

# Neural signatures of autism

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**Functional magnetic resonance imaging of brain responses to biological motion in children with autism spectrum disorder (ASD), unaffected siblings (US) of children with ASD, and typically developing (TD) children has revealed three types of neural signatures: (i) state activity, related to the state of having ASD that characterizes the nature of disruption in brain circuitry; (ii) trait activity, reflecting shared areas of dysfunction in US and children with ASD, thereby providing a promising neuroendophenotype to facilitate efforts to bridge genomic complexity and disorder heterogeneity; and (iii) compensatory activity, unique to US, suggesting a neural system-level mechanism by which US might compensate for an increased genetic risk for developing ASD. The distinct brain responses to biological motion exhibited by TD children and US are striking given the identical behavioral profile of these two groups. These findings offer far-reaching implications for our understanding of the neural systems underlying autism.**

endophenotype | functional magnetic resonance imaging

**A**utism spectrum disorder (ASD) is a strongly genetic, highly prevalent neurodevelopmental disorder characterized by striking social deficits (1, 2). Among the most scientifically challenging features of ASD are its phenotypic heterogeneity and genetic variability, which constrain successful identification of genes underlying the clinical syndrome. Despite these challenges, we hypothesize that the various factors contributing to the expression of ASD might exert their effects through a circumscribed set of neuroanatomical structures (3); that is, it is possible that the simplest and potentially most powerful signature of ASD will be found at the level of brain systems. Such “neural signatures” of ASD may serve as critical endophenotypes to facilitate the study of the pathophysiological mechanisms underlying this devastating and highly prevalent neurodevelopmental disorder.

Originally described in the psychiatric literature by Gottesman and Shields (4), endophenotypes (i.e., phenotypes not obvious to the unaided eye) provide quantifiable characteristics (e.g., behavioral, physiological, neuropsychological) that reflect genetic liability for a disease. Endophenotypes exist midstream between genotypes and clinical phenotypes in both affected individuals and their unaffected relatives (4–6). As such, they offer the potential to bridge gaps between diagnostic categories of complex diseases, such as neurodevelopmental and psychiatric disorders, and genetic mechanisms (4). Endophenotypes reveal more basic components of a complex phenotype and thus are thought to be more closely related to the underlying pathophysiology than the collection of downstream clinical symptoms. Therefore, genetic factors contributing to endophenotypes are considered more easily identifiable, due to the increased proportion of the variance explained at a given genetic locus compared with that explained by the traditional clinical endpoint. Research on the identification of genetically meaningful, clinically informed endophenotypes, such as activity in brain regions supporting key aspects of social perception, is likely to provide important insight into the underlying components of the core features of ASD and facilitate complementary approaches to genetic studies.

As intrinsically social creatures, humans typically exhibit robust visual sensitivity to other people’s movements (7). This is

well illustrated by the discovery that point-light displays (i.e., videos created by placing lights on the major joints of a person and filming them moving in the dark), although relatively impoverished stimuli, contain sufficient information to identify the kind of motion being produced (e.g., walking, dancing, reaching), as well as the identity of the agent (8). Visual sensitivity to biological motion is an evolutionarily well-conserved and ontogenetically early-emerging mechanism that is fundamental to adaptive social engagement (9); for example, newly hatched chicks recognize biological motion in point-light displays (10), and 2-d-old human infants preferentially attend to biological motion in point-light displays (11). Preferential attention to biological motion is thought to be critical for filial attachment (12) and is seen as a precursor to subsequent social development, including the ability to perceive emotion (13) and to attribute intentions to others (14).

Given the centrality of biological motion perception to social interaction, recent evidence of disrupted biological motion perception in toddlers with autism is particularly noteworthy. Using eye tracking, Klin et al. (9) demonstrated that a group of 2-y-old children with autism failed to orient preferentially toward point-light displays of canonical biological motion. Instead, their viewing behavior was well explained by preferential attention to non-social audiovisual contingencies that were ignored by typically developing children and developmentally delayed children without autism. Moreover, disrupted perceptual sensitivity to biological motion has been documented in older children with ASD (15). Neuroimaging studies examining the neural correlates of point-light biological motion perception in adults with and without ASD have consistently implicated the posterior superior temporal sulcus (pSTS) region as an area of dysfunction (16, 17). Given that ASD is a neurodevelopmental disorder, studying the early stages of this atypical neural response to biological motion is critical. Identifying disruptions in the brain mechanisms for biological motion perception in children with ASD might provide insight into an ongoing developmental process whereby early abnormalities in social engagement shape (and are shaped by) the neural processes that support social interactions.

During a 5.5-min functional magnetic resonance imaging (fMRI) scan, 4- to 17-y-old children and adolescents viewed coherent and scrambled point-light animations of biological motion in a blocked design. Three groups of children were studied: (i) children with ASD ( $n = 25$ ), (ii) unaffected siblings of children with ASD (US;  $n = 20$ ), and (iii) typically developing children (TD;  $n = 17$ ). Comparing the activation to biological motion versus scrambled motion among the three groups identified three kinds of brain activity: (i) state activity, reflecting ASD (regions showing reduced differential activation to biological versus scrambled motion in ASD relative to TD and US); (ii) trait ac-

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**Table 1. Group characterization and matching variables**

Measure	TD	US	ASD
Sex, males: females, n	12:5	9:11	20:5
Age, years, (range)	10.9 (3.1) [4.6–16.7]	11.3 (2.8) [6.6–16.9]	11.8 (3.6) [4.0–17.7]
SRS, total raw score	23.7 (14.5)	18.9 (15.3)	98.7 (23.5)
Vineland-II Communication*	102.5 (15.8)	102.0 (12.9)	78.3 (10.5)
Receptive	15.1 (3.4)	15.2 (2.3)	10.4 (2.0)
Expressive	15.5 (2.9)	15.3 (2.1)	11.1 (2.4)
Written	15.3 (2.7)	14.7 (3.1)	12.2 (2.7)
Vineland-II Daily Living*	93.1 (10.4)	93.6 (10.9)	78.5 (11.0)
Personal	13.5 (2.6)	13.2 (3.7)	10.5 (2.0)
Domestic	13.0 (1.6)	13.4 (2.6)	10.9 (3.0)
Community	15.3 (2.3)	15.5 (2.3)	12.8 (3.2)
Vineland-II Social*	102.7 (9.0)	99.6 (11.3)	73.5 (9.8)
Interpersonal Relationships	15.6 (1.9)	14.9 (1.9)	9.6 (1.9)
Play and Leisure Time	15.2 (2)	14.8 (2.1)	10.4 (2.6)
Coping Skills	15.3 (1.6)	14.4 (2.4)	10.6 (2.3)
DAS-II Global Composite Ability <sup>†</sup>	114.1 (16.3)	115.8 (7.9)	100.2 (19.7)
Verbal	111.7 (14.1)	118.2 (15.4)	99.9 (21.4)
Specialized Non-Verbal Composite	110.1 (17.5)	113.8 (15.1)	98.2 (17.7)
WASI Full-Scale IQ <sup>†</sup>	113.6 (9.7)	112.9 (15.2)	
Verbal	112.5 (12.4)	108.4 (15.0)	
Performance	112.6 (8.0)	114.6 (17.2)	
Amount of movement, mm <sup>‡</sup>	0.9 (0.7)	1.4 (0.9)	1.1 (0.6)

Unless noted otherwise, values are reported as average score, with SD in parentheses.

\*Vineland-II raw scores were not available for four participants (two TD, one US, and one ASD). The Vineland-II Survey Edition was substituted for five ASD participants.

<sup>†</sup>Either the DAS-II (15 TD, 6 US, and 25 ASD) or WASI (2 TD and 14 US) was administered to establish average cognitive abilities.

<sup>‡</sup>Average amount of movement in six planes of motion.

tivity, reflecting the genetic vulnerability to develop ASD (regions showing reduced differential activation in ASD and US relative to TD); and (iii) compensatory activity (regions showing enhanced differential activation unique to US). State activity characterizes the nature of disruption in brain circuitry in ASD at the neural systems level, whereas trait activity reflects shared areas of dysfunction in US and children with ASD, thereby providing a robust endophenotype for ASD. Compensatory activity refers to activity unique to US, which might reflect the operation of a neural system-level mechanism by which US overcome an increased genetic risk for developing ASD.

As illustrated in Table 1, the three groups of participants were matched on chronological age and were of similar cognitive ability, all within the average range. Cognitive ability was assessed using either the Differential Ability Scale (DAS-II) (18) or the Wechsler Abbreviated Scale of Intelligence (WASI) (19). The children with ASD were diagnosed with autism ( $n = 9$ ), Asperger's syndrome ( $n = 7$ ), or pervasive developmental disorder—not otherwise specified ( $n = 9$ ) using the gold standard Autism Diagnostic Observation Schedule (ADOS) (20), the Autism Diagnostic Interview—Revised (ADI-R) (21), and experienced clinical judgment (Table 2). Notably, our US and TD groups were matched on the Social Responsiveness Scale (SRS) (22) and the Vineland Adaptive Behavior Scales II (23). This rigorous matching ensured that both groups were unaffected by ASD and demonstrated equivalent levels of social responsiveness. In addition, strict exclusion criteria were used for the TD and US groups to rule out other developmental disorders and the “broader autism phenotype” (BAP) (24) in each participant, as well as in first- and second-degree relatives of the US participants; Table 3 provides the complete list of exclusion criteria. We reasoned that by excluding US and TD participants with subtle social and communicative abnormalities, trait activity could then be interpreted as reflecting a vulnerability to develop ASD, as opposed to being epiphenomenal to the presence of subthreshold ASD symptoms. Our samples included proband-sibling pairs ( $n = 5$  pairs) as well as unrelated

probands ( $n = 19$ ) and US participants ( $n = 14$ ). Because all of the US participants passed screening for ASD or BAP, and only five US participants were related to probands in the ASD group, we minimized an important potential confound: identifying regions reflecting shared genetic variance unrelated to ASD. Had all of our participants been proband-sibling pairs, then this confound might have limited the scope of our conclusions. Written informed consent was obtained from each participant's parent(s), and verbal assent was obtained from each participant. The Yale School of Medicine's Human Investigations Committee approved the study.

## Results

As illustrated in Figs. 1 and 2, conjunction analyses of the biological motion > scrambled motion contrast identified (*i*) state

**Table 2. ASD group characterization**

Measure	Average (SD)
ADOS Calibrated Severity Score ( $n = 22$ )*	7.0 (1.5)
ADOS Mod2, Total ( $n = 3$ )	15.0 (5.0)
Social	11.3 (3.8)
RRB	3.7 (2.1)
ADOS Mod2, Total ( $n = 21$ )	11.5 (3.4)
Social	8.8 (2.9)
RRB	2.7 (1.7)
ADOS Mod4, Total ( $n = 1$ )	15.0
Social	13
RRB	2
ADI-R ( $n = 22$ ) <sup>†</sup>	
Social	21.9 (3.9)
Communication (verbal)	18.2 (3.0)
RRSB	5.6 (2.5)
Age of onset, years	3.3 (0.9)

\*The ADOS calibrated severity score (40) was computed only for 22 participants age 4–16 y.

<sup>†</sup>The ADI-R was not available for 3 participants.

**Table 3. Exclusion criteria**

**TD and US exclusion criteria**

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 (except sibling of proband with ASD in the case of US).
3. An individual education plan for special education services, including speech/language therapy, occupational therapy, and social skills therapy.
4. Low or moderately low score on any domain of the Vineland Adaptive Behavior Scale-II.
5. Total T score >76 (severe range) on the SRS.
6. Clinical impression suggesting ASD, other developmental delay/disorder, or psychiatric disorder by the highly experienced multidisciplinary clinical team at Yale Child Study Center Characterization Core.

**Additional US exclusion criteria**

1. Parents with elevated spousal ratings on the SRS or self-ratings on the BAP-Q (22).

activity (TD > ASD  $\cap$  US > ASD) localized to the right amygdala, ventromedial prefrontal cortex (vmPFC), left ventrolateral prefrontal cortex (vlPFC), right pSTS, and bilateral fusiform gyri (FG); (ii) trait activity (TD > ASD  $\cap$  TD > US) localized to the left dorsolateral prefrontal cortex (dlPFC), right inferior temporal gyrus (ITG), and bilateral FG (anterior to and nonoverlapping

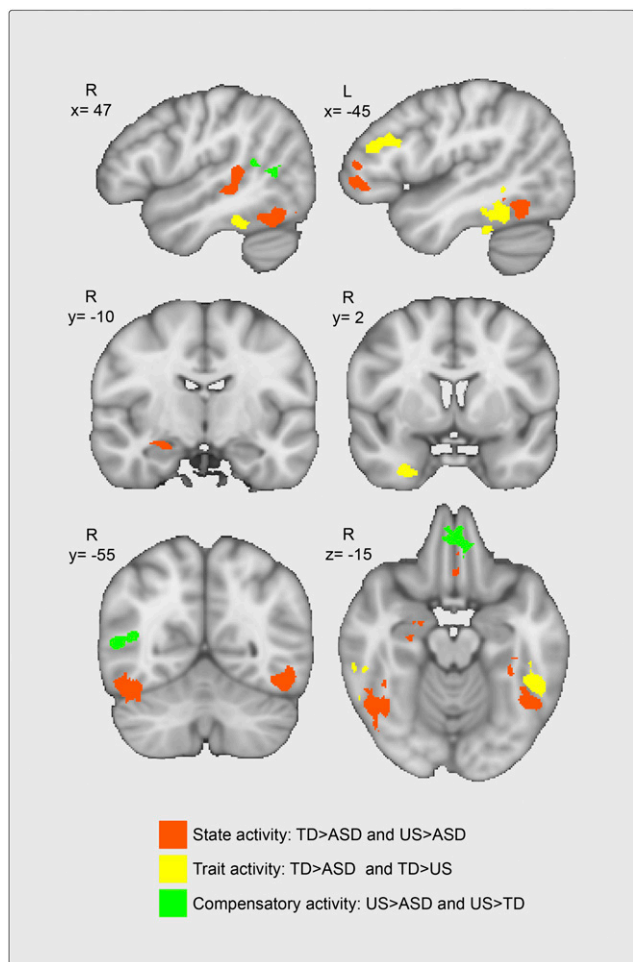
with the portions of the FG identified as state activity); and (iii) compensatory activity (US > TD  $\cap$  US > ASD) localized to the right hemisphere pSTS (caudal to and nonoverlapping with the portion of the right hemisphere pSTS identified as exhibiting state activity) and the vmPFC (anterior and inferior to the portion of vmPFC identified in our state activity analysis). Table 4 lists the weighted centers and the extent of activation for these regions. Region-of-interest analyses excluding the subset of five proband-sibling pairs revealed equivalent patterns of results to those involving the full sample.

Correlation analyses revealed no significant associations between state activity and cognitive ability in the children with ASD, indicating that differences in cognitive ability likely do not account for the state activity findings. Correlation analyses between SRS scores (an index of the severity of social deficits associated with ASD) and activity from the state, trait, and compensatory regions revealed several significant relationships (Fig. 3). As illustrated in Fig. 3A, in the ASD group, we found a negative correlation between SRS score and activity in the right pSTS region identified in our analysis of state activity ( $r = 0.502$ ,  $P < 0.01$ ). In the US group, we found a negative correlation between SRS score and trait activity ( $r = -0.403$ ,  $P < 0.05$ ) (Fig. 3B). As shown in Fig. 3C and D, in the TD group, we found negative correlations between SRS score and activity in the trait marker region of the left dlPFC ( $r = -0.433$ ,  $P < 0.05$ ) and state activity in the left vlPFC ( $r = -0.420$ ,  $P < 0.05$ ).

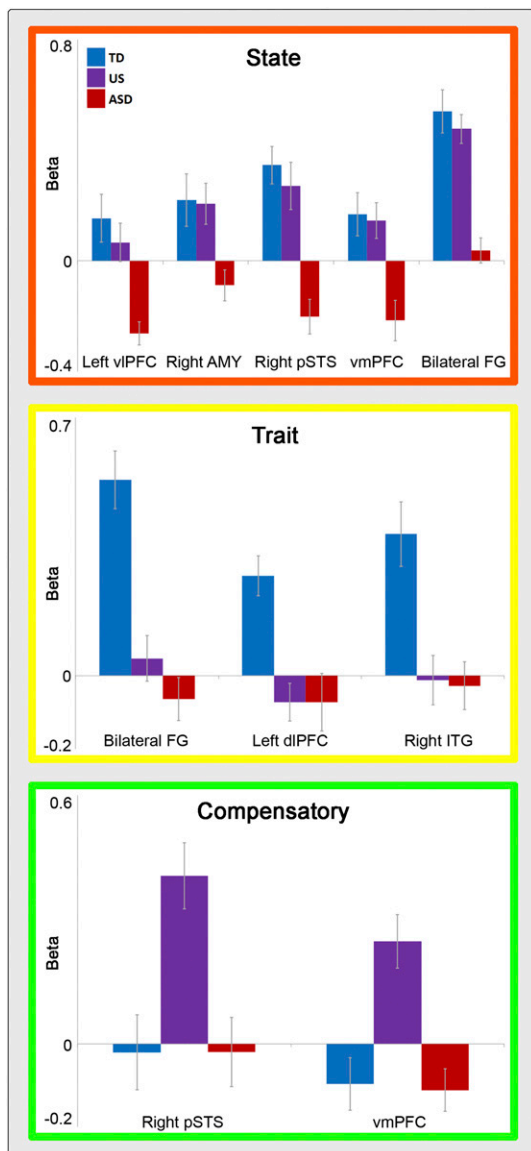
**Discussion**

This study makes key contributions to the understanding of ASD in the identification of state activity, trait activity, and compensatory activity.

**State Activity.** The identification of state activity extends previous research implicating the right amygdala, right pSTS, bilateral FG, left vlPFC, and vmPFC in adults with ASD, by showing that dysfunction in these regions is already present in school-age children with ASD (25–29). This is an important advance in the field, given that previous reports of atypical neural response to biological motion included only adult subjects (16, 17). In addition, activity in the state-defined right pSTS was associated with the severity of social deficits in individuals with ASD. Individuals with higher SRS scores exhibited less activation to biological motion within the right pSTS. This finding suggests that activity in the pSTS might serve as a biological marker to subdivide the autism spectrum on the basis of severity. Furthermore, activity in the state-defined region of the left vlPFC was found to reflect the level of social responsiveness of the TD children, indicating a coupling of social behavior and brain mechanisms for social perception. The evidence of dysfunction in brain mechanisms for social perception in young children with ASD explains previous behavioral findings of disrupted biological motion perception (9). Given that social interaction relies on the accurate perception of other people's actions, state activity indicating regions of dys-



**Fig. 1.** Localization and response patterns of state, trait, and compensatory activity. Conjunction analyses of the biological motion > scrambled motion contrasts ( $P < 0.0025$ ,  $k = 20$ ) identified state activity (orange map) localized to the left ventrolateral prefrontal cortex, right amygdala (AMY), right posterior superior temporal sulcus, ventromedial prefrontal cortex, and bilateral fusiform gyri. Trait activity (yellow map) was localized to the bilateral fusiform gyrus, left dorsolateral prefrontal cortex, and right inferior temporal gyrus. Compensatory activity (green map) was localized to the right posterior superior temporal sulcus and ventromedial prefrontal cortex.



**Fig. 2.** Response patterns of state, trait, and compensatory activity. Average beta values ( $y$  axis) from the biological > scrambled contrast as a function of region classification. (*Top*) Beta values from the regions of state-related activity (orange border). (*Middle*) Beta values from the trait-related activations (yellow border). (*Bottom*) Beta values from the compensatory activations (green border). Error bars represent the SEM.

function associated with the manifestation of ASD provides a significant step toward more fully characterizing the biological underpinnings of this neurodevelopmental disorder.

**Trait Activity.** In accordance with Gottesman and Gould's characterization of endophenotypes (6), trait activations, including those in the left dlPFC, right ITG, and bilateral FG, were shared between affected individuals (ASD group) and first-degree relatives (US group). These findings are particularly noteworthy because we explicitly ruled out the BAP in the US group, in contrast to previous studies (30, 31). This implies that our neuroimaging paradigm offers a remarkable level of sensitivity that transcends clinical evaluation. Although the US group was indistinguishable from the TD group at the behavioral level, the trait activity findings reveal similar neural signatures in the US and ASD groups. Concordant with this interpretation, social responsiveness was

**Table 4.** Centers and extent of activation for state, trait, and compensatory activity

Region	$x$	$y$	$z$	Extent*
<b>State regions</b>				
Left ventrolateral prefrontal cortex	-42	41	2	1,196
Ventromedial prefrontal cortex	-4	33	-11	533
Right posterior temporal sulcus	45	-31	4	1,184
Right amygdala	24	-11	-13	315
Right fusiform gyrus	43	-52	-18	2,276
Left fusiform gyrus	-42	-49	-12	1,943
<b>Trait regions</b>				
Right inferior temporal gyrus	27	2	-31	648
Left dorsolateral prefrontal gyrus	-43	24	25	860
Right fusiform gyrus	47	-36	-19	652
Left fusiform gyrus	-47	-42	-15	1,519
<b>Compensatory regions</b>				
Right posterior temporal sulcus	47	-52	11	703
Ventromedial prefrontal cortex	-2	41	-14	646

\*The number of active 1-mm cubic voxels.

associated with overall trait activity in the US group and with trait-defined left dlPFC in the TD group. Furthermore, whereas the state regions could arise as an effect of having ASD, the trait activity cannot be explained in this way; rather, this trait activity likely reflects the genetic vulnerability to develop ASD (32). An alternative explanation—that trait activity merely reflects the experience of living with someone with ASD—is unlikely, because age did not correlate with trait activity, and because our results did not differ as a function of whether the US participant was older or younger than his or her sibling with ASD. Notably, these regions emerged during biological motion perception, emphasizing the link between atypical social perception and a predisposition to ASD.

The key implication of our trait activity findings is that we provide a functional neuroendophenotype that should help bridge the gene–behavior gap and thereby accelerate the search for pathophysiological mechanisms. A central goal in autism research is to map out a mechanistic understanding of the disorder from the gene level to the individual's behavior. The neuroendophenotype described herein represents altered functioning of neural circuits during social perception (a key aspect of dysfunction in ASD) in individuals at increased genetic risk for developing ASD. With this in hand, collaborative work can perhaps use this quantitative endophenotype to conduct genome-wide association studies to identify candidate genetic mechanisms and associated pathophysiological pathways.

**Compensatory Activity.** Our US group exhibited unique areas of activation in the vmPFC and the right pSTS, regions previously implicated in aspects of social perception and social cognition (33, 34). These regions might reflect the absence of additional genetic or environmental factors that confer risk for ASD. Alternatively, they could represent a process through which brain function was altered over development to compensate for an increased genetic risk to develop ASD. We found that the activity in these regions did not vary with chronological age. Thus, it is possible that the compensatory regions reflect the outcome of a process occurring earlier in development, during a sensitive period for the development of brain mechanisms for social perception. This might be likely, given that autism is a developmental disorder that emerges during the first years of life, well before age 4 y (the youngest age studied in this sample). Nonetheless, we cannot yet draw firm conclusions regarding the compensatory activity. Indeed, longitudinal research in younger children is



**MRI Data Acquisition.** Scanning was performed on a Siemens MAGNETOM Trio, A Tim System 3T scanner at the Yale Magnetic Resonance Research Center, Yale School of Medicine. T1-weighted anatomical images were acquired using an MPRAGE sequence (repetition time, 2,530 ms; echo time, 3.34 ms; field of view, 25.6 cm; image matrix,  $64^2$ ;  $1 \times 1 \times 1$  mm). For each run, 164 whole-brain functional images were acquired using a single-shot, gradient-recalled echo planar pulse sequence (repetition time, 2,000 ms; echo time, 25 ms; flip angle,  $60^\circ$ ; field of view, 22 cm; image matrix,  $64^2$ ; voxel size,  $3.2 \times 3.2 \times 3.2$  mm; 34 slices) sensitive to blood oxygenation level-dependent contrast.

**Data Analyses.** Data were analyzed with Brain Voyager QX version 2.0.8.1480 (Brain Innovation). All 10 volumes before the onset of the first stimulus event were discarded, to allow for T1 equilibrium. Preprocessing of the functional data included interleaved slice time correction using cubic spline interpolation, 3D motion correction using trilinear/sinc interpolation, linear trend removal, and temporal high-pass filtering to remove low-frequency non-linear drifts of three or fewer cycles per time course (2.8 s). On examination of estimated motion plots and cine loops, participants with  $>3.5$  mm of deviation or rotation from the estimated center of mass in any direction were excluded. Functional data sets were coregistered to the Talairach-transformed (36), within-session, T1-weighted anatomical images. Eight nuisance variables were removed via linear regression, including six motion parameters and two time course signals drawn from  $9\text{-mm}^3$  regions of interest in white matter (Talairach coordinate  $-26, -13, 31$ ) and the left ventricle (Talairach coordinate  $-19, -35, 15$ ), both of which were verified in each participant's normalized anatomical image.

A multiparticipant statistical analysis was run in which a model predictor was defined by convolving an ideal boxcar response with a double gamma

function model of the hemodynamic response (37) across each 24-s trial. Whole-brain random-effects direct group comparisons of the biological motion  $>$  scrambled motion contrast were performed in the following four comparisons: TD  $>$  ASD, TD  $>$  US, US  $>$  ASD, and US  $>$  TD. Areas of activation were identified at a voxel-wise uncorrected level of  $P < 0.05$ . A cluster threshold of  $k > 20$  contiguous voxels was used to correct for multiple comparisons (38, 39). This cluster threshold was calculated for each group comparison with a corrected threshold of  $\alpha < 0.05$  using a Brain Voyager QX cluster-level statistical threshold estimator plug-in. After 5,000 iterations of a Monte Carlo simulation, an  $\alpha$  value was assigned to each cluster size based on its relative frequency. Restricting the number of active voxels to 20 contiguous voxels within each group comparison resulted in a  $<5\%$  chance of discovering false-positive voxels in the key analyses. Three separate conjunction analyses were performed to identify regions of state (TD  $>$  ASD  $\cap$  US  $>$  ASD), trait (TD  $>$  ASD  $\cap$  TD  $>$  US), and compensatory (US  $>$  TD  $\cap$  US  $>$  ASD) activity. These regions were identified at a voxel-wise uncorrected level of  $P < 0.0025$  and a cluster threshold of  $k > 20$ . Correlation analyses between SRS scores and state, trait, and compensatory activity were conducted at the one-tailed level given our a priori hypotheses regarding the relationship of social function and brain mechanisms for biological motion perception.

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