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Evaluation of Quantified Social Perception Circuit Activity as a Neurobiological Marker of Autism Spectrum Disorder

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Abstract

IMPORTANCE—Autism spectrum disorder (ASD) is marked by social disability and is associated with dysfunction in brain circuits supporting social cue perception. The degree to which neural functioning reflects individual-level behavioral phenotype is unclear, slowing the search for functional neuroimaging biomarkers of ASD.

OBJECTIVE—To examine whether quantified neural function in social perception circuits may serve as an individual-level marker of ASD in children and adolescents.

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Study concept and design: Pelphrey, Kaiser.

Acquisition, analysis, or interpretation of data: All authors.

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DESIGN, SETTING, AND PARTICIPANTS—The cohort study was conducted at the Yale Child Study Center and involved children and adolescents diagnosed as having ASD and typically developing participants. Participants included a discovery cohort and a larger replication cohort. Individual-level social perception circuit functioning was assessed as functional magnetic resonance imaging brain responses to point-light displays of coherent vs scrambled human motion.

MAIN OUTCOMES AND MEASURES—Outcome measures included performance of quantified brain responses in affected male and female participants in terms of area under the receiver operating characteristic curve (AUC), sensitivity and specificity, and correlations between brain responses and social behavior.

RESULTS—Of the 39 participants in the discovery cohort aged 4 to 17 years, 22 had ASD and 30 were boys. Of the 75 participants in the replication cohort aged 7 to 20 years, 37 had ASD and 52 were boys. A relative reduction in social perception circuit responses was identified in discovery cohort boys with ASD at an AUC of 0.75 (95% CI, 0.52–0.89; $P = .01$); however, typically developing girls and girls with ASD could not be distinguished ($P = .54$). The results were confirmed in the replication cohort, where brain responses were identified in boys with ASD at an AUC of 0.79 (95% CI, 0.64–0.91; $P < .001$) and failed to distinguish affected and unaffected girls ($P = .82$). Across both cohorts, boys were identified at an AUC of 0.77 (95% CI, 0.64–0.86) with corresponding sensitivity and specificity of 76% each. Additionally, brain responses were associated with social behavior in boys but not in girls.

CONCLUSIONS AND RELEVANCE—Quantified social perception circuit activity is a promising individual-level candidate neural marker of the male ASD behavioral phenotype. Our findings highlight the need to better understand effects of sex on social perception processing in relation to ASD phenotype manifestations.

Autism spectrum disorder (ASD) is a collection of potentially severe childhood neurodevelopmental conditions affecting 1 in 54 boys and 1 in 252 girls.¹ Although ASD is characterized by a heterogeneous range of behavioral symptoms, including early-onset difficulties in communication and restricted repetitive behavior,² difficulty with social interaction is a unifying feature of the condition.³

Typically developing (TD) children preferentially attend to point-light displays of biological motion in the form of a moving human within the first days of life.⁴ Two- and 3-year-old children diagnosed as having ASD, however, do not orient toward such point-light displays.^{5,6} This behavioral deficit remains in affected older children,^{7,8} adolescents, and young adults.^{8–10}

Sensitivity to biological motion is underpinned by neural circuits prepared to benefit from species-typical input^{4,11,12} and plays a central role in the development of social engagement⁶ including the development of emotion perception¹³ and the attribution of intentions to others.¹⁴ Consistent with the ASD behavioral phenotype, brain responses to biological motion are reduced in regions supporting social perception, such as the fusiform gyrus and superior temporal sulcus, in affected children,¹⁵ adolescents, and adults.^{9,10,16} Moreover, unaffected siblings of children with ASD share regions of dysfunction with affected children,^{15,17} suggesting that social perception circuit functioning may reflect vulnerability rather than an acute clinical behavioral manifestation. Taken together, the literature points to a

pervasive dysfunction in social perception circuits associated with the social deficits characteristic of ASD. Indeed, dysfunction in brain circuits supporting social perception is among the most replicated functional brain differences between ASD and TD individuals across experimental paradigms.¹⁸

The identification of biomarkers is a key challenge in psychiatry.¹⁹ Biomarkers can inform diagnosis and prognosis, but also improve our understanding of pathogenesis and pathophysiological mechanisms, predicting disease progression and monitoring therapy.²⁰ Despite the strong interest in neuroimaging markers of ASD, the degree to which quantified neural activity in social perception circuits reflects individual-level disorder state is unclear. We previously noted that the observed reduction in brain responses to biological motion in affected children may be sufficiently robust to potentially serve as an individual level marker of ASD.²¹ To examine the practical usefulness of this putative marker, we collected and examined brain responses in a larger replication cohort that included a relatively large number of affected girls (total $n = 14$).

Methods

Participants

Participants from a discovery cohort¹⁵ and a new, replication cohort were included in the study (Table 1). Written informed consent was obtained from each participant's parent(s) or legal guardian according to the Declaration of Helsinki for a protocol that was approved by the Yale School of Medicine Human Investigations Committee. All children had normal or corrected-to-normal (via magnetic resonance imaging-compatible glasses) vision. Typically developing children were excluded based on (1) diagnosed, referred, or suspected ASD, schizophrenia, or other developmental or psychiatric disorder; (2) first- or second-degree relative with diagnosed, referred, or suspected ASD; (3) an individual education plan for special education services, including speech/language therapy, occupational therapy, and social skills therapy; (4) clinical impression suggesting ASD, other developmental delay/disorder, or psychiatric disorder by the highly experienced multidisciplinary clinical team in the Child Study Center; (5) total $t > 76$ on the Social Responsiveness Scale (SRS) (discovery cohort only); and (6) low or moderately low score on any domain of the Vineland Adaptive Behavior Scale-II (discovery cohort only).

Clinical Measures

Autism spectrum disorder in children was diagnosed by an expert clinician, whose judgment was informed by the Autism Diagnostic Observation Schedule²² and the Autism Diagnostic Interview-Revised.²³ Cognitive ability was assessed using the Differential Ability Scale.²⁴ Social behavior was characterized using the SRS,²⁵ and, in the discovery cohort, the Vineland Adaptive Behavior Scale-II.

Participant Matching

To exclude potential effects of cognitive ability differences in the replication cohort, we created subgroups matched on Differential Ability Scale scores. We alternated removal of

the highest scoring TD male participant and the lowest scoring male participant with ASD until a group difference t test $P > .90$ was obtained (Table 1).

Experimental Design

During scanning, children viewed coherent and scrambled point-light displays of animated biological motion created from motion-capture data with 16 different capture points. The coherent motion displays (12 individual, 3- to 4-second animations) featured an unfamiliar adult male actor performing movement sequences relevant to early childhood experiences such as playing pat-a-cake.⁶ Twelve scrambled motion animations were created by randomly selecting 16 points from across the 12 different biological motion animations and plotting their trajectories on a black background. Thus, the coherent and scrambled displays contained the same local motion information, but only the coherent displays contained the configuration of a person.²⁶ Stimuli were presented using E-Prime 2.0 software (Psychological Software Tools). Six randomly selected coherent motion clips and 6 randomly chosen scrambled motion clips were presented once each in an alternating-block design (time per block, 24 seconds). The experiment began and ended with a 20-second fixation period (total time, 328 seconds). The movies were presented without audio. The children were asked to watch the videos and were reminded to remain still and alert.

Magnetic Resonance Imaging Data Acquisition

On a Siemens MAGNETOM Tim Trio 3T scanner system, T1-weighted anatomical images were acquired using an MPRAGE sequence (repetition time, 1900 milliseconds; echo time, 2.96 milliseconds; field of view, 256 mm; image matrix, 256 mm²; voxel size, 1×1×1 mm; 160 slices). Functional runs consisted of 164 whole-brain functional images acquired using a single-shot gradient recalled echo planar pulse sequence sensitive to blood oxygenation level-dependent contrast (repetition time, 2000 milliseconds; echo time, 25 milliseconds; flip angle, 60°; field of view, 22 cm; image matrix, 64 mm²; voxel size, 3.4 × 3.4 × 4.0 mm; 34 slices).

Functional Magnetic Resonance Imaging Data Preprocessing

Data were preprocessed with BrainVoyager QX (BrainInnovation). All 10 volumes before the onset of the stimulus event were discarded to allow for T1 equilibrium. Preprocessing of the functional data included interleaved slice time correction using cubic spline interpolation, 3-dimensional motion correction using trilinear/sinc interpolation, linear trend removal, and temporal high-pass filtering to remove low-frequency nonlinear drifts. Estimated motion plots and cine loops were inspected for head motion greater than 2 mm of translation in any direction or 2° of rotation about any axis. To reduce potential unspecific effects owing to head motion, we removed volume acquisitions where movement between 2 consecutive volumes exceeded 1 mm or integrated movement across 4 volumes exceeded 2 mm. Functional data sets were coregistered to the Talairach-transformed,²⁷ within-session, T1-weighted anatomical images.

General Linear Model Analysis

A general linear model analysis was conducted for each participant on all voxels within a whole-brain mask defined on the Montreal Neurological Institute template brain normalized to Talairach space. Regressors were defined as boxcar functions with values of 1 during each condition and 0 otherwise, convolved with a double-gamma hemodynamic response function.²⁸ Predictors depicting motion in all 6 parameters were included as predictors of no interest.

Group-Level Analyses

First, we defined the circuit involved in processing observed human motion as the set of regions of interest that were significantly activated for the contrast (coherent vs scrambled motion) in TD children and children with ASD combined. Second, a direct group comparison for ASD compared with TD of the coherent vs scrambled motion contrast was performed to assess group-level differences. Finally, to examine potential nonspecific visual effects, such as group differences in attending to the stimuli, we identified regions of interest associated with visual attention to movement²⁹ based on the contrast (coherent + scrambled motion > baseline) in TD children and children with ASD combined. The results were assessed at conventional voxelwise uncorrected levels ($P < .0001$ or $P < .01$, as indicated) and corrected for multiple comparisons at the cluster level through the BrainVoyager QX cluster-level statistical threshold estimator plugin (1000 iterations, $\alpha < .05$).^{30,31}

All group-level random effects analyses were conducted in the replication cohort only because group-level differences have been examined in the discovery cohort previously.¹⁵ To limit bias toward any group, we performed the analyses in equal numbers of TD participants and participants with ASD combined ($n = 74$). To this end, we excluded 1 randomly selected ASD participant.

Individual-Level Analyses

Individual-level brain responses were assessed as the (coherent > scrambled motion) contrast β values averaged across all voxels within the set of the biological motion regions of interest. To limit any group-difference bias, we only examined regions of interest defined for the main effect of children with ASD and TD children combined. The average β values were then entered into a receiver operating characteristic curve analysis. We used permutation testing with 10 000 iterations to assess the likelihood of obtaining the results owing to chance. The analysis was conducted in both sexes combined and in girls and boys only.

Correlation Analysis

We computed the Pearson partial linear correlation coefficient between average β values in the biological motion perception circuit and SRS scores in TD children and children with ASD combined, while controlling for age, and assessed P values under the hypothesis of no correlation against the 1-sided alternative of a nonzero negative correlation. In children with ASD, we also examined correlations between average β values and motion, cognitive ability, and Autism Diagnostic Observation Schedule²² and the Autism Diagnostic Interview-Revised²³ scores.

Results

Replication Cohort Group-Level Analyses

The random effects replication cohort group analysis for (coherent > scrambled motion) reproduced well-documented regional activations to biological motion, including large clusters in bilateral fusiform gyri (FG), extending into the posterior superior temporal sulcus in the right hemisphere, and the occipital gyrus ($n = 74$; $P < .0001$, $k > 6$; Table 2; Figure, A; eFigure in the Supplement).^{32,33}

The comparison of TD vs ASD confirmed previously observed hypoactivations in ASD in the right FG, left FG, inferior temporal gyrus, left middle temporal gyrus, and the left inferior frontal gyrus ($P < .01$; $k > 17$; Table 2).^{9,10,15,16} We found no significant results for the ASD > TD contrast.

We found no significant effects in regions associated with visual attention (eResults in the Supplement). There were some group differences in head motion (eResult in the Supplement); however, these likely had limited effects on the results (eDiscussion in the Supplement).

Reduced Individual-Level Responses in Social Perception Circuits in Affected Boys

Average biological motion circuit p values for the main effect of coherent vs scrambled motion and children with ASD and TD children combined identified individual discovery cohort ASD cases at a significant area under the receiver operating characteristic curve (AUC) of 0.70 (95% CI, 0.51–0.84; $P = .02$). However, this effect was driven entirely by boys who were identified at an AUC of 0.75 (95% CI, 0.52–0.89; $P = .01$), whereas girls with ASD and TD girls could not be distinguished (AUC = 0.50; 95% CI, 0.00–1.00; $P = .54$) (Figure, B–D; Table 3). These results were confirmed in the replication cohort, where the AUC was significant in both sexes combined (AUC = 0.66; 95% CI, 0.52–0.78; $P = .01$), high in boys at (AUC = 0.79; 95% CI, 0.64–0.86; $P < .001$), and at chance levels in girls (AUC = 0.39; 95% CI, 0.16–0.66; $P = .82$). In replication cohort boys, the results could not be explained by group differences in cognitive ability: when matched on Differential Ability Scale scores, the AUC was 0.83 (95% CI, 0.64–0.95; $P < .001$). In both cohorts combined, the overall AUC in boys remained high at 0.77 (95% CI, 0.64–0.86; $P < .001$) with a sensitivity of 76% and a specificity of 76%. Neither sample size nor motion explained the relatively low AUC in girls (eResults and eTables 1–3 in the Supplement).

Post hoc analyses showed that the right FG and posterior superior temporal sulcus cluster contributed most in detecting boys with ASD in both the discovery and replication cohorts with AUCs of 0.74 (95% CI, 0.50–0.89) and 0.79 (95% CI, 0.65–0.90), respectively, closely followed by the left FG, with AUCs of 0.71 (95% CI, .49–0.87) and 0.75 (95% CI, 0.57–0.87), respectively (Table 3). No region was significant in girls (all $P > .50$).

Association With Social Behavior

We found significant inverse correlations between average brain activity in the social perception circuit and social behavior difficulties (SRS scores), corrected for age, in

discovery cohort boys ($r = -0.43$, $P = .01$), replication cohort boys ($r = -0.35$, $P = .006$), and boys of both cohorts combined ($r = -0.36$, $P = .001$). However, in girls, no significant correlations were identified (all $P > .05$) (Figure, E). Brain responses did not correlate with cognitive ability, motion, Autism Diagnostic Observation Schedule, or Autism Diagnostic Interview-Revised in any group (all $P > .10$).

Discussion

A simple 1-value measure of neural activity in social perception circuits identified boys affected by ASD with sensitivity and specificity of 76% across 2 cohorts; however, affected and TD girls could not be distinguished. Our results suggest that previously observed group-level hypoactivations in social perception brain regions are sufficiently robust and consistent to serve as a promising individual-level neural marker of social deficits associated with ASD in boys.

Social Perception in ASD

Impaired responses to social stimuli characterize the ASD behavioral phenotype and are among the most reproduced functional brain differences.^{3,18} The literature is largely based on studies in males, however, and our results support a potential sexually dimorphic neural reflection of the condition. Whether the observed sex differences are a consequence of methodological issues, such as relatively low number of girls or dissimilar disorder manifestations, is unclear. Nevertheless, posterior superior temporal sulcus responses to socioaffective stimuli increase in magnitude with age in TD girls but not in boys,³⁴ suggesting an effect of sex in the development of social perception processing. Such differences in developmental patterns may also contribute to the lack of correlation between brain responses and SRS scores in girls. Further studies examining larger samples of girls diagnosed as having ASD and other disorders sharing sociocognitive behavioral phenotypes (eg, anorexia nervosa³⁵) are required to elucidate the underlying mechanisms.

Methodological Issues and Limitations

By extracting only the average brain response from a pre-defined region of interest, we alleviated the problem of between-participants voxel-to-voxel mapping, which may be particularly detrimental in groups of varying head size. Nevertheless, more sophisticated approaches, eg, allowing simultaneous inclusion of regional responses across multiple brain regions, are likely to further improve both the power and robustness of the marker.

Our participants were not matched on cognitive ability. However, the results in a matched subsample of boys did not differ compared with the unmatched full sample, and β values did not correlate with Differential Ability Scale scores. Thus, brain responses to biological motion may be a robust marker in boys of varying cognitive ability. Similarly, we did not limit heterogeneity resulting from varying head sizes, ages, and puberty; factors that when appropriately accounted for may improve the sensitivity and specificity of the proposed marker. Finally, we did not exclude replication cohort children on the basis of social behavior alone: the replication cohort included TD children with high SRS scores and children with ASD with low SRS scores, resulting in an overlap between the 2 groups

(Figure, E and F). Recognizing the phenotypic heterogeneity in both ASD and typical development, we allowed for a potentially more challenging but also more realistic task of identifying individual children fulfilling the criteria for ASD.

We did not examine participants' eye movements or directly control for nonspecific effects related to visual attention. The lack of eye tracking is a potentially severe limitation because the broad alterations in visual attention associated with ASD³⁶ may have contributed to social perception circuit hypoactivations. However, unaffected and affected participants did not differ in brain responses in visual attention regions, so it is unlikely that any unspecific visual attention deficits contributed significantly to the performance of the proposed marker.

Usefulness of a Functional Biomarker

The proposed marker fulfills proposed criteria for neuroimaging-based biomarkers (eDiscussion the Supplement). Nevertheless, the intense search for a viable ASD biomarker has hitherto been largely fruitless,³⁷ and the heterogeneous nature of the condition likely renders identification of a single diagnostic marker intractable.³⁸ A growing body of studies have highlighted the promise of resting-state functional brain imaging in developing candidate biomarkers of autism.^{39,40} The proposed marker may complement such markers by providing a quantified measure of evoked social perception circuit functionality. Brain function is actively shaped throughout life in an intricate interplay between genetics and the environment, and a functional marker may be used to monitor these plastic processes and to guide interventions targeted to improve function in specific circuits via behavioral treatments⁴¹ and pharmacological challenges.⁴²

Conclusions

Functional markers are crucial in charting brain developmental trajectories and for early detection of deviations in vulnerable groups. A functional biomarker may be able to detect associated neural deviations before behavioral changes occur. In fact, the proposed paradigm targets low-level social perception stimuli relevant to all stages of development: 2-day-old infants preferentially attend to point-light displays of biological motion,⁴ and the posterior temporal cortex responds to social cues within days after birth.¹¹ Moreover, infants and toddlers at risk for ASD show early-stage atypical behavioral and neural responses.^{43–45} Consequently, quantified function of social brain circuits should be a promising candidate neural marker of ASD across all age groups. The Yale Child Study group is committed to studying brain responses in young patients and control children, with designated facilities such as a mock scanner. Nonetheless, recognizing the challenges associated with scanning younger children, we are studying responses to biological motion using functional near infrared spectroscopy in toddlers. The present finding of robust individual-level differences pave the road toward refined studies specifically targeting such early neural markers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

Question

Can quantified neural function in social perception circuits identify autism spectrum disorder?

Findings

In this functional magnetic resonance imaging study that included 2 independent cohorts with a total of 114 children and adolescents, social perception circuit activity distinguished boys with and without autism spectrum disorder at a sensitivity and specificity of 76% each, whereas girls with and without autism could not be distinguished.

Meaning

Quantified social perception circuit function is a promising candidate for an individual-level neural marker of the male autism spectrum disorder behavioral phenotype.

Figure. Performance of Quantified Social Perception Circuit Activity in Detecting Autism Spectrum Disorder

A, The social perception circuit defined in the replication cohort, autism spectrum disorder and typically developing combined, from the group-level main effect for the contrast (coherent>scrambled motion) ($P < .0001$, $k > 6$). Receiver operating characteristic curves for detecting children diagnosed as having autism spectrum disorder based on social perception circuit response levels for girls (B), all boys (C), and boys matched on cognitive ability (D). The association between social perception circuit response levels (average β values) and social behavior (Social Responsiveness Scale scores) for girls (E) and boys (F). The open squares and circles indicate typically developing responses, and the closed squares and

circles indicate autism spectrum disorder responses. The r and P values indicate tests for negative partial correlations, corrected for age. AUC indicates area under the receiver operating characteristic curve.

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Table 1.Characteristics of the Study Participants^a

Characteristic	Mean (SD) [Range]					
	Discovery Cohort		Replication Cohort			
	TD (n = 12)	ASD (n = 18)	P Value	TD (n = 25)	ASD (n = 27)	P Value
Boys						
Age	10.75 (2.82) [6.55–16.69]	11.91 (3.85) [4.03–17.70]	.38	11.52 (3.05) [7.08–17.83]	11.45 (2.82) [7.08–17.67]	.97
DAS	111.12 (16.15) [78.00–140.00]	99.39 (20.85) [72.00–141.00]	.12	105.46 (17.69) [76.00–137.00]	91.33 (23.27) [41.00–132.00]	.03
SRS	25.67 (16.32) [2.00–54.00]	95.67 (22.00) [48.00–130.00]	<.001	29.20 (23.50) [2.00–90.00]	98.70 (30.21) [37.00–147.00]	<.001
ADOS	NA	10.89 (2.65) [7.00–15.00]	NA	NA	12.85 (5.33) [5.00–25.00]	NA
ADI-R	NA	21.69 (4.16) [14.00–26.00]	NA	NA	22.15 (3.63) [13.00–29.00]	NA
Movement, mm ^b	0.84 (0.74) [0.34–2.96]	1.30 (0.66) [0.24–2.36]	.05	2.18 (1.99) [0.14–8.14]	1.54 (1.70) [0.16–7.07]	.21
Boys matched on DAS						
Age	NA	NA	NA	11.53 (3.16) [7.08–17.83]	11.03 (2.66) [7.08–15.92]	.59
DAS	NA	NA	NA	99.32 (14.12) [76.00–120.00]	99.27 (16.62) [77.00–132.00]	.99
SRS	NA	NA	NA	33.16 (24.84) [3.00–90.00]	98.27 (30.19) [37.00–147.00]	<.001
ADOS	NA	NA	NA	NA	12.20 (5.01) [5.00–21.00]	NA

Characteristic	Mean (SD) [Range]					
	Discovery Cohort			Replication Cohort		
	TD (n = 12)	ASD (n = 18)	P Value	TD (n = 25)	ASD (n = 27)	P Value
ADI-R	NA	NA	NA	NA	22.41 (3.76) [13.00–29.00]	NA
Movement, mm ^b	NA	NA	NA	2.24 (1.98) [0.20–8.14]	1.65 (1.83) [0.23–7.07]	.34
Girls	TD (n = 5)	ASD (n = 4)		TD (n = 13)	ASD (n = 10)	
Age	11.35 (3.97) [4.56–13.75]	11.58 (2.62) [9.02–14.50]	.92	11.51 (2.75) [7.42–15.58]	10.73 (4.61) [4.92–20.25]	.62
DAS	122.25 (15.82) [101.00–137.00]	94.00 (13.93) [84.00–114.00]	.04	93.85 (12.75) [77.00–115.00]	98.80 (14.41) [83.00–123.00]	.39
SRS	20.80 (6.91) [10.00–28.00]	95.50 (26.29) [66.00–121.00]	.001	32.92 (25.11) [10.00–93.00]	84.30 (27.53) [38.00–123.00]	<.001
ADOS	NA	14.25 (5.56) [9.00–22.00]	NA	NA	10.80 (5.12) [4.00–22.00]	NA
ADI-R	NA	23.00 (4.69) [18.00–27.00]	NA	NA	18.60 (5.56) [9.00–27.00]	NA
Movement, mm ^b	1.17 (0.77) [0.46–2.10]	1.30 (1.19) [0.45–3.05]	.84	0.81 (0.75) [0.19–3.01]	4.24 (5.20) [0.67–17.54]	.03

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised (total score); ADOS, Autism Diagnostic Observation Schedule (total score); ASD, autism spectrum disorder; DAS, Differential Ability Scale (global composite scores); NA, not applicable; SRS, Social Responsiveness Scale (total raw score); TD, typically developing.

^aMissing data: DAS in 1 replication TD child and 2 discovery TD children; SRS in 1 discovery ASD child; ADOS in 1 replication ASD child; ADI in 2 discovery ASD children; movement in 2 replication ASD children.

^bMaximum amount of movement in 6 planes of motion.

Table 2.
Group-Level Biological Motion (Coherent > Scrambled Biological) Perception Analyses

Group Contrasts	Region	Talairach Coordinates			<i>t</i> Value	<i>P</i> Value	Extent
		x	y	z			
ASD + TD ^a	Right FG/pSTS	38	-59	-12	6.80	<.001	169
	Left FG	-40	-38	-15	8.03	<.001	168
	Left OG	-25	-96	-9	5.34	<.001	13
ASD vs TD ^b	Right FG	41	-56	-9	4.47	<.001	53
	Left FG	-37	-53	-9	4.36	<.001	85
	Left MTG	-34	-2	-27	4.68	<.001	41
	Left IFG	-34	34	-6	3.53	<.001	18
	Left cerebellum	-19	-65	-24	4.09	<.001	26
		-34	-50	-24	3.88	<.001	18

Abbreviations: ASD, autism spectrum disorder; FG, fusiform gyrus; IFG, inferior frontal gyrus; MTG, middle temporal gyrus; OG, occipital gyrus; pSTS, posterior superior temporal sulcus; TD, typically developing.

^aGroup-level activations in all replication cohort children for main effect of coherent vs scrambled motion ($P < .0001$, $k > 6$).

^bGroup-level coherent vs scrambled motion activation reductions in replication cohort children autism spectrum disorder relative to typically developing children (ASD vs TD; $P < .01$, $k > 17$).

Table 3.

Performance of Quantified Brain Activity in Detecting Autism Spectrum Disorder

Sex	Cohort	Whole Circuit		Right FG/pSTS		Left FG		Left OG	
		AUC	P Value	AUC	P Value	AUC	P Value	AUC	P Value
Boys	Discovery	.750	.01	.740	.01	.710	.03	.630	.12
	Replication	.790	<.001	.800	<.001	.748	.001	.643	.04
	Replication matched ^a	.825	<.001	.821	<.001	.806	<.001	.644	.063
Girls	All	.770	<.001	.770	<.001	.730	<.001	.643	.02
	Discovery	.500	.54	.500	.56	.450	.450	.550	.45
	Replication	.390	.82	.450	.65	.315	.933	.308	.94
All		.421	.79	.488	.56	.361	.907	.369	.89

Abbreviations: AUC, area under the receiver operating characteristic curve; FG, fusiform gyrus; pSTS, posterior superior temporal sulcus; OG, occipital gyrus; pSTS, posterior superior temporal sulcus.

^aMatched on cognitive ability (Diffrential Ability Scale scores).