revealed a decreased rightward asymmetry of network efficiencies with increasing age in the TD group, but not in the ASD group. More specifically, the TD group did not exhibit an age-related increase in network efficiency in the right hemisphere, but the ASD group did. For the left hemisphere, no difference between the groups was observed for the developmental trajectory of network efficiencies. Intriguingly, within the ASD group, more severe restricted and repetitive

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https://doi.org/10.1016/j.euroneuro.2017.11.018

behavior in ASD was found to be correlated with less rightward asymmetry of network local efficiency. These findings provide suggestive evidence of atypical network topological asymmetries and offer important insights into the abnormal development of ASD brains.

1. Introduction

As a severe neurodevelopmental disorder, autism spectrum disorder (ASD) is characterized by impairments in language and social interaction and by the presence of repetitive and stereotypical behaviors (American Psychiatric Association, 2000; Kanner, 1943). Various psychopathological hypotheses have been proposed for ASD, one of which involves hemispheric asymmetry/lateralization (Kleinhans et al., 2008). According to this hypothesis, there should be a loss or inversion of typical patterns of brain lateralization/asymmetry in ASD patients (Floris et al., 2013; Lo et al., 2011).

Numerous lines of neuroimaging evidence have supported this hypothesis. For example, early PET studies showed atypical or reversed cerebral blood flow in frontal language regions (Chiron et al., 1995; Müller et al., 1999; Ohnishi et al., 2000). Functional MRI techniques further revealed ASD-related atypical rightward lateralization of functional language, motor, and visuospatial networks, as well as of the default-mode network (Cardinale et al., 2013; Floris et al., 2016b; Lindell and Hudry, 2013; Nielsen et al., 2014). Structurally, there have been reports of abnormal volumetric asymmetry patterns observed in frontal and temporal lobes in ASD (Herbert et al., 2002; Herbert et al., 2005; Rojas et al., 2002; Rojas et al., 2005). In addition, white matter (WM) tracts, e.g., the arcuate fasciculus (AF) and uncinate fasciculus (UF), have been reported to exhibit atypical asymmetry patterns of diffusion MRI indices (e.g., FA) in ASD (Fletcher et al., 2010; Knaus et al., 2010; Lo et al., 2011). Furthermore, a few studies reported significant correlations between atypical asymmetry and behavioral/cognitive deficits in ASD. For instance, there was a significant correlation between the motor performance and hemispheric lateralization: more rightward asymmetry of the functional correspondence within the motor network was associated with poorer motor performance in ASD patients (Floris et al., 2016a).

In recent years, multimodal MRI techniques have been extensively applied to model the human brain as a complex network of brain regions connected by anatomical tracts or functional associations, with graph theoretical approaches being subsequently used to reveal the topological organization for the constructed brain networks (Iturria-Medina et al., 2007; Rubinov and Sporns, 2010). Several studies have demonstrated whole-brain network topological differences between ASD and typically developing (TD) individuals, e.g., differences in network clustering, path length, modularity, and rich-club/hub organization (Itahashi et al., 2014; Li et al., 2014a; Rudie et al., 2013).

In addition to the whole-brain network topological organization, hemispheric network topologies are also of great importance. In particular, they can provide a novel network topological perspective for studying brain asymmetries. Several reports have revealed significant topological asymmetries between hemispheric structural networks in healthy populations (Iturria-Medina et al., 2011; Li et al., 2014b; Ratnarajah et al., 2013). In ASD studies, a few studies have started to examine atypical asymmetries of network connections/nodes between the two hemispheres (Conti et al., 2016). However, the asymmetries of topological properties for the entire hemispheric networks remain largely unexplored.

To clarify these properties, the present study applied diffusion MRI to specifically investigate the asymmetries of network topology between the two hemispheres in ASD. Given the well-demonstrated anomalous brain developmental trajectory in ASD, as well as the reported developmental changes in topological asymmetries of hemispheric networks in healthy subjects (Caeyenberghs and Leemans, 2014; Zhong et al., 2017), we hypothesized a significant age-dependent alteration in the network topological asymmetries in ASD compared with TD individuals. Such differences in asymmetry might serve as structural substrates for specific types of cognitive/behavioral deficits in ASD. Specifically, we constructed hemispheric WM networks in a relatively large cohort ranging in age from young childhood to young adults, using the newly released Autism Brain Imaging Data Exchange II (ABIDE II) database. Graph theoretical approaches were then applied to quantify multiple topological parameters for hemispheric WM networks.

2. Experimental procedures

2.1. Participants

All samples were selected from the ABIDE II project (Di Martino et al., 2017). There were five imaging sites containing both T1 and diffusion-weighted images. In total, this database contains 155 ASD individuals and 129 TD individuals with the two image modalities. As with other ABIDE studies (Alaerts et al., 2015; Di Martino et al., 2014; Haar et al., 2016), the inclusion criteria for sample selection in the present study were as follows: (i) right-handed males; (ii) individuals with higher full-scale IQ (FSIQ) scores ($>$ 70); (iii) no medication; and (iv) younger than 26 years old. Given the much higher ASD incidence in male than female and the gender effects on the asymmetry, only males were included in this study. There are total 141 subjects (69 ASD patients; 72 TD individuals) meet these inclusion criteria. Next, visual inspection for image quality control excluded 11 individuals (9 ASD patients; 2 TD individuals), whose images have severe image artifacts, head motion, or missing slices. Finally, all individuals from the same imaging site were further excluded if the site had less than 15 individuals in total according to above criteria. In the end, 128 individuals (58 ASD patients; 70 TD individuals) from four imaging sites were entered into our analysis in the present study (for details, see Table 1S). The 4 imaging sites were Trinity Center for Health Sciences (TCHS), San Diego State

Please cite this article as: Wei, L., et al., Aberrant development of the asymmetry between hemispheric brain white matter networks in autism spectrum disorder. European Neuropsychopharmacology (2017), https://doi.org/10.1016/j.euroneuro.2017.11.018