HHS Public Access

Author manuscript

Autism Res. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Autism Res. 2016 January ; 9(1): 43–54. doi:10.1002/aur.1494.

Local brain connectivity across development in autism spectrum disorder: A cross-sectional investigation

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Abstract

Lay Abstract—There is a general consensus that autism spectrum disorder (ASD) is accompanied by alterations in brain connectivity. Much of the neuroimaging work has focused on assessing long-range connectivity disruptions in ASD. However, evidence from both animal models and postmortem examination of the human brain suggests that local connections may also be disrupted in individuals with ASD. Here we investigated the development of local connectivity across three age cohorts of individuals with ASD and typically developing (TD) individuals. We find that in typical development, children exhibit high levels of local connectivity across the brain, while adolescents exhibit lower levels of local connectivity, similar to adult levels. On the other hand, children with ASD exhibit marginally lower local connectivity than TD children, and adolescents and adults with ASD exhibit levels of local connectivity comparable to that observed in neurotypical individuals. During all developmental stages -- childhood, adolescence, and adulthood -- individuals with ASD exhibited lower local connectivity in brain regions involved in sensory processing and higher local connectivity in brain regions involved in complex information processing. Further, higher local connectivity in ASD corresponded to more severe ASD symptomatology. Thus we demonstrate that local connectivity is disrupted in autism across development, with the most pronounced differences occurring in childhood.

Scientific Abstract—There is a general consensus that autism spectrum disorder (ASD) is accompanied by alterations in brain connectivity. Much of the neuroimaging work has focused on assessing long-range connectivity disruptions in ASD. However, evidence from both animal models and postmortem examination of the human brain suggests that local connections may also be disrupted in individuals with the disorder. Here we investigated how regional homogeneity (ReHo), a measure of similarity of a voxel's timeseries to its nearest neighbors, varies across age in individuals with ASD and typically developing (TD) individuals using a cross-sectional design. Resting-state fMRI data obtained from a publicly available database were analyzed to determine group differences in ReHo between three age cohorts: children, adolescents, and adults. In typical development, ReHo across the entire brain was higher in children than in adolescents and adults. In contrast, children with ASD exhibited marginally lower ReHo than TD children, while adolescents and adults with ASD exhibited similar levels of local connectivity as age-matched neurotypical individuals. During all developmental stages, individuals with ASD exhibited lower

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local connectivity in sensory processing brain regions and higher local connectivity in complex information processing regions. Further, higher local connectivity in ASD corresponded to more severe ASD symptomatology. These results demonstrate that local connectivity is disrupted in ASD across development, with the most pronounced differences occurring in childhood. Developmental changes in ReHo do not mirror findings from fMRI studies of long-range connectivity in ASD, pointing to a need for more nuanced accounts of brain connectivity alterations in the disorder.

Keywords

autism; brain development; resting state functional MRI; regional homogeneity

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social interaction and social communication deficits, and the presence of restricted and repetitive behaviors (American Psychiatric Association, 2013). Individuals with ASD exhibit atypical patterns of brain connectivity as measured both with *in vivo* neuroimaging techniques and post-mortem investigation (Minshew and Williams, 2007). The majority of previous research has focused on examining long-range connectivity aberrances in ASD (Kana et al., 2011; Vissers et al., 2012). In childhood, long-range functional brain connections are largely over-connected (Supekar et al., 2013; Uddin et al., 2013). On the other hand, adults with ASD can exhibit long-range functional under-connectivity (Just et al., 2012). Recent work has also demonstrated that by adulthood, long-range connectivity differences are no longer detectable compared with neurotypical adults (Nomi and Uddin, 2015; Tyszka et al., 2014). In contrast to the extensive work on long-range connectivity in ASD, less attention has been focused on assessing short-range connectivity alterations in the disorder.

Evidence for short-range connectivity abnormalities was first demonstrated by structural and post-mortem studies of individuals with ASD. Early in life, beginning between 2 to 3 years, there is increased grey and white matter cerebral volume in children with ASD compared with age-matched typically developing (TD) children (Courchesne et al., 2001) and developmentally delayed children (Sparks et al., 2002). By adulthood, the brain volume discrepancy normalizes, as adults and adolescents with ASD and healthy controls have similar brain matter volume (Aylward et al., 2002; Courchesne et al., 2001). Based on these results, one of the earliest theories of autism emerged, purporting that the disorder is characterized by local (or short-range) over-connectivity and disrupted long-range connectivity (Belmonte et al., 2004; Courchesne and Pierce, 2005). Specifically, it was observed that the frontal cortex in ASD may be excessively connected to itself, while connections between the frontal cortex and distal brain regions may be poorly synchronized (Courchesne and Pierce, 2005). Previous local connectivity studies of ASD have produced mixed findings (Paakki et al., 2010; Shukla et al., 2010). In a systematic review of the limited data on local connectivity, little empirical support was found for the theory of local over-connectivity in ASD (Vissers et al., 2012). Due to the lack of data and inconsistency in the literature, there is a need for further study of local connectivity in ASD across the lifespan.

It has recently been noted that developmental trajectories of functional connectivity in ASD are incompletely understood, and that over- and under-connectivity findings may be age-specific (Uddin et al., 2013). In parallel with the observation that a developmental perspective may clarify the nature of brain connectivity aberrations in autism, recently developed analytic techniques are enabling more sophisticated examination of local functional connectivity. One approach, termed regional homogeneity (ReHo), can be used to measure the degree of short-range (local) connectivity within a discrete region of the brain (Zang et al., 2004). ReHo analysis of local connectivity uses Kendall's coefficient of concordance (Kendall and Gibbons, 1990), a measure of coherence between one voxel and the surrounding 26 voxels in the brain. This metric has high test-retest reliability (Zuo et al., 2013), which is an important factor for establishing brain-behavior correlations and studying clinical populations (Zuo and Xing, 2014). This measure can help answer questions about brain development in autism that have been difficult to answer thus far due to the sample limitations in postmortem studies.

While the functional significance of ReHo is still under investigation, it has been shown that areas comprising the default mode network (Raichle et al., 2001) have the highest regional homogeneity in the brain (Jiang et al., 2014; Long et al., 2008; Wu et al., 2007; Zang et al., 2004). Jiang and colleagues (2014) reported that in primary sensory areas such as the ventral visual stream, lower regional homogeneity values indicate higher information processing complexity, while higher values indicate primary information processing. In higher-order association areas such as the posteromedial cortex, lower regional homogeneity values indicate the subregion's connectivity to lower-order information processing areas, whereas higher values indicate that subregion's connectivity to multimodal association areas. All of the aforementioned results have only been demonstrated in adults. Lopez-Larson and colleagues (2011) studied the development of ReHo in TD individuals and reported an age-related decrease in regional homogeneity across grey matter in the brain. It is possible that this reflects increases in pruning in the developing brain, and thus decreases in the strength of local connectivity.

There are few studies of regional homogeneity in ASD (Di Martino et al., 2014; Jiang et al., in press; Maximo et al., 2013; Paakki et al., 2010; Shukla et al., 2010) and none have examined developmental changes in ReHo in ASD. This analysis has great potential to test the short-range over-connectivity hypothesis in autism and the extent to which such findings are linked with distinct developmental stages. Current ReHo studies of ASD reveal inconsistent results, reporting both higher and lower regional homogeneity compared with TD participants. Some studies report lower ReHo in the middle frontal gyrus (Paakki et al., 2010; Shukla et al., 2010) while others report higher ReHo in this area (Jiang et al., in press; Maximo et al., 2013) in ASD. The right insula, an area that has been implicated in autism (Uddin and Menon, 2009), shows lower regional homogeneity in ASD (Jiang et al., in press; Paakki et al., 2010). Similar to the discrepancies of results in long-range functional connectivity analyses (Uddin et al., 2013), some of the inconsistent results for ReHo may be accounted for by adopting a developmental perspective. Jiang et al. (in press) found that in the left precuneus, individuals with ASD had increased ReHo with age, while typical controls exhibited decreased ReHo with age. These authors also found positive correlations with ASD symptom severity and local connectivity in the middle frontal gyrus and superior

temporal sulcus. These initial studies highlight the potential importance of ReHo analyses in autism and how they can inform our understanding of local connectivity measures, as well as how they can complement long-range connectivity analyses.

There is a dearth of studies of ASD considering brain connectivity in a developmental context (Di Martino et al., 2014; Uddin et al., 2013). The present study addresses this gap in the literature by measuring ReHo in three cohorts of individuals with ASD and TD individuals stratified by age. Additionally, we assess whether ReHo is correlated with a behavioral measure of symptom severity in the ASD group. Following the abnormal pattern of brain growth in autism (Courchesne et al., 2001), we predict there will be abnormally higher local connectivity in children with autism, but this difference will normalize through adolescence to adulthood.

Methods

Participants

Data from the Autism Brain Imaging Data Exchange http://fcon_1000.projects.nitrc.org/indi/abide/ (ABIDE, Di Martino et al., 2014) contributed by New York University Langone Medical Center was analyzed. The present study included 106 total participants. There were 53 participants each in the ASD and TD groups. Participants were further stratified into Child (< 11 years, $n = 36$), Adolescent (11–18 years, $n = 40$), and Adult (≥18 years, $n = 30$) groups. Inclusion in the ASD group was determined by: 1) a clinician's DSM-IV-TR diagnosis of Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder Not-Otherwise-Specified, 2) meeting the clinical cut-off on the Autism Diagnostic Observation Schedule (total score > 7, ADOS, Lord et al., 1989), and when possible, 3) confirmation with the Autism Diagnostic Interview-Revised (ADI-R, Lord et al., 1994). Ninety percent of the ASD sample met criteria on the ADOS for an ASD, and the remaining 5 participants met criteria on the ADI for autism. Typically developing (TD) children had no current Axis-I disorders, assessed with the Schedule of Affective Disorders and Schizophrenia for Children- Present and Lifetime version for both the parent and child (KSADS-PL, Kaufman et al., 1997). For neurotypical adults (18 and older), the absence of Axis-I disorders were determined by the Structured Clinical Interview for DSM-IV-TR Axis-I Disorders, Non-Patient Edition (SCID-I/NP, First et al., 1995) and the Adult ADHD Clinical Diagnostic Scale (ACDS, Adler and Spencer, 2004). Full-scale (FSIQ), verbal (VIQ), and performance (PIQ) IQ were assessed for each participant with the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999). The ASD and TD participants were matched within age cohort on FSIQ, VIQ, PIQ, gender, and head motion (measured by mean framewise displacement [FD], Power et al., 2012). The sample consisted of all right-handed participants, as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). Children and adolescents with ASD were given the Social Communication Questionnaire (SCQ, Berument et al., 1999) as a measure of autism symptom severity. See Table 1 for a summary of participant demographics.

The NYU institutional review board approved all procedures for data collection and sharing. Written informed consent was obtained from each participant.

Data Acquisition

Data were acquired at NYU with a 3 Tesla Allegra (TR = 2000 ms; TE = 15 ms; flip angle = 90°; FOV = 240 mm; voxel size = 3×3×4 mm; number of slices = 33; 4 mm slice thickness). For resting state scans, participants were asked to keep their eyes open and fixate on a cross hair. Resting state scans lasted 6 minutes for a total of 180 volumes. High-resolution T1 weighted structural scans were also acquired for each participant using a magnetization prepared gradient echo sequence (TR = 2530 ms; TE = 3.25 ms; inversion time = 8.07 minutes; flip angle = 7 °; 128 slices; 1 volume FOV = 256 mm). For further details regarding scanning protocols, see Di Martino et al. (2014).

Data Preprocessing

Data preprocessing was conducted using the Data Preprocessing Assistant for Resting-State fMRI-Advanced edition (DPARSF-A, Yan and Zang, 2010), which combines functions of FSL (FMRIB Centre, University of Oxford, www.fmrib.ox.ac.uk/fsl) and SPM (http://www.fil.ion.ucl.ac.uk/spm). Participants were excluded based on excessive motion (i.e., if their rotational or translational motion exceeded 2 mm or 2 degrees). Motion in the six rigid directions (translational and rotational x, y, and z) are presented for each diagnostic group within each age cohort in Supplementary Table 1. Diagnostic groups within each age cohort did not differ significantly in their motion in any of the six directions. In order to achieve the most test-retest reliable ReHo calculations, we followed the data processing suggestions from Zuo and colleagues (2014). Functional images underwent removal of the first 4 time points (Di Martino et al., 2014), slice time correction, spatial realignment, nuisance covariate regression (linear trends, Friston 24 motion parameters, white matter (WM), and cerebrospinal fluid (CSF) signal), band-pass filtering (.01–.08 Hz), normalization to a standard MNI152 template, and motion scrubbing at a .5 mm threshold (Power et al., 2012). Structural images underwent brain extraction, manual coregistration to the functional image, and segmentation into grey matter, WM, and CSF components. Quality control steps where data were visually inspected occurred after: brain extraction, coregistration, normalization, and ReHo map calculation. All participants had no more than 20% of time points removed after the scrubbing procedure, and diagnostic groups did not differ significantly on percentage of data removed within age cohorts (see Table 1). In order to determine whether the motion correction procedures (Friston 24 regression and scrubbing procedure) affect the results, we also employed a minimal motion preprocessing pipeline. This pipeline was identical to the original, but instead of using a Friston 24 regression and scrubbing, only the six rigid motion parameters were regressed from the data. Results from this alternate pipeline are presented in Supplementary Materials.

Regional Homogeneity Analyses

Regional homogeneity (ReHo) was calculated by computing Kendall's coefficient of concordance for one voxel and the surrounding 26 voxels (Kendall and Gibbons, 1990):

$$W=\frac{\sum (R_i)^2-n(\overline{R})^2}{\frac{1}{12}K^2(n^3-n)}$$

where W is the KCC among the 27 voxels, R_i is the sum rank of the ith time point, $\bar{R} = ((n + 1)K/2)$ is the mean of the R_i's, K is the number of time series within a measured cluster (here, $K = 27$; one given voxel plus 26 of its neighbors), n is the number of ranks (the number of volumes) (Song et al., 2008; Zang et al., 2004). The number of volumes differs for each ReHo calculation due to motion scrubbing, so n ranges from 146 to 176. Values range from perfectly concordant ($W = 1$) to not concordant at all ($W = 0$).

Following ReHo calculation, maps were smoothed with a 6 mm Gaussian kernel as in previous work (Maximo, 2013; Shukla, 2010). Because ReHo values at the brain edge would inherently be including voxels outside of brain space, ReHo values were only calculated for every voxel within an eroded brain mask to remove invalid data at the brain edges. Global mean ReHo was calculated by computing the mean ReHo for the entire brain (within the eroded mask) for each subject. One map in the adolescent group and one map in the adult group had signal dropout in the ventral brain, thus distorting the ReHo map. Therefore, the ventral brain and cerebellum were masked in these two subjects before bringing them to group analyses.

Average ReHo maps were computed within each diagnostic and age cohort (6 total maps) and their global means were computed. No standardization procedure was performed here in order to preserve the interpretable KCC values and to detect global group differences, as in previous publications (Lopez-Larson et al., 2011; Maximo et al., 2013). A 2 × 3 ANCOVA was calculated to assess the main effect of diagnosis (ASD or TD), age cohort (Child, Adolescent, Adult), and their interaction on global mean ReHo values. Because each age cohort had a different percentage of data scrubbed due to motion, the percentage of data scrubbed was used as a covariate in the model.

Individual ReHo maps were standardized by dividing original KCC values by the global mean for each individual to ensure valid comparisons between subjects. Differences in ReHo between ASD and TD groups within each age group using the standardized maps were assessed with an independent samples t-test using SPM8. Statistically significant clusters were determined by Gaussian random field theory, with a $p < .01$ voxel-level threshold and $p < .05$ cluster-level threshold, as in previous publications (Di Martino et al., 2014; Jiang et al., in press).

Brain-Behavior Relationships

A multiple linear regression model was used to assess the relationship between global mean ReHo for individuals and SCQ values in the ASD group for children and adolescents. SCQ data were unavailable for adults. Two outliers were removed from the analysis, as their global mean ReHo scores were 3+ SD above the mean. No bivariate outliers were detected. Because age groups were not matched on percentage data scrubbed, percentage data scrubbed was controlled for in the model. To determine whether a global mean ReHo-by-age interaction was present, the model also included an interaction term comparing children to adolescents. The interaction term was calculated by multiplying the centered global mean ReHo values by the dummy coded age variable. The model was entered in these steps: 1) percentage data scrubbed 2) global mean ReHo, centered 3) age: dummy-coded 4) interaction term: global mean ReHo-by-age.

Results

Patterns of both higher and lower regional homogeneity in the ASD group compared with the TD group were observed in comparisons across all age cohorts. Results were largely consistent across the two preprocessing pipelines, but more extensive group differences emerged after implementation of the scrubbing procedure. In order to best account for motion differences within the sample, the results presented here are from the scrubbing pipeline. See Table 2 for all diagnostic group differences. Supplementary Table 2 and Supplementary Figures 1, 2, and 3 contain results from the minimal preprocessing pipeline.

ReHo in Children with ASD and TD Children

When comparing children in the ASD and TD groups, we observed higher ReHo in the ASD group in the right precentral gyrus, superior temporal gyrus, and inferior frontal gyrus and lower ReHo in the left accumbens, lateral occipital cortex, and cerebellar lobule VI (Figure 1). The pattern in children with ASD appears to be higher ReHo in more anterior regions and lower ReHo in posterior regions. Here, anterior refers to regions anterior to the central sulcus, such as frontal lobe, anterior temporal lobe, basal ganglia, and the amygdala. Posterior regions refer to regions posterior to the central sulcus, such as parietal cortex, occipital cortex, posterior temporal lobe, and the cerebellum.

ReHo in Adolescents with ASD and TD Adolescents

Comparing adolescents in the ASD and TD groups, we observed higher ReHo in the ASD group in the right operculum, amygdala, and cerebellar lobule IX and lower ReHo in left posterior cingulate, primary somatosensory cortex, and bilateral cuneus (Figure 2). ReHo differences appear to be more heterogeneous in the adolescent sample compared with the child and adult groups, as a clear anterior-posterior ReHo dissociation did not emerge.

ReHo in Adults with ASD and Neurotypical Adults

Lastly, comparing adults in the ASD and neurotypical groups, we observed higher ReHo in the ASD group in the right temporal pole and bilateral supplementary motor cortices and lower ReHo in bilateral cerebellar regions (Figure 3). Similar to the child cohort, the ASD group had higher ReHo in more anterior regions of the brain and lower ReHo in posterior regions compared with age-matched neurotypical adults.

Diagnosis x Age Group Interactions

When comparing the effect of diagnosis and age group on global mean ReHo measures, there were no significant main effects of diagnosis or age group. There was a significant interaction of diagnosis and age group, $F(2, 99) = 3.42$, $p = .037$, partial $\eta^2 = .07$ (Figure 4). Global mean ReHo values were marginally higher for TD children ($M = .434$, $SD = .03$) than children with ASD ($M = .418$, $SD = .03$), $F(1, 34) = 3.28$, $p = .079$. Global mean ReHo values were not significantly different between diagnostic groups in adolescents or adults.

Brain-Behavior Relationships

The multiple regression model with all four predictors was not significant, $F(4, 28) = 1.27$, $p > .05$. Global mean ReHo values were positively associated with SCQ total score in both children and adolescents with HFA, $t(30) = 2.16$, $p = .039$, $\beta = .40$. The interaction between age group and global mean ReHo values was not significant in predicting SCQ scores (Figure 5, Table 3).

Discussion

It has been proposed that the brains of individuals with ASD exhibit local over-connectivity (Courchesne and Pierce, 2005). However, many open questions remain with regards to the nature, anatomical location, and developmental expression of this over-connectivity. Here we explored local connectivity across development in ASD and TD individuals using a cross-sectional design. This data-driven approach allowed us to examine whether there are short-range connectivity differences in ASD and how this may change across the lifespan. We found that in children and adults, individuals with ASD exhibited higher local connectivity compared with age-matched TD individuals in anterior areas of the brain, particularly within the frontal cortex. In children and adults, individuals with ASD tended to have lower local connectivity in posterior brain areas such as the occipital cortex and cerebellum. In contrast, the adolescent group exhibited a heterogeneous grouping of higher and lower values of local connectivity throughout the brain. Specifically, in adolescents with ASD there was lower local connectivity in occipital and parietal regions and higher local connectivity in the operculum and cerebellum compared with TD adolescents.

Implications for brain development in ASD

The developmental trajectory of local brain connectivity in ASD was largely similar to that of TD individuals. The overall ReHo in TD individuals was high in childhood, lower in adolescence, and remained low in adulthood. These results replicate the findings of Lopez-Larson and colleagues (2011), who found that local connectivity decreases with age. In individuals with ASD, ReHo was lowest during childhood and reached typical levels by adolescence. The findings in TD individuals support the hypothesis that the development of local brain connections are emphasized in childhood, then later switch to support global connectivity (Fair et al., 2009). This is in line with other reports of weakening of short-range functional connections with typical development (Supekar et al., 2009).

The emerging pattern of ReHo differences between the ASD and TD groups reveals higher ReHo in ASD in higher-level processing areas of the brain and lower ReHo in primary processing areas. In typical brain development, primary sensory areas tend to mature first and higher-level processing areas develop later to integrate information from the primary information processing areas (Gogtay et al., 2004). If lower ReHo values correspond to higher functional integration and complexity of information processing (Jiang et al., 2014), perhaps primary information processing areas in ASD are less segregated, while higher-level processing areas are more segregated and less functionally integrated in ASD compared with TD individuals. While those with ASD exhibit differences in brain organization in terms of regional specialization and integration compared to neurotypical individuals, this may not

reflect an abnormality in information processing. It is possible that in ASD, primary information processing areas require the input of other brain regions to successfully complete a task, thus resulting in higher-than-expected functional integration, and thus lower ReHo values. Similarly, higher-level information processing areas may be more specialized to complete tasks than in neurotypical individuals, resulting in lower-than-expected ReHo values.

These findings partially support the frontal lobe hypothesis of autism, in which the frontal cortex is locally over-connected while fronto-parietal regions are underconnected (Courchesne and Pierce, 2005). Courchesne and Pierce (2005) present evidence of frontal lobe enlargement, disrupted minicolumn organization, and hyperimmune activation in children as young as 2 years. As would be predicted by the frontal lobe hypothesis, we find that children and adults with ASD exhibited local over-connectivity in frontal regions such as premotor cortex and the inferior frontal gyrus. Likewise, children and adults with ASD exhibited decreased local connectivity in the cerebellum, a region consistently implicated in ASD (Shakiba, 2014). Like frontal regions, the cerebellum shows hyperimmune activation in ASD, as shown by postmortem studies (Vargas et al., 2005).

The results for adolescents, however, do not fit the frontal lobe over-connectivity model. This may be due to the heterogeneous nature of brain development for children in this age range (here, 11 to 18). There is a mixture of pre- and post-pubertal children in this age range, thus leading to differences in the stage of brain development and potentially influencing the heterogeneity of the results. Functional connectivity patterns in the brain undergo protracted periods of change during puberty (Blakemore et al., 2010), a time that coincides with drastic changes in social, cognitive, and affective processes. It is known that pubertal status affects both brain structure and function. For example, white matter integrity as measured with callosal thickness is greater in more sexually mature children (Chavarria et al., 2014). Functional activation studies provide evidence for dissociable effects of pubertal hormones and age on the adolescent brain (Galván et al., 2012; Goddings et al., 2012). Pubertal stage has also been shown to affect volume of subcortical limbic structures (Blanton et al., 2012). At present, nothing is known regarding how pubertal stage affects brain connectivity in ASD, and whether the effects are different from those observed in the typically developing brain. These remain important questions for future work, in which pubertal stage of participants will need to be explicitly characterized.

Given that children and adults with ASD exhibited similar regions of aberrant local connectivity, an alternative explanation for the wide-spread differences in local connectivity in adolescents may be the unique pattern of brain development during the adolescent period. As opposed to representing a linear intermediate between child and adult brain development, the brains of adolescents exhibit a distinct profile of maturity (Casey et al., 2008). This is due to the presence of a mature limbic system, responding to emotional and rewarding stimuli, but an underdeveloped prefrontal control system, which can inhibit the strong impulses generated by subcortical structures (Casey et al., 2008). The unique developmental period of adolescence may account for local connectivity results in the current study that do not mirror findings from children and adults.

Comparison with previous ReHo studies of ASD

Previous studies of ReHo in ASD have revealed inconsistent results (Di Martino et al., 2014; Jiang et al., in press; Maximo et al., 2013; Paakki et al., 2010; Shukla et al., 2010). This study is the first to investigate ReHo in a developmental context in both typically developing individuals and individuals with ASD. By stratifying the participants by age, we were able to examine developmental changes in local connectivity and how they may be different in ASD. The present study replicated many of the findings of the Shukla et al. (2010) study. For example, here we also report that individuals with ASD have higher ReHo in the right superior temporal gyrus, inferior frontal gyrus, and the amygdala and lower ReHo in the left posterior cingulate and lateral occipital cortices. We report ASD-related increases in ReHo in bilateral supplementary motor cortices, which overlaps with the right dorsal superior frontal cortex, as reported by Di Martino et al. (2014). While two studies reported ASD-related decreases in ReHo in the right insula (Jiang et al., in press; Paakki et al., 2010), the present study conversely reports ASD-related increases in ReHo in the right opercular cortex extending to the insula. Maximo et al. (2013) reported ASD-related decreases in ReHo in higher-order areas such as the posterior cingulate cortex and medial prefrontal lobe and ASD-related increases in ReHo in primary visual areas. The present study did not replicate findings from the Maximo et al. (2013) study. Instead, we report findings of general ASD-related *decreases* in ReHo in primary information areas, such as visual and somatosensory cortices, and ASD-related *increases* in ReHo in higher-order association areas such as the frontal cortex and operculum/insula.

Inconsistencies between the present findings and the extant ReHo literature in ASD may be explained by several factors. The discordant results may be due to the heterogeneity of symptomatology in ASD, which could lead to non-representative samples in some of the studies. Keown and colleagues (2013) observed a different pattern of local connectivity results between adolescents with higher-symptoms and lower-symptoms of ASD within the high-functioning spectrum. This suggests that local connectivity patterns are sensitive to differences in ASD symptomatology, also demonstrated by the brain behavior relationships established by this study and others (Jiang et al., in press; Maximo et al., 2013). Some of the discrepancies might also be explained by the wide range of ages sampled in past studies. Further, differences might be accounted for by differences in methodology such as ReHo cluster size (e.g., 7 compared to 27), smoothing kernel, and threshold cutoffs for significant clusters.

Underlying causes of over-connectivity

The altered trajectory of local connectivity in ASD may be related to faulty synaptic pruning. Animal studies show that in typical development, the brain initially produces more synapses than are necessary throughout primary, secondary, and associative cortices (Rakic et al., 1986). Following this surge in synapse production, synaptic pruning occurs via a competitive selection for important connections. Synchronous activity between neurons tends to strengthen their connections, while asynchronous activity leads to synaptic pruning and a loss of connection between those neurons (Purves and Lichtman, 1980). Recent post-mortem studies have demonstrated ASD-related reductions in synaptic pruning in the temporal lobe between childhood and adolescence compared to typically developing

controls (Tang et al., 2014). Based on work with mouse models of autism, Tang and colleagues (2014) proposed that reduced synaptic pruning may be caused by enhanced local excitatory connectivity via a reduction in the removal of synapses, or autophagy.

Jiang et al. (2014) reported that ReHo metrics follow the hierarchical pattern of organization across various brain networks, including the visual system. Higher ReHo values corresponded to lower-level visual processing areas like Broadmann area 17, and values continue to decrease along the ventral visual stream through Broadmann areas 20 and 21. They purport that higher ReHo values indicate a reduced complexity of information processing and increased functional segregation. Perhaps the developmental decline in overall ReHo in TD individuals indicates increased functional integration of brain regions as the brain matures. Further, the abnormal development of local connectivity in ASD may reflect differences in functional segregation and integration of brain areas.

Brain-Behavior Relationships

In both children and adolescents with ASD, higher overall local connectivity was related to poorer social communication skills. Jiang et al. (in press) also found a positive relationship between local connectivity in discrete brain regions and ADOS total, communication, and stereotyped behavior scores. This consistent brain-behavior relationship supports the importance of studying local connectivity in ASD. Higher local connectivity in children and adolescents may reflect lower functional integration of brain areas, which is perhaps associated with more severe ASD symptomatology. It may seem counterintuitive that (marginally) higher local connectivity in childhood is more typical but is also associated with greater ASD symptomatology. These results can be reconciled by assuming differences in information processing strategies in the brains of individuals with ASD and TD individuals. For example, the brains of individuals with ASD may require more functional integration (i.e., lower local connectivity) in order to operate at optimal levels, while brains of TD individuals may maintain higher functional segregation (i.e., higher local connectivity) in childhood.

Limitations

ReHo is not a direct measure of local connectivity, so results should be interpreted cautiously when drawing parallels to neural correlates. Due to the cross-sectional nature of the study, results should be interpreted cautiously when drawing conclusions about the development of local connectivity. Future studies should employ a longitudinal design to confirm the developmental trajectory found in the present study and explicitly characterize the pubertal stage of participants to determine the relationship between sexual maturity and development of local connectivity. We were limited to studying brain-behavior relationships in children and adolescents because our measure of symptom severity, the SCQ, was not available for the adult sample. Future research should characterize the relationship between local connectivity and ASD symptomatology throughout development, extending into adulthood.

Conclusions

Local connectivity development in ASD does not follow the same trajectory as in typically developing individuals. Anterior brain regions, including high-level processing areas, tend to have higher local connectivity, while posterior regions, including primary information processing areas, exhibit lower local connectivity in ASD compared to TD individuals. This aberrant local connectivity is related to poorer social communication skills. These findings support the frontal lobe dysfunction (Courchesne and Pierce, 2005) and disrupted connectivity theories (Kana et al., 2011) of autism and add to a growing literature demonstrating widespread connectivity abnormalities in ASD.

We demonstrate age-specific patterns of local connectivity alterations in ASD for the first time. In the adolescent group, findings were more heterogeneous than the child and adult groups, perhaps due to the fact that the adolescent group comprised a mixed group of pre- and post-pubertal children. Children with autism show atypicalities in pubertal development, with reports of both precocious (Majewska et al., 2014) and delayed onset (Knickmeyer et al., 2006). Previous neuroimaging studies have combined pre- and post-pubertal children together, and have not stratified samples based on pubertal stage. As a consequence, at present, nothing is known about pubertal development and brain connectivity in autism despite the known effects of sex hormones and puberty on brain structure and function. Future work should aim to assess the effects of pubertal stage on brain connectivity in ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant sponsor: National Institute of Mental Health, Slifka/Ritvo Innovation in Autism Research Award, NARSAD Young Investigator Grant

Grant number: K01MH092288

This work was supported by award K01MH092288 from the National Institute of Mental Health, a Slifka/Ritvo Innovation in Autism Research Award, and a NARSAD Young Investigator Grant to L.Q.U. Funding for the data collection of the NYU ABIDE data set was supported by the NIH (K23MH087770; R21MH084126; R01MH081218; R01HD065282), Autism Speaks, The Stavros Niarchos Foundation, The Leon Levy Foundation, and an endowment provided by Phyllis Green and Randolph Cowen.

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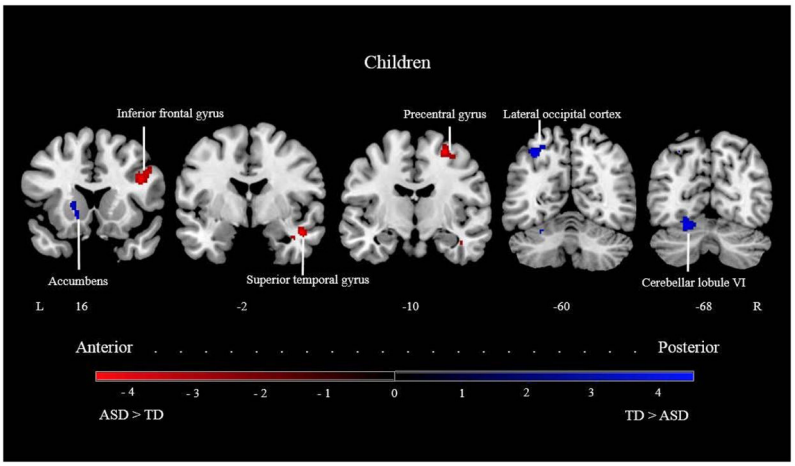

Figure 1.

Higher regional homogeneity in anterior regions of the brain and lower ReHo in posterior regions in children with ASD.

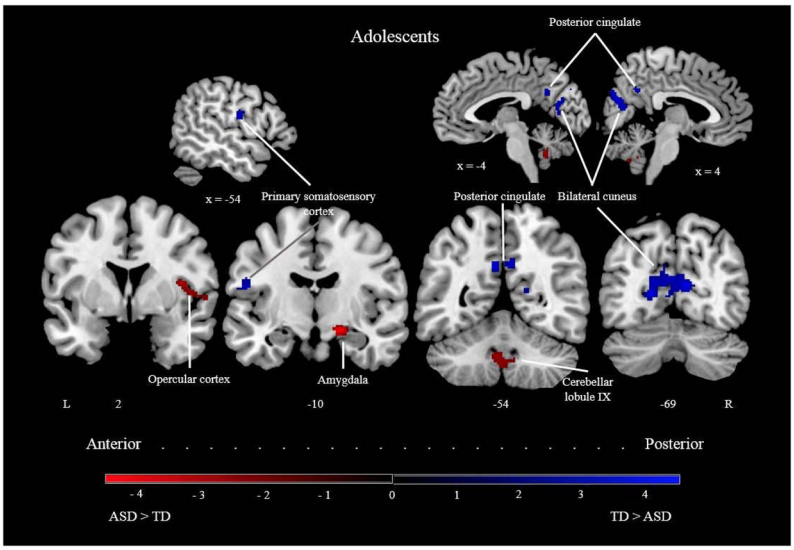

Figure 2.

Heterogeneous differences in the adolescent group with both higher and lower regional homogeneity throughout the brain in the ASD group.

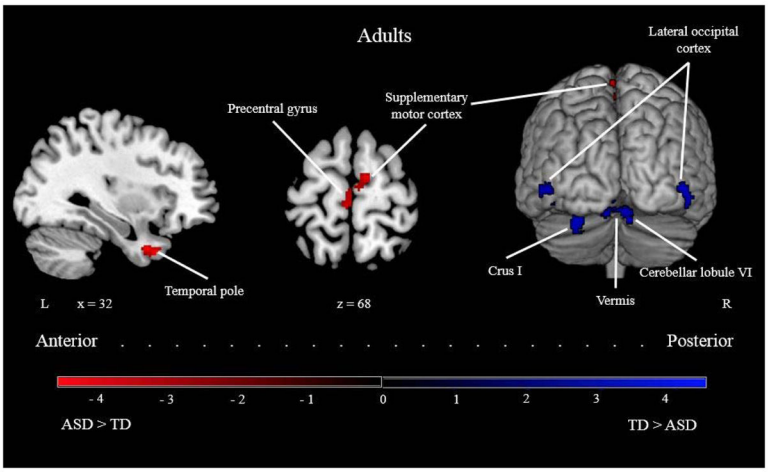

Figure 3.

Higher regional homogeneity in anterior regions of the brain and lower ReHo in posterior regions in adults with ASD, mirroring results in the child group.

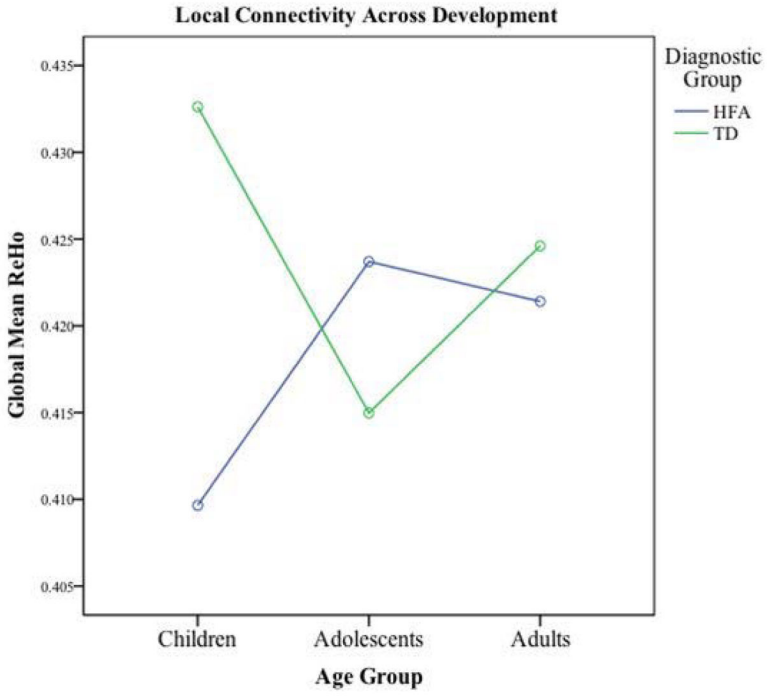

Figure 4.

Global mean regional homogeneity values for each diagnostic group within children, adolescent, and adult age cohorts. We found a significant age group-by-diagnosis interaction.

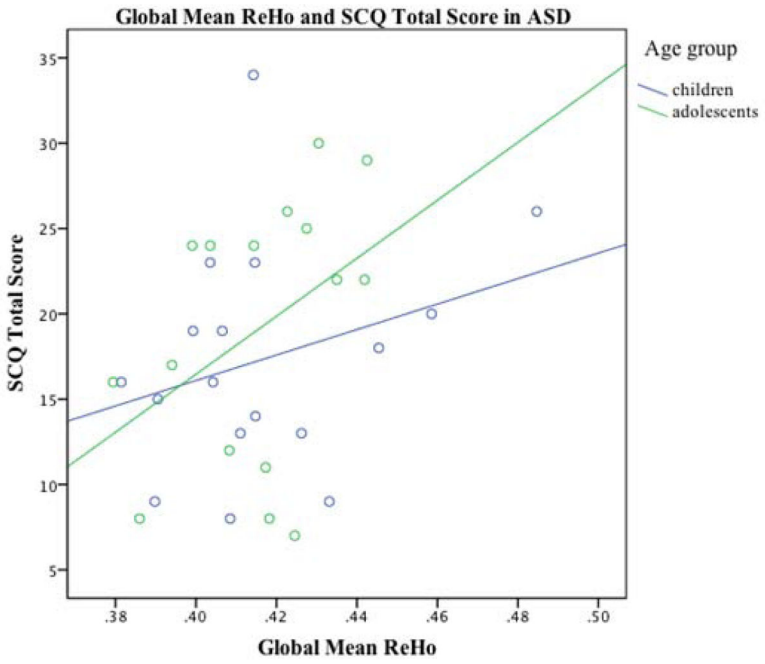

Figure 5.

Global mean regional homogeneity was positively associated with SCQ total score in the ASD group for both children and adolescents.

Table 1

Sample characteristics and diagnostic group differences.

	ASD		TD		
Children	**Mean(SD)**	**Range**	**Mean(SD)**	**Range**	***t*-value**
Gender	17 M/1 F	-	15 M/3 F	-	$\chi^2 = .60$
Age in years	9.26 (1.28)	7.13–10.96	9.32 (1.35)	7.19–10.86	−0.142
Full-scale IQ	112.44 (20.60)	84–148	112.72 (13.79)	80–138	−0.048
Verbal IQ	108.72 (15.16)	77–137	113.22 (12.94)	91–131	−0.958
Perceptual IQ	114.94 (23.08)	84–149	109.29 (15.35)	72–135	0.85
Mean ReHo	.418 (.03)	.38–.48	.434 (.03)	.39–.51	$-1.181^{\dagger}$
Data removed scrubbing (%)	3.80 (3.98)	0–12.99	2.20 (2.40)	0–7.91	1.459
Mean FD	.17 (.06)	.06–.28	.14 (.05)	.08–.26	1.601
ADOS Total	10.33 (4.23)	6–21	-	-	-
SCQ	17.35 (6.68)	8–34	3.50 (2.62)	1–8	5.61^{***}
Adolescents					
Gender	16 M/4F	-	16 M/4F	-	-
Age in years	13.58 (1.86)	11.01–17.88	14.28 (1.78)	11.03 – 17.70	−1.21
Full-scale IQ	104.55 (15.86)	78–132	104.95(15.67)	80–134	−0.08
Verbal IQ	103.5 (15.56)	79–139	107.35 (13.5)	80–132	−0.84
Perceptual IQ	104.85 (16.58)	79–132	101.15 (17.33)	67–137	0.69
Mean ReHo	.426 (.04)	.38–.54	.412 (.02)	.37–.46	1.49
Data removed scrubbing (%)	2.40 (3.95)	0–16.38	1.02 (1.32)	0–3.95	1.49
Mean FD	.15 (.06)	.07–.33	.12 (.05)	.04–.20	$1.87^{\dagger}$
ADOS Total	12.05 (4.65)	5–22	-	-	-
SCQ	19.24 (7.58)	7–30	2.77 (2.55)	0–9	8.36^{***}
Adults					
Gender	11 M/4 F	-	11 M/4 F	-	-
Age in years	25.57 (6.32)	18.58–39.10	24.20 (4.16)	19.13–30.78	0.70
Full-scale IQ	108.53 (15.18)	80–137	111.07 (11.04)	91–139	−0.52

	ASD		TD		
Children	**Mean(SD)**	**Range**	**Mean(SD)**	**Range**	***t*-value**
Verbal IQ	107.73 (18.55)	73–136	110.13 (11.27)	96–140	−0.43
Perceptual IQ	107.60 (11.70)	88–129	109.87 (11.00)	87–129	−0.55
Mean ReHo	.417 (.03)	.36–.46	.418 (.02)	.38–.45	−0.08
Data removed scrubbing (%)	.72 (1.18)	0–3.95	.11 (.32)	0–1.13	1.91†
Mean FD	.11 (.04)	.06–.16	.10 (.04)	.05–.20	0.73
ADOS Total	11.33 (4.17)	5–18	-	-	-
SCQ	-	-	-	-	-

$^{\dagger}p < .10$;

$^{***}p < .001$

FD: framewise displacement; ADOS: Autism Diagnostic Observation Schedule-IV; SCQ: Social Communication Questionnaire.

Table 2

Differences in ReHo between diagnostic groups within child, adolescent, and adult cohorts.

Children		**MNI coordinates**			**peak t-value**	**cluster size**
ASD>TD	**Cortical**	x	y	z		
	R precentral	28	−10	60	4.16	143
	R IFG	42	16	26	4.03	104
	R STG/WM	48	−2	−20	4.31	112
TD>ASD	**Cortical**					
	L lateral occipital	−34	−60	50	3.97	134
	Subcortical					
	L accumbens	−14	16	−6	3.17	87
	Cerebellar					
	L cerebellum lobule VI	−20	−68	−18	3.75	159
Adolescents						
ASD>TD	**Cortical**					
	R opercular cortex/insula	40	2	10	3.85	63
	Subcortical					
	R amygdala	18	−10	−14	5.47	67
	Cerebellar					
	L cerebellum IX	−4	−54	−36	3.16	120
TD>ASD	**Cortical**					
	Bilateral cuneus	18	−62	18	4.58	78
	L posterior cingulate	−6	−54	32	3.69	86
	L S1	−54	−8	20	3.66	63
Adults						
ASD>TD	**Cortical**					
	R temporal pole	32	16	−38	4.02	67
	R SMA/L precentral	8	−10	68	3.75	119
TD>ASD	**Cortical**					
	R lateral occipital	46	−66	−2	3.69	69
	L temporal-occipital/fusiform	−40	−60	−10	3.95	118

Children		MNI coordinates			peak t-value	cluster size
	Cerebellar					
	Vermis and Bilateral					
	Lobule VI	−2	−70	−14	4.44	268
	L Crus I	−28	−72	−28	3.8	116

IFG: inferior frontal gyrus; STG: superior temporal gyrus; WM: white matter; S1: primary somatosensory cortex; SMA: supplementary motor area.

Table 3

Multiple regression model of global mean ReHo values' association with autism symptom severity in children and adolescents with ASD.

Regression.		**Dependent Variable: SCQ scores**		
		B	**β**	**t**
Step1	Percent Data Scrubbed	−0.01	0.00	−0.02
Step2	Percent Data Scrubbed	−0.37	−0.17	−0.93
	Mean ReHo	127.68	0.40	2.16*
Step3	Percent Data Scrubbed	−0.30	−0.14	−0.72
	Mean ReHo	124.53	0.39	2.07*
	Age- Dummy Coded	1.31	−0.09	−0.51
Step4	Percent Data Scrubbed	−0.21	−0.10	−0.46
	Mean ReHo	169.40	0.54	1.77†
	Age- Dummy Coded	−1.87	−0.13	−0.68
	SCQ and Age Interaction	−75.56	−0.20	−0.61

† $p < .10$,

* $p < .05$; SCQ: Social Communication Questionnaire