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Decreased amygdala functional connectivity in adolescents with autism: A resting-state fMRI study

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ABSTRACT

The human brain undergoes dramatic changes in amygdala-related functional connectivity network during adolescence. Given that the amygdala is a vital component of the "social brain", the *Amygdala Theory of Autism* has been proposed to account for atypical patterns of socio-emotional behavior in autism. Most of the previous neuroimaging evidence has concentrated on local functional or structural abnormalities of the amygdala in relation to social deficits in autism, rather than on its integrated role as part of larger brain networks. To examine whether functional integration pattern of the amygdala is altered in autism, the current study examined sixty-five adolescent subjects (30 autism and 35 healthy controls, 12–18 years old) from two independent datasets (UCLA and Leuven) of the Autism Brain Imaging Data Exchange. Whole-brain resting-state functional connectivity maps seeded in the amygdala were calculated and compared between patient and control groups. Compared with healthy controls, adolescents with autism showed decreased functional connectivity between the amygdala and subcortical regions in both datasets, including the bilateral thalamus and right putamen. These findings support the *Amygdala Theory of Autism*, demonstrating altered functional connectivity pattern associated with the amygdala in autism, and provide new insights into the pathophysiology of autism.

1. Introduction

Autism is a neurodevelopmental syndrome accompanied by impaired social interaction and communication, restricted repetitive and stereotyped behavior and interests (American Psychiatric Association, 2013). Social deficits are the critical features that differentiate autism from other developmental disorders (Rapin and Tuchman, 2008), and might also explain the emergence of other symptoms during development in autism (Schultz, 2005). The core manifestations of social deficits in autism include poor eye contact, lack of social or emotional reciprocity, impairment in the use of non-verbal behaviors and failure to develop age-appropriate peer relationships (American Psychiatric Association, 2013; Lord et al., 2013). With the high prevalence (estimated at about 1 in 68 children) and increasing tendency of the prevalence (Baio, 2014), there is an urgent need to identify the pathophysiological mechanisms that could explain the social behavioral impairments in autism in a unified way.

Several theories have been proposed to elucidate the atypical patterns of social deficits observed in this population (Baron-Cohen, 1997; Hobson, 1993; Schultz, 2005). Previous studies have shown that social intelligence (Humphrey, 1976), dissociable from general intelligence, is a function of activity in the so-called social brain. It comprises a network of brain areas that include the amygdala, orbitofrontal cortex (OFC), superior temporal sulcus and gyrus (STS/G), medial prefrontal cortex, anterior cingulate cortex, temporoparietal junction, inferior frontal gyrus, anterior insula, hippocampus, anterior temporal lobes and fusiform gyrus (Adolphs, 2003, 2009; Barak and Feng, 2016; Brothers, 2002; Gotts et al., 2012; Patriquin et al., 2016). The amygdala has been identified as a central component in the neural circuits underlying social behaviors, especially in social emotional processing (Phelps and Ledoux, 2005). Together with the fact that social deficits are viewed as the primary autism symptomatology (American Psychiatric Association, 2013), Baron-Cohen et al. proposed a theory that the amygdala is one of potential key neural regions in the pathophysiology of autism (Baron-Cohen et al., 2000). Structure and function abnormalities in the amygdala might result in the social

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behavior deficits in the development course of autism (Baron-Cohen et al., 2000).

Subsequent studies supported the theory providing evidence from face perceptual tasks (Critchley et al., 2000; Pierce et al., 2001), gaze fixation (Dalton et al., 2005), and morphology studies (Aylward et al., 1999; Nacewicz et al., 2006; Schumann et al., 2004; Stanfield et al., 2008). Specifically, individuals with autism showed no or reduced activation in the amygdala when processing facial expressions (Critchley et al., 2000; Pierce et al., 2001). At the same time, diminished gaze fixation in autism is associated with the hypoactivation in the amygdala (Dalton et al., 2005). Preliminary morphology studies of the amygdala in autism also reported abnormal amygdala volume in individuals with autism compared with control group (Aylward et al., 1999; Nacewicz et al., 2006; Schumann et al., 2004; Stanfield et al., 2008).

Preliminary functional studies focusing on regional brain activation in autism during the performance of various tasks have reported abnormal activity in a diverse set of brain regions, such as the amygdala (Critchley et al., 2000; Pierce et al., 2001), anterior cingulate cortex (Hall et al., 2014; Shafritz et al., 2008), fusiform face area (FFA) (Piggot et al., 2004; Wang et al., 2004) and superior temporal sulcus (Gervais et al., 2004). These studies collectively showed that the behavioral symptoms of autism correlated with a variety of brain areas rather than a single brain region and indicates that the brain mechanism underlying autism is more likely to be non-localized abnormalities. While regional activation characterizations provide initial understandings of the neuropathology underpinning autism, a comprehensive approach that depicts coordination among different brain areas may better explain the diverse behavioral impairments in autism.

Previous longitudinal and cross-sectional studies have reported age-specific anatomic abnormalities in autism. It is proposed that there is abnormal overgrowth of the brain in autism at early ages, but decrease in structural volumes and neuron numbers during adolescence and young adulthood (Courchesne et al., 2011). Adolescence is a transitional period from childhood to adulthood with changes in explorative and emotive behaviors associated with the onset of pubertal maturation, increase social demands and offset of the control of caretakers (Casey et al., 2010). It is also a time associated with increased prevalence of psychopathology involving the regulation of behavior and emotion (Steinberg, 2008). During adolescence, typical developmental individuals shift social focus from parents to peers and develop peer relationships, reflected in the activation within social brain network, including the amygdala (Picci and Scherf, 2015). However, formation of friendship in adolescents with autism are more based upon common interests instead of social demands. Prominent social communicative impairments in autism might limit the ability to form peer relationships initiatively. Additionally, neural and developmental abnormalities in adolescence serves as a “second hit” during the development of autism, which result in a failure to transition into adult levels of adaptive functioning (Picci and Scherf, 2015). As a result, we chose the specific developmental stage —adolescence — to explore the abnormalities of the amygdala in autism.

Recently, the advent of functional connectivity methods, which measure the synchronization of the activity between different brain regions as inter-regional coordination, provide further insight into the neurobiological mechanism of autism. Previous fMRI studies investigating functional connectivity of the amygdala in autism found inconsistent altered connectivity during the face processing tasks with different brain areas, such as FFA (Kleinhans et al., 2008), ventromedial prefrontal cortex (Swartz et al., 2013) and middle temporal gyrus (Monk et al., 2010). These contrasting results might partly be attributed to several factors including differences in task strategy and task performance. Spontaneous low-frequency fluctuations (LFF) in the blood oxygenation level-dependent (BOLD) signal during resting-states, reflecting the intrinsic neural baseline activity of the brain, might better reveal the etiology of autism (Biswal et al., 1995; Damoiseaux et al., 2006). Exploring brain networks during the resting state has emerged as a new method for investigating cognitive and affective dysfunction in neuropsychiatric disorders and eliminates the limitations (e.g. potential task performance confounders) of conventional task-based fMRI studies (Menon, 2011; Woodward and Cascio, 2015; Zhang et al., 2015). Resting-state functional connectivity studies have identified several brain regions that showed altered connectivity with the amygdala in autism. Previous functional connectivity study seeded in the insula have reported reduced connectivity with the amygdala in high-functioning autism in the age range between 12 and 20 years (Ebisch et al., 2011). Hypoconnectivity between amygdala and cortical regions were found in adolescents and adults with autism compared with healthy controls (Rausch et al., 2015). Research examining developmental changes in large-scale network functional connectivity reported reduced connectivity between amygdala/subcortical network and default mode network in adolescents with autism, as well as increased connectivity within amygdala/subcortical network in children with autism (Nomi and Uddin, 2015). However, to the best of our knowledge, no previous studies have exclusively investigated the resting-state functional connectivity patterns of the amygdala—an integrated region within multiple networks of brain regions (Pessoa, 2008)—in adolescents with autism. Based on the amygdala-related findings associated with social interaction symptoms mentioned above, it's plausible to conclude that the functional integration of amygdala plays an important role in social impairments of autism. Therefore, understanding the intrinsic functional connectivity patterns of the amygdala in autism might provide a more complete picture of the autism brain.

In the current study, we utilized two independent datasets from the Autism Brain Imaging Data Exchange (ABIDE, http://fcon_1000.projects.nitrc.org/indi/abide/) and conducted seed-based resting-state functional connectivity analyses to explore the functional connectivity patterns associated with the amygdala in participants with autism. Considering the developmental model of functional connectivity in autism (i.e. reduced functional connectivity in adolescents and adults with autism compared with age-matched controls, while increased functional connectivity in children with autism) (Uddin et al., 2013), we hypothesized that the resting-state functional connectivity patterns of the amygdala would be decreased in adolescents with autism. In addition, we examined the relation between social interaction symptom severity and altered amygdala functional connectivity to establish a more precise link between social behavior and brain function in this population.

2. Methods

2.1. Subjects

The original rsfMRI and phenotypic data were collected from ABIDE. Data analyzed in our study were limited to:

1. Age range of 12–18 years.
2. Subjects diagnosed with autism, excluding subjects with Asperger syndrome, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified (PDD-NOS).
3. Subjects diagnosed with no psychiatric neurological comorbidity, including but not limited to attention deficit/hyperactivity disorder (ADHD), schizophrenia, epilepsy, anxiety or depressive disorder.
4. Data with resting-state images providing near-full brain coverage, detailed and valid clinical scale information.
5. Individuals with head motion within 2 mm translation and 2° of rotation.
6. Individuals with > 50% of their time points left after scrubbing.
7. Sites with more than 10 subjects per group after the above exclusions.

Table 1
Sample characteristics of the subjects.

Characteristics	Site	Autism (n=18)	Controls (n=19)	*p*-value	Site	Autism (n=12)	Controls (n=16)	*p*-Value
Age (year)	UCLA	15.0 ± 1.8	14.0 ± 1.5	0.07[a]	Leuven	13.7 ± 1.2	14.3 ± 1.6	0.29[a]
Gender (male/female)		17/1	16/3	0.32[b]		9/3	12/4	1[b]
Handedness (right/left)		17/1	18/1	0.97[b]		10/2	13/3	0.89[b]
FIQ		103.1 ± 13.1	104.2 ± 9.8	0.77[a]		96.3 ± 13.8	110.4 ± 8.6	0.003[a,*]
FD		0.09 ± 0.04	0.07 ± 0.03	0.13[a]		0.11 ± 0.06	0.10 ± 0.03	0.45[a]
Scrubbed time points (%)		9.39 ± 10.34	5.65 ± 7.96	0.22[a]		9.69 ± 14.09	2.97 ± 3.68	0.08[a]
ADI_R_SOCIAL		19.6 ± 5.0	–	–		–	–	–
ADOS_SOCIAL		6.3 ± 2.7	–	–		–	–	–

Test for differences between groups (two-tailed):
ADI_R_SOCIAL: reciprocal social interaction subscore (A) total for ADI_R.
ADOS_SOCIAL: social total subscore of the classic ADOS.
[a] Two-sample *t*-test.
[b] χ^2 test.
[*] Significant difference between groups ($p < 0.05$).

Given that psychiatric neurological comorbidity might obscure the amygdala-related functional connectivity in individuals with autism, subjects diagnosed with other psychiatric neurological comorbidity, including but not limited to ADHD, schizophrenia, epilepsy, anxiety or depressive disorder, were excluded from the current study. Altered functional connectivity of amygdala have been reported in these psychiatric disorders, which might mask the functional connectivity findings in autism. For example, disrupted intrinsic amygdala functional connectivity patterns were observed in adolescents with generalized anxiety disorder (Roy et al., 2013).

Two datasets, Leuven University (Leuven) and University of California, Los Angeles (UCLA), which met the above criteria, were used. Thirty-seven subjects (19 healthy controls, 18 autism) from UCLA and twenty-eight subjects (16 healthy controls, 12 autism) from Leuven were included in the study.

Detailed demographic and clinical characteristics (social subscore of Autism Diagnostic Interview-Revised (ADI_R) and Autism Diagnostic Observation Schedule (ADOS)) of the subjects are summarized in Table 1. Only UCLA dataset provide social subscore of ADI_R and ADOS. Missing data of full-scale intelligence quotient (FIQ) were estimated by averaging performance and verbal intelligence quotient. No significant differences in gender, age, handedness, mean framewise displacement (FD) or scrubbed time points were found between the two groups in both datasets ($p > 0.05$). However, FIQ scores of individuals with autism were significantly lower than those of the healthy controls in the Leuven dataset (p=0.003), while there was no significant difference in FIQ between the two groups in the UCLA dataset ($p > 0.05$). More details of informed consent and site-specific protocols are available at http://fcon_1000.projects.nitrc.org/indi/abide/.

2.2. Data acquisition

MRI scans at UCLA were performed on a 3 T Siemens scanner. An echo-planar imaging (EPI) sequence was used to obtain the blood oxygenation level-dependent (BOLD) images of the entire brain in 34 slices [TR/TE=3000/28 ms, number of volumes=120, voxel size=3×3×4 mm^3, flip angle=90°, slice thickness=4 mm without gap]. Each resting-state scan lasted for 6 min. MRI scans at Leuven were performed on a 3 T Philips scanner. An EPI sequence was used to obtain the BOLD images of the entire brain in 32 slices [TR/TE=1667/33 ms, number of volumes=250, voxel size=3.59×3.59×4 mm^3, flip angle=90°, slice thickness=4 mm without gap]. Each resting-state scan lasted for 6.9 min.

2.3. Data preprocessing

All data preprocessing was performed using the advanced edition of the Data Processing Assistant for Resting-State fMRI (DPARSF *A*) (Yan and Zang, 2010). The first ten images were removed to account for instability of the initial signal and the adaptation of the subjects to the scanner. Images were corrected for errors in slice timing, realigned to correct for motion (subjects with translation greater than 2 mm or rotation greater than 2° about three axes were excluded), spatially normalized to the standard echo-planar imaging template in Montreal Neurological Institute (MNI) stereotaxic space (Collins, 1998), resampled to 3×3×3 mm^3, smoothed with a Gaussian kernel of 8×8×8 mm^3 (full width at half maximum, FWHM) and then detrended. Possible sources of undesired signals were regressed out as nuisance covariates, including Friston 24 motion parameters (Satterthwaite et al., 2012; Yan et al., 2013), white matter signal and cerebrospinal fluid signal. Global signal was also regressed out as it has been shown to improve the specificity of functional connectivity analysis (Fox et al., 2009) and can improve the correction of motion artifacts (Yan et al., 2013). The resulting images were then temporally band-pass filtered (0.01–0.08 Hz). In consideration that functional connectivity measures are extremely sensitive to even small amounts of head motion (Power et al., 2012), we conducted motion scrubbing procedure by removing frames with FD > 0.5 mm; individuals with > 50% of their time points left were included in the analysis. No significant differences in the remaining time points were found between the autism and healthy control groups in both datasets (Table 1).

2.4. Data analysis

Primary seed-based functional connectivity analysis was performed for the left and right amygdala, respectively. The amygdala masks were extracted from the automated anatomical labeling (AAL) template provided by statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/) (Tzourio-Mazoyer et al., 2002). Pearson's correlation analysis was computed between the amygdala seed and the whole brain in a voxel-wise manner. For statistical normality, correlation coefficients were normalized by the Fisher's *Z* transformation:

$$Z = \frac{1}{2}\sqrt{n-3}\,[\ln(1+R) - \ln(1-R)]$$

where n is time points, and R is correlation coefficients. The *Z* values entered into the following analysis.

Random effect one-sample *t*-test was performed on the individual *Z* values by SPM8 in a voxel-wise manner to determine the brain regions showing significant functional connectivity to the amygdala of each group within a whole brain grey matter mask in SPM8. Then the false discovery rate (FDR) control was conducted to control the expected proportion of falsely rejected hypotheses (Benjamini and Hochberg, 1995) ($p < 0.05$). Since global mean signal regression can induce

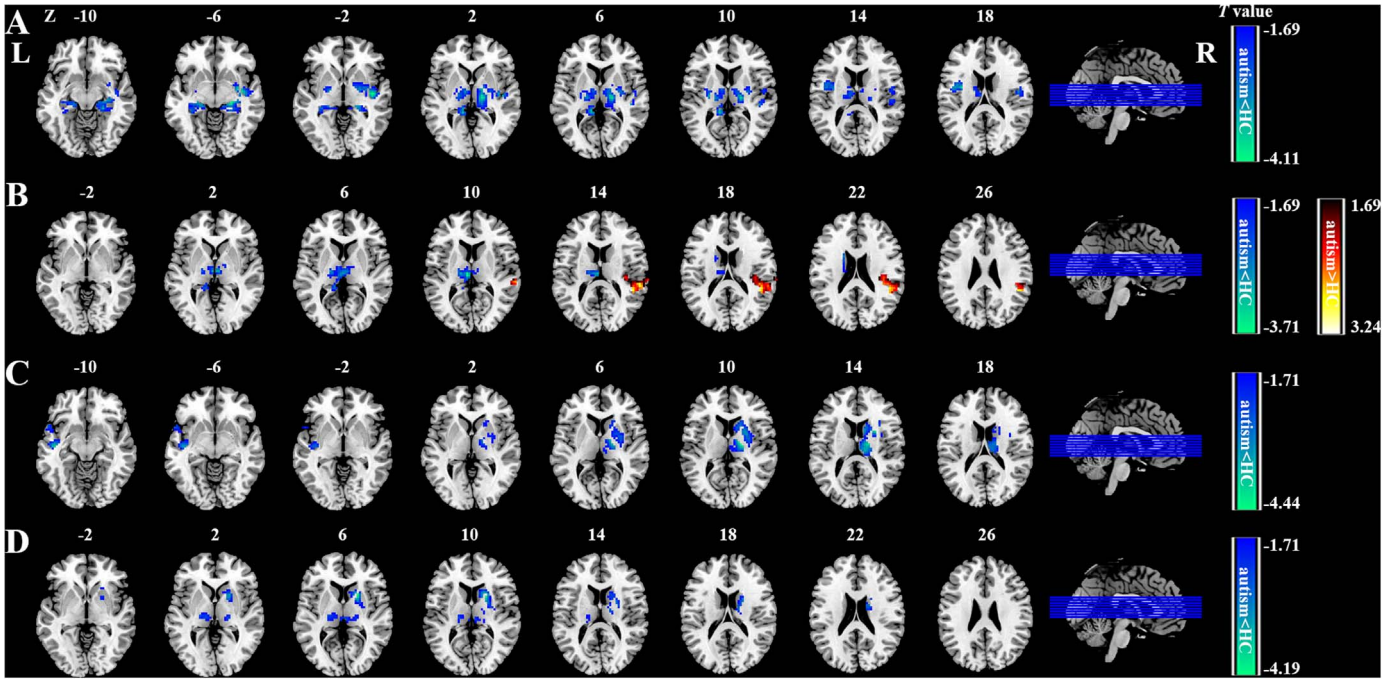

Fig. 1. Altered functional connectivity of the amygdala in individuals with autism. Altered functional connectivity of the left amygdala (A) and the right amygdala (B) in autism compared with healthy controls (HC) in UCLA. Altered functional connectivity of the left amygdala (C) and the right amygdala (D) in autism compared with HC in Leuven (AlphaSim Correction, $p < 0.05$).

negative correlations (Murphy et al., 2009), this study was restricted to regions that were significantly positively correlated with the amygdala.

The *Z* values of functional connectivity entered into a random effect two-sample *t*-test in SPM8 in a voxel-wise manner within the union regions of the autism group and the healthy control group to determine the brain regions showing significantly different inter-group functional connectivity of the amygdala, removing the effects of age, sex and FIQ. Significantly different functional connectivity to the amygdala were determined with a corrected threshold of $p < 0.05$ (voxel threshold of $p < 0.05$, AlphaSim Correction) for both datasets (Song et al., 2011). The minimum corrected cluster sizes were k=228 (left amygdala, UCLA), k=197 (right amygdala, UCLA), k=241 (left amygdala, Leuven), and k=276 (right amygdala, Leuven) with parameters: FWHM=(14.665, 14.049, 15.181) mm, FWHM=(14.597, 14.357, 14.735) mm, FWHM=(15.602, 14.918, 13.048) mm, FWHM=(14.255, 14.324, 14.704) mm, respectively. The analysis above was conducted separately for each dataset. We then extracted the overlap regions which showed significant difference between autism and healthy controls in the two datasets for subsequent analyses.

2.5. Correlations with autism symptom severity

Given that only UCLA dataset provide social subscore of ADI_R and ADOS, correlation analysis explored potential relationships between autism social deficits severity measured by the scores on ADI-R and ADOS social domain displayed in Table 1 and altered inter-regional functional connectivity between the amygdala and overlap regions for UCLA dataset. The existence of a linear relationship between functional connectivity extracted as the average functional connectivity *Z* values of all voxels within each overlap cluster (i.e. right thalamus, right putamen and left thalamus) and social interaction symptom severity was tested using Pearson's correlation coefficient with a threshold of $p < 0.05$.

2.6. Reproducible analyses of potential confounds

2.6.1. Analysis on 'scrubbed' data

Since previous research has shown that functional connections tend to stabilize around 5 min (Van Dijk and Tvenkataraman, 2010) and a 50% cutoff for scrubbed volumes is rather liberal, we conducted reproducible analysis using subjects who have more than 5 min of resting-state data with the same method as mentioned in the manuscript to assess the effect of motion scrubbing on resting-state fMRI data. 26 subjects (11 autism and 15 healthy controls) from UCLA and 26 subjects (10 autism and 16 healthy controls) from Leuven entered the subsequent analysis. No significant difference in the rest of time points was found between patient and control groups in both datasets. Whole-brain resting-state functional connectivity maps seeded in the amygdala were calculated and compared between patient and control groups.

2.6.2. Analysis using different smooth strategies

To demonstrate the robustness of our findings against FWHM values, we verified the results smoothing with a Gaussian kernel of 4×4×4 mm^3 and 6×6×6 mm^3 (full width at half maximum, FWHM), respectively. All the other data preprocessing and processing methods remained the same as the main text. Whole-brain resting-state functional connectivity maps seeded in the amygdala were calculated and compared between patient and control groups.

3. Results

3.1. Functional connectivity of amygdala in dataset 1: UCLA

One-sample *t*-test results in UCLA were presented in supplementary Fig. S1. Two-sample *t*-test results of functional connectivity analysis in the UCLA dataset showed that individuals with autism, compared with healthy controls, had decreased functional connectivity between the left amygdala and several regions, such as the bilateral thalamus, bilateral hippocampus, bilateral rolandic operculum, right fusiform gyrus and right insula. In addition, participants with autism

Table 2
Brain regions showing significantly different functional connectivity of the amygdala between autism and healthy controls in the UCLA dataset.

Seed	Cluster	Regions	Hemisphere	Number of voxels	MNI coordinates			*T* value
					x	y	z	
Left amygdala	autism < healthy controls							
	Cluster 1	Fusiform gyrus	R	701	21	3	−45	−3.44
		Hippocampus	R		24	−24	−6	−3.98
		Insula	R		42	−12	−3	−4.11
		Pallidum	R		15	0	0	−3.31
		Parahippocampal gyrus	R		24	−33	−9	−3.32
		Putamen	R		33	−6	−6	−3.61
		Rolandic operculum	R		48	−9	18	−2.92
		Superior temporal gyrus	R		42	−15	0	−3.83
		Thalamus	R		15	−18	0	−3.99
	Cluster 2	Cerebelum_4 & 5	L	461	−21	−39	−27	−3.41
		Hippocampus	L		−12	−39	9	−3.48
		Rolandic operculum	L		−42	−3	18	−3.18
		Thalamus	L		−18	−18	6	−3.02
Right amygdala	autism > healthy controls							
	Cluster 1	Rolandic operculum	R	214	42	−33	24	2.68
		Supramarginal gyrus	R		48	−42	27	2.90
		Superior temporal gyrus	R		45	−42	15	3.24
	autism < healthy controls							
	Cluster 1	Thalamus	L	205	−6	−21	12	−3.71
		Thalamus	R		3	−15	3	−3.02

R, right; L, left.

showed increased functional connectivity between the right amygdala and the right rolandic operculum, right supramarginal gyrus and right superior temporal gyrus, as well as decreased connectivity between the right amygdala and the bilateral thalamus (Fig. 1 and Table 2).

3.2. Functional connectivity of amygdala in dataset 2: Leuven

In the Leuven dataset, one-sample *t*-test results were presented in supplementary Fig. S2. Significant decreases in functional connectivity of the left amygdala with the left superior temporal gyrus, right caudate, right putamen and right thalamus were observed in autism compared with control group. Additionally, individuals with autism showed significantly decreased functional connectivity between the right amygdala and the right caudate, right putamen and bilateral thalamus (Fig. 1 and Table 3).

3.3. Overlap of altered functional connectivity between two datasets

The overlap of amygdala-related functional connectivity alterations between Leuven and UCLA datasets includes decreased connectivity between the left amygdala and the right thalamus and right putamen, and decreased connectivity between the right amygdala and the left thalamus (Fig. 2 and Table 4).

3.4. Correlations with autism symptom severity

The functional connectivity between the left amygdala and the right thalamus and right putamen for autism was negatively related to symptom severity for reciprocal social interaction subscore of ADI-R in the UCLA dataset (r=−0.49, p=0.04; r=−0.56, p=0.016, uncorrected, respectively). No other significant correlation between connectivity and social deficits severity was found in this study (Fig. 2).

Table 3
Brain regions showing significantly different functional connectivity of the amygdala between autism and healthy controls in the Leuven dataset.

Seed	Cluster	Regions	Hemisphere	Number of voxels	MNI coordinates			*T* value
					x	y	z	
Left amygdala	autism < healthy controls							
	Cluster 1	Temporal pole: superior temporal gyrus	L	336	−24	6	−21	−3.26
		Superior temporal gyrus	L		−45	−12	−12	−3.83
	Cluster 2	Caudate	R	352	12	9	12	−3.43
		Putamen	R		24	9	12	−4.14
		Thalamus	R		18	−12	12	−4.44
Right amygdala	autism < healthy controls							
	Cluster 1	Caudate	R	290	18	15	9	−3.23
		Putamen	R		21	12	6	−4.19
		Thalamus	L		−18	−21	9	−2.51
		Thalamus	R		18	−12	12	−2.70

R, right; L, left.

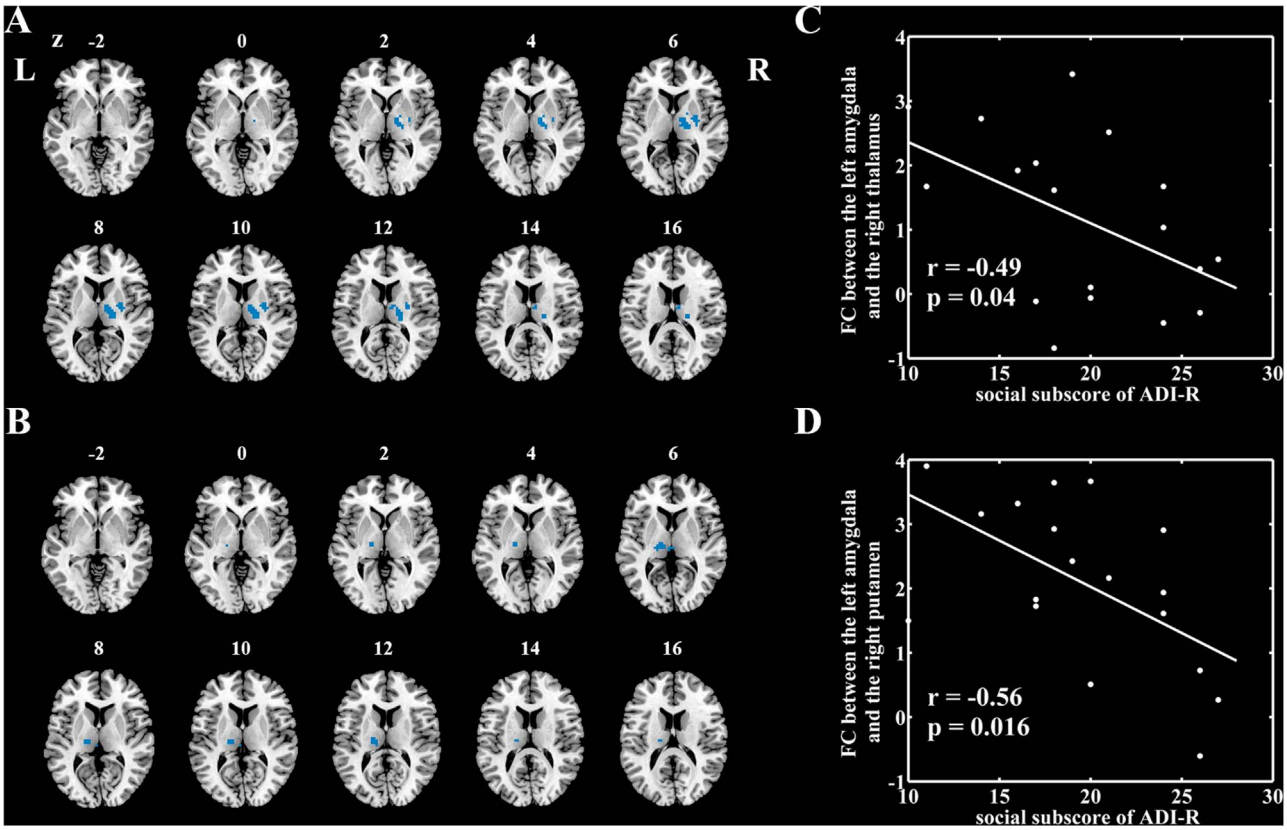

Fig. 2. Overlap of altered functional connectivity (FC) between Leuven and UCLA. Compared with healthy controls, individuals with autism exhibited decreased functional connectivity between the left amygdala and right thalamus and right putamen (A), as well as decreased functional connectivity between the right amygdala and left thalamus (B). Correlation analysis between the functional connectivity and autism symptom severity demonstrated that the functional connectivity between the left amygdala and the right thalamus (C), as well as the right putamen (D) in autism was negatively related to symptom severity assessed with social subscore of ADI_R in the UCLA dataset.

Table 4
Overlap of altered functional connectivity in individuals with autism compared with healthy controls of Leuven and UCLA.

Seed	Cluster	Regions	Hemisphere	Number of voxels	Labels
Left amygdala	autism < healthy controls				
	Cluster 1	Thalamus	R	66	VL/VA/ LP/VPL
	Cluster 2	Putamen	R	24	
Right amygdala	autism < healthy controls				
	Cluster 1	Thalamus	L	35	VL/VPL/ LP/MD

R, right; L, left. VL: ventral lateral nucleus; VA: ventral anterior nucleus; LP: lateral posterior nucleus; VPL: ventral posterior lateral nucleus; MD: medial dorsal nucleus.

3.5. Reproducible analyses of potential confounds

3.5.1. Analysis on 'scrubbed' data

The overlap results of two datasets are illustrated in supplementary Fig. S3, which replicated most of the functional connectivity findings in the primary analyses. Compared with healthy controls, individuals with autism exhibited decreased functional connectivity between the left amygdala and right thalamus and right putamen in both datasets (AlphaSim Correction, $p < 0.05$).

3.5.2. Analysis using different smooth strategies

Overlap results showed that decreased functional connectivity between the left amygdala and right thalamus are highly reproducible no matter using 4-mm or 6-mm smooth (supplementary Fig. S4; AlphaSim Correction, $p < 0.05$).

4. Discussion

This study examined the functional connectivity patterns of amygdala in autism using resting-state fMRI data collected from two institutions. The overlap results demonstrated that adolescents with autism have decreased functional connectivity between the left amygdala and the right thalamus and right putamen compared to healthy controls, and decreased connectivity between the right amygdala and the left thalamus, which testify our hypothesis. Particularly, decreased functional connectivity between the left amygdala and right thalamus was robust to alternate preprocessing strategies. At the same time, discrepant functional connectivity patterns between two datasets were observed in several brain regions, including the fusiform gyrus, hippocampus, insula, pallidum, parahippocampal gyrus, superior temporal gyrus, rolandic operculum, supramarginal gyrus, cerebellum, temporal pole and caudate. Correlation analysis showed that consistent functional connectivity between the left amygdala and the right thalamus, as well as the right putamen, were negatively correlated with abnormalities in social interaction function in the autism group. This brain-behavior relationship indicates a disease-related change tendency of functional connectivity in autism. These findings associated with amygdala are consistent with the *Amygdala Theory of Autism* (Baron-Cohen et al., 2000) and developmental model on functional connectivity in autism (Uddin et al., 2013), and provide new evidence to understand the pathophysiological mechanism of social deficits in autism.

The amygdala is a collection of nuclei, and exhibit unique functional connectivity files with other cortical and subcortical regions throughout the brain, which underlie a wide variety of affective and cognitive processes (Ledoux, 2007; Ledoux, 2000). Furthermore, atypical functional connectivity associated with amygdala have been implicated in a

wide range of psychiatric disorders with affective and cognitive deficits, such as anxiety, depression, schizophrenia, and autism (Cullen et al., 2014; Hoptman et al., 2010; Rausch et al., 2015; Roy et al., 2013). These findings demonstrated the potential of amygdala functional connectivity for indexing typical and atypical development of emotion-related brain circuitry.

Functional brain circuits mature with age and dramatic changes in relation to amygdala circuitry occur in emotional behaviors during the development (Gee et al., 2013). The amygdala functional connectivity experiences peculiar maturation during adolescence (Gabard-Durnam et al., 2014). Specifically, the remarkably transition time of amygdala-related functional connectivity from childhood to adolescence is around 10 and 11 years old, and amygdala-cortical functional connectivity absence during childhood occur during adolescence in typical development individuals (Gabard-Durnam et al., 2014). Differentiated amygdala-related functional connectivity patterns between childhood and adulthood also stressed the developmental importance during adolescence (Qin et al., 2012). Adolescence is a transitional period from childhood to adulthood with changes in emotional behaviors (Casey et al., 2010), as well as increased prevalence of psychiatric disorders involving the regulation of behavior and emotion (Steinberg, 2008). Exploring the functional connectivity patterns of amygdala in this period can provide a better understanding of atypical development associated with social deficits in autism brain.

4.1. Decreased functional connectivity between the amygdala and thalamus in autism

The thalamus is traditionally regarded as a “sensory gate” receiving afferents from sensory receptors and projecting sensory information to target regions. Apart from olfaction, almost all the sensory circuits relay in the thalamus. The ventral posterior lateral nucleus (VPL) served as the somatosensory relay for the body; the ventral anterior nucleus (VA) and ventral lateral nucleus (VL) are associated with motor control pathways; the lateral posterior nucleus (LP) is interconnected with parietal lobe and receives some inputs from the visual system; the medial dorsal nucleus (MD) connected with the amygdala via the ventroamygdalofugal pathway is involved in memory, especially the executive aspects (Nolte and Sundsten, 2002).

The amygdala receive afferents from the thalamus carrying a great deal of sensory inputs, and also send efferents to the thalamus. The reciprocal connections of the amygdala suit it perfectly for the perception of outside objects and situations and making appropriate emotional responses (Nolte and Sundsten, 2002). Neuroanatomical and functional evidence testified the existence of two parallel routes (i.e. a thalamo-cortical-amygdala and a thalamo-amygdala pathway) to the amygdala in salient sensory information processing (Garrido et al., 2012; Ledoux, 2000). It's noteworthy that the subcortical pathway may serve as a more widespread role in sensory information processing, not restricted to emotionally salient stimuli (fear, happy or neutral).

In this study, compared with healthy controls, adolescents with autism exhibited significantly decreased functional connectivity between the amygdala and the thalamus. Thalamic abnormalities in autism have been reported in a large number of recent studies (Friedman et al., 2003; Hardan et al., 2006; Haznedar et al., 2006; Starkstein et al., 2000; Tamura et al., 2010; Tsatsanis et al., 2003). Recent studies also reported anatomical and functional amygdala abnormalities in autism (Baron-Cohen et al., 2000; Critchley et al., 2000; Dalton et al., 2005; Dziobek et al., 2010; Stanfield et al., 2008). The abnormalities in thalamus and amygdala may contribute to the aberrant functional integration between them, and the underconnectivity may lead to dysfunctional sensory processing in autism. In typical development, sensory inputs from the thalamus can reach the amygdala via the direct subcortical connection and fire the amygdala to make an expeditious evaluation of behavioral importance in sensory information (Garrido et al., 2012). The functional inconsistency in individuals with autism might result in abnormal sensory information about outside world and further lead to improper emotional response to the social world.

Correlation analysis showed that decreased functional connectivity between the left amygdala and the right thalamus was negatively related with the scores on ADI-R social domain. The social subscore of ADI-R assesses the symptom severity of social interaction in autism, and higher scores indicate more severe social deficits. In individuals with autism, the functional connectivity between amygdala and thalamus was significantly below the level of healthy controls. Further, the lower functional connectivity between these regions tends to appear with more severe autism social deficits. The relationship between functional integration and symptom severity indicates disease-related change tendency in participants with autism, and might provide new lines for understanding the neural mechanisms underlying social deficits in autism.

4.2. Decreased functional connectivity between the amygdala and putamen in autism

The putamen, together with the caudate nucleus and pallidum composed the dorsal striatum. Previous studies suggest that the role of the putamen is not only involved in motor behavior, but also associated with learning and memory, especially the stimulus-response habits learning and memory (Packard and Knowlton, 2002). Although infrequently examined, abnormalities in putamen have been detected in autism. Lower relative glucose metabolic rate was reported in the putamen in adults with autism spectrum disorders (Mehmet Haznedar et al., 2006). In another study, the putamen was reported to have reduced numerical density of neurons in individuals with autism (Wegiel et al., 2014).

Studies of the past decades have provided substantial evidence that amygdala regulates the acquisition, storage and consolidation of emotionally arousing memory (Ledoux, 2000; McGaugh, 2004). The decreased functional connectivity between the left amygdala and the right putamen found in the present study may be implicated in the form of emotionally arousing memory. Some recent models proposed that the memory deficits is a basic deficit in the processing of complex information in individuals with autism (Minshew and Goldstein, 2001). Individuals with autism were demonstrated to have differing profile of memory function in autism compared with controls (Williams et al., 2006). The dysfunction of the connection between the amygdala and the putamen might lead to the emotion-related memory deficits, which results in the deficits in the processing of complex social information. Additionally, the correlation trend between reduced functional connectivity and social deficits severity observed in autism might imply the special role of functional connectivity associated with the amygdala in the pathophysiology of autism.

4.3. Discrepant functional connectivity findings associated with the amygdala in two datasets

Albeit consistent findings associated with the amygdala were found in the current study, discrepant findings also need to be noticed in multisite studies. These two datasets manifested discrepant functional connectivity patterns in several brain regions, including the fusiform gyrus, hippocampus, insula, pallidum, parahippocampal gyrus, superior temporal gyrus, rolandic operculum, supramarginal gyrus, cerebellum, temporal pole and caudate. In light of the fact that fMRI acquisition sequences differed both in spatial and time resolution between two datasets, these discrepant findings might partly be attributed to the inter-scanner variability (Friedman et al., 2006; Glover et al., 2012), though we processed data separately to reduce these differences. Additionally, inter-group differences in demographics (e.g. FIQ) in two sites, which have been treated as covariates in the statistic models, might also introduce undesirable inter-site

variability. Such factors might obscure the desirable group differences and weaken the efficiency of multi-site studies (Glover et al., 2012).

Since social impairment is the most common clinical sign in individuals with autism, examining brain circuits involved in social information processing might explain the mechanisms underlying social-cognitive deficits in autism. The amygdala, fusiform gyrus, hippocampus, insula, temporal pole, supramarginal gyrus and superior temporal gyrus have been implicated in social cognition process and pertain to social brain network (Adolphs, 2003, 2009; Barak and Feng, 2016; Brothers, 2002; Gotts et al., 2012; Patriquin et al., 2016). Converging neuroimaging evidence has shown that abnormal social perception and cognition in autism rest upon the specific impairments in social brain network (Barak and Feng, 2016; Elsabbagh and Johnson, 2016; Gotts et al., 2012). Those social brain regions selectively involved in social processing and interconnect other social brain areas to make up the social information processing system (Adolphs, 2003). Altered functional connectivity or synchronization between the amygdala and the rest areas of social brain network in autism in the current study provides new evidence for abnormal social brain circuits. Impairments in the social brain network might lay the foundation for atypical features of social cognition process in individuals with autism (Barak and Feng, 2016; Elsabbagh and Johnson, 2016; Gotts et al., 2012).

Previous resting-state functional connectivity study of the amygdala in healthy controls detected a wide variety of brain regions connected with the amygdala, including striatum, parahippocampal gyrus and cerebellum (Gabard-Durnam et al., 2014; Roy et al., 2009). The functional interaction between the amygdala and striatum is involved in detecting emotional stimuli and making adaptive decisions (Charpentier et al., 2015). Altered functional connectivity between the amygdala and striatum in the current study might reflect impairments in social emotional processing.

Anxiety and depression are common comorbidities in individuals with autism (Ghaziuddin et al., 2002; White et al., 2009), especially occur at a high risk in adolescence (Picci and Scherf, 2015). Disrupted amygdala functional connectivity patterns associated with the striatum and cerebellum were reported in adolescents with generalized anxiety disorder (Roy et al., 2013). Moreover, decreased functional connectivity between the amygdala and parahippocampal gyrus was associated with depression symptom in adolescents with major depressive disorder (Cullen et al., 2014). The amygdala functional connectivity network abnormalities might provide new lines for investigating the neural substrates underlying anxiety and depression symptom in adolescents with autism.

4.4. Limitations

Some limitations of our study should be mentioned. First, we conducted multiple comparisons in correlation analysis, however, none of examined relationships survived correction. Considering the relatively large correlation coefficients values in correlation analysis results (Cohen, 1988, 1992), failure to survive multiple comparisons might partly be attributed to the relative small number of autism individuals with ADOS and ADI scores. The relationship between altered functional connectivity and social deficits severity observed in the autism group should be verified in future studies. Second, better ways of regressing out irrelevant factors between different sites should be found to increase the reliability of multisite research. Third, previous functional connectivity study demonstrated reduced amygdala-cortical connectivity in elder subjects with autism (adolescents and adults) (Rausch et al., 2015). Though the current study did replicated decreased amygdala connectivity patterns in adolescents with autism, the regions that showed altered functional connectivity were not replicated. Differential brain regions found in these two studies might partly be attributed to the different developmental stages included in the study. This also highlight the significance of research on the functional connectivity of amygdala in autism during adolescence. Future longitudinal studies might be particularly fruitful to examine the developmental effect on amygdala functional connectivity in autism. In addition, the cause of these functional abnormalities is also unknown. The structural connectivity should be explored to gain a deeper insight into the neurophysiopathology underlying autism.

4.5. Conclusions

In summary, subjects with autism showed decreased functional connectivity of the amygdala compared with typical developmental individuals, which provided new support for the *Amygdala Theory of Autism*. Our findings demonstrated amygdala-related functional connectivity abnormalities in autism during adolescence, a critical transition period from childhood to adulthood. Since functional brain connectivity might vary across age in individuals with autism (Uddin et al., 2013), future longitudinal studies in autism could explore the amygdala functional connectivity abnormalities by taking different developmental stages into account. Further, altered amygdala functional connectivity patterns found in the current study might provide new lines for understanding neural mechanisms underlying autism.

Conflicts of interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pscychresns.2016.10.005.

References

Adolphs, R., 2003. Cognitive neuroscience of human social behaviour. Nat. Rev. Neurosci. 4 (3), 165–178.
Adolphs, R., 2009. The social brain: neural basis of social knowledge. Annu. Rev. Psychol. 60 (1), 693–716.
American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub.
Aylward, E., Minshew, N., Goldstein, G., Honeycutt, N., Augustine, A., Yates, K., et al., 1999. MRI volumes of amygdala and hippocampus in non–mentally retarded autistic adolescents and adults. Neurology 53 (9), (2145-2145).
Baio, J., 2014. Developmental disabilities monitoring network surveillance year 2010 principal investigators; Centers for Disease Control and Prevention (CDC). Prevalence of autism spectrum disorder among children aged 8 years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveill. Summ. 63, 1–21.
Barak, B., Feng, G., 2016. Neurobiology of social behavior abnormalities in autism and Williams syndrome. Nat. Neurosci. 19, 6.
Baron-Cohen, S., 1997. Mindblindness: An Essay on Autism and Theory of Mind. MIT press.
Baron-Cohen, S., Ring, H.A., Bullmore, E.T., Wheelwright, S., Ashwin, C., Williams, S., 2000. The amygdala theory of autism. Neurosci. Biobehav. Rev. 24 (3), 355–364.
Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. B 57, 289–300.
Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar mri. Magn. Reson.

Med. 34 (4), 537–541.
Brothers, L., 2002. The social brain: a project for integrating primate behavior and neurophysiology in a new domain. Found. Soc. Neurosci., 367–385.
Casey, B., Duhoux, S., Cohen, M.M., 2010. Adolescence: what do transmission, transition, and translation have to do with it? Neuron 67 (5), 749–760.
Charpentier, C.J., Martino, B.D., Sim, A.L., Sharot, T., Roiser, J.P., 2015. Emotion-induced loss aversion and striatal-amygdala coupling in low-anxious individuals. Soc. Cogn. Affect. Neurosci. 11 (4), 569–579.
Cohen, J., 1988. Statistical power analysis for the behavioral sciences (2nd Edition). Biometrics.
Cohen, J., 1992. A power primer. Psychol. Bull. 112 (1), 155–159.
Collins, D.L., Zijdenbos, A., Kollokian, V., Sled, J.G., Kabani, N.J., Holmes, C.J., Evans, A.C., 1998. Design and construction of a realistic digital brain phantom. IEEE Trans. Med. Imaging 17, 463–468.
Courchesne, E., Campbell, K., Solso, S., 2011. Brain growth across the life span in autism: age-specific changes in anatomical pathology. Brain Res. 1380, 138–145.
Critchley, H.D., Daly, E.M., Bullmore, E.T., Williams, S.C., Van Amelsvoort, T., Robertson, D.M., et al., 2000. The functional neuroanatomy of social behaviour Changes in cerebral blood flow when people with autistic disorder process facial expressions. Brain 123 (11), 2203–2212.
Cullen, K.R., Westlund, M.K., Klimes-Dougan, B., Mueller, B.A., Houri, A., Eberly, L.E., et al., 2014. Abnormal amygdala resting-state functional connectivity in adolescent depression. JAMA Psychiatry 71 (10), 1138–1147.
Dalton, K.M., Nacewicz, B.M., Johnstone, T., Schaefer, H.S., Gernsbacher, M.A., Goldsmith, H.H., et al., 2005. Gaze fixation and the neural circuitry of face processing in autism. Nat. Neurosci. 8 (4), 519–526.
Damoiseaux, J., Rombouts, S., Barkhof, F., Scheltens, P., Stam, C., Smith, S.M., et al., 2006. Consistent resting-state networks across healthy subjects. Proc. Natl. Acad. Sci. USA 103 (37), 13848–13853.
Dziobek, I., Bahnemann, M., Convit, A., Heekeren, H.R., 2010. The role of the fusiform-amygdala system in the pathophysiology of autism. Arch. Gen. Psychiatry 67 (4), 397–405.
Ebisch, S.J.H., Gallese, V., Willems, R.M., Mantini, D., Groen, W.B., Romani, G.L., et al., 2011. Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. Hum. Brain Mapp. 32 (7), 1013–1028.
Elsabbagh, M., Johnson, M.H., 2016. Autism and the social brain: the first-year puzzle. Biol. Psychiatry.
Fox, M.D., Zhang, D., Snyder, A.Z., Raichle, M.E., 2009. The global signal and observed anticorrelated resting state brain networks. J. Neurophysiol. 101 (6), 3270–3283.
Friedman, L., Glover, G.H., Consortium, T.F., 2006. Reducing interscanner variability of activation in a multicenter fMRI study: controlling for signal-to-fluctuation-noise-ratio (SFNR) differences. Neuroimage 33 (2), 471–481.
Friedman, S., Shaw, D., Artru, A., Richards, T., Gardner, J., Dawson, G., et al., 2003. Regional brain chemical alterations in young children with autism spectrum disorder. Neurology 60 (1), 100–107.
Gabard-Durnam, L.J., Flannery, J., Goff, B., Gee, D.G., Humphreys, K.L., Telzer, E., et al., 2014. The development of human amygdala functional connectivity at rest from 4 to 23 years: a cross-sectional study. Neuroimage 95, 193–207.
Garrido, M.I., Barnes, G.R., Sahani, M., Dolan, R.J., 2012. Functional evidence for a dual route to amygdala. Curr. Biol. 22 (2), 129–134.
Gee, D.G., Humphreys, K.L., Flannery, J., Goff, B., Telzer, E.H., Shapiro, M., et al., 2013. A developmental shift from positive to negative connectivity in human amygdala-prefrontal circuitry. J. Neurosci. 33 (10), 4584–4593.
Gervais, H., Belin, P., Boddaert, N., Leboyer, M., Coez, A., Sfaello, I., et al., 2004. Abnormal cortical voice processing in autism. Nat. Neurosci. 7 (8), 801–802.
Ghaziuddin, M., Ghaziuddin, N., Greden, J., 2002. Depression in persons with autism: implications for research and clinical care. J. Autism Dev. Disord. 32 (4), 299–306.
Glover, G.H., Mueller, B.A., Turner, J.A., Erp, T.G.M.V., Liu, T.T., Greve, D.N., et al., 2012. Function biomedical informatics research network recommendations for prospective multicenter functional MRI studies. J. Magn. Reson. Imaging 36 (1), 39–54.
Gotts, S.J., Simmons, W.K., Milbury, L.A., Wallace, G.L., Cox, R.W., Martin, A., 2012. Fractionation of social brain circuits in autism spectrum disorders. Brain 135 (Pt 9), 2711–2725.
Hall, G.B., Szechtman, H., Nahmias, C., 2014. Enhanced salience and emotion recognition in autism: a PET study. Am. J. Psychiatry.
Hardan, A.Y., Girgis, R.R., Adams, J., Gilbert, A.R., Keshavan, M.S., Minshew, N.J., 2006. Abnormal brain size effect on the thalamus in autism. Psychiatry Res.: Neuroimaging 147 (2), 145–151.
Haznedar, M., Buchsbaum, M., Hazlett, E., LiCalzi, E., Cartwright, C., Hollander, E., 2006. Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. Am. J. Psychiatry 163 (7), 1252–1263.
Hobson, R.P., 1993. Autism and the Development of Mind. Psychology Press.
Hoptman, M.J., D'Angelo, D.D., Mauro, C.J., Shehzad, Z.E., Kelly, A.M., Castellanos, F.X., et al., 2010. Amygdalofrontal functional disconnectivity and aggression in schizophrenia. Schizophr. Bull. 36 (5), 1020–1028.
Humphrey, N.K., 1976. The social function of intellect. Grow. Points Ethol., 303–317.
Kleinhans, N.M., Richards, T., Sterling, L., Stegbauer, K.C., Mahurin, R., Johnson, L.C., et al., 2008. Abnormal functional connectivity in autism spectrum disorders during face processing. Brain 131 (4), 1000–1012.
Ledoux, J., 2007. The amygdala. Curr. Biol. 17 (20), R868–R874.
Ledoux, J.E., 2000. Emotion circuits in the brain. Annu. Rev. Neurosci. 23 (2), 155–184.
Lord, C., Cook, E.H., Leventhal, B.L., Amaral, D.G., 2013. Autism spectrum disorders. Autism: The Science of Mental Health, 28, 217
Mehmet Haznedar, M., Buchsbaum, M., Hazlett, M.S., LiCalzi, E.A., Cartwright, E.M., C, Hollander, E., 2006. Volumetric analysis and three-dimensional glucose metabolic mapping of the striatum and thalamus in patients with autism spectrum disorders. Am. J. Psychiatry 163 (7), 1252–1263.
McGaugh, J.L., 2004. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu. Rev. Neurosci. 27, 1–28.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn. Sci. 15 (10), 483–506.
Minshew, N.J., Goldstein, G., 2001. The pattern of intact and impaired memory functions in autism. J. Child Psychol. Psychiatry 42 (08), 1095–1101.
Monk, C.S., Weng, S.-J., Wiggins, J.L., Kurapati, N., Louro, H.M., Carrasco, M., et al., 2010. Neural circuitry of emotional face processing in autism spectrum disorders. J. Psychiatry Neurosci. 35 (2), 105.
Murphy, K., Birn, R.M., Handwerker, D.A., Jones, T.B., Bandettini, P.A., 2009. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 44 (3), 893–905.
Nacewicz, B.M., Dalton, K.M., Johnstone, T., Long, M.T., McAuliff, E.M., Oakes, T.R., et al., 2006. Amygdala volume and nonverbal social impairment in adolescent and adult males with autism. Arch. Gen. Psychiatry 63 (12), 1417–1428.
Nolte, J., Sundsten, J., 2002. The Human Brain: An Introduction to its Functional Anatomy 5. Mosby St. Louis.
Nomi, J.S., Uddin, L.Q., 2015. Developmental changes in large-scale network connectivity in autism. Neuroimage Clin. 7, 732–741.
Packard, M.G., Knowlton, B.J., 2002. Learning and memory functions of the basal ganglia. Annu. Rev. Neurosci. 25 (1), 563–593.
Patriquin, M.A., DeRamus, T., Libero, L.E., Laird, A., Kana, R.K., 2016. Neuroanatomical and neurofunctional markers of social cognition in autism spectrum disorder. Hum. Brain Mapp..
Pessoa, L., 2008. On the relationship between emotion and cognition. Nat. Rev. Neurosci. 9 (2), 148–158.
Phelps, E.A., Ledoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48 (2), 175–187.
Picci, G., Scherf, K.S., 2015. A two-hit model of autism: adolescence as the second hit. Clin. Psychol. Sci. J. Assoc. Psychol. Sci. 3 (3).
Pierce, K., Müller, R.-A., Ambrose, J., Allen, G., Courchesne, E., 2001. Face processing occurs outside the fusiformface area'in autism: evidence from functional MRI. Brain 124 (10), 2059–2073.
Piggot, J., Kwon, H., Mobbs, D., Blasey, C., Lotspeich, L., Menon, V., et al., 2004. Emotional attribution in high-functioning individuals with autistic spectrum disorder: a functional imaging study. J. Am. Acad. Child Adolesc. Psychiatry 43 (4), 473–480.
Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage 59 (3), 2142–2154.
Qin, S., Young, C.B., Supekar, K., Uddin, L.Q., Menon, V., 2012. Immature integration and segregation of emotion-related brain circuitry in young children. Proc. Natl. Acad. Sci. USA 109 (20), 7941–7946.
Rapin, I., Tuchman, R.F., 2008. Autism: definition, neurobiology, screening, diagnosis. Pediar. Clin. North Am. 55 (5), 1129–1146, (viii).
Rausch, A., Zhang, W., Haak, K.V., Mennes, M., Hermans, E.J., Oort, E.V., et al., 2015. Altered functional connectivity of the amygdaloid input nuclei in adolescents and young adults with autism spectrum disorder: a resting state fMRI study. Mol. Autism 7 (1), 1–13.
Roy, A.K., Fudge, J.L., Kelly, C., Perry, J.S.A., Daniele, T., Carlisi, C., et al., 2013. Intrinsic functional connectivity of amygdala-based networks in adolescent generalized anxiety disorder. J. Am. Acad. Child Adolesc. Psychiatry 52 (3), 10.
Roy, A.K., Shehzad, Z., Margulies, D.S., Kelly, A.M.C., Uddin, L.Q., Gotimer, K., et al., 2009. Functional connectivity of the human amygdala using resting state fMRI. Neuroimage 45 (2), 614–626.
Satterthwaite, T.D., Wolf, D.H., Loughead, J., Ruparel, K., Elliott, M.A., Hakonarson, H., et al., 2012. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. Neuroimage 60 (1), 623–632.
Schultz, R.T., 2005. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. Int. J. Dev. Neurosci. 23 (2), 125–141.
Schumann, C.M., Hamstra, J., Goodlin-Jones, B.L., Lotspeich, L.J., Kwon, H., Buonocore, M.H., et al., 2004. The amygdala is enlarged in children but not adolescents with autism; the hippocampus is enlarged at all ages. J. Neurosci. 24 (28), 6392–6401.
Shafritz, K.M., Dichter, G.S., Baranek, G.T., Belger, A., 2008. The neural circuitry mediating shifts in behavioral response and cognitive set in autism. Biol. Psychiatry 63 (10), 974–980.
Song, X.W., Dong, Z.Y., Long, X.Y., Li, S.F., Zuo, X.N., Zhu, C.Z., et al., 2011. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 6 (9), e25031.
Stanfield, A.C., McIntosh, A.M., Spencer, M.D., Philip, R., Gaur, S., Lawrie, S.M., 2008. Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. Eur. Psychiatry 23 (4), 289–299.
Starkstein, S.E., Vazquez, S., Vrancic, D., Nanclares, V., Manes, F., Piven, J., et al., 2000. SPECT findings in mentally retarded autistic individuals. J. Neuropsychiatry Clin. Neurosci. 12 (3), 370–375.
Steinberg, L., 2008. A social neuroscience perspective on adolescent risk-taking. Dev. Rev. 28 (1), 78–106.
Swartz, J.R., Wiggins, J.L., Carrasco, M., Lord, C., Monk, C.S., 2013. Amygdala habituation and prefrontal functional connectivity in youth with autism spectrum disorders. J. Am. Acad. Child Adolesc. Psychiatry 52 (1), 84–93.

Tamura, R., Kitamura, H., Endo, T., Hasegawa, N., Someya, T., 2010. Reduced thalamic volume observed across different subgroups of autism spectrum disorders. Psychiatry Res.: Neuroimaging 184 (3), 186–188.
Tsatsanis, K.D., Rourke, B.P., Klin, A., Volkmar, F.R., Cicchetti, D., Schultz, R.T., 2003. Reduced thalamic volume in high-functioning individuals with autism. Biol. Psychiatry 53 (2), 121–129.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15 (1), 273–289.
Uddin, L.Q., Supekar, K., Menon, V., 2013. Reconceptualizing functional brain connectivity in autism from a developmental perspective. Front. Hum. Neurosci., 7.
Van Dijk, K.R., Tvenkataraman, H., 2010. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. J. Neurophysiol. 103 (1), 297–321.
Wang, A.T., Dapretto, M., Hariri, A.R., Sigman, M., Bookheimer, S.Y., 2004. Neural correlates of facial affect processing in children and adolescents with autism spectrum disorder. J. Am. Acad. Child Adolesc. Psychiatry 43 (4), 481–490.
Wegiel, J., Flory, M., Kuchna, I., Nowicki, K., Ma, S., Imaki, H., et al., 2014. Stereological study of the neuronal number and volume of 38 brain subdivisions of subjects diagnosed with autism reveals significant alterations restricted to the striatum, amygdala and cerebellum. Acta Neuropathol. Commun. 2, 141.
White, S.W., Oswald, D., Ollendick, T., Scahill, L., 2009. Anxiety in children and adolescents with autism spectrum disorders. Clin. Psychol. Rev. 29 (3), 216–229.
Williams, D.L., Goldstein, G., Minshew, N.J., 2006. The profile of memory function in children with autism. Neuropsychology 20 (1), 21.
Woodward, N.D., Cascio, C.J., 2015. Resting-state functional connectivity in psychiatric disorders. JAMA Psychiatry 72, 8.
Yan, C.-G., Cheung, B., Kelly, C., Colcombe, S., Craddock, R.C., Di Martino, A., et al., 2013. A comprehensive assessment of regional variation in the impact of head micromovements on functional connectomics. Neuroimage 76, 183–201.
Yan, C.-G., Zang, Y.-F., 2010. DPARSF: a MATLAB toolbox for "Pipeline" data analysis of resting-state fMRI. Front Syst. Neurosci. 4, 13.
Zhang, Y., Zhu, C., Chen, H., Duan, X., Lu, F., Li, M., et al., 2015. Frequency-dependent alterations in the amplitude of low-Frequency fluctuations in social anxiety disorder. J. Affect. Disord. 174, 329–335.