Hypo- and hyper-connectivity in default mode network related to social impairment in tweens with autism spectrum disorder

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Abstract

Background. Autism spectrum disorder is a neurodevelopmental disorder, marked by impairment in social communication and restricted, repetitive patterns of behavior, interests, or activities. Accumulating data suggests that alterations in functional connectivity might contribute to these deficits. Whereas functional connectivity in resting state fMRI is expressed by several resting-state networks, for this study we examined only few of them: auditory, language, salience and default mode networks. Our particular interest was in the default mode network (DMN), given its age dependent alterations of functional connectivity and its relation to social communication.

Methods. Since the studies investigating young children (6-8 years) with autism have found hypo-connectivity in DMN and studies on adolescents (12-16 years old) with autism have found hyper-connectivity in the DMN, we were interested in connectivity pattern during the age of 8 to 12, so we investigated the role of altered intrinsic connectivity in 16 children (mean age 9.75 ±1.6 years) with autism spectrum disorder compared to 16 typically developing controls in the DMN and other resting-state networks.

Results. Our results show that, compared to controls, the group with autism spectrum disorder showed signs of both hypo- and hyper-connectivity in different regions of the resting-state networks (Precuneus network and DMN) related to social communication.

Conclusion. We suggests that transition period from childhood to adolescence carries the complexity of functional connectivity from both age groups (children and adolescents). Regions that showed differences in functional connectivity were discussed in relation to social communication difficulties.

Keywords: ASD, social communication, resting state fMRI, Functional connectivity, ABIDE, Default Mode Network

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder, characterized by impairment in social communication and restricted, repetitive patterns of behaviors, interests or activities (American Psychiatric Association, 2013) and it is one of the most frequent neurodevelopmental disorders in children (Fombonne, 2009). Knowledge on the etiology is rapidly progressing, but no definite cause has been identified yet (Currenti, 2010). As a result, diagnosis currently depends on elaborate behavioral examination, making it difficult to diagnose children at a young age (Crais, Watson, Baranek, & Reznick, 2006). Therefore, research on possible biological markers of ASD is of great importance.

Non-invasive neuroimaging techniques are being increasingly used to obtain biomarkers for psychiatric disorders (Linden, 2012). Functional connectivity (FC) studies investigate patterns of synchronized activity between brain regions, associated with specific behavioral processes. This approach is particularly convenient when applied to functional magnetic resonance imaging (fMRI), a technique that is able to localize brain activity with a great spatial resolution. Several task-based fMRI studies have found evidence of reduced brain connectivity in patients with ASD during various cognitive tasks (Uddin, Supekar, & Menon, 2013). However, when scanning patients, task-based fMRI studies have a few important drawbacks that must be considered: task complexity and comprehension, interpretation of the result, long scanning time and ect (Fox & Greicius, 2010). Therefore, it may be beneficial to look at resting-state fMRI (rs-fMRI) studies. Using this technique, subjects are asked to lie still and rest during the fMRI scan; and we have a richer source of signals, a better signal to noise ratio and multiple cortical systems can be studied at once.

In rs-fMRI studies spontaneous variations in the BOLD signal are the focus of interest (Greicius, 2008). Temporally correlated signal variations of different brain regions are thought to correspond to distinct functional resting-state networks (Beckmann, DeLuca, Devlin, & Smith, 2005). For few resting-state networks, a relation with social communication has been already demonstrated, among which the auditory network (Russo, 2008), the language network (Carter, Williams, Minshew, & Lehman, 2012), the salience network (Toyomaki & Murohashi, 2013) and the default mode network (DMN) (Li, Mai & Liu, 2014; Mars et al., 2012). Since most evidence is found on the role of the DMN in social communication, this network will be our main focus.

Many researchers found evidence of reduced intrinsic FC within the DMN in individuals with ASD (Cherkassky, Kana, Keller, & Just, 2006; Kennedy & Courchesne, 2008; Von dem Hagen, Stoyanova, Baron-Cohen, & Calder, 2013). These findings have led to the under-connectivity hypothesis of ASD, which postulates a link between the symptoms of ASD and hypo-connectivity in the brain. Three studies have found a negative correlation between different behavioral measures of ASD and resting-state FC, indicating that lower FC was related to increased social impairments (Assaf et al., 2010; Monk et al. 2009; Weng et al. 2010). However, these results are based on studies with adolescents and adults. Since the onset of ASD is in the early developmental period (American Psychiatric Association, 2013), we looked at studies

focusing on childhood of ASDs. Rather than confirming the under-connectivity hypothesis, studies on children with ASD found evidence of intrinsic hyper-connectivity (Lynch et al., 2013; Supekar et al., 2013). At a whole-brain level, hyper-connectivity was linked to worse social impairment [22] and the same relation was found when focusing on the DMN specifically (Weng et al., 2010).

The discrepancies between the research findings on children, adolescents and adults with ASD have led to the developmental perspective. Throughout development, FC in the DMN changes, resulting in a more integrated network (Fair et al., 2008). Nomi and Uddin (2015) found evidence of age specific patterns of functional connectivity in the DMN and other networks. Also a study by Washington et al. (2014) showed that the maturation of the DMN is disturbed in children with ASD. Therefore each of the studies we have mentioned above was focusing on a particular age group. Given that our interest is to find a biomarker for middle childhood ('tweens) ASD, the period that was investigate less, we will concentrate on children above the age of eight and below thirteen. One of the difficulties of such studies on children with ASD is attaining a large subject sample. Thus recently, the importance of data sharing has become more prominent and multiple publicly available neuroimaging databases have arisen, among which the Autism Brain Imaging Data Exchange (ABIDE) (Di Martino et al., 2013). ABIDE is an online database for rs-fMRI images, available from individuals with ASD and age-matched TD. For this study, structural MRI and rs-fMRI images were downloaded from the database.

Searching for a biomarker of tweens with ASD, the focus of this study will be on resting-state FC in the DMN and its relation to social communication in children with autism. Since our sample consists only of children, we expect to find regions of the DMN that are hyper-connected in the ASD group, as was found in other rs-fMRI studies (Lynch et al., 2013; Supekar et al., 2013). However, our age group also comprises subjects from ten to thirteen years old, who are transitioning from childhood to early adolescence. Given that studies on adolescents mostly found evidence of hypo-connectivity in the DMN (Assaf et al., 2010; Weng et al., 2010), we also expect to find regions that are hypo-connected in the ASD group.

Materials & Methods

Participants

Phenotypical data of all children younger than thirteen was downloaded from the ABIDE database (fcon_1000.projects.nitrc.org/indi/abide/). Subjects with an unknown diagnosis or comorbidity were excluded from the dataset. Full scale IQ (FIQ) and Verbal scale IQ (VIQ) were measured with the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) or the Wechsler Intelligence Scale for Children (WISC, Wechsler, 1949). Several questionnaires were used to measure the presence and severity of autistic symptoms in patients and controls, among which the Social Responsiveness Scale (SRS, Constantino, & Gruber, 2005) and the Social Communication Questionnaire (SCQ, Rutter, Bailey, & Lord, 2003). Social communication deficits of the patients were further assessed with the Autism Diagnostic Observation Schedule (ADOS, Lord et al., 2000) and the Autism Diagnostic Interview-Revised (ADI-R, Lord, Rutter, & Le Couteur, 1994), which are currently the ‘gold standard’ for diagnosing ASD (Falkmer, Anderson, Falkmer, & Horlin, 2013). All children and their parents agreed to participate in the study. For the final sample, selection of the controls was based on subjects having completed the SCQ and the SRS. Selection of the patients was based on the

completion of the ADOS, the SCQ and the SRS. These inclusion criteria led to a group of patients (n=16, age 7-12) and a group of controls (n=16, age 6-12). The two groups did not differ in terms of age, FIQ or performance scale IQ (PIQ). Table 1 provides details of the subject characteristics.

Table 1

fMRI Data Preprocessing

For each subject, 180 images of the BOLD signals were obtained and preprocessing of the signals was performed in MATLAB R2013a (Mathworks), using Statistical Parametric Mapping 12 (SPM12, Welcome Department of Cognitive Neurology, University of College London, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). First, images were realigned to a reference image to correct for head motion. To separate grey and white matter and cerebro-spinal fluids, normalized anatomical images were then segmented using Tissue Probability Maps. Bias correction for more uniform intensities within different types of tissues was also performed. Next, coregistration was applied for intermodal registration of functional images to anatomy affine transformation, using Normalized Mutual Information. Functional images were then spatially normalized into standard Montreal Neurological Institute (MNI) space, using the tissue probability map template. To improve signal-to-noise ratio, spatial smoothing was applied, using a Gaussian kernel of full-width-half-maximum of 8 mm. REST toolbox (Song et al., 2010) was used to remove the linear trend and data was filtered, including only frequencies between 0.01 and 0.09 HZ. Finally, to evaluate the extent of head motion, framewise displacement (FWD) was calculated for each subject (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) to keep subjects with motion values above the 0.5 mm threshold.

Independent Component Analysis (ICA)

Group spatial ICA was carried out for all subjects within GIFT software (http://icatb.sourceforge.net, version 1.3), to detect resting-state networks. First, principal component analysis is applied to reduce the individual subjects' data in dimension. Secondly, the estimation of independent sources is performed using the Infomax algorithm (Bell and Sejnowski, 1995), resulting in spatially independent functional maps. The final stage is a back reconstruction of the individual subject image maps and time courses from the raw data (Calhoun, Adali, Pearlson, & Pekar, 2001). ICA was run 20 times and results were clustered by ICASSO. Automatic component labeller was used to perform a spatial template matching procedure, using the resting state (RSN) network templates of the GIFT toolbox, in order to individuate resting-state networks. Besides afterwards RSNs were visually inspected and only the networks of interest were chosen.

Group Comparison

To investigate differences in resting-state FC between the two groups, a two-sample t-test was conducted for each selected component, using network-specific masks from the GIFT toolbox. All group tests were controlled for age and head movement (FWD) as covariates and a significance of the results was set to a threshold of $p<0.05$ corrected for multiple comparisons

194 using family-wise error (FWE). This analysis generated functional connectivity maps exhibiting
195 significant group differences for each resting-state network.

196 **Results**

197 *Independent Component Analysis*

198 The number of independent components estimated using the minimum description length
199 (DML) criteria, was 69. We chose to decompose data into 20 components, because this is a
200 common degree of clustering/splitting when applying ICA to rs-fMRI data (Smith et al., 2009).
201 Selection of the components was based on their relation with social communication, resulting in
202 the DMN (Li et al., 2014), the salience network (Toyomaki, & Murohashi, 2013), the auditory
203 network (Russo, 2008) and the language network (Carter et al., 2012). When several
204 components represented the same networks, the component with the highest correlation
205 coefficient with the template was selected for further analysis. The precuneus network was also
206 included in our selection, since it is also a part of the ventral DMN.

Table 2

Group Comparison

A two-sample t-test revealed group differences in FC only in two from seven preselected networks. The left precuneus (PrC), in the precuneus network and the left superior frontal gyrus (SFG), in the dorsal DMN, both showed stronger FC in ASD. In the latter network, TD showed increased FC in the left and right medial frontal gyrus (FG). Regions with significant group differences in resting-state FC are shown in Table 2.

Discussion

Evidence for Both Hyper- and Hypo-connectivity

The results of the group comparison revealed signs of both hyper- and hypo-connectivity, providing support for our hypothesis. The recent study by Cheng, Rolls, Gu, Zhang and Feng (2015) found significant differences in FC between patients with ASD and controls in many of the regions as we did, supporting our results. In this study, data from children, adolescents and adults were combined for analysis. The age-specific differences in FC in the DMN and other networks (Nomi and Uddin, 2015), could explain why they found evidence of both hyper- and hypo-connectivity. Even though our subject sample contained only children, we speculated that the oldest children could already be transitioning from childhood to early adolescence. Therefore, we expected to find evidence of both hyper- and hypo-connectivity and this was confirmed by our findings.

Further support for this hypothesis comes from the developmental perspective of functional connectivity. Based on the discrepancies between the findings in studies on children, adolescents and adults, a review by Uddin et al. (2013) proposed a developmental perspective, with puberty as the critical period in brain development. The trajectories of FC oppose each other with age by increasing in normal controls and decreasing in ASD group. Furthermore the period of puberty is lacking data on functional connectivity, thus only two possible scenarios about FC in ASD are presented: 1) linear decrease in functional connectivity from childhood to adolescence, or 2) a sharp decrease in FC with a slow increase in connectivity afterwards.

Concerning the DMN, Fair et al. (2008) showed that this network became more integrated with increasing age. Another study also found evidence for differences in FC in the DMN, when comparing children, adolescents and adults (Nomi & Uddin, 2015). They found hyper-connectivity in frontal pole (part of DMN) in children with ASD bellow 11 years old, and no differences in older children with ASD compared with typically developing controls. A longitudinal study compared the FC of children in the DMN and central executive network (CEN), at ages between 9 and 11 and later between the ages of 12 and 14 (Sherman et al., 2014). They found that with age participants showed increased integration inside the investigated networks and increase segregation between these networks. Even though there was evidence that the DMN is functionally connected by age 10, the network continued to strengthen in early adolescence. The significant differences in FC between the ages of 10 and 13 could explain why we found both weaker and stronger FC in children with ASD, since our subject sample did not make a distinction between early childhood, late childhood and early adolescence.

A totally different explanation for the group differences comes from the study of Hahamy, Behrmann and Mala (2015). They showed that there was a regression to the mean effect in the FC of patients with ASD, meaning that very high and low voxel values are attenuated, compared to the same voxel values in controls. This effect resulted from greater individually distinct distortions in connectivity patterns. These idiosyncratic spatial distortions also could explain why both hyper- and hypo-connectivity can be found in individuals with ASD.

Aberrant FC in Different Regions Related to Social Communication

The left PrC

The first major finding of the group comparison was that the left PrC in the precuneus network was hyper-connected in children with ASD. Two studies on self-processing demonstrated the importance of this region during self-description tasks (Kircher et al., 2000; Kircher et al., 2002). A study by Lombardo, Barnes, Wheelwright, & Baron-Cohen (2007) showed that such self-referential cognitive skills were impaired in adults with ASD. Moreover, the study also found evidence of impaired empathy in adults with ASD and they established a link between the impaired self-referential cognition and the impaired empathy. Activation of the PrC during tasks involving empathy, forgiveness (Farrow et al., 2001) and emotion attribution (Ochsner et al., 2004) was also demonstrated. Overall, these studies have established a link between the PrC and various aspects of social functioning.
Further multiple studies have identified the PrC as a region with aberrant FC in subjects with ASD (Assaf et al., 2010; Cheng et al., 2015; Lynch et al., 2013). However, these studies found evidence of hypo-connectivity of the PrC in adolescents, adults and children of our investigated age group, as opposed to the hyper-connectivity that we found. Results of these studies indicated that symptom severity increased, as FC in the PrC decreased. Altogether, hyper-connectivity that we found in the left PrC in children with ASD is a relatively new finding, but converging evidence suggests that aberrant FC in this region is associated with a deficit in suppressing DMN and the social communication difficulties of subjects with ASD (Christakou et al 2013).

The left SFG

A second region of the dorsal DMN showing significant group differences was the left superior frontal gyrus. Children with ASD showed increased FC, compared to controls. The role of the left SFG in language performance in subjects with ASD was demonstrated in a task-based fMRI study (Knaus, Silver, Lindgren, Hadjikhani, & Tager-Flusberg, 2008). Nevertheless hyper-connectivity in the SFG is not a new finding; similar results were found by two other rs-fMRI studies (Weng et al., 2010, Cheng et al., 2015). In the study of Weng et al. (2010), adolescents with ASD displayed stronger FC between the PCC and other regions of the DMN, including the SFG. Additionally they found that stronger FC between these two regions was associated with poorer non-verbal communicative abilities in adolescents with ASD. Contrastingly, poorer social functioning was associated with weaker FC between the PCC and the SFG. A similar relation was revealed by the study of Cheng et al. (2015), who found that FC between the left SFG and the middle temporal gyrus (MTG) was negatively correlated with the ADOS

communication scores of subjects with ASD. These studies provide support for our finding that the left SFG is hyper-connected in subjects with ASD and they imply the role of this region in the social communication deficits of subjects with ASD.

The left and right medial FG

Group comparison of FC in the dorsal DMN revealed that the left and right medial frontal gyrus were hypo-connected in children with ASD. A study on the neural correlates of self-knowledge (Ochsner et al., 2005) demonstrated the importance of the medial FG during self-appraisal and a Lombardo et al. (2007) suggested that this self-processing could be linked with the interpersonal problems of people with ASD. In a different study (Pelphrey, Morris, McCarthy, & LaBar, 2007) differences in activation were seen between participants with ASD and controls during a perception task of angry and fearful faces. More activation was displayed by the controls in different regions, including the left medial FG. Along with difficulties in social interaction, one of the first signs of ASD is a delay in language development (American Psychiatric Association, 2013) and a study by Gaffrey et al. (2007) showed that the medial FG plays a role in language performance in individuals with ASD.

The studies above all demonstrate the importance of the medial FG during various social communication tasks. However, these studies involve differences in activation of the medial FG, opposed to differences in FC. No previous study has found evidence of aberrant resting-state FC in subjects with ASD in this region, as was shown by our results, but a study on Theory of Mind (ToM) did found group differences in FC in the medial FG (Kana, Keller, Cherkassky, Minshew, & Just, 2009). Children with ASD have difficulties with representing the mental states of others, called the ToM, causing a great disadvantage when trying to predict the behavior of others (Baron-Cohen, Lesie, Frith, 1985). The study by Kana et al. (2009) demonstrated that the medial FG was activated during these ToM tasks, but significantly less activation in this region was seen in adults with ASD. Moreover, the ASD group showed reduced FC between frontal ToM regions of the brain, including the medial FG, and posterior ToM regions.

In sum, resting-state hypo-connectivity in the medial FG is a new finding. Nonetheless, multiple studies have established the importance of this region in social communication abilities and demonstrated that the medial FG often showed aberrant activation or FC in subjects with ASD.

Conclusions

We investigated a group of tweens (8-12 years old) with ASD and matched controls using resting state fMRI. On behavioural level groups significantly differed in social communication measures, though resting state fMRI data analysis showed both hyper- and hypo-connectivity only in the regions of default mode network, confirming previously reported alterations found relevant for two different age groups (6-8 and 12-15 years old).

We suggest that during a transition period from childhood to adolescence functional hyper-connectivity persists together with the upcoming first signs of hypo-connectivity in DMN. This way hyper-connectivity in left precuneus and left SFG gradually decreases and hypo-connectivity in bilateral MFG becomes stronger.

For future research, it would be interesting to explore the relation between resting-state FC and behavioral measures of autism. In order to avoid the problem of circularity, data-analysis should be done on a set of data that is independent of the data used in the selection process (Abott,

2009). Furthermore, longitudinal studies on the evolution of resting-state FC in the brain of children with autism could tell us more about the dynamics of the differences in development of the brain.

Limitations and Future Directions

The first limitation of our study is the small sample size (n=32). As a result of our strict selection criteria, many participants were excluded from our sample. Therefore, the findings of our study should be considered preliminary until replicated. A second limitation is that our study included only high-functioning patients with ASD, limiting generalizability of our results to the diagnostic category as a whole. A third limitation is that we did not make a distinction between late childhood and early adolescence. It is recommended for future research to focus on an even more specific age group than we did, given the differences in FC throughout development (Sherman et al., 2014). Another limitation is that multi-site databases, such as ABIDE, despite their great value, contain some inherent limitations. Large heterogeneity in acquisition parameters, research protocols and subject populations could reduce sensitivity. Therefore, it is recommended to replicate results in an individual dataset. Finally, since this was an exploratory study, we could not correlate FC of the different regions with the behavioral measures of social communication, to avoid double dipping (Abott, 2009).

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Table 1. Subjects' characteristics.

	ASD (n=16)	Controls (n=16)	T-test: p-value
Age	9.75 (1.62)	9.73 (1.62)	0.96
Sex (male:female)	14:2	11:5	
Full scale IQ	107.5 (13.55)	114.44 (11)	0.12
Verbal scale IQ	103.62 (16.41)	114.69 (13.61)	0.046*
Performance scale IQ	110.06 (16.41)	110.75 (9.95)	0.89
SRS total score	91.56 (24.92)	21.13 (9.82)	<0.001***
SCQ total score	16.63 (8.37)	3.25 (2.14)	<0.001***
ADOS communication	3.5 (1.71)		
ADOS social interaction	7.13 (2.6)		
ADOS total score	10.62 (4.19)		
ADI-R social total score	19.19 (5.88)		
ADI-R verbal total score	15.69 (4.92)		

Note. Data are mean (SD).

Table 2. Regions showing group differences in resting-state functional connectivity.

Anatomical region	Comparison	x	y	z	max t	Cl. size
Precuneus network						
Left precuneus	ASD>Controls	-14	-72	38	4.89	19(40)
Dorsal Default Mode Network						
Left superior frontal gyrus	ASD>Controls	-16	52	34	6.34	85(86)
Right medial frontal gyrus	Controls>ASD	2	54	4	5.81	33(161)
Left medial frontal gyrus	Controls>ASD	-8	58	0	4.89	77(161)

Note. *The table depicts MNI coordinates for peak activation voxel in each region with significant differences in FC between groups, t scores from random effects analyses across all participants and cluster size information. Threshold was p<0.05 (FWE).*