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Increased Functional Connectivity Between Subcortical and Cortical Resting-State Networks in Autism Spectrum Disorder

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Abstract

Importance—Individuals with autism spectrum disorder (ASD) exhibit severe difficulties in social interaction, motor coordination, behavioral flexibility, and atypical sensory processing, with considerable interindividual variability. This heterogeneous set of symptoms recently led to investigating the presence of abnormalities in the interaction across large-scale brain networks. To date, studies have focused either on constrained sets of brain regions or whole-brain analysis, rather than focusing on the interaction between brain networks.

Objectives—To compare the intrinsic functional connectivity between brain networks in a large sample of individuals with ASD and typically developing control subjects and to estimate to what extent group differences would predict autistic traits and reflect different developmental trajectories.

Design, Setting, and Participants—We studied 166 male individuals (mean age, 17.6 years; age range, 7-50 years) diagnosed as having *DSM-IV-TR* autism or Asperger syndrome and 193 typical developing male individuals (mean age, 16.9 years; age range, 6.5-39.4 years) using

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resting-state functional magnetic resonance imaging (MRI). Participants were matched for age, IQ, head motion, and eye status (open or closed) in the MRI scanner. We analyzed data from the Autism Brain Imaging Data Exchange (ABIDE), an aggregated MRI data set from 17 centers, made public in August 2012.

Main Outcomes and Measures—We estimated correlations between time courses of brain networks extracted using a data-driven method (independent component analysis). Subsequently, we associated estimates of interaction strength between networks with age and autistic traits indexed by the Social Responsiveness Scale.

Results—Relative to typically developing control participants, individuals with ASD showed increased functional connectivity between primary sensory networks and subcortical networks (thalamus and basal ganglia) (all $t > 3.13$, $P < .001$ corrected). The strength of such connections was associated with the severity of autistic traits in the ASD group (all $r > 0.21$, $P < .0067$ corrected). In addition, subcortico-cortical interaction decreased with age in the entire sample (all $r < -0.09$, $P < .012$ corrected), although this association was significant only in typically developing participants (all $r < -0.13$, $P < .009$ corrected).

Conclusions and Relevance—Our results showing ASD-related impairment in the interaction between primary sensory cortices and subcortical regions suggest that the sensory processes they subserve abnormally influence brain information processing in individuals with ASD. This might contribute to the occurrence of hyposensitivity or hypersensitivity and of difficulties in top-down regulation of behavior.

Introduction

Brain abnormalities in autism spectrum disorder (ASD) are present at different scales of anatomical organization, ranging from cortical layers^{1,2} and minicolumns^{3,4} to large-scale distributed brain networks.^{5–9} There is increasing consensus that these abnormalities reflect atypical interactions across multiple neural systems, rather than a problem affecting isolated brain regions.^{10–18} Abnormalities in the development and interaction across brain networks could arise from early disruptions of local neuronal circuitry, signaled by abnormal laminar organization² and reduced size of cortical minicolumns.^{3,19} The latter in particular is likely to reflect disrupted functional segregation between minicolumns, giving rise to local overconnectivity between minicolumns.^{3,11} Excessive local information processing would positively reinforce and stabilize local physical connections while at the same time negatively affect the development of efficient long-range connections due to delays in information transfer between distant brain regions, failure to differentiate signal from noise, and reduced synchrony in the activity of distant clusters of minicolumns^{11,20–23} (see the initial figure in the study by Belmonte et al²² for a graphical depiction of the effect of local overconnectivity coupled with long-range underconnectivity). At the network level, the cascading causal effect of local overconnectivity on long-range disconnectivity could result in decreased functional integration within networks and functional segregation between networks,^{24–26} as well as persistent subcortico-cortical overconnectivity.^{8,27}

Within this perspective, functional neuroimaging studies focused on 2 levels of anatomical organization. Examining the interaction between specific brain regions with functional

magnetic resonance imaging (fMRI), functional connectivity studies have shown that ASD is associated with abnormal connectivity within cortico-cortical networks supporting language, 28–30 working memory,^{31,32} visual attention,³³ face recognition,^{34,35} salience detection,⁷ and social cognition.^{36–39} Abnormal subcortico-cortical connectivity has also been evidenced by studies^{18,27,40–43} focusing on the basal ganglia and the thalamus. Considering the topological properties of the whole-brain network, graph theoretical studies^{44–47} consistently reported alterations in the efficiency of information transfer both at the local and the global level in ASD. While these investigations have contributed to characterize the disconnection model of ASD,^{11,13,15,48} one largely underexamined domain regards the investigation of between-network interactions in ASD.

To date, few studies have examined between-network interactions in ASD, reporting reduced connectivity between the saliency network and a medial temporal lobe network in young adults with ASD⁴⁹ and between a frontoparietal network and a cingulate gyrus network in children with ASD.⁵⁰ While these studies provide initial evidence about abnormalities in between-network interactions in ASD, they focused on a limited number of networks selected a priori⁴⁹ and did not analyze the interaction with sensory networks.⁵⁰

Herein, we aimed to systematically explore the interaction between brain networks in individuals with ASD using independent component analysis (ICA)^{51–53} on resting-state fMRI (rs-fMRI). This technique allows one to extract functional networks that resemble brain networks recruited during task performance.^{54–56} We quantify interactions between brain networks using the temporal correlation of their spontaneous activity at rest, and we estimate to what extent group differences would predict autistic traits and reflect different developmental trajectories. Our study uses a large sample of participants selected from the Autism Brain Imaging Data Exchange (ABIDE), a recently launched publicly available database of 1112 structural and rs-fMRI data sets acquired on 539 participants with ASD and 573 age-matched controls,⁵⁷ aggregated from 17 international sites.

The wide heterogeneity of symptoms associated with ASD led us to hypothesize the presence of abnormal patterns of interaction between multiple brain networks, ranging from sensory and motor processing to higher-order cognitive functions. We also hypothesized that group differences in between-network interaction would be associated with the degree of autistic traits and with delayed or arrested development of cortico-cortical interactions and persistent subcortico-cortical connectivity.

Methods

Included Participants From the ABIDE Database

From the ABIDE database, we included all male individuals with a *DSM-IV-TR* diagnosis of either autism or Asperger syndrome, collectively referred to as the ASD group and typically developing (TD) control subjects. Participant inclusion criteria were as follows: (1) the data sets included a T1-weighted image (an rs-fMRI acquisition of 180 time points with near full-brain coverage), (2) a full-scale IQ higher than 70, and (3) a mean framewise displacement (FD)⁵⁸ of less than 0.34, corresponding to 2 SDs above the whole-sample mean. These criteria yielded 359 participants (166 ASD and 193 TD) from 8 sites, matched

by age ($t_{357} = 0.86$, $P = .39$), full-scale IQ ($t_{357} = -0.93$, $P = .35$), mean FD ($t_{357} = 1.67$, $P = .09$), and eye status (open or closed) in the scanner ($\chi^2_{21} = 0.05$, $P = .81$). Demographic information for the final sample ($N = 359$) is summarized in Table 1. Further details about demographics, diagnostic criteria, and a selection flowchart for the final sample are provided in eFigure 1, eFigure 2, and eTable 1 in the Supplement. Institutional review board approval was provided by each data contributor. Detailed recruitment and assessment protocols and inclusion criteria are available on the ABIDE website. The ABIDE data set was made public in August 2012 and can be accessed at: http://fcon_1000.projects.nitrc.org/indi/abide/.

Independent Component Analysis

Image processing was carried out using FSL63–65 and in-house written software (<https://github.com/sblnin/rsfnc>). Computations were performed on the Millipede cluster at the University of Groningen (Groningen, the Netherlands) to take advantage of parallel computing for processing a data set of this magnitude. After preprocessing of the rs-fMRI data (detailed in the eMaterials in the Supplement), spatially independent components (ICs) were extracted using FSL MELODIC software.⁶⁶ The number of components was estimated by the MELODIC algorithm. Temporally concatenated probabilistic ICA^{53,66} was carried out 25 times on randomized subsets of 112 participants (7 in the TD group plus 7 in the ASD group for each of the 8 sites). The resulting spatial components were entered in a meta-ICA⁶⁷ to extract robust and reproducible resting-state networks (RSNs).

Components Selection

The meta-ICA estimated 52 spatial components. Among these, we selected RSNs according to their spatial distribution, consistency with previous rs-fMRI studies,^{7,54,67–69} and resemblance to functional networks recruited by task-based fMRI experiments.^{54,55,70} This selection was complemented by calculating for each spatial component the reproducibility across the 25 temporally concatenated probabilistic ICAs and the overlap with gray matter (eMaterials and eFigures 3, 4, 5, 6, and 7 in the Supplement). This led to the identification of 19 RSNs that were the focus of subsequent analyses (Figure 1 and Table 2). Excluded components are shown in eFigure 3 in the Supplement.

The meta-independent component analysis on 359 participants (166 autism spectrum disorder group and 193 typically developing group) extracted 52 independent components (ICs), 19 of which were selected for functional network connectivity analyses using a semisupervised procedure detailed in the eMaterials in the Supplement. For each IC, we indicate the component order in the results of the meta-independent component analysis, reflecting the amount of variance explained by that IC (in decreasing order), along with an anatomical labeling. The expanded IC abbreviations are listed in Table 2. Discarded ICs are shown in eFigure 3 in the Supplement. The similarity of these resting-state networks with those previously found by Smith et al⁵⁴ and Biswal et al⁶⁷ was quantified by means of spatial correlation and is shown in eFigure 7 in the Supplement.

Functional Network Connectivity

Each RSN's summary time course was estimated at the participant level by spatial regression of the full set of 52 components from the meta-ICA against each participant's

preprocessed rs-fMRI data.⁷¹ Although we focused our analyses on the 19 identified RSNs, we used the full set of components for spatial regression to account for potential effects of noise captured by the non-RSN components ($n = 33$). Each RSN summary time course was then band-pass filtered (0.08-0.009 Hz).⁷² We calculated functional network connectivity (FNC)^{73–75} using the Pearson correlation coefficient between each and every other summary time course. This resulted in an FNC matrix with the dimensions of 19 times 19 (RSNs) times 359 (participants). Group differences in FNC were estimated for each pair of RSNs in a general linear model that included age, IQ, and eye status at scan. Seven covariates were added to capture the mean FNC differences across sites and one to capture the global mean. Finally, the mean participant FD was added as a covariate to minimize the effects of motion.^{57,76} Inference was carried out using nonparametric permutation testing (FSL randomize [20 000 permutations]). The significance threshold was corrected for multiple comparisons using false discovery rate (FDR).⁷⁷ In addition, we repeated the analyses using data despiking⁷⁸ and a more stringent group matching for motion ($P = .36$) to assess whether group differences in FNC could depend on residual differences in motion between groups (see eMaterials in the Supplement). We then focused on RSN pairs showing significant group differences in FNC after correction to investigate their association with autistic traits and with different developmental trajectories.

Association Between FNC and the Social Responsiveness Scale

We examined whether FNC group differences could predict autistic traits, measured using the Social Responsiveness Scale (SRS).^{61,62} We correlated SRS raw scores with FNC in the whole sample and in each group separately, after groupwise demeaning of SRS scores and regressing out age, full-scale IQ, site of acquisition, eye status at scan, and mean FD. This was performed separately for each pair of RSNs with a significant group difference in FNC. The SRS scores were groupwise demeaned to prevent that correlations with FNC across groups could be confounded by group differences in SRS scores. Inference was carried out using FSL randomize, and the final results were corrected for multiple comparisons using the FDR. This analysis was restricted to the 67% of ASD ($n = 111$) and 56% of TD ($n = 108$) participants for whom SRS data were available (Table 1).

Association Between FNC and Age

We examined whether group differences in FNC would be associated with different neurodevelopmental trajectories. We correlated age with FNC in the whole sample and in each group separately, after regressing out full-scale IQ, mean FD, site of acquisition, and eye status (open or closed) at scan. We then tested the hypotheses of decreased negative correlation of FNC with age in ASD for subcortico-cortical interactions and of decreased positive correlation of FNC with age in ASD for cortico-cortical interactions. As in the previous analysis, inference was carried out using nonparametric permutation testing (FSL randomize [20 000 permutations]), and the results were corrected with the FDR.

Results

ICA and Components Selection

The number of ICs estimated in the 25 temporally concatenated probabilistic ICAs ranged from 22 to 30 (median, 27). The subsequent meta-ICA extracted 52 ICs, among which we selected 19 RSNs for further analyses (Figure 1 and Table 2). These 19 RSNs featured significantly higher reproducibility ($t_{50} = 4.90$, $P < .0000052$ by 2 independent-samples t tests) and proportion of gray matter within or outside their spatial extent ($t_{50} = 1.95$, $P < .03$) compared with the 33 discarded components (eFigure 3 in the Supplement). The spatial distribution of most of our 19 RSNs was consistent with that of RSNs identified in previous work^{7,54,67–69} (eFigure 7 in the Supplement), including sensory networks (IC1, IC5, IC16, IC19, and IC29), fronto-temporo-parietal networks (IC24 and IC25), subcortical structures (IC17), cerebellum (IC3 and IC13), paralimbic regions (IC9 and IC33), saliency⁷⁹ (IC23), and default-mode network (IC10, IC15, and IC27).

Group Differences in FNC

Relative to the TD group, the ASD group exhibited a significantly increased ($P < .001$, $q[\text{FDR}] = 0.05$) positive interaction between the RSN encompassing basal ganglia and thalamus (IC17) with several cortical networks (with $q[\text{FDR}]$ indicating the upper bound in the expected proportion of false positives) (Figure 2). Most of these cortical RSNs included regions in the primary somatosensory (IC5 and IC29), auditory (IC16), and visual (IC8) cortices, as well as the superior temporal sulcus (STS) and left inferior frontal gyrus (IFG) (IC24). An anterior cerebellar RSN (IC13) was also overconnected with the STS and left IFG (IC24) and with dorsal somatosensory and motor cortices (IC5). The ASD group showed decreased FNC only in the interaction between ventral sensorimotor cortices (IC29) and temporoparietal regions centered on the primary auditory cortex (IC16). Results from further analyses performed using data despiking and a more stringent group matching for motion make it unlikely that these group differences depended on differences in motion between groups (eMaterials, eFigure 8, and eTable 2 in the Supplement). Additional analyses on the effect of the sample size are reported in the eMaterials and eFigure 9 in the Supplement.

Association Between FNC Abnormalities and the SRS

In the ASD group, autistic traits measured with the SRS scores were positively associated with FNC between the subcortical RSN (IC17) and both dorsal IC5 ($r = 0.21$) and ventral IC29 ($r = 0.25$) primary somatosensory and motor cortices ($P < .0067$ for both, $q[\text{FDR}] = 0.05$) (Table 3, Figure 3, eFigure 10, and eTable 4 in the Supplement). Conversely, the strength of cortico-cortical interaction between auditory (IC16) and ventral somatosensory (IC29) cortices was negatively associated with autistic traits in TD controls only ($r = -0.11$, $P < .0006$, $q[\text{FDR}] = 0.05$).

Association Between FNC Abnormalities and Age

Functional network connectivity between the subcortical RSN (IC17) and networks encompassing primary visual (IC8), auditory (IC16), and ventral somatosensory (IC29)

regions significantly decreased with age in TD participants ($P < .009$, $q[\text{FDR}] = 0.05$) (Table 4). While the effect was maintained in the entire sample of ASD plus TD groups ($P < .012$, $q[\text{FDR}] = 0.05$), in the ASD group the negative association between age and subcortico-cortical FNC was weaker than in the TD group and not significant (Table 4, eFigure 11, and eTable 5 in the Supplement). However, this difference did not yield significant group interactions. Conversely, FNC between anterior cerebellum (IC13) and dorsal somatosensory and premotor cortices (IC5) significantly increased with age in TD participants ($P < .0077$, $q[\text{FDR}] = 0.05$) and in the entire sample ($P < .0009$, $q[\text{FDR}] = 0.05$). Finally, FNC between anterior cerebellum (IC13) and STS plus left IFG (IC24) significantly increased with age in the ASD group ($P < .0008$, $q[\text{FDR}] = 0.05$) and in the entire sample ($P < .0014$, $q[\text{FDR}] = 0.05$).

Discussion

Increased Subcortico-Cortical FNC

Relative to TD controls, in participants with ASD a subcortical RSN encompassing basal ganglia and thalamus showed increased functional connectivity with 5 cortical RSNs, most of which included primary sensory cortices (results at $P < .05$ uncorrected are presented in eFigures 12, 13A, 13B, and 14 in the Supplement). Our findings concur with previous studies in ASD that reported increased functional connectivity between regions in the primary sensory cortices and in the striatum,^{27,41,43,80,81} as well as increased⁴⁰ thalamo-cortical connectivity (but see Nair et al⁴² for thalamo-cortical underconnectivity). A comparison of our results with those reported in the inaugural ABIDE article⁵⁷ is provided in the eMaterials in the Supplement.

The evidence of subcortico-cortical overconnectivity mostly targeting primary sensory cortices provides a framework to conceptualize the presence of sensory abnormalities in ASD. A growing clinical and experimental literature reports atypical sensory processing in ASD,^{82–86} qualified as hyporeactivity or hyperreactivity to sensory stimuli^{82,84} and enhanced sensory perceptual processing and discrimination.^{87,88} Accordingly, the newly released *DSM-5* manual⁸⁹ now also includes hyporeactivity or hyperreactivity to sensory stimulation as a diagnostic criterion, acknowledging that sensory abnormalities are central in the symptomatology of ASD. Our results suggest that the presence of atypical sensory processing in ASD could stem from an abnormal, possibly excessive influence of basic sensory features of the environment on information processing in the brain, which could override higher-order cognitive processes in determining the relevance of different sources of information for behavior. At the neural level, this situation could be engendered by an abnormally high sensory input from subcortical nuclei to the cortex, reflected indirectly by our findings of subcortico-cortical overconnectivity even at rest. A similar conjecture by Belmonte and colleagues¹⁰ proposed that in ASD the impairment of low-level mechanisms for filtering irrelevant and unwanted sensory stimuli would prompt the development of compensatory mechanisms that operate at a later, less efficient stage of processing. The recently reported⁷ overconnectivity within the saliency network in ASD might reflect the development of compensatory mechanisms aimed at counteracting the overwhelming

amount of sensory input reaching the cortex due to impaired gating circuits at the subcortical level.^{7,90,91}

It is remarkable that the RSN pairs where we detect group differences in FNC are likely to reflect, at least in part, the activity of projections from deep cerebellar nuclei to the cerebral cortex and from the striatum to the thalamus. The hypothesis of an imbalance in the ratio of excitatory to inhibitory activity in ASD had been proposed by Rubenstein and Mezerich,⁹² and even earlier studies^{93–95} consistently reported loss of Purkinje cells in the cerebellum. There is now a growing body of evidence suggesting that the disruption of γ -aminobutyric acid–ergic signaling contributes to the pathophysiology of ASD.^{23,96–98} Importantly, stereotyped behaviors appear to be related to dysfunctions in γ -aminobutyric acid signaling,⁹⁹ while insistence on sameness is associated with caudate overgrowth.¹⁰⁰ Additionally, very recent evidence from in vivo proton magnetic resonance spectroscopy showed a decreased ratio of γ -aminobutyric acid to creatinine in the cerebellum and in the primary sensory and motor cortices of individuals with ASD.^{101,102} Therefore, the increased interaction we observed between subcortical and cortical regions might reflect an abnormally low inhibitory activity, rather than an abnormally high excitatory activity. For instance, the cortico-cerebellar overconnectivity that we detected could stem from a disinhibition of the deep cerebellar nuclei due to the loss of Purkinje cells.²² This conjecture, however, awaits testing with methods different from fMRI because the fMRI signal may confuse excitation and inhibition.¹⁰³

Association Between FNC Abnormalities and Autistic Traits Measured With SRS

We observed that in ASD subcortico-cortical overconnectivity was related to increased severity of autistic traits as measured with the SRS. Scores on the SRS clearly distinguish individuals with ASD from TD controls at the group level (in our sample, $t_{174}^* = 19.00$, $P < 1.412e-44$, with the asterisk indicating the df adjusted for unequal variance between groups). At the same time, this measure reflects that autistic traits (1) are present in a continuous gradient of severity in the general population,⁶¹ (2) have an increased likelihood to manifest in family members of ASD participants with a negative diagnosis of ASD,^{62,104,105} and (3) express variability both between and within groups.¹⁰⁶ Resting-state fMRI has been shown to capture variability in autistic traits indexed by SRS in neurotypical adults.¹⁰⁷ We show that FNC between subcortical and primary somatosensory and motor networks, which is abnormally high in individuals with ASD, was correlated to the severity of autistic traits in the whole sample, as well as within the ASD group. This suggests that this FNC measure is able to capture variability both between and within group described by the SRS scores.

Concerning the nature of the association between SRS and FNC that we report herein, studies^{91,108,109} in sensorimotor gating in ASD proposed that difficulties in inhibiting repetitive behaviors could stem from problems in filtering out irrelevant sensory stimuli. Deficits in sensorimotor gating in ASD appear to be rooted in structural abnormalities in fronto-striatal and cerebellar circuits¹⁰⁸ and are strongly associated with the presence of repetitive behaviors.⁹¹ The association we have identified between SRS scores and subcortico-cortical connectivity involving somatosensory and motor cortices is compatible with the idea of a relationship between sensory abnormalities and repetitive behaviors.

However, this hypothesis should be corroborated by future studies investigating the association between subcortical-sensorimotor overconnectivity and direct measures of sensory symptoms in ASD⁸⁴ and by task-based fMRI studies specifically probing these sensory and motor processes.

Association Between FNC Abnormalities and Age

Consistent with prior literature,¹¹⁰ examining the developmental trajectory of between-network overconnectivity revealed that subcortico-cortical connectivity significantly decreased with age in the sample of participants. This suggests that during development cortical processing becomes decreasingly determined by processes elicited by sensory stimuli, emotions, and interoceptive feelings.¹¹⁰ The relationship between subcortico-cortical FNC was negative within each group and did not significantly differ across groups, although the correlation was significant only for TD participants. Therefore, while our results concur with previous studies^{27,40,41,43,80,81} in reporting a persistent subcortico-cortical overconnectivity across different age groups in ASD, such overconnectivity in the ASD participants we examined decreased with age at a rate that failed to show significant differences from that recorded in the TD participants.

Limitations

Our study has several limitations. First, the correlation approach in functional connectivity does not provide directional information. Such information will be crucial to determine whether the observed subcortico-cortical hyperconnectivity reflects cortical compensatory mechanisms aimed at regulating the information flow from sensory organs, increased information flow from the thalamus to the cortex, or both.

Second, the weak association between FNC and SRS potentially reflects the wide interindividual variability in ASD. Gathering richer phenotypical information is needed to yield a multivariate characterization of the association between phenotypic and neuroimaging parameters.^{111,112}

Third, our group differences in the FNC center around an RSN encompassing basal ganglia and thalamus. Given the neuroanatomical heterogeneity of different structures within this RSN, it is remarkable that ICA does not further decompose this network. This limits the level of detail that can be achieved using spatially independent components and highlights the complementary role of region-based and network-based functional connectivity studies.^{113,114}

Conclusions

We report that hyperconnectivity between subcortical regions and sensory cortices is a central feature in ASD. This hyperconnectivity was related to the degree of autistic traits in the examined sample of individuals with ASD. We propose that such hyperconnections could relate to abnormal sensory processing in that they represent an alteration of the normal equilibrium between sensory information stemming from the thalamus and top-down influence from higher-order cortices.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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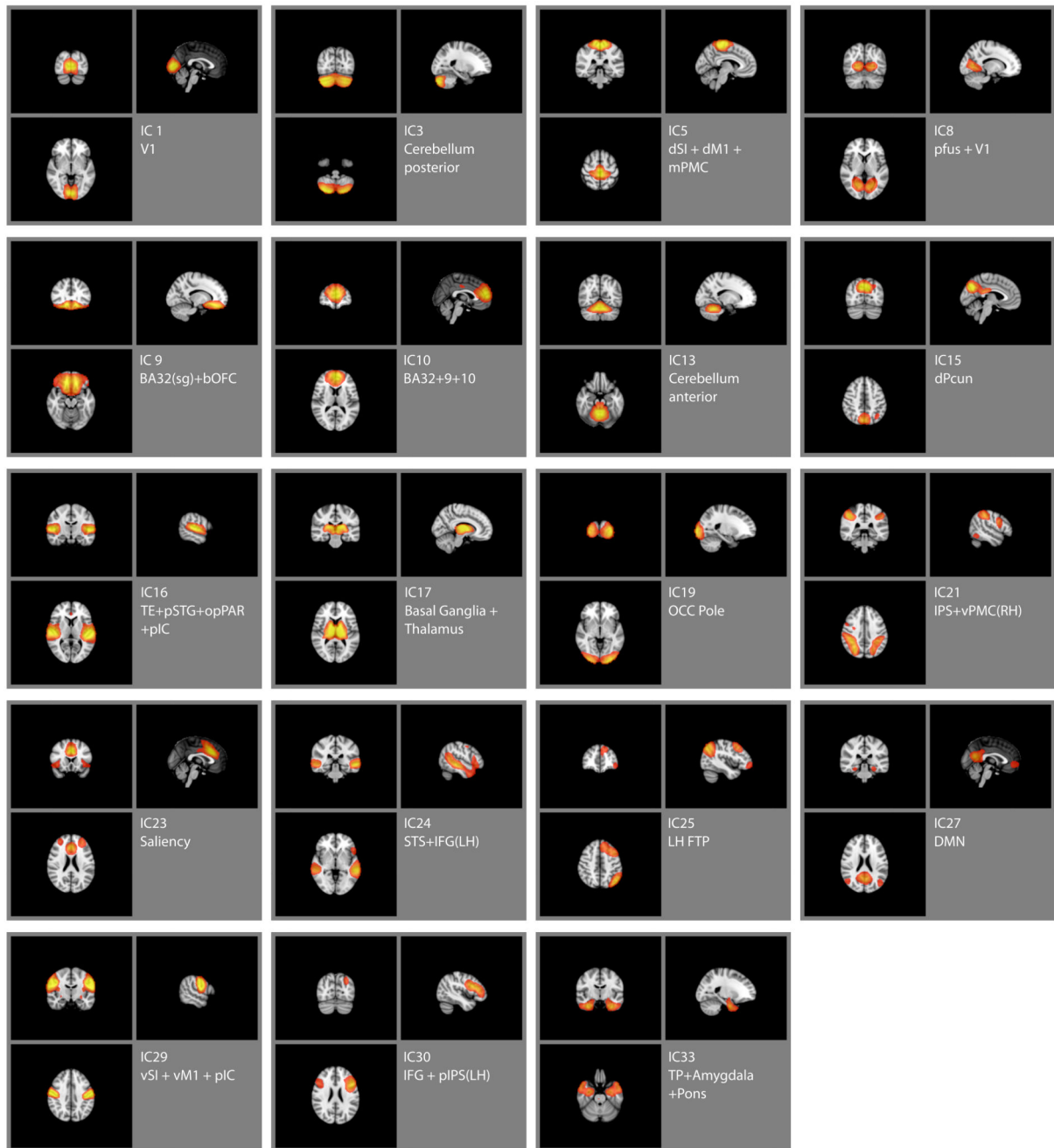


Figure 1. Components selected for FNC analysis

The metaICA on 359 participants (166 ASD + 193 TD) extracted 52 independent components (IC), 19 of which were selected for FNC analyses using a semi-supervised procedure detailed in the eMaterials. For each IC, we indicate the component order in the results of the metaICA, reflecting the amount of variance explained by that IC (in decreasing order), along with an anatomical labeling. Abbreviations are listed in Table 2. Discarded ICs are shown in eFigure 3. The similarity of these RSNs with those previously found in Biswal

et al. (2010)⁶³ and in Smith et al. (2009)⁵⁴ was quantified by means of spatial correlation, and is reported in eFigure 7.

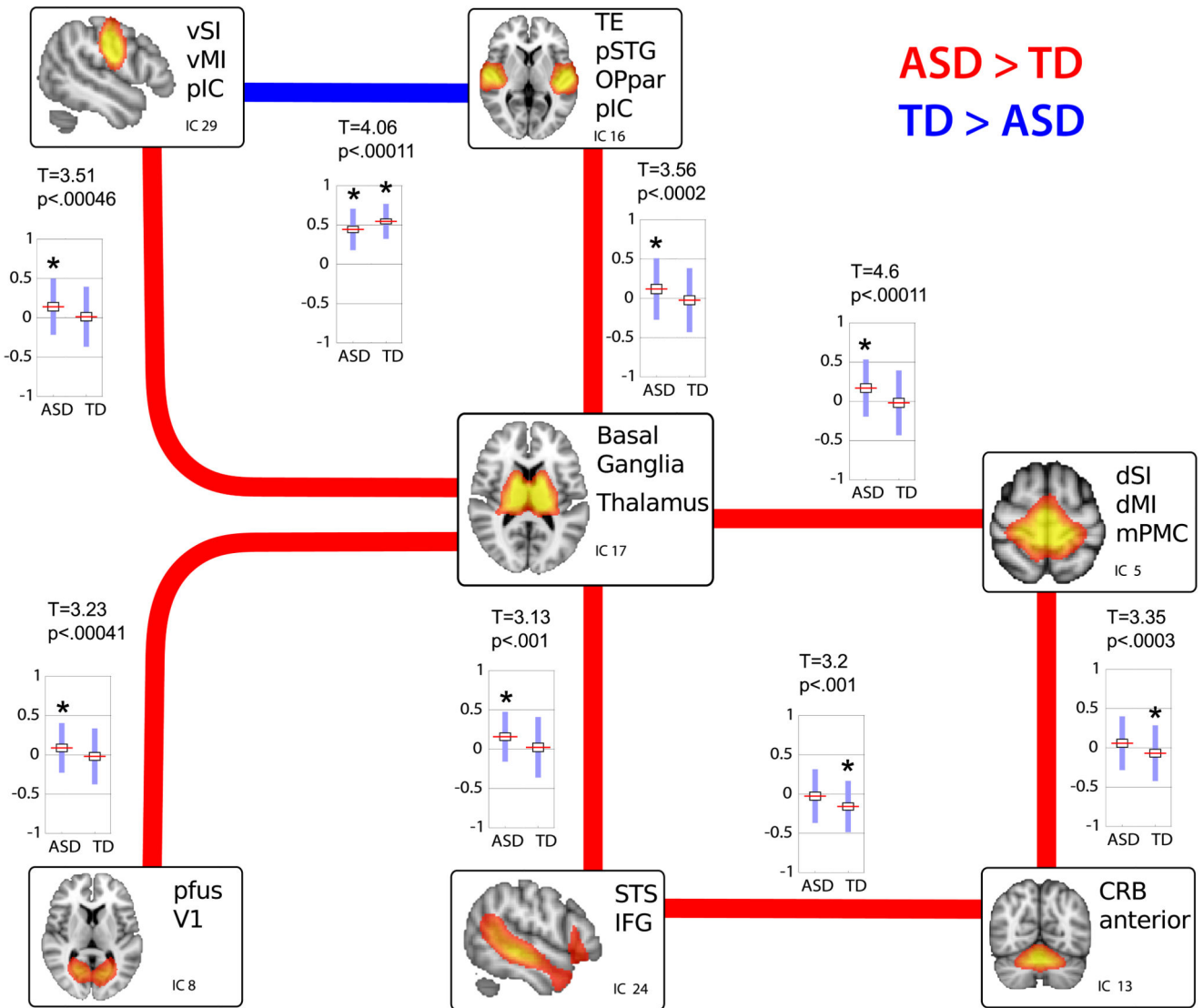


Figure 2. Group differences in between-network connectivity

Group differences in FNC strength are shown as lines (red indicates increased FNC in ASD with respect to TD participants, blue the reverse situation) together with boxplots of the Pearson correlation values per each group. Boxplots report the mean (red line), standard deviation (blue bars) and standard error of the mean (black rectangle around the mean) of group-level FNC values. Stars above the boxplots indicate those cases in which the mean FNC was found significantly different from zero (at $q(\text{FDR})=.05$ - see also eTable 5). Results were obtained by comparing the between-network functional connectivity of 166 ASD and 193 TD participants, using nonparametric permutation testing (20,000 permutations) and correcting the final results with $q(\text{FDR})=.05$, leading to a final threshold of $p<0.001$. Converting the correlation scores to Z values using Fisher r to Z transformation yielded almost identical results (see eFigure 5).

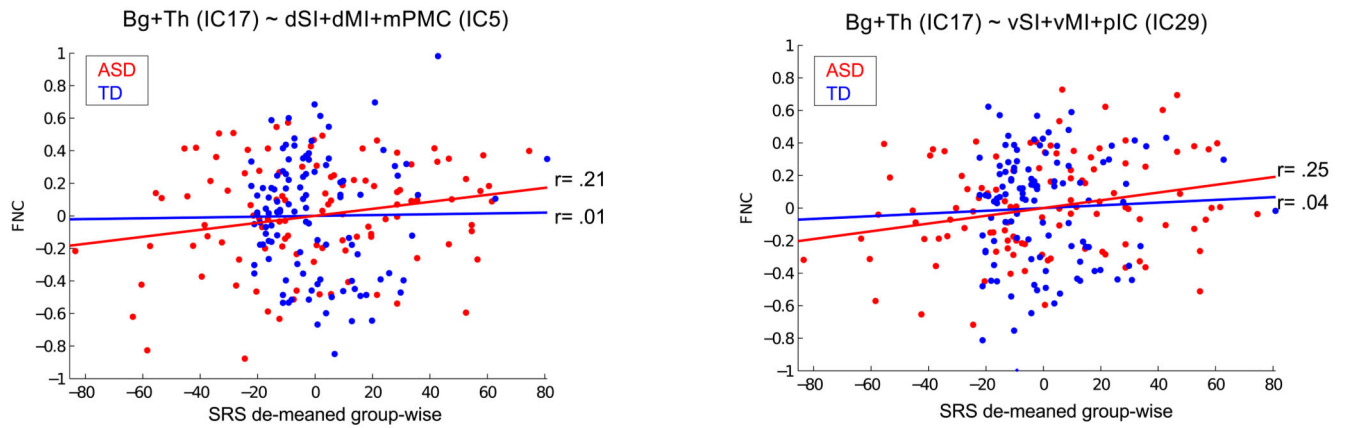


Figure 3. Correlation between somatosensory-subcortical FNC and group-wise demeaned SRS scores

These scatterplots illustrate the association between FNC and SRS (after group-wise demeaning) in ASD (red) and TD (blue) participants for the interaction between the subcortical RSN and the two RSNs centered around the ventral (IC29) and dorsal (IC5) primary somatosensory and motor cortex. The association between SRS scores and FNC was found significant only for the ASD group after correction with $q(\text{FDR})=.053$. These results were confirmed by repeating the analysis using robust regression ($p<.024$, $q(\text{FDR})=.05$). The lines in the scatterplot represent the linear fit within each group: red for ASD, blue for TD. Detailed statistics for these within-group correlations, as well as for the correlation analysis in the entire sample, are reported in the Table 3. Scatterplots and statistics for the correlation of SRS with other FNC scores are reported in eFigure 8 and eTable 2.

Table 1
Participants demographics.

	Mean (SD) [Range]	
	Autism Group (N = 166)	Control Group (N = 193)
Age, years	17.6 (7.6) [7-50]	16.9 (6.6) [6.5-39.4]
Full-scale IQ	109.6 (16.16) 71-148	111 (13.1) [73-146]
ADI-R Social (N=93)	19.7(5.3)[7-28]	N/A
ADI-R Verbal (N=94)	15.6(4.5)[2-25]	N/A
ADI-R Repetitive Behavior (N=93)	5.8(2.58)[0-12]	N/A
ADOS Total (N=171)	10.7(5.3)[0-22]	N/A
ADOS Communication (N=170)	3.5(1.9)[0-8]	N/A
ADOS Social (N=171)	7.1(3.8)[0-14]	N/A
ADOS Repetitive Behaviour (N=142)	1.7(1.6)[0-8]	N/A
SRS (N _{ASD} = 111; N _{TD} = 108)	89.4 (32.4) [6-164]	22.2 (18.1) [0-103]

Abbreviations: SD = standard deviation; ADI-R = Autism Diagnostic Interview-Revised 113; ADOS = Autism Diagnostic Observation Schedule 114; SRS = Social Responsiveness Scale 75, 76. Participants from the following sites from ABIDE were included in the final sample of 359 participants: Leuven (sample 1), NYU, OLIN, PITT, Stanford, SDSU, USM, Yale. The number of participants for whom raw scores in ADOS, ADI-R and SRS are available in the current version of the Composite Phenotypic File (Phenotypic_V1_0b.csv) is reported in brackets.

Table 2
Localization of the 19 Resting State Networks (RSN) used for FNC analysis.

IC number	Spatial location	Abbreviation
IC 1	Primary visual cortex	V1
IC 3	Cerebellum posterior	pCRB
IC 5	dorsal primary sensory cortex + dorsal primary motor cortex + medial premotor cortex	dSI + dM1 + mPMC
IC 8	posterior Fusiform gyrus + Primary Visual Cortex	pfus + V1
IC 9	subgenual BA32 + basal orbitofrontal cortex	BA32(sg) + bOFC
IC 10	BA32 + BA9 + BA10	BA32+9+10
IC 13	Cerebellum anterior	CRB anterior
IC 15	dorsal precuneus	dPeun
IC 16	primary auditory cortex + posterior superior temporal gyrus (including a portion of planum polare) + parietal operculum + posterior insular cortex	TE + pSTG + opPAR + pIC
IC 17	Basal Ganglia + Thalamus	BG+Th
IC 19	Occipital pole	OCC pole
IC 21	Intraparietal sulcus + RH ventral premotor cortex	IPS + vPMC(RH)
IC 23	Dorsal anterior insula + middle frontal gyrus + medial cingulate + preSMA	Saliency
IC 24	Superior temporal sulcus + LH inferior frontal gyrus	STS + IFG(LH)
IC 25	LH inferior parietal cortex + LH middle frontal gyrus + LH middle temporal gyrus + LH frontal pole + LH preSMA (Left Fronto-Temporo-Parietal network)	LH FTP
IC 27	BA32 + retrosplenial cortex + precuneus + angular gyrus (Default Mode Network)	DMN
IC 29	ventral primary sensory cortex + ventral primary motor cortex + posterior insular cortex	vSI + vMI + pIC
IC 30	Inferior frontal gyrus/sulcus + LH posterior intraparietal sulcus	IFG + pIPS (LH)
IC 33	Temporal pole + basolateral Amygdala + Pons	TP+Amy+Pons

Table 3
Association between FNC and SRS scores (group-wise demeaned)

Network pair	ASD	TD	whole sample	group difference (z)
Bg+Th ~ dSI/MI/mPMC	0.21^a	0.01	0.09^c	1.43 ^d
Bg+Th ~ vSI+vMI+pIC	0.25^a	0.04	0.13^c	1.51 ^d
TE+pSTG+PARop+pIC ~ vSI+vMI+pIC	-0.04	-0.11^b	-0.07^c	.54
CRB anterior ~ STS+LH IFG	0.13	-0.07	0.06^c	1.5 ^d

Values in the 'ASD', 'TD' and 'whole sample' columns report the Pearson correlation coefficient between FNC and group-wise demeaned SRS scores, after regressing out FIQ, site of acquisition, eyes open/closed at scan, and mean FD. The corresponding scatterplots are presented in Figure 3 and eFigure 8. We report in this table only RSN interactions where results were significant. The complete results and scatterplots for all examined RSN interactions are presented in eTable2 and eFigure 8.

Abbreviations: **Bg+Th** (IC17): Basal Ganglia + Thalamus; **dSI+dMI+mPMC** (IC5): dorsal primary somatosensory + primary motor cortex + medial premotor cortex; **vSI+vMI+pIC** (IC29): ventral primary somatosensory + primary motor cortex + posterior insular cortex; **TE+pSTG+PARop+pIC** (IC16): primary auditory cortex + posterior superior temporal gyrus + parietal operculum + posterior insular cortex; **CRB anterior** (IC13): anterior Cerebellum; **STS+LH IFG** (IC24): superior temporal sulcus + left inferior frontal gyrus.

^a p<.0067 (corrected with q(FDR)=.053)

^b p<.0006 (corrected with q(FDR)=.05)

^c p<.007 (corrected with q(FDR)=.05)

^d p<.077 uncorrected

Table 4
Association Between Functional Network Connectivity and Age^a

Network pair	ASD	TD	whole sample	group difference (z)
Bg+Th ~ pfus + V1	-0.06	-0.13^b	-0.10^c	0.69
Bg+Th ~ TE+pSTG+PARop+pIC	-0.06	-0.13^b	-0.09^c	0.67
Bg+Th ~ vSI+vMI+pIC	-0.04	-0.18^b	-0.11^c	1.31
CRB anterior ~ STS+LH IFG	0.18^a	0.08	0.14^c	0.87
CRB anterior ~ dSI+dMI+mPMC	0.14	0.11^b	0.12^c	0.27

Values in the 'ASD', 'TD' and 'whole sample' columns report the Pearson correlation coefficient between FNC and age, after regressing out FIQ, site of acquisition, eyes open/closed at scan, and mean FD. We report in this table only RSN interactions where results were significant. The complete results and scatterplots for all examined RSN interactions are presented in eTable3 and eFigure 9.

Abbreviations: **Bg+Th** (IC17): Basal Ganglia + Thalamus; **pfus + V1** (**IC8**): posterior fusiform gyrus + primary visual cortex; **TE+pSTG+PARop+pIC** (IC16): primary auditory cortex + posterior superior temporal gyrus + parietal operculum + posterior insular cortex; **vSI+vMI+pIC** (IC29): ventral primary somatosensory + primary motor cortex + posterior insular cortex; **STS+LH IFG** (IC24): superior temporal sulcus + left inferior frontal gyrus; **CRB anterior** (IC13): anterior Cerebellum.

^a p<.0008 (corrected with q(FDR)=.05)

^b p<.009 (corrected with q(FDR)=.05)

^c p<.012 (corrected with q(FDR)=.05)