Archival Report

Biological Psychiatry: CNNI

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

http://dx.doi.org/10.1016/j.bpsc.2016.09.002

Autism spectrum disorder (ASD) is a pervasive developmental disorder defined by impairments in reciprocal social communication and patterns of rigid or repetitive behavior. However, a growing body of evidence suggests that ASD is also associated with more basic sensorimotor impairment (1–3), which is increasingly linked to core symptoms (4–6). The brain's hierarchical organization suggests that these complex behavioral symptoms could be downstream of the more basic sensorimotor impairment, but this has yet to be empirically tested.

Individuals with autism also often experience comorbid neurological symptoms that reflect problems with cortical excitability and arousal, including seizures and sleep disturbances (7). These clinical observations, along with experimental evidence from electroencephalography (8) and genetic models (9), have contributed to the theory that a fundamental problem in ASD is a relative increase in excitatory and decrease in inhibitory functional activity in the brain (10).

Both sensorimotor and cortical excitability differences in ASD implicate the thalamus. The thalamus is an important site for gating afferent sensory input to the cortex, modulating efferent motor signals, and regulating the overall level of cortical activity. Its functional organization comprises multiple parallel loops with dense reciprocal connections to nearly all regions of the cerebral cortex. These relays have been demonstrated to not only dynamically modulate subcortical-cortical communication, but also play an important role in modulating corticocortical signaling (11). Thus, the connectivity between thalamus and cerebral cortex affects multiple critical processes that are relevant for the behavioral symptoms that define ASD, as well as for the current theory of excitatory/inhibitory imbalance in ASD.

Recent studies have used resting-state functional magnetic resonance imaging (RS-fMRI) to map functional connectivity between the cortex and thalamus, and examine thalamocortical connectivity in individuals with ASD. RS-fMRI is particularly useful in clinical populations such as those with ASD because of its task-free nature (12). A study using large cortical seeds corresponding to the primary anatomical targets of the

thalamus (13) reported overconnectivity between the thalamus and temporal lobe (14) alongside underconnectivity between the thalamus and other cortical regions. Nair *et al*. (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 (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 (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 (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.

METHODS AND MATERIALS

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 (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 (18); most also included the Autism Diagnostic Interview-Revised (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 (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 ($\chi^2_{12} = 373.68$, $p = 1.39 \times 10^{-72}$). Demographic and neuroimaging data quality metrics are presented in Table 1. Demographic data, broken down by site, are presented in Supplemental Table S2.

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

Table 1. Sample Demographics

	Autism Spectrum Disorder (n = 228)		Typically Developing (n = 228)		Statistics	
	Mean	SD	Mean	SD	t	p
Age, Years	16.6	6.1	16.6	6.0	0.65	.948
Full-Scale IQ	103.4	17.0	111.3	13.3	5.49	<.001
RS-fMRI Data Quality Metrics						
Percent scrubbed volumes	5.34	5.19	4.91	5.00	0.91	.362
Prescrubbing RMS FD	0.22	0.13	0.21	0.12	0.47	.641
Postscrubbing RMS FD	0.16	0.05	0.15	0.04	0.93	.351
Prescrubbing DVARS	2.95	1.03	2.97	1.02	0.23	.816
Postscrubbing DVARS	2.25	0.74	2.25	0.73	0.05	.960

Male:female ratio for each group was 199:29. Full-scale IQ was estimated by averaging verbal and performance IQ for 18 subjects. No IQ data were available for 4 autism spectrum disorder individuals.

DVARS, temporal derivative of root mean square variance; FD, framewise displacement; RMS, root mean square; RS-fMRI, resting-state functional magnetic resonance imaging.