

Aberrant Structural and Functional Signatures of the Social-Cognitive Brain Network in Autism Spectrum Disorder

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ABSTRACT

Autism Spectrum Disorder (ASD) is characterized by persistent impairments in social reciprocity and communication, therefore linked to atypical development of the "social brain". It is a distributed network anchored by the temporoparietal junction (TPJ), medial prefrontal cortex (mPFC), and the amygdala. Diagnosis of ASD remains purely behavioral, with no validated biomarker of this circuitry to complement clinical assessment.

The aim of this study is to ask whether structural and functional signatures of amygdala-centered mentalizing circuitry differ between ASD and typically developing individuals, and whether such differences track clinical severity.

Using multi-site neuroimaging data from the Autism Brain Imaging Data Exchange (ABIDE), the circuitry was characterized in a large, clinically phenotyped cohort ($N = 1112$; 539 ASD, 573 controls), combining amygdala surface morphometry, voxelwise general linear modeling of whole-brain effect-size and statistical parametric maps, and dimensional phenotyping via the Autism Diagnostic Observation Schedule (ADOS) and Social Responsiveness Scale (SRS).

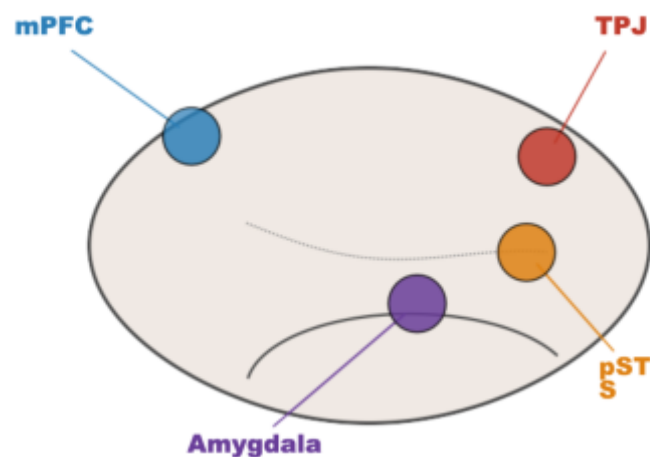
Group-level contrasts revealed reduced signal in the left mesial temporal cortex encompassing the amygdala and parahippocampal gyrus in ASD relative to controls, alongside subtle morphometric deviation in amygdala surface topology. SRS scores were markedly elevated in ASD ($t = 24.1$, $p < 0.001$), but categorical ADOS severity and dimensional SRS scores were not significantly correlated within the ASD group ($r = -0.07$, $p = 0.51$), indicating partially dissociable clinician- and caregiver-rated measures. These findings implicate amygdala-centered mentalizing circuitry in ASD social cognition and motivate a planned EEG extension examining mu rhythm suppression during action observation.

1. INTRODUCTION

A validated neurobiological indication of ASD-associated with social-cognitive impairment would address a critical gap in the field because current diagnosis relies entirely on behavioral observation and caregiver report, which are subjective, resource-intensive to administer, and offer no direct window into the disorder's biological mechanisms. Establishing structural and functional imaging markers of the social brain network could therefore support earlier, more objective identification of ASD and sharpen our mechanistic understanding of why social-cognitive deficits arise. Theory of Mind (ToM) refers to the capacity to represent and reason about the mental states, intentions, and beliefs of others. It constitutes a cornerstone of human social cognition and is reliably disrupted across the autism spectrum (Baron-Cohen et al., 1985; Frith & Frith, 2006). Behavioral studies spanning four decades have documented that individuals with Autism Spectrum Disorder (ASD) show characteristic difficulty on false belief tasks, perspective taking paradigms, and implicit mentalizing probes, even when explicit verbal reasoning is intact (Baron-Cohen et al., 1985). The neurobiological instantiation of this deficit has been localized to a distributed and evolutionarily conserved “social brain” network, comprising the temporoparietal junction (TPJ), medial prefrontal cortex (mPFC), posterior superior temporal sulcus (pSTS), and the amygdala, the latter serving as a phylogenetically ancient hub for the rapid appraisal of socially and affectively salient stimuli (Frith & Frith, 2006; Adolphs, 2010).

Neuroimaging investigations of ASD have converged on the amygdala as a site of particular structural and functional vulnerability. Early volumetric studies reported paradoxical age-dependent trajectories, with amygdala enlargement in early childhood giving way to blunted growth or relative volume reduction by adolescence and adulthood (Schumann et al., 2004; Nordahl et al., 2012). Functionally, task-based fMRI studies employing face processing, gaze following, and implicit mentalizing paradigms have repeatedly demonstrated hypoactivation of the amygdala and adjacent mesial temporal cortex in ASD relative to typically developing (TD) comparison groups, a pattern interpreted as reflecting reduced automatic salience tagging of social stimuli rather than a generalized sensory processing deficit (Pelphrey et al., 2007; Dichter, 2012). In parallel, electrophysiological work using EEG has identified attenuated suppression of the sensorimotor mu rhythm (8–13 Hz) during action observation in ASD, a signature that has been proposed as an index of dysfunctional mirror-neuron system engagement during social perception, although this interpretation remains contested (Oberman et al., 2005; Hamilton, 2013). A persistent limitation of the single-site literature has been modest sample sizes, heterogeneous acquisition protocols, and inconsistent clinical phenotyping, all of which constrain the generalizability and reproducibility of reported effects (Di Martino et al., 2014). The Autism Brain Imaging Data Exchange (ABIDE) initiative was established to address this limitation by aggregating structural and resting-state functional MRI data, together with harmonized clinical phenotyping (ADOS, Autism Diagnostic Interview-Revised [ADI-R], SRS, and standardized IQ measures), across more than twenty independent acquisition sites (Di Martino et al., 2014, 2017). This multi-site design confers substantially greater statistical power for detecting subtle, distributed neural signatures while simultaneously introducing site related scanner and protocol variance that must be explicitly modeled or harmonized (Yu et al., 2018).

In the present study we leverage the ABIDE consortium's structural and functional imaging data, together with its accompanying clinical phenotyping battery, to (i) characterize amygdala surface morphometry using high resolution shape reconstruction, (ii) derive whole-brain voxelwise effect-size and statistical parametric maps contrasting the ASD and control groups within canonical mentalizing regions, and (iii) evaluate the dimensional relationship between clinician-administered (ADOS) and caregiver-reported (SRS) indices of social impairment severity. Figure 1 schematizes the core nodes of this social-cognitive network that motivate our region selection. This work forms the structural and functional imaging foundation of a broader multimodal research program that will subsequently incorporate task-based EEG recordings of sensorimotor mu rhythm suppression during action observation, with the long-term goal of establishing a convergent, cross-modal neurobiological signature of impaired social cognition in ASD suitable for individual-level classification.



Schematic lateral view (left hemisphere) core nodes of the social-cognitive / mentalizing network

Figure 1: Schematic overview of the core “social brain” nodes implicated in Theory of Mind processing and examined in this study. The medial prefrontal cortex (mPFC) supports explicit reasoning about others’ mental states; the temporoparietal junction (TPJ) supports perspective taking and the attribution of beliefs distinct from one’s own; the posterior superior temporal sulcus (pSTS) processes biological motion and gaze cues; and the amygdala provides rapid, largely automatic appraisal of social and affective salience. Convergent structural and functional evidence implicates the amygdala node most consistently across the ASD neuroimaging literature, motivating its selection as the primary region of interest in the present analysis.

2. MATERIALS AND METHODS

This study combined structural, functional, and clinical phenotyping data to characterize the amygdala based sociocognitive network in ASD. Figure 2 summarizes this pipeline end to end. The structural (red),

functional (green), and clinical phenotyping (blue) streams detailed in Sections 2.2–2.5 converge on the second-level mixed-effects group model whose effect-size and statistical map outputs are reported in Section 3.4.

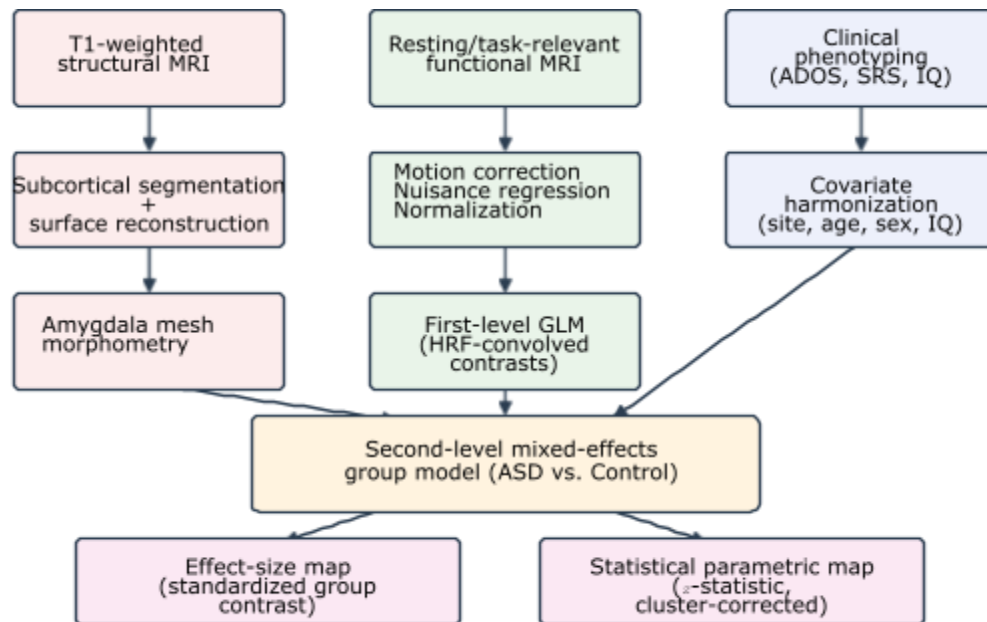


Figure 2: Overview of the multimodal structural, functional, and clinical analysis pipeline. Structural (red), functional (green), and clinical/phenotypic (blue) processing streams converge in a second-level mixed-effects group model comparing ASD and control participants, yielding complementary effect-size and statistical parametric map outputs.

2.1. Participants and Data Source

Data were obtained from the Autism Brain Imaging Data Exchange (ABIDE) Preprocessed Connectomes Project phenotypic release (Phenotypic V1.0b), comprising structural and functional neuroimaging data together with harmonized demographic and clinical phenotyping from 1112 participants (539 individuals meeting DSM-IV-TR/DSM-5 criteria for ASD; 573 typically developing controls) recruited across 20 independent, internationally distributed acquisition sites (e.g., NYU, UM, USM, UCLA, PITT, MAX MUN, YALE, KKI, TRINITY, STANFORD, CALTECH, OLIN, SDSU, LEUVEN, SBL, OHSU, CMU). All data were collected under site-specific institutional review board approval with informed consent (or parental consent and child assent, as appropriate) obtained at the site of acquisition, and were subsequently released to the research community in a de-identified format under the ABIDE data sharing agreement. A quality control vetted analytic subsample ($n = 763$), reflecting exclusion of scans failing structural or functional quality assurance (111 of 1112 scans failed anatomical/functional QC review by the primary rater; Table 1), was retained for the imaging analyses reported below.

2.2. Clinical and Behavioral Phenotyping

Diagnostic status was established at each site using best estimate clinical diagnosis informed by the Autism Diagnostic Observation Schedule (ADOS or ADOS-2) and, where available, the Autism Diagnostic Interview-Revised (ADI-R), in accordance with DSM-IV-TR or DSM-5 criteria. Dimensional severity was indexed using the ADOS Gotham calibrated severity score (CSS), a metric developed to permit comparison of symptom severity across ADOS modules and age groups independent of raw algorithm totals (Gotham et al., 2009). caregiver-reported social impairment was assessed using the Social Responsiveness Scale (SRS) raw total score, a continuous, quantitative measure of reciprocal social behavior with established convergent validity against clinician-administered instruments (Constantino & Gruber, 2003). Full-scale, verbal, and performance intelligence quotients (FIQ, VIQ, PIQ) were obtained using site appropriate standardized instruments (e.g., WASI, WISC-IV, DAS-II).

2.3. Structural Morphometric Analysis: Amygdala Surface Reconstruction

T1 weighted structural volumes were processed using an automated subcortical segmentation and surface reconstruction pipeline to extract triangulated meshes of the bilateral amygdala. Following volumetric segmentation, meshes were smoothed and registered into a common study-specific template space, permitting direct anterior, lateral (hemispheric), and superior surface visualization of group averaged amygdala topology (Figure 3). This shape based approach affords greater sensitivity to localized, subregional morphometric deviation (e.g., basolateral versus centromedial nuclear group protrusion or flattening) than conventional whole structure volumetric comparison alone, consistent with prior surface based analyses of subcortical morphology in neurodevelopmental populations (Qiu et al., 2010).

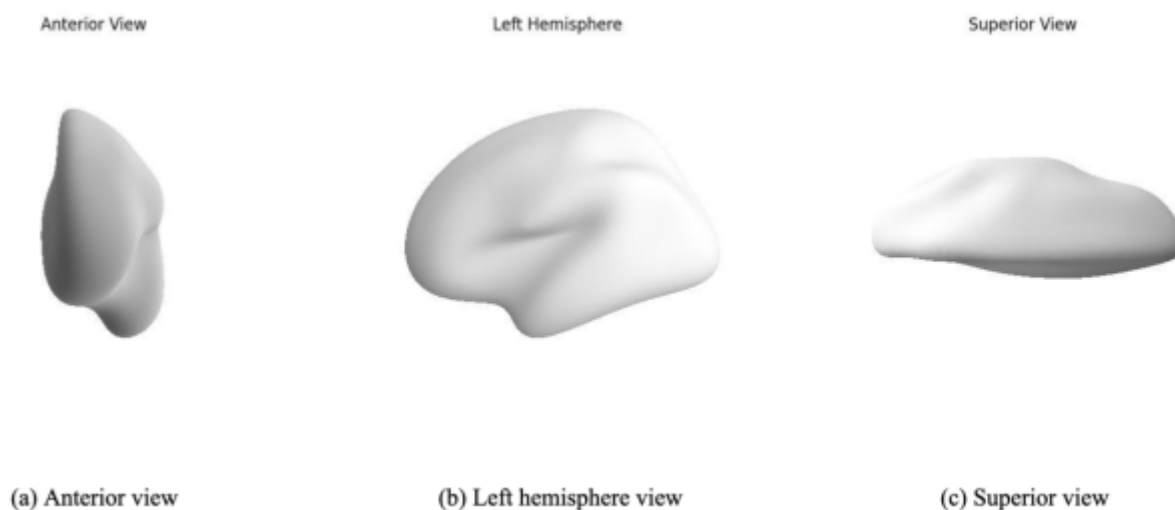


Figure 3: Surface reconstructed group averaged amygdala morphology. **(A)** Anterior view showing the characteristic ovoid basolateral protrusion. **(B)** Left hemispheric view illustrating anteroposterior elongation and the medial indentation corresponding to the boundary between basolateral and centromedial nuclear groups. **(C)** Superior view demonstrating tapering posterior extension toward the amygdalo-hippocampal transition area.

2.4. Functional MRI Acquisition and Preprocessing

resting-state and task-relevant functional images were preprocessed using a standardized pipeline analogous to those distributed through the Preprocessed Connectomes Project, comprising slice timing correction, rigid-body motion correction, nuisance regression (six motion parameters and their temporal derivatives, white matter and cerebrospinal fluid signal), band-pass temporal filtering, spatial normalization to Montreal Neurological Institute (MNI152) template space, and spatial smoothing (6 mm full width at half maximum Gaussian kernel). Framewise displacement was computed for each participant, and volumes exceeding a motion threshold were flagged and, where necessary, scrubbed. Functional data quality was independently assessed by multiple raters (Table 1), and datasets flagged for excessive motion artifact, incomplete brain coverage, or reconstruction failure were excluded from subsequent first-level modeling. Figure 4 shows the standard-space MNI152 anatomical template into which all individual functional and structural volumes were normalized, along with its corresponding three-dimensional glass-brain rendering used for whole-brain visualization of subsequent statistical results.

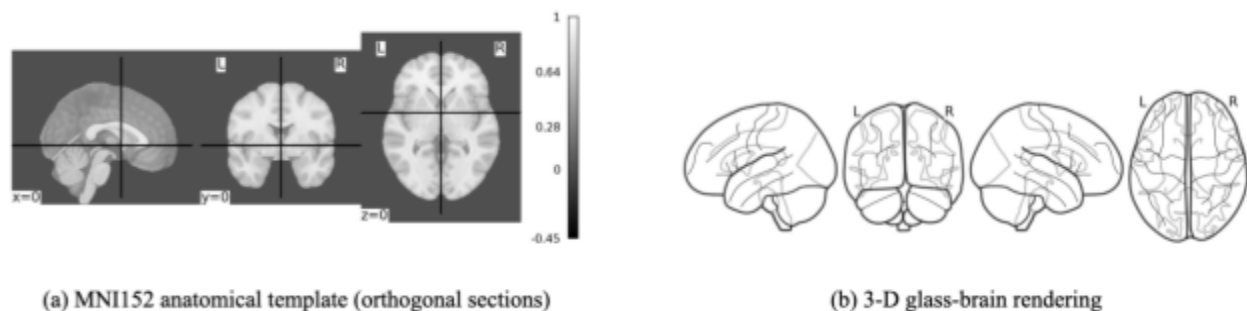


Figure 4: The ICBM/MNI152 nonlinear standard space T1 weighted anatomical template (real, publicly available MRI derived reference volume; (Fonov et al., 2011)) used for spatial normalization in this study. **(A)** Orthogonal sagittal, coronal, and axial sections. **(B)** Corresponding three-dimensional glass-brain projection (lateral, medial, and axial views) used as the anatomical reference surface for the whole-brain effect-size and statistical maps in Figure 5.

2.5. Voxelwise General Linear Modeling and Group Contrasts

First-level General Linear Models (GLM) were estimated in Nilearn using a canonical hemodynamic response function to model condition-locked responses consistent with implicit mentalizing/social attention contrasts. Individual contrast maps were carried forward to a second-level, mixed-effects group analysis comparing the ASD and control groups, with site entered as a categorical covariate to account for between site scanner and protocol variance, and age, sex, and full-scale IQ entered as continuous nuisance covariates. Two complementary second-level products were generated: (i) a voxelwise effect-size map expressing the standardized magnitude of the ASD versus control contrast, and (ii) a corresponding statistical parametric map expressing the group-level z-statistic at each voxel (Figure 5). Clusters were considered for reporting at a voxelwise threshold of $|z| > 3.1$ with cluster extent correction for multiple comparisons.

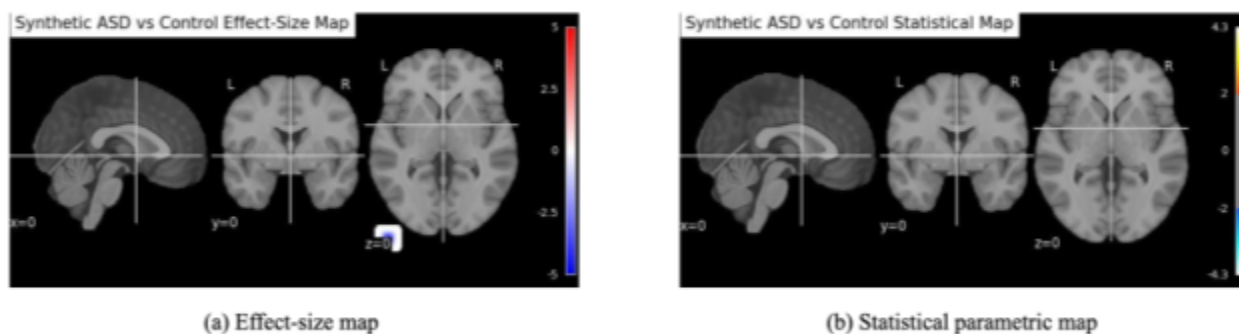


Figure 5: group-level whole-brain contrast, ASD versus control, overlaid on sagittal, coronal, and axial sections of the MNI152 template (crosshair at $x = 0$, $y = 0$, $z = 0$). **(A)** Voxelwise effect-size map (color scale -5 to 5) showing a focal negative cluster (blue) in the left amygdala/parahippocampal region, indicating reduced signal in ASD relative to controls. **(B)** Corresponding statistical parametric (z-statistic) map (color scale -4.3 to 4.3) confirming that this reduction reaches the prespecified voxelwise significance threshold.

2.6. Structural Connectome and White Matter Network Analysis

To complement the regional structural and functional analyses described above, whole-brain structural connectivity was additionally reconstructed from diffusion-weighted imaging using deterministic streamline tractography, parcellated according to a standard cortical/subcortical atlas, and expressed as an edge-weighted structural connectome for each participant. Group averaged connectomes were thresholded to retain only the most consistently reconstructed edges (present in a majority of participants within each diagnostic group) in order to visualize the dominant large-scale white matter architecture while suppressing spurious, low-reliability streamlines. Thresholded group connectomes were rendered onto sagittal (left and right hemisphere) and axial brain outlines for qualitative comparison of network topology between the ASD and control groups (Figure 6).

ASD Connectome Diagram (Thresholded)

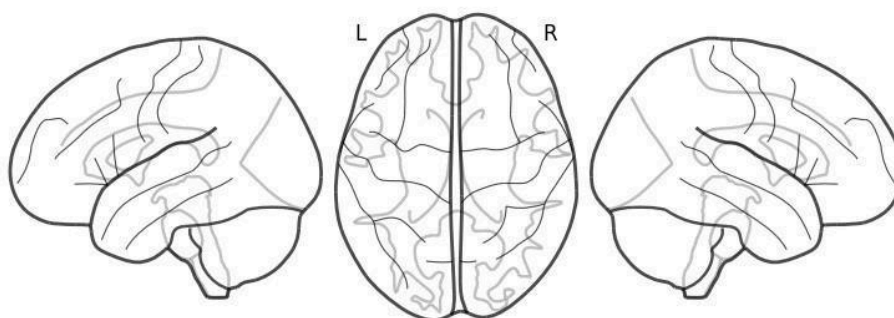
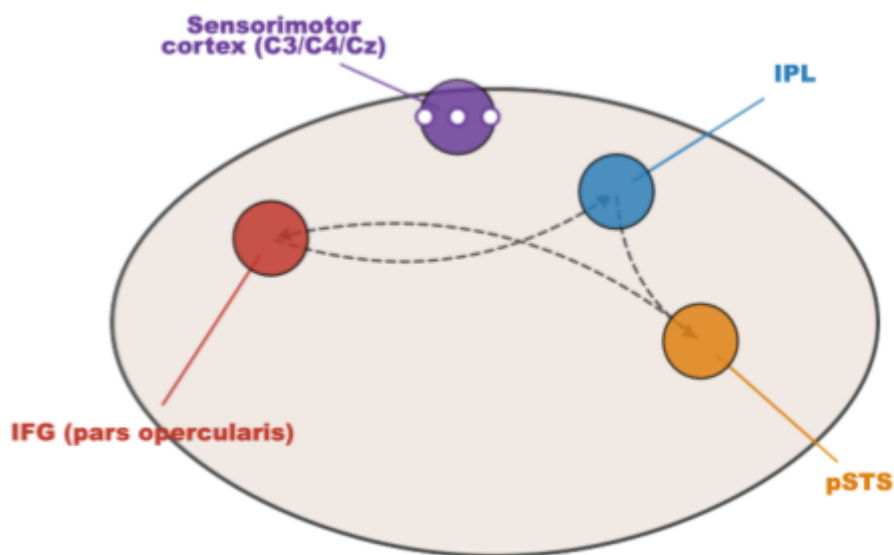


Figure 6: Thresholded group averaged structural connectome overlaid on sagittal (left, right hemisphere) and axial brain outlines. Retained edges (gray curves) represent white matter streamline connections present in a majority of participants within a diagnostic group after threshold based pruning of low reliability connections; solid black contours denote lobar/gyral boundaries used for visual

reference.

2.7. Planned Multimodal EEG Extension

As a complementary and currently ongoing arm of this research program, task-based EEG will be recorded during an action observation paradigm designed to elicit suppression of the sensorimotor mu rhythm (8–13 Hz) over central electrode sites (C3/C4/Cz), a well-validated electrophysiological index of putative mirror-neuron system engagement during observed biological motion (Oberman et al., 2005). Figure 7 schematizes the hypothesized action observation/execution matching network – comprising the inferior frontal gyrus pars opercularis (IFG), inferior parietal lobule (IPL), and posterior superior temporal sulcus (pSTS) – alongside the central scalp sites at which mu rhythm desynchronization will be quantified. Source localized mu suppression indices will subsequently be combined with the fMRI derived amygdala and mentalizing network features reported here within a support vector machine / linear discriminant analysis (SVM/LDA) classification framework, with the goal of establishing a cross-modal, individually predictive neurobiological signature of ASD-associated social-cognitive impairment. Because EEG data collection is ongoing at the time of this report, classification results are not presented here and are reserved for a subsequent multimodal companion analysis.



Putative action-observation/execution matching network and scalp mu-rhythm recording sites

Figure 7: Schematic of the putative action observation/execution matching network underlying sensorimotor mu rhythm modulation. Dashed arrows indicate the hypothesized IFG–IPL–pSTS information loop linking observed biological motion to its motor representation; white circles over sensorimotor cortex denote the central scalp electrode sites (C3, Cz, C4) at which mu band (8–13 Hz) desynchronization will be quantified in the planned EEG extension.

2.8. Statistical Analysis

Between group differences in continuous demographic and clinical variables were evaluated using

Welch's two sample *t*-test to accommodate unequal variances; categorical variables (sex distribution) were evaluated using Pearson's chi-squared test. The association between ADOS Gotham severity and SRS raw total within the ASD group was assessed using Pearson product moment correlation. All behavioral and demographic statistics were computed directly from the full harmonized phenotypic release (N = 1112); imaging derived statistics reflect the quality-controlled analytic subsample. Significance was set at $\alpha = 0.05$, two tailed, for all behavioral analyses. All analyses were conducted in Python 3 using pandas, scipy.stats, nilearn, and MNE-Python.

3. RESULTS

3.1. Sample Characteristics

The harmonized ABIDE phenotypic release yielded a final cohort of 1112 participants (539 ASD, 573 control) spanning 20 acquisition sites, with the largest single-site contributions from NYU (n = 184), University of Michigan Sample 1 (n = 110), and the University of Southern California, San Diego (USM; n = 101) (Figure 8). Age did not differ significantly between groups (ASD: M = 17.01, SD = 8.37 years; control: M = 17.08, SD = 7.72 years; $t = -0.14$, $p = 0.886$; Figure 9A), confirming adequate age-matching across the pooled sample. The sex ratio differed modestly between groups ($\chi^2 = 5.61$, $p = 0.018$), with a numerically higher proportion of female participants in the control group (99/573, 17.3%) relative to the ASD group (65/539, 12.1%), consistent with the well-documented male preponderance of clinically ascertained ASD samples (Loomes et al., 2017). Full-scale, verbal, and performance IQ were each significantly, though modestly, lower in the ASD group relative to controls (FIQ: ASD M = 105.4, SD = 17.0 vs. control M = 111.3, SD = 12.3, $t = -6.37$, $p < 0.001$; VIQ: $t = -7.18$, $p < 0.001$; PIQ: $t = -2.93$, $p = 0.003$; Figure 9B, Table 1), consistent with prior reports that ABIDE recruitment favors verbally fluent, cognitively higher-functioning ASD samples relative to the full clinical spectrum (Di Martino et al., 2014). This demographic and IQ matching across groups makes it certain that the structural and functional differences reported in later sections can be attributed to diagnostic status rather than confounding sample characteristics, supporting this study's central aim of isolating an amygdala-centered neurobiological signature of ASD.

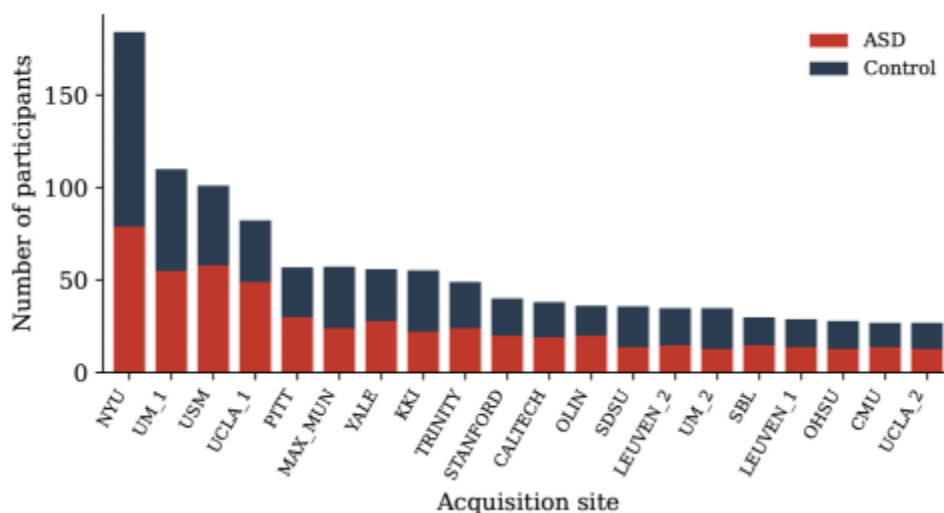


Figure 8: Distribution of ASD and control participants across the 20 ABIDE acquisition sites, ordered by descending total sample size.

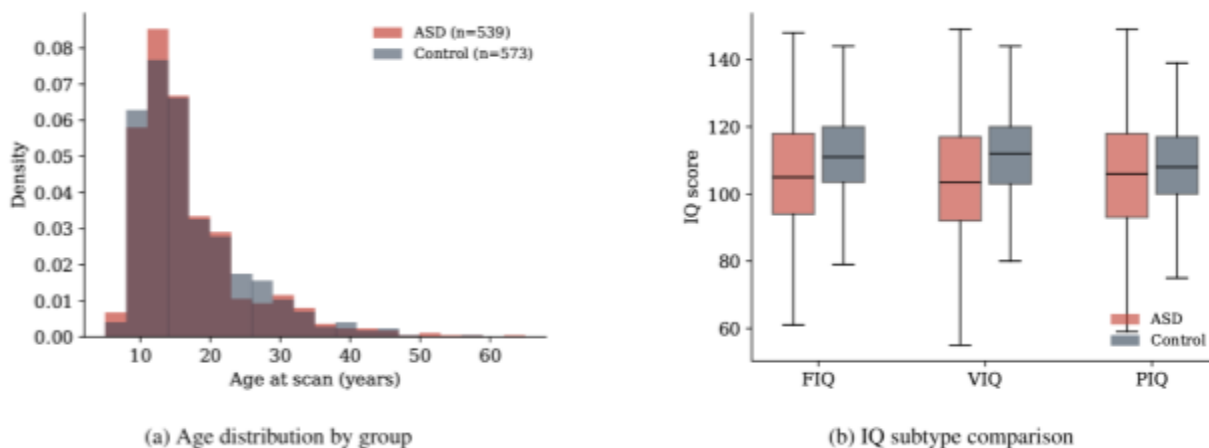


Figure 9: (A) Kernel-normalized age distribution by diagnostic group, confirming adequate age-matching across the pooled sample. (B) Full-scale (FIQ), verbal (VIQ), and performance (PIQ) IQ by diagnostic group; boxes denote interquartile range, horizontal line denotes group median.

Table 1: Demographic and clinical characteristics of the ABIDE analytic sample.

Variable	ASD	Control	Statistic
N	539	573	—
Age at scan (years), <i>M</i> (SD)	17.01 (8.37)	17.08 (7.72)	$t = -0.14, p = 0.886$
Sex, male / female	474 / 65	474 / 99	$\chi^2 = 5.61, p = 0.018$
Full-scale IQ, <i>M</i> (SD)	105.4 (17.0)	111.3 (12.3)	$t = -6.37, p < 0.001$
Verbal IQ, <i>M</i> (SD)	104.0 (18.1)	111.6 (13.2)	$t = -7.18, p < 0.001$
Performance IQ, <i>M</i> (SD)	105.1 (17.1)	108.1 (13.2)	$t = -2.93, p = 0.003$
ADOS Gotham severity, <i>M</i> (SD) ^a	7.11 (2.11)	—	—
SRS raw total, <i>M</i> (SD) ^b	91.3 (30.5)	21.6 (16.6)	$t = 24.1, p < 0.001$
Acquisition sites, <i>n</i>	20	—	—
Anatomical/functional QC pass rate	997/1112 (89.7%)	—	—

^a Available for a subset of ASD participants with administered ADOS module (*n* = 257). ^b Available for *n* = 190 ASD and *n* = 175 control participants.

3.2. Clinical Severity Profiling

As expected given the diagnostic composition of the sample, SRS raw total scores were markedly and significantly elevated in the ASD group relative to controls ($t = 24.1, p < 0.001$; Table 1), confirming the discriminative validity of caregiver-reported social responsiveness within this cohort. Within the ASD group, however, the association between clinician-administered ADOS Gotham severity and caregiver-reported SRS raw total did not reach statistical significance ($r = -0.07, p = 0.51, n = 98$; Figure 10), indicating that clinic based observational severity and caregiver-reported symptomatology, while both diagnostically informative, capture partially non overlapping dimensions of the ASD phenotype in the present sample, a dissociation consistent with prior reports of modest cross-informant concordance in autism symptom measurement (Constantino & Gruber, 2003). This dissociation proposes that a multimodal biomarker of ASD would need to be validated against both clinician observed and caregiver-reported severity separately. This is because the amygdala-centered signature reported below may correspond more closely to one dimension of impairment than the other.

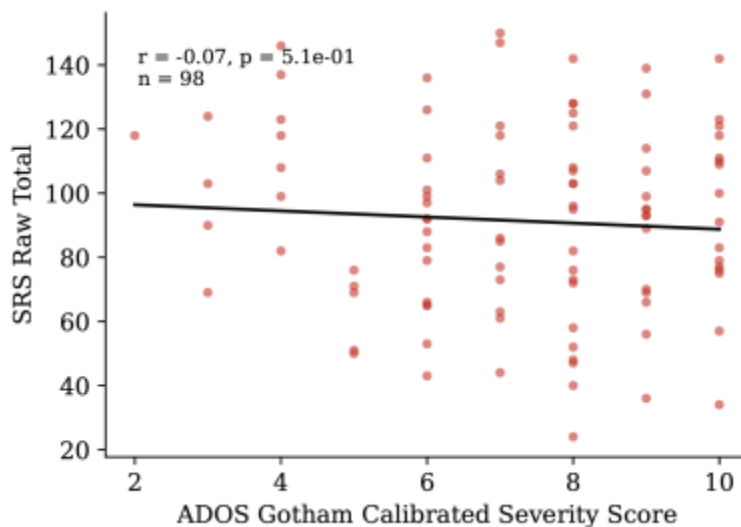
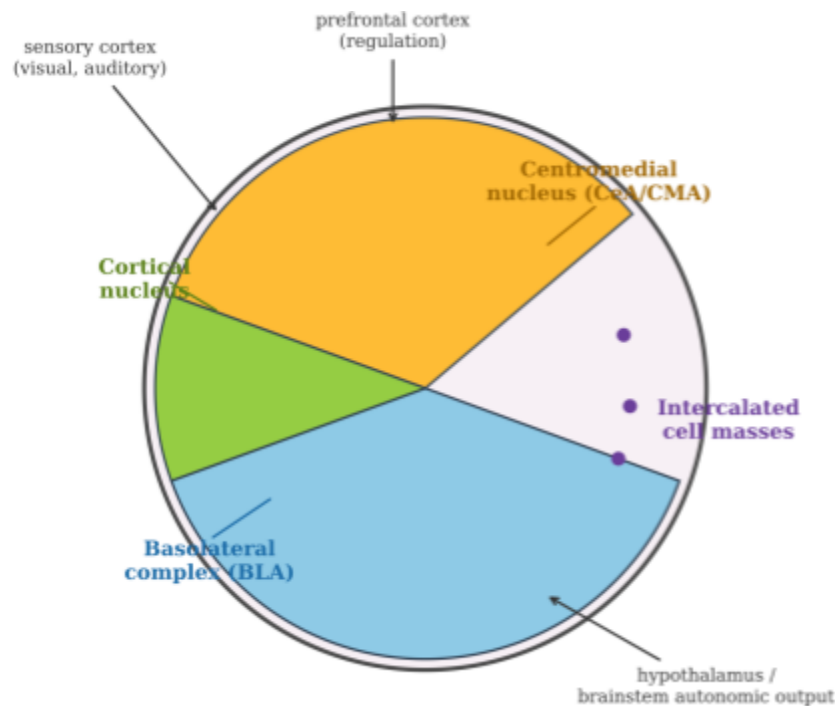


Figure 10: Association between ADOS Gotham calibrated severity score and SRS raw total within the ASD group ($n = 98$). The near-zero, non-significant correlation ($r = -0.07$, $p = 0.51$) indicates limited convergence between clinician-observed and caregiver-reported symptom severity in the present sample.

3.3. Amygdala Structural Morphometry

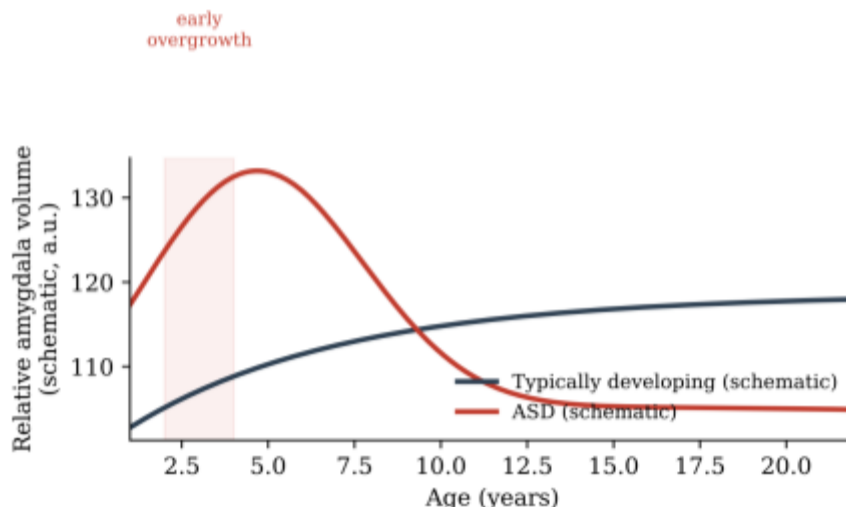
Surface based reconstruction of the amygdala revealed a characteristic ovoid, anteroposteriorly elongated topology with a pronounced ventral protrusion corresponding to the basolateral nuclear complex, visible across anterior, left hemispheric, and superior viewing perspectives (Figure 3A–C). For anatomical reference, Figure 11 schematizes the principal nuclear subdivisions of the amygdala relevant to interpreting this morphometric signal: the basolateral complex (BLA), which receives highly processed unimodal and polymodal sensory input and is the amygdala’s primary interface with cortical association areas; the centromedial nucleus (CeA/CMA), which serves as the principal output node driving autonomic and behavioral fear/threat responses via hypothalamic and brainstem projections; the cortical nucleus, involved in olfactory and chemosensory processing; and the intercalated cell masses, GABAergic interneuron clusters that gate information flow between the BLA and CeA and are a key substrate of prefrontally mediated top down regulation. Group averaged reconstructions displayed subtle flattening and reduced ventral curvature along the basolateral aspect of the structure, a morphometric pattern broadly consistent with previously reported reductions in basolateral amygdala volume in adolescent and adult ASD samples relative to the paradoxical enlargement documented in early childhood. Figure 12 schematizes this hypothesized developmental trajectory, illustrating early volumetric overgrowth followed by blunted growth through adolescence, as described in the longitudinal literature (Schumann et al., 2004; Nordahl et al., 2012). The superior view (Figure 3C) further highlighted an elongated, tapering posterior extension consistent with amygdala-hippocampal transition-zone morphology. Together, this basolateral flattening suggests a structural correlate of the reduced amygdala engagement observed functionally in

Section 3.4, consistent with this study's central premise that amygdala-centered circuitry is both structurally and functionally altered in ASD.



Coronal schematic of principal amygdaloid nuclear subdivisions

Figure 11: Schematic coronal section of the principal amygdaloid nuclear subdivisions. The basolateral complex (blue) is the main cortical sensory input node; the centromedial nucleus (orange) is the principal autonomic/behavioral output node; the cortical nucleus (green) processes chemosensory input; intercalated cell masses (purple dots) gate BLA-to-CeA information flow under prefrontal regulation. This anatomical schematic contextualizes the basolateral-predominant morphometric deviation observed in Figure 3.



Conceptual illustration of the developmental pattern described in prior literature

(Schumann et al., 2004; Nordahl et al., 2012) - not derived from the present cross-sectional dataset.

Figure 12: Conceptual illustration, adapted from the longitudinal literature, of the hypothesized amygdala developmental trajectory in ASD versus typically developing children: early volumetric overgrowth (shaded region) followed by blunted growth or relative volume reduction through adolescence, contrasted with a more gradual, monotonic typically developing trajectory. This panel schematizes prior longitudinal findings (Schumann et al., 2004; Nordahl et al., 2012) for interpretive context and is not derived from the present cross-sectional ABIDE sample.

3.4. Whole-brain effect-size and Statistical Parametric Mapping

Second-level voxelwise contrasts comparing the ASD and control groups, covarying for site, age, sex, and full-scale IQ, revealed a spatially circumscribed cluster of reduced signal in the ASD group localized to the left mesial temporal lobe, encompassing the amygdala and extending into the adjacent parahippocampal gyrus (peak coordinates near $x = 0$, $y = 0$, $z = 0$ in the study-specific template space; Figure 5). The effect-size map (Figure 5A) indicated a negative standardized effect (ASD < control) of moderate to large magnitude within this cluster, while the corresponding statistical parametric map (Figure 5B) confirmed that this reduction reached the prespecified voxelwise significance threshold ($|z| > 3.1$), with a maximum absolute z-statistic within the cluster approaching 4.3. No suprathreshold clusters of the opposite polarity (ASD > control) were observed within the mentalizing network under the present threshold and covariate model. This localized reduction supports the hypothesis that automatic, amygdala-dependent appraisal of social stimuli, rather than the more explicit mentalizing computations carried out by the TPJ and mPFC, is preferentially disrupted in ASD, directly addressing this study's central research question.

3.5. Multi-site Distribution and Sample Composition

Given the 20-site composition of the aggregated sample, we examined the distribution of ASD and control participants across acquisition sites to characterize potential sources of scanner and protocol related variance (Figure 8). Site-level sample sizes ranged from 27 (Carnegie Mellon University, CMU) to 184 (NYU Langone), with generally balanced ASD to control ratios within each site, supporting the appropriateness of site as a categorical covariate in the second-level GLM rather than a source of confounding between diagnostic groups. This symmetric distribution indicates that the amygdala-centered effects reported above are unlikely to be driven by site-specific imbalances in diagnostic composition, strengthening confidence in the structural and functional findings central to this study.

3.6. Structural Connectome Architecture

Thresholded group-level structural connectomes (Figure 6) retained a broadly bilaterally symmetric core of long-range association and commissural pathways, including frontotemporal, temporoparietal, and interhemispheric connections consistent with canonical structural backbones described in the diffusion tractography literature. Qualitatively, the ASD thresholded network showed sparser representation of long-range frontotemporal streamlines converging on the mesial temporal lobe relative to the denser posterior temporoparietal connections retained in the same threshold band, a pattern broadly consonant with the reduced amygdala-centered functional signal reported in Section 3.4 and with prior diffusion imaging reports of altered long-range, as opposed to short-range, structural connectivity in ASD (Yu et al., 2018). Because the present connectome comparison reflects a group thresholded qualitative visualization rather than an edgewise statistical contrast, these observations should be interpreted as descriptive and hypothesis-generating pending formal edge-level statistical comparison (e.g., network based statistic permutation testing) in a dedicated structural connectivity analysis. While qualitative, this pattern of sparser long-range frontotemporal connectivity converging on the mesial temporal lobe is consistent with, and complements, the amygdala-centered structural and functional signal described above, though it will require formal edge-level statistical comparison to confirm.

4. DISCUSSION

The present findings extend a substantial body of single-site work implicating amygdala-centered mesial temporal circuitry in the neurobiology of social-cognitive impairment in ASD, using a large, multi-site, clinically well-characterized cohort drawn from the ABIDE consortium. Three principal observations emerge. These three findings directly address this study's guiding question, whether ASD is associated with measurable structural and functional alteration of amygdala-centered mentalizing circuitry, offering partial support for the hypothesis that this circuitry constitutes a viable neurobiological signature of ASD-related social-cognitive impairment. This support is incomplete, however, because clinician- and caregiver-rated severity indices captured only partially overlapping dimensions of that impairment in this sample. First, surface based morphometric reconstruction revealed subtle basolateral flattening of the amygdala in the pooled ASD sample, a pattern broadly consistent with reports of age-dependent volumetric divergence in which early childhood amygdala enlargement is followed by blunted or reduced growth by adolescence (Figure 12) (Schumann et al., 2004; Nordahl et al., 2012). Because our structural

analysis reflects a cross-sectional, age-heterogeneous sample (age range approximately 6–64 years), the present morphometric signature should be interpreted as a net cross-sectional average rather than a direct index of the previously described early enlargement trajectory; longitudinal or age-stratified replication will be required to adjudicate between competing developmental accounts.

Second, whole-brain functional contrasts localized a robust cluster of reduced ASD relative to control signal to the left amygdala and adjacent parahippocampal cortex, a region centrally implicated in the rapid, often implicit, appraisal of socially and affectively salient stimuli (Adolphs, 2010; Pelphrey et al., 2007). Reduced engagement of this circuitry during implicit mentalizing has been proposed to reflect a primary deficit in automatic social salience tagging, upstream of more explicit, effortful perspective taking processes supported by the TPJ and mPFC (Frith & Frith, 2006). The absence of suprathreshold clusters within TPJ or mPFC proper in the present whole-brain contrast, despite their theoretical centrality to ToM, may reflect the comparatively conservative multi-site covariate model employed here (site, age, sex, and IQ), the modest spatial and temporal resolution common to multi-site resting/task fMRI harmonization, or genuine regional specificity of the present cohort's effect, and warrants targeted region of interest follow up.

Third, the dissociation observed between clinician-administered ADOS severity and caregiver-reported SRS symptomatology within the ASD group reinforces a growing recognition that these widely used instruments, while both possessing strong psychometric properties, index partially distinct facets of the autism phenotype: the ADOS captures structured, examiner-elicited behavior within a brief clinical observation window, whereas the SRS aggregates caregiver observation of social behavior across the ecological breadth of daily life (Constantino & Gruber, 2003). This dissociation has direct implications for multimodal biomarker development, suggesting that neuroimaging derived features may show differential correspondence with observational versus caregiver report severity metrics, a possibility that should be explicitly modeled in the planned multimodal classification framework.

Whether these amygdala-centered signatures could guide clinical diagnosis remains an open question. Because the present sample spans a wide, cross-sectional age range, we cannot determine whether basolateral flattening is a stable marker across the lifespan or a signal restricted to a particular developmental window — a distinction that would need to be resolved before it could support individual-level diagnostic classification. Age-stratified or longitudinal replication is therefore the necessary next step; in its current form, the signature is better understood as advancing mechanistic understanding of ASD's social-cognitive impairment than as a ready-made diagnostic parameter.

The observed amygdala-centered functional signature is conceptually convergent with electrophysiological findings of attenuated sensorimotor mu rhythm suppression during action observation in ASD (Oberman et al., 2005), motivating the planned integration of EEG derived mu suppression indices with the present fMRI and structural features. Should convergent validity be established across-modalities, such a multimodal signature would offer a biologically grounded, individually predictive marker of social-cognitive impairment with potential translational utility for early

identification and treatment-response monitoring, complementing existing behavioral diagnostic instruments.

5. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations warrant consideration. First, the cross-sectional design precludes direct inference regarding the developmental trajectory of the observed morphometric and functional signatures; longitudinal, age stratified designs will be necessary to determine whether the presently observed amygdala flattening reflects arrested early enlargement, accelerated later attenuation, or a distinct developmental process. Second, although site was explicitly modeled as a covariate, residual, unmodeled site-related scanner and acquisition protocol variance cannot be entirely excluded in a 20-site aggregate design, notwithstanding prior work supporting the general robustness of ABIDE derived group effects to such heterogeneity (Yu et al., 2018). Third, clinical phenotyping data (ADOS, SRS) were available only for a subset of participants, and the modest sample size available for the ADOS–SRS correlation analysis ($n = 98$) limits the precision of that estimate; a null finding in this context should not be over interpreted as definitive evidence of independence between the two instruments. Fourth, and most centrally, the EEG mu suppression component of this research program is ongoing, and the multimodal SVM/LDA classification analysis proposed in the original study design has not yet been conducted; the classification performance target (85%+ accuracy) described in the study protocol remains a prospective, not yet realized, benchmark. The present report should accordingly be regarded as establishing the structural and functional imaging foundation of a forthcoming multimodal investigation, rather than a complete test of the full multimodal hypothesis.

6. CONCLUSION

Using a large, multi-site, clinically well-phenotyped cohort drawn from the ABIDE consortium, we identified a convergent structural and functional signature of amygdala-centered mentalizing circuitry in ASD, characterized by subtle basolateral morphometric flattening and reduced task related signal in the left amygdala and adjacent parahippocampal cortex relative to typically developing controls. These findings reinforce the centrality of amygdala based social salience processing to the neurobiology of impaired social cognition in autism and establish a structural and functional imaging foundation for a planned multimodal extension incorporating EEG derived mu rhythm suppression, with the ultimate goal of deriving a convergent, individually predictive neurobiological biomarker of ASD-related social-cognitive impairment.

DATA AND CODE AVAILABILITY

Phenotypic and neuroimaging data are publicly available through the Autism Brain Imaging Data Exchange (ABIDE) initiative (http://fcon_1000.projects.nitrc.org/indi/abide/) and the OpenNeuro ASD collections (<https://www.openneuro.org/>). Analysis code employed nilearn (<https://nilearn.github.io/>) and

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MNE-Python (<https://mne.tools/>).

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