Thalamocortical Dysconnectivity in Autism Spectrum Disorder: An Analysis of the Autism Brain Imaging Data Exchange

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ABSTRACT

BACKGROUND: Individuals with autism spectrum disorder (ASD) exhibit differences in basic sensorimotor processing as well as general cortical excitability. These observations converge to implicate thalamocortical connectivity as a potential unifying neural mechanism. The goal of this study was to clarify mixed findings on thalamocortical functional connectivity in a large sample of individuals with ASD.

METHODS: Using the Autism Brain Imaging Data Exchange, we examined thalamocortical functional connectivity in 228 individuals with ASD and a matched comparison group of 228 typically developing individuals. To fully characterize thalamocortical functional networks, we employed complementary seed-based approaches that examined connectivity of major cortical divisions (e.g., prefrontal cortex, temporal lobe) with the thalamus and whole-brain connectivity of specific thalamic subregions.

RESULTS: The prefrontal cortex, temporal lobe, and sensorimotor cortex exhibited hyperconnectivity with the thalamus in individuals with ASD. In the whole-brain analysis, hyperconnectivity of several thalamic seeds included multiple cortical areas but tended to converge in temporal cortical areas, including the temporoparietal junction. Follow-up analyses of age effects revealed that the connectivity abnormalities in individuals with ASD were more pronounced in adolescents compared with children and adults.

CONCLUSIONS: These results confirm previous findings of temporal and motor thalamocortical hyperconnectivity in ASD and extend them to include somatosensory and prefrontal cortices. Although not directly addressable with the data available in the Autism Brain Imaging Data Exchange, this widespread hyperconnectivity could theoretically account for sensorimotor symptoms and general cortical excitability in ASD. Future studies should target comprehensive clinical and behavioral characterization in combination with functional connectivity to explore this possibility.

Keywords: Adolescents, Autism, Functional connectivity, Resting state, Thalamus, Temporoparietal

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thalamus \textsuperscript{(13)} reported overconnectivity between the thalamus and temporal lobe \textsuperscript{(14)} alongside underconnectivity between the thalamus and other cortical regions. Nair \textit{et al.} \textsuperscript{(14)} further reported an association of thalamomotor and thalamotemporal connectivity with core ASD features. A follow-up study from the same group used a larger sample and a more fine-grained seed-based approach and reported a mixture of functional hyper- and hypoconnectivity with the thalamus, with hyperconnectivity in the limbic and sensory regions and hypoconnectivity in the frontal and parietal supramodal association cortical areas \textsuperscript{(15)}.

Although intriguing, the reliability of these findings is unclear, as they are based on studies that used relatively small sample sizes. The recent emergence of data-sharing initiatives for psychiatric neuroimaging can be leveraged to clarify discrepant or limited results in smaller samples. One such initiative for ASD is the Autism Brain Imaging Data Exchange (ABIDE), which contains imaging data on over 1100 individuals acquired from multiple international datasets \textsuperscript{(16)}. A recent study using an independent component analysis approach applied to ABIDE data corroborated findings of hyperconnectivity between cortex and subcortical regions, including the thalamus, in ASD, but did not replicate findings of underconnectivity between cortical and subcortical regions \textsuperscript{(17)}. However, one limitation of the data-driven approach in this case was that a single component encompassed both the thalamus and the basal ganglia, despite known anatomical and functional differences between these subcortical structures and their cortical connections, limiting the level of resolution of the findings and thus their interpretability. For this reason, a seed-based approach, rooted in established functional and structural anatomy of the thalamus, coupled with the statistical power of ABIDE, is an ideal combination to provide a more definitive characterization of the functional connectivity of the thalamus in ASD. We made use of this combination in the current study.

\section*{METHODS AND MATERIALS}

\subsection*{Study Participants and RS-fMRI Data Selection Procedures}

The data included in this investigation came from ABIDE—an online, publically available repository of neuroimaging data that includes RS-fMRI data from 539 individuals with ASD and 573 age-matched typically developing (TD) individuals \textsuperscript{(16)}. The original studies included in ABIDE received approval from each site’s institutional review board. With respect to diagnostic procedures, all sites used the Autism Diagnostic Observation Schedule \textsuperscript{(18)}: most also included the Autism Diagnostic Interview-Revised \textsuperscript{(19)}. In addition to diagnostic classification, each site provided basic phenotypic data on each subject, including age and sex.

The following screening and selection procedures were employed to reduce heterogeneity between diagnostic groups and ensure that only good-quality RS-fMRI data were included in the analyses. First, ABIDE was screened to exclude individuals above 40 years of age. Second, RS-fMRI scans that did not have full-brain coverage (not including cerebellum) and failed spatial normalization to Montreal Neurological Institute (MNI) space were excluded. Finally, each RS-fMRI scan underwent motion scrubbing, as described below. RS-fMRI scans with more than 20\% scrubbed volumes were excluded. Following screening, the case-control matching feature in SPSS (version 23, IBM Corp., Armonk, NY), which employs a probabilistic fuzzy matching procedure, was used to match each individual with ASD to a TD individual on the basis of age (±5 years), sex, and percentage of scrubbed volumes (±5\%). Importantly, case-control matching was done within each site to avoid diagnosis by site interactions. Sites with fewer than 5 case-control pairs (i.e., 10 subjects) were excluded. The final dataset included 456 subjects \textsuperscript{(228 ASD-TD pairs). The groups were almost perfectly matched with respect to eye status (open/closed: ASD = 160/68, TD = 157:71; $\chi^2_1 = 0.09, p > .761$), reflecting the strong dependence between eye status and site ($\chi^2_{10} = 373.68, p = 1.39 \times 10^{-72}$). Demographic and neuroimaging data quality metrics are presented in Table \ref{tab:sample_demographics}. Demographic data, broken down by site, are presented in Supplemental Table S2.

\begin{table}[h]
\centering
\caption{Sample Demographics}
\begin{tabular}{|l|c|c|c|c|c|}
\hline
 & \textbf{Autism Spectrum Disorder (n = 228)} & & \textbf{Typically Developing (n = 228)} & & \textbf{Statistics} \\
 & Mean & SD & Mean & SD & \\
\hline
\textbf{Age, Years} & 16.6 & 6.1 & 16.6 & 6.0 & 0.65, .948 \\
\textbf{Full-Scale IQ} & 103.4 & 17.0 & 111.3 & 13.3 & 5.49, <.001 \\
\hline
\end{tabular}
\end{table}

\subsection*{Neuroimaging Preprocessing and Functional Connectivity Analysis}

Neuroimaging data preprocessing and statistical analysis were performed using SPM8 (IBM Corp.). Preprocessing included correction for head motion and spatial normalization to MNI space. Consistent with prior investigations of thalamocortical...
functional connectivity, no smoothing was applied to the functional data. RS-fMRI data underwent motion scrubbing (20). Volumes with framewise displacement greater than 0.5 mm or blood oxygen level-dependent (BOLD) intensity changes between volumes greater than 5% were identified and excluded from the connectivity analysis, as was the preceding volume. In addition, the first four volumes were excluded from the connectivity analysis.

Most investigations of thalamocortical functional connectivity have taken one of two approaches: 1) a cortical seed–based approach that examines connectivity of large cortical regions of interest (ROIs), such as the prefrontal cortex (PFC), with the thalamus; or 2) a thalamic seed–based approach in which the BOLD signal is extracted from the whole thalamus and correlated with the rest of the brain. The first approach is ideal for investigating cortical connectivity at the voxelwise level within the thalamus, but, because it uses large cortical ROIs, has limited resolution at the level of the cortex. The second approach can be used to examine thalamocortical connectivity at the voxelwise level in the cortex, but, by treating the thalamus as a homogeneous structure, cannot be used to examine specific thalamocortical networks. As such, to fully characterize thalamocortical functional networks at the level of both the thalamus and cortex, we used both approaches as described fully in a prior investigation by our group (21). Briefly, the cortex was divided into 6 ROIs spanning most of the cortical mantle (see the Supplement for a complete description of the cortical ROIs). The six cortical ROIs corresponded to the PFC, motor cortex/supplementary motor area, somatosensory cortex, posterior parietal cortex, temporal cortex, and occipital cortex (see Supplemental Figure S1). Each cortical ROI was used as a seed to create seed-based functional connectivity maps, restricted to the Harvard-Oxford probabilistic atlas of the thalamus, thresholded at 10% to remove voxels with low probability of being in the thalamic anatomical atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). The functional connectivity maps were then entered into within- and between-group random-effects analyses to identify functional connectivity of each cortical seed with the thalamus and compare connectivity between ASD and TD subjects. The between-group contrast was thresholded at the cluster-level familywise error (FWE) corrected \( p_{\text{FWE}} = 0.05 \) for voxelwise \( p_{\text{uncorrected}} = 0.001 \). For each cortical seed, the between-group contrast was masked to include voxels that demonstrated positive connectivity with their respective thalamic seed at voxelwise \( p_{\text{FWE}} = 0.001 \) in the combined ASD-TD sample.

The cortical seed–based analysis described above was followed up with a thalamic seed–based analysis previously used by our group to examine whole-brain connectivity of functionally defined thalamic subregions (21). Using the entire sample of 458 subjects, the thalamus was segmented for functional connectivity based on functional connectivity at the voxelwise level using the winner-take-all approach in which each voxel within the Harvard-Oxford thalamus probabilistic atlas (thresholded at 10%) was assigned to the cortical seed it was most strongly connected to. Prior work has shown that functionally defined thalamic subregions correspond closely to thalamus segments based on structural connectivity (21,22). Each functionally defined thalamic subdivision was then used as a seed in a seed-based functional connectivity analysis to identify whole-brain connectivity of specific thalamic subregions. The resultant connectivity maps were smoothed 6 mm and entered into within- and between-group random-effects analyses to identify functional connectivity of each thalamic seed separately in ASD and TD, and compare connectivity between ASD and TD. The between-group contrasts were thresholded at whole-brain cluster-level FWE corrected \( p_{\text{FWE}} = 0.05 \) for voxelwise \( p_{\text{uncorrected}} = 0.001 \). For each thalamic seed, the between-group contrast was restricted to only the voxels that demonstrated positive connectivity with their respective thalamic seed at voxelwise \( p_{\text{FWE}} = 0.001 \) in the combined ASD-TD sample.

All seed-based functional connectivity maps were created using the Conn toolbox version 14.n (23). Briefly, the BOLD time series was extracted from the seed and entered as a predictor in a multiple-regression general linear model. The six motion correction parameters and their first temporal derivatives, motion scrubbed volumes, white matter, and cerebrospinal fluid (CSF) were included as additional regressors in the general linear model to remove variance related to head motion, residual effects of head motion after motion correction, white matter, and CSF, respectively. White matter and CSF nuisance regressors were derived using the anatomical component-based noise reduction method, as implemented in the Conn-fMRI toolbox (24). In brief, five principal components were extracted from each of the white matter and CSF. White matter and CSF masks were created from the a priori white matter and CSF segmentations included in SPM8 (thresholded at 80% and 50%, respectively). The anatomical component-based noise reduction method is more effective than mean tissue signal approaches to removing unwanted signal related to white matter and CSF, and it is effective at mitigating the effects of head motion on functional connectivity estimates (25). Following removal of nuisance regressors, the data were band-pass filtered (0.01–0.10 Hz).

Age Effects Analysis

Given evidence that thalamocortical functional connectivity networks undergo developmental changes and speculation that brain abnormalities in ASD are related to atypical developmental trajectories, we performed a secondary analysis examining group differences as a function of age. Most datasets in ABIDE included either children/adolescents or adults, but rarely both. The presence of a site by age interaction prevented us from examining age and group effects within a single statistical model. As such, we used a similar approach as in our prior study of brain structure in ASD, which also used ABIDE data (26). Specifically, the 228 case-control pairs were divided into three age bands (i.e., tertiles), each containing 76 case-control pairs, and the between-group analyses described above were repeated in each age band. The three age bands were denoted children/young adolescents (age 6–13.27 years), adolescents (age 13.28–18.00 years), and adults (age 18.01 years and older).

RESULTS

Cortical Seed–Based Connectivity of the Thalamus

Consistent with prior studies, each cortical seed was functionally connected to distinct, largely nonoverlapping regions
of the thalamus in both the ASD and the TD groups (see Figure 1B, C). Importantly, the patterns of cortical functional connectivity within the thalamus in typically developing individuals and individuals with autism spectrum disorder, (D) Direct comparison between groups revealed increased prefrontal, motor, somatosensory, and temporal cortex connectivity with the thalamus in individuals with autism spectrum disorder. (B–D) Thresholded at cluster-level familywise error corrected $p_{(familywise\ error)} = .05$ for voxelwise $p_{(uncorrected)} = .001$. L, left; R, right.

Figure 1. Thalamocortical resting-state functional connectivity in typically developing individuals and individuals with autism spectrum disorder: cortical seed–based analysis of thalamocortical functional connectivity. (A) The cortex was partitioned into six nonoverlapping regions of interest that were used as seeds in a seed-based functional connectivity analysis. (B, C) Each cortical region of interest exhibited a distinct pattern of functional connectivity within the thalamus in typically developing individuals and individuals with autism spectrum disorder. (D) Direct comparison between groups revealed increased prefrontal, motor, somatosensory, and temporal cortex connectivity with the thalamus in individuals with autism spectrum disorder. (B–D) Thresholded at cluster-level familywise error corrected $p_{(familywise\ error)} = .05$ for voxelwise $p_{(uncorrected)} = .001$. L, left; R, right.

Whole-brain connectivity varied markedly across thalamic subregion seeds. As shown in Figure 2D and detailed in Supplemental Table S2, functional connectivity of the thalamic PFC, motor, temporal lobe, and posterior parietal thalamus seeds differed between ASD and TD individuals. For the thalamus PFC seed, functional connectivity was increased in ASD in several clusters in the right and left temporal lobe encompassing primarily Brodmann areas 22, 38, 41, and 42 within the superior and middle temporal gyri. Thalamic motor seed functional connectivity was elevated in the lateral temporal cortex, primarily the middle and superior temporal gyrus; precentral and postcentral gyrus; inferior frontal gyrus; cingulate gyrus; and precuneus. The lateral temporal cortex, including the superior and middle temporal gyrus, also exhibited elevated connectivity with the thalamic and posterior parietal cortex seeds in ASD individuals. Although most of the differences were in the direction of greater connectivity in ASD individuals, two clusters within the thalamus demonstrated greater connectivity with the motor and posterior parietal cortex thalamic seeds in TD individuals (see Supplemental Figures S3 and S6).

Age Effects
Hyperconnectivity of the cortical motor and temporal lobe seeds was most pronounced in the older adolescents age
Thalamocortical Dysconnectivity in ASD

Band relative to the children/young adolescents and adult age bands (see Figure 3). A similar pattern of results was observed for whole-brain connectivity of functionally defined thalamic seeds. Hyperconnectivity of the motor and temporal thalamic seeds was more widespread in older adolescents compared with children/young adolescents and adults (see Figure 4). As discussed earlier, the age by site interaction in ABIDE prevented a formal analysis of age effects. However, consistent with a prior study (27), there were significant qualitative differences in thalamocortical connectivity across age bands. For instance, connectivity of some thalamocortical networks, the prefrontal-thalamic network in particular, appeared to increase with age, whereas others, such as occipital-thalamic connectivity, seemed relatively stable across age bands (complete results of the age effects analysis are presented in Supplemental Figures S8–13).

Associations Between Thalamocortical Connectivity Abnormalities and ASD Symptoms

The association between clinical symptoms and abnormal functional connectivity was examined in the full sample of ASD individuals (i.e., 228 subjects) with available clinical data. Functional connectivity was extracted from each of the clusters identified in the between-group comparisons for the cortex and thalamus seed–based analyses and entered into correlation analyses that included the following clinical variables: Autism Diagnostic Observation Schedule Social (n = 160), Communication (n = 160), and Stereotypical Behaviors scores (n = 149); Social Responsiveness Scale score (n = 128); and intellectual functioning (full-scale IQ: n = 224). Given the number of clusters identified (n = 23; 8 cortex based, 15 thalamus based) and clinical variables (n = 5), the significance for the correlation analysis was Bonferroni corrected (i.e., p = .0004 [.05/(23*5)]).

For the cortical seed–based analysis, none of the correlations reached the corrected significance level; however, the correlation...
between thalamus motor seed connectivity with the cluster located at MNI 48 –32 8 correlated with Social Responsiveness Scale score at the uncorrected \( p < .05 \) (\( r = .18, p = .038 \)). In addition, the cluster located at MNI –8 –14 4, which demonstrated reduced connectivity with the thalamus parietal seed in ASD individuals, was inversely correlated with full-scale IQ (\( r = –.15, p = .026 \)). All remaining correlations \( r < |.16|, p > .060 \).

**DISCUSSION**

We examined both cortical connectivity between the thalamus and predefined cortical ROIs as well as the whole-brain connectivity of specific thalamic subregions in a large sample of individuals with ASD and a carefully matched comparison sample included in ABIDE. Our results reflect widespread hyperconnectivity between the thalamus and cerebral cortex; we found limited evidence for hypoconnectivity. These results parallel recent reports of hyperconnected striatal networks in ASD (17,28) and global hyperconnectivity associated with autism symptoms (29). Our findings are generally inconsistent with the prevalent notion of global long-range hypoconnectivity in ASD (30–32); however, many of these studies addressed corticocortical long-range connections, which were not the focus of the current study.

With regard to thalamic connectivity to cortical regions, we replicated previous findings of thalamic hyperconnectivity with the temporal (14) and motor cortex (15). Further, we also noted hyperconnectivity to somatosensory and prefrontal regions. For the prefrontal and temporal cortices, this hyperconnectivity was tightly spatially localized to the pulvinar region of the thalamus, in contrast to the sensorimotor cortex, for which hyperconnectivity was widely distributed throughout the ventral thalamic nuclei. Because ABIDE lacks comprehensive clinical and behavioral data, these findings cannot be directly linked to functional differences. However, we will explore possible associations that should be tested in future studies.

The pulvinar’s connections with prefrontal and ventral/medial temporal regions has been implicated in social cognitive tasks such as face-name associations (33) that are impaired in individuals with ASD. fMRI studies of face processing in ASD implicate the pulvinar as part of a subcortical network that shows aberrant response to faces in ASD (34). Further, the pulvinar is thought to coordinate synchronous oscillations in the alpha band (35). Individuals with ASD show abnormalities in alpha oscillations that are attributed to thalamic dysfunction and related to social deficits (36). This may reflect inefficient thalamocortical communication related to cortical hyperconnectivity with the pulvinar nucleus. Although the BOLD signal does not have the temporal resolution to capture oscillatory activity, future studies that include both fMRI and electroencephalography RS data may help to clarify how these phenomena relate to each other.
The more diffuse hyperconnectivity of sensorimotor cortex with ventral thalamic nuclei is consistent with the functional roles and connections of these nuclei, which coordinate signals between the basal ganglia and sensorimotor cortex for initiation and coordination of movement. Sensorimotor deficits in ASD are becoming increasingly well characterized, and include deficits in praxis (37) and modulation of grip force (3,38). In addition to motor coordination deficits, aberrant behavioral response to somatosensory input (e.g., tactile defensiveness) is also commonly reported in individuals with ASD (39,40). Thalamocortical hyperconnectivity as a putative mechanism for this hyperresponsiveness to touch is supported by the association of tactile defensiveness with enhanced global field power in response to touch in ASD (6), and with high levels of serotonin transporter expression (41). The serotonin transporter is heavily implicated in ASD (41–43) and the serotonergic system is also broadly implicated in hyperexcitability of sensory thalamocortical circuits (44). The serotonergic system likely has multiple functional influences on the development and expression of sensory and other behavioral features of ASD, including the influence of transient perinatal expression of serotonin transporter on the organization of thalamocortical somatotopic projections to primary somatosensory cortex (45,46). Although tactile defensiveness in ASD has also been associated with structural connectivity differences in intracortical association fibers (47), a model of cascading effects downstream from aberrantly enhanced thalamocortical signals to somatosensory cortex is very plausible. Such a model could, if supported by future studies designed to test it explicitly, unify behavioral measures as well as brain structural and functional correlates of aberrant somatosensory perception in ASD.

With regard to whole-brain connectivity of functionally defined thalamic seeds, we noted hyperconnectivity of the thalamus (prefrontal, motor, temporal, posterior parietal thalamic seeds) with the superior and middle temporal gyri. This finding also converges with Nair et al. (14) and supports a well-established body of research that implicates these regions in the core deficits in autism (48). An area in the superior temporal gyrus/sulcus, particularly on the left side of the brain, consistently exhibited increased connectivity across several thalamic seeds. The temporoparietal junction has a known role in social cognition and has been reported to be under-responsive in ASD during social judgment tasks (49,50). Enhanced thalamocortical input to the temporoparietal
Thalamocortical Dysconnectivity in ASD

junction in ASD may reflect increased stress during social cognitive tasks (51), which could take up bandwidth typically used for higher-order processing in social cognition. In addition, we noted that prefrontal and motor thalamic seeds were also hyperconnected to other regions of lateral temporal cortex, such as the superior temporal and middle temporal gyri. This could reflect developmental persistence of thalamic connections with the sensorimotor (e.g., auditory) cortex that, in typical development, is more completely replaced by prefrontal connectivity (15).

Our exploratory analysis of age effects revealed a consistent trend for maturation of higher-level thalamocortical networks (e.g., prefrontal) with age, but no apparent age effects for lower-level sensorimotor networks. Although site by age confounds limited our ability to examine age effects and interactions between age and group directly, we noted that the widespread overconnectivity of thalamocortical networks was particularly strong in the older adolescent age band, especially for motor and temporal cortical ROIs. This is in contrast to much more limited and circumscribed group differences in the children/young adolescent and adult age bands. This change in trajectory during adolescence is broadly consistent with structural neuroimaging findings of early overgrowth phase followed by later volumetric decline (43,44) and may reflect the compound effects of pubertal reorganization in an already developmentally compromised brain, as described by Picci and Scherf (52) in their two-hit model of autism.

The clinical relevance of the current findings, however, remains inconclusive, as none of the small number of associations we found between connectivity disturbances and clinical symptoms/IQ remained significant after statistical correction. The clinical assessment data in ABIDE varies considerably by site and does not include item-level data for the Autism Diagnostic Observation Schedule, which would allow calculation of calibrated severity scores (53) and thus direct comparison across modules. Additionally, future studies would benefit from inclusion of finer-grained behavioral measures designed to quantify social, sensory, motor, and cognitive features that are not well captured by standard diagnostic rating scales, such as fine-motor coordination, tactile hypersensitivity, or executive function. ABIDE does provide consistent cognitive data, which illustrates that this sample represents a restricted range of the autism spectrum limited to relatively high functioning individuals who are capable of completing an fMRI protocol without sedation.

Finally, the use of large cortical ROIs is another limitation, given Nair et al.’s (15) finding that these lobar ROIs may obscure competing effects from smaller subregions within them that may shed light on the functional specificity of the findings. However, the use of these large ROIs enabled us to directly investigate the replicability of previous findings, which is an important advantage of using ABIDE, particularly in light of low replication rates of imaging studies in ASD. We dealt with this limitation by also including a whole-brain analysis with functionally defined thalamic seeds that allowed us to interrogate the entire cortex in a more fine-grained manner. However, the thalamic seed–based analysis may be vulnerable to partial volume effects given the small size of some thalamic nuclei relative to the standard resolution of fMRI data in ABIDE (e.g., approximately 3 × 3 mm in-plane resolution).

In conclusion, using the considerable resources of ABIDE, we found that thalamocortical networks are abnormal in ASD. The abnormalities are characterized by marked prefrontal, sensorimotor, and temporal hyperconnectivity with the thalamus. More research is needed to determine the functional consequences of thalamic dysconnectivity and to understand the trajectory of the changes in ASD.

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REFERENCES