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Developmental changes in large-scale network connectivity in autism

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ABSTRACT

Background: Disrupted cortical connectivity is thought to underlie the complex cognitive and behavior profile observed in individuals with autism spectrum disorder (ASD). Previous neuroimaging research has identified patterns of both functional hypo- and hyper-connectivity in individuals with ASD. A recent theory attempting to reconcile conflicting results in the literature proposes that hyper-connectivity of brain networks may be more characteristic of young children with ASD, while hypo-connectivity may be more prevalent in adolescents and adults with the disorder when compared to typical development (TD) (Uddin et al., 2013). Previous work has examined only young children, mixed groups of children and adolescents, or adult cohorts in separate studies, leaving open the question of developmental influences on functional brain connectivity in ASD.
Methods: The current study tests this developmental hypothesis by examining within- and between-network resting state functional connectivity in a large sample of 26 children, 28 adolescents, and 18 adults with ASD and age- and IQ-matchedTD individuals for the first time using an entirely data-driven approach. Independent component analyses (ICA) and dual regression was applied to data from three age cohorts to examine the effects of participant age on patterns of within-networkwhole-brain functional connectivity in individuals with ASD compared with TD individuals. Between-network connectivity differences were examined for each age cohort by comparing correlations between ICA components across groups.
Results: We find that in the youngest cohort (age 11 and under), children with ASD exhibit hyper-connectivity within large-scale brain networks as well as decreased between-network connectivity compared with age-matchedTD children. In contrast, adolescents with ASD (age 11–18) do not differ from TD adolescents in within-network connectivity, yet show decreased between-network connectivity compared with TD adolescents. Adults with ASD show no within- or between-network differences in functional network connectivity compared with neurotypical age-matched individuals.
Conclusions: Characterizing within- and between-network functional connectivity in age-stratified cohorts of individuals with ASD and TD individuals demonstrates that functional connectivity atypicalities in the disorder are not uniform across the lifespan. These results demonstrate how explicitly characterizing participant age and adopting a developmental perspective can lead to a more nuanced understanding of atypicalities of functional brain connectivity in autism.

1. Introduction

Early neuroimaging research comparing functional brain connectivity in individuals with autism spectrum disorder (ASD) and typically developing (TD) individuals led to the hypo-connectivity hypothesis proposing that fronto-posterior connectivity deficits are partly responsible for cognitive deficits in ASD(Belmonte et al., 2004; Just et al., 2004). Previous task-based functional magnetic resonance imaging (fMRI) studies primarily using region-of-interest (ROI) analyses found support for the hypo-connectivity theory (Just et al., 2012; Minshew and Williams, 2007). These experiments found hypo-connectivity within the temporal–parietal junction in a theory of mind task (Kana et al., 2009), the limbic system in a face perception task (Kleinhans et al., 2008), between the frontal and parietal regions in a working memory task (Koshino et al., 2005), and between the frontal, parietal and occipital regions in a cognitive control task (Solomon et al., 2009). However, later task-based fMRI studies found hyper-connectivity in connections involving the posterior superior temporal sulcus in visual search tasks (Shih et al., 2011), the medial temporal lobe in face perception tasks (Welchew et al., 2005), within the left hemisphere in a source recognition task (Noonan et al., 2009), between the inferior frontal gyrus, and between the inferior parietal lobule and the superior temporal sulcus in

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semantic judgments and letter decision tasks (Shih et al., 2010). These results suggested that ASD could also be characterized by hyper-connectivity, providing evidence against a pure hypo-connectivity account (Kana et al., 2011).

Recently, resting-state fMRI (rsfMRI), has emerged as a powerful tool for examining intrinsic functional brain connectivity in clinical pediatric populations. Resting-state fMRI offers two advantages over task-based fMRI. First, it allows easier data collection from special populations such as young children with ASD, who have difficulties with long task-based fMRI experiments (Yerys et al., 2009). Second, it identifies underlying intrinsic functional networks that are not confounded by differences in task performance or strategy differences commonly found between individuals with ASD and neurotypical controls. Resting-state fMRI typically involves instructing participants to rest for 5–8 min while blood oxygen level dependent (BOLD) signals are acquired with MRI. By focusing on temporal correlations of the BOLD signal between functionally coupled brain regions, it is possible to identify intrinsically connected functional networks that are not confounded by cognitive tasks (Biswal et al., 1995; Bressler and Menon, 2010).

Resting state fMRI studies in neurotypical individuals have identified several major intrinsically connected networks related to visual, motor, auditory, memory and executive processes (Damoiseaux et al., 2006). Research examining individuals with ASD has recently focused on hypo- and hyper-connectivity differences observed in two major large-scale brain networks. The default mode network (DMN) consists of key nodes in the posterior cingulate cortex (PCC), the medial temporal lobes (MTL) and the medial prefrontal cortex (MPFC) and is active in self-related tasks such as autobiographical memories or social tasks such as theory of mind (Fox and Raichle, 2007; Spreng et al., 2009). The salience network (SN) involves the anterior insula (AI) and the anterior cingulate cortex (ACC) and is thought to regulate switching of endogenous and exogenous attention to relevant stimuli that helps in guiding behavior (Uddin, 2015). Studies using rsfMRI have found both hypo- and hyper-connectivity of these and other functional networks when comparing individuals with ASD with neurotypical (NT) individuals. Hypo-connectivity in ASD compared with TD individuals has been identified in connections between the insula and amygdala (Ebisch et al., 2011) and most consistently between connections of nodes within the DMN(Assaf et al., 2010; Ebisch et al., 2011; Kennedy and Courchesne, 2008a; Monk et al., 2009; Weng et al., 2010). Hyper-connectivity in ASD compared with TD individuals has been identified in motor and visual networks, as well as the DMN and SN(Uddin et al., 2013; Washington et al., 2014), and between striatal areas and the insula (Di Martino et al., 2011). Finally, one study has even demonstrated extremely small to no differences in functional connectivity in ASD compared with neurotypical adults (Tyszka et al., 2014), producing additional conflicting evidence.

Although methodological differences surely contribute to the mixed findings in the literature (Muller et al., 2011), a more recent idea attempting to reconcile these discrepant findings proposes that hyper-connectivity may be more characteristic of young children with ASD, while hypo-connectivity may begin to emerge in adolescence and persist into adulthood. In a review of the rsfMRI functional connectivity literature in ASD it is suggested that studies demonstrating hyper-connectivity have typically examined children less than 12 years of age, while studies demonstrating hypo-connectivity have typically examined adolescents and adults over the age of 12 (Uddin et al., 2013). The authors proposed that a developmental account hypothesizing early childhood hyper-connectivity and later adolescent and adult hypo-connectivity in ASD compared with TD could partially account for the mixed functional connectivity findings in the literature.

Previous functional connectivity studies have focused on a single age group (e.g., childhood, adolescence, or adulthood), mixed age groups (e.g., combining childhood and adolescence, or adolescence and adulthood), or used a linear regression correlational approach across a single group of subjects containing various age ranges (Assaf et al., 2010; Kennedy and Courchesne, 2008b; Monk et al., 2009). Several studies exploring whole-brain connectivity have included subjects with a wide range of ages, allowing for the possibility that a certain age group was driving the functional connectivity findings in the results (Assaf et al., 2010; Gotts et al., 2012). Therefore, an important gap in the literature concerns the principled examination of functional connectivity alterations in ASD across different developmental stages. In the current work we stratify individuals into age cohorts to directly test if some of the mixed findings throughout the literature can be accounted for by explicitly sorting groups of ASD and TD participants according to their ages.

An additional aspect of network connectivity that has received less attention in ASD research is how correlations between networks compare to that observed in the neurotypical population. Previous research has shown that the DMN, referred to as a 'task-negative network' (TNN), typically exhibits negative correlations with task-positive networks (TPN) such as the dorsal attention network (DAN) (Fox et al., 2005). The TNN nomenclature refers to the fact that nodes of the DMN typically show reductions in activity when a participant is focused on a task demanding exogenous attention while TPN refers to the fact that nodes of the DAN typically show increases in activity during such a task. Thus these networks are often referred to as "anti-correlated" because when a TPN is active the TNN is not, and vice versa. The relationship between these networks relates to behavioral performance in the neurotypical population (Kelly et al., 2008), but is not well understood in ASD. Characterization of relationships between these two networks may have important implications for understanding brain dynamics in ASD.

A challenge to synthesizing the functional connectivity literature in autism is that several studies have used ROI-based analyses that are difficult to compare with each other, as they are often linked to hypotheses about specific functional circuits (Abrams et al., 2013; Kennedy and Courchesne, 2008b; Lynch et al., 2013). The current study sought to compare whole-brain functional connectivity in ASD and TD individuals using an entirely data-driven approach. We explored the nature and extent of functional differences both within- and between-networks when comparing ASD and TD individuals across three age groups — children (under 11), adolescents (11–18), and adults (over 18). In order to assess within-network group differences in functional connectivity, we used independent component analysis (ICA) (Beckmann et al., 2005) across three different age groups to examine if the developmental trajectory of hyper- to hypo-connectivity in children to adults respectively, as predicted by Uddin and colleagues (Uddin et al., 2013) would be present. To assess between-network group differences in functional connectivity, we applied a network analysis to examine how correlations between networks potentially differ across the three age groups. This approach of exploring within- and between-network functional connections was adapted to elucidate how large-scale brain networks in ASD compare to those observed in age-matchedTD individuals across development.

2. Methods

2.1. Participants

We used data from the Autism Brain Imaging Data Exchange (ABIDE), a publicly available data set (http://fcon_1000.projects.nitrc.org/indi/abide/) (Di Martino et al., 2014). Only data collected at the New York University Langone Medical Center were utilized to avoid cross-study methodological acquisition differences. To explore the effects of participant age on functional connectivity, we divided the data into three age groups of ASD and TD participants: young children under 11 years of age ($n = 52$), adolescents from 11–18 years of age ($n = 56$), and adults over 18 years of age ($n = 36$; Table 1). Individuals with ASD had a clinical DSM-IV diagnosis of Autistic Disorder, Asperger's syndrome, Pervasive Developmental Disorder Not-Otherwise Specified (PDD-NOS) while TD participants were required to have no Axis-I disorders based on the KSADS-PL questionnaire.