

1 What is the best brain state to predict autistic traits?

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1 **Abstract**

2 Autism is a heterogeneous condition, and functional magnetic resonance imaging-based studies
3 have advanced understanding of neurobiological correlates of autistic features. Nevertheless,
4 little work has focused on the optimal brain states to reveal brain-phenotype relationships. In
5 addition, there is a need to better understand the relevance of attentional abilities in mediating
6 autistic features. Using connectome-based predictive modelling, we interrogate three datasets to
7 determine scanning conditions that can boost prediction of clinically relevant phenotypes and
8 assess generalizability. In dataset one, a sample of youth with autism and neurotypical
9 participants, we find that a sustained attention task (the gradual onset continuous performance
10 task) results in high prediction performance of autistic traits compared to a free-viewing social
11 attention task and a resting-state condition. In dataset two, we observe the predictive network
12 model of autistic traits generated from the sustained attention task generalizes to predict
13 measures of attention in neurotypical adults. In dataset three, we show the same predictive
14 network model of autistic traits from dataset one further generalizes to predict measures of social
15 responsiveness in data from the Autism Brain Imaging Data Exchange. In sum, our data suggest
16 that an in-scanner sustained attention challenge can help delineate robust markers of autistic
17 traits and support the continued investigation of the optimal brain states under which to predict
18 phenotypes in psychiatric conditions.

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1 **Introduction**

2 Autism spectrum disorder (referred to as “autism” hereafter) affects approximately 1% of
3 children around the world¹ and is characterized by difficulties with social communication and
4 interaction, restricted and repetitive behaviors, and sensory atypicalities². There is a need to
5 better appreciate the neurobiological correlates of autistic traits in youth, which will help
6 improve understanding of the condition and might aid potential clinical utility. Furthermore,
7 there is a growing movement to characterize conditions like autism along dimensions of
8 function³⁻⁷.

9 There are numerous approaches to characterize the brain-based correlates of autism traits
10 using functional magnetic resonance imaging (fMRI) connectivity data, in which measures of
11 similarity of the blood-oxygen-level-dependent (BOLD) signal are computed between different
12 regions of interest⁸. In particular, prediction-based studies—using functional connectivity data to
13 predict a phenotype—have proven promising. For instance, case-control studies have focused on
14 classifying those with autism compared to neurotypical participants, showing that high prediction
15 accuracy can be achieved on the basis of functional connectivity differences⁹⁻¹⁸. Another
16 approach predicts continuous measures of a phenotype (a symptom scale or a behavioral test
17 score)¹⁸⁻²¹. One method of dimensional prediction is connectome-based predictive modelling
18 (CPM)^{22,23}, which seeks to identify the functional connections most strongly predictive of a
19 given phenotype. Groups using CPM in autism samples have identified brain-behavior correlates
20 of clinician-rated autism symptoms^{24,25}, and other traits, such as behavioral inhibition²⁶, social
21 responsiveness^{24,27}, and attentional states²⁸.

22 Nevertheless, which conditions yield the best predictive modeling performance is still
23 largely understudied. Most studies have typically focused on resting-state fMRI, in which

1 participants rest quietly in the scanner. However, in neurotypical participants, the importance of
2 scanning condition (e.g., ‘brain state’) is being recognized²⁹⁻³² for prediction of various
3 phenotypes, including intelligence³³⁻³⁵, attention^{36,37}, working memory^{38,39}, personality traits⁴⁰,
4 cognition and emotion scores⁴¹, as well as for emphasizing individual differences in connectivity
5 patterns⁴². These studies suggest that predicting out-of-scanner phenotypes using connectivity
6 measured during task performance tend to increase prediction accuracy particularly when the
7 task probes some aspect of the out-of-scanner item of interest (e.g., memory tasks in the scanner
8 tend to result in higher prediction of memory performance outside the scanner³⁸).

9 In addition, there are a number of elegant studies showing that in-scanner attention tasks
10 can be used to inform the neurobiological organization of autism⁴³⁻⁴⁷. There are also other brain
11 imaging studies suggesting an overlap between the functional networks mediating ADHD and
12 autism^{24,48}. At a behavioral level, the co-occurrence of autism and attention-deficit/hyperactivity
13 disorder (ADHD) symptoms has long been acknowledged⁴⁹⁻⁵².

14 Motivated by the importance of tasks in assessing phenotypes, as well as the importance
15 of attention in autism, here we consider brain state-associated improvements in prediction
16 performance in a sample of youth with autism and neurotypical participants. Using data from
17 three different scanning conditions—a task requiring sustained attention, a task requiring
18 selective social attention (SSA), and resting-state data—we applied CPM to probe brain-behavior
19 relationships. Specifically, the gradual onset continuous performance task (gradCPT)^{36,53,54} tests
20 the ability to sustain attention to constantly changing stimuli. The SSA task captures ability to
21 process dynamic, multimodal faces within a complex visual scene, which represents one of the
22 best replicated eye-tracking biomarkers in autism⁵⁵⁻⁵⁹. The task was designed such that speech

1 (SP) and eye contact (EC) were varied, allowing us to assess the effect of each condition on
2 prediction performance.

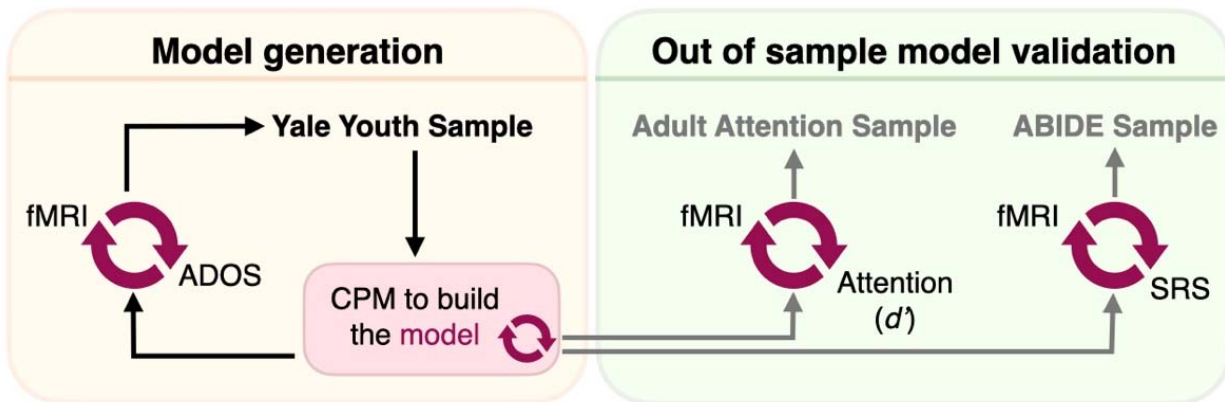
3 We hypothesized that consistent with the social features of autism, prediction
4 performance of autistic traits would be highest in the SSA task and would increase with the
5 presence of increased social cues. Specifically, we expected that the condition containing both
6 eye contact and speech (EC+SP+) would yield the strongest prediction performance. We
7 hypothesized that the next highest prediction performance would result from the sustained
8 attention task, due to the restricted and repetitive behaviors observed in autism, and that both
9 tasks would outperform resting-state data. To determine if results were robust, we used two other
10 datasets to determine if successful models can generalize to external samples. One of the datasets
11 was used to assess the model's generalizability in predicting performance on an attention task;
12 the other dataset was used to assess prediction of other autistic features.

13

14 **Results**

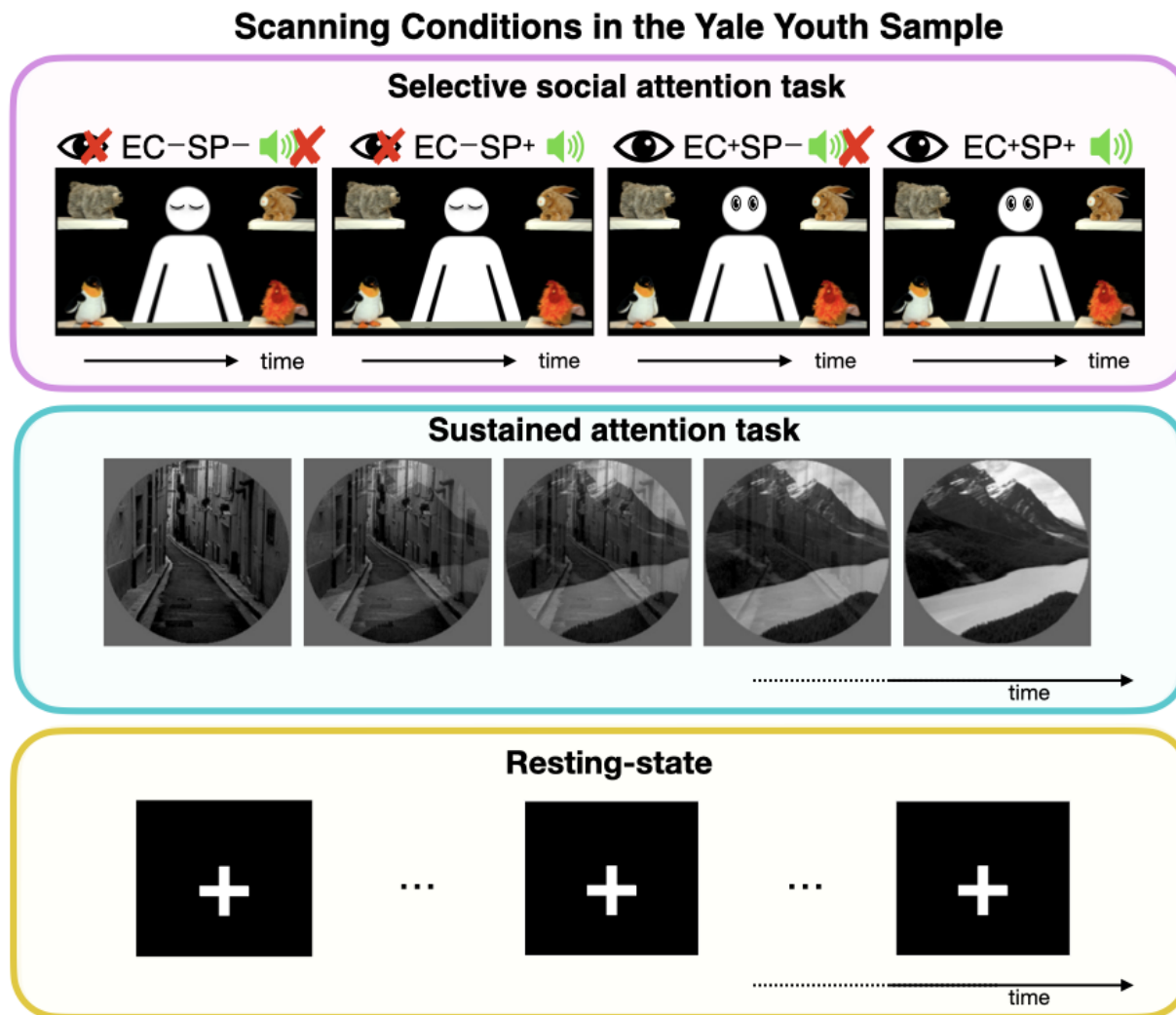
15 *Overview*

16 Three samples were used in this work (Figure 1). The first dataset comprised 63 subjects
17 from a sample described previously (mean age = 11.7 years, st. dev. = 2.8 years; 29 females;
18 mean IQ = 107.8, st. dev. = 15.1)^{28,60}. Twenty participants had autism; 11 other participants had
19 a neurodevelopmental condition (five had attention-deficit/hyperactivity disorder (ADHD), two
20 had anxiety disorder, and four were classified as belonging to the broader autism phenotype)⁶¹.
21 Hereafter, we refer to this dataset as the “Yale youth sample.” Autism symptoms were scored
22 using the Autism Diagnostic Observation Schedule-2 (ADOS-2)⁶².



1
2 Figure 1. An overview of the datasets used in this study. The Yale youth sample was the first
3 dataset used. FMRI connectivity data from different scanning conditions (task and rest) were
4 used to generate connectome-based predictive models of Autism Diagnostic Observation
5 Schedule (ADOS) scores (red circular arrows denote a brain-behavior predictive model). A
6 summary predictive model was then generated and applied to the adult attention sample. The
7 goal of this step was to determine whether the model generalized to predict attention phenotypes
8 (d') in an external dataset. The summary model was also applied to ABIDE to determine if the
9 model predicted SRS scores in an external sample. ABIDE, autism brain imaging data exchange;
10 ADOS, Autism Diagnostic Observation Schedule; CPM, connectome-based predictive model; d' ,
11 d-prime (attention phenotype in the Adult Attention Sample); SRS, social responsiveness scale.
12

13 Participants in the Yale youth sample completed three different scanning conditions
14 (Figure 2; see Methods for further description of each task). We note that the SSA clips were
15 counterbalanced across participants; the other scan conditions were not (Supplemental Materials;
16 Supplemental Figure 1). A standard preprocessing approach was used to generate
17 connectomes^{33,63-65} from the different scanning conditions using a 268-node atlas²². For each
18 subject, the mean time-course of each region of interest (“node” in graph theory) was computed,
19 and the Pearson correlation coefficient was calculated between each pair of nodes to achieve a
20 symmetric 268 x 268 matrix of correlation values representing “edges” (connections between
21 nodes) in graph theory. The Pearson correlation coefficients were then transformed to z -scores
22 via a Fisher transformation, and only the upper triangle of the matrix was considered, yielding
23 35,778 unique edges.



1
2 Figure 2. A schematic showing the scanning conditions used in the Yale youth sample. Top
3 panel: free-viewing selective social attention task. Four conditions were shown to participants:
4 no eye contact, no speech (EC-SP-); no eye contact, with speech (EC-SP+); eye contact, with no
5 speech (EC+SP-); and eye contact, with speech (EC+SP+). Note we have obscured the actress in
6 the preprint version for confidentiality. Middle panel: the gradual onset continuous performance
7 task (gradCPT) was used as a sustained attention task. Grayscale pictures of cities and mountains
8 were presented with images gradually transitioning from one to the next; button presses were
9 required for city scenes and withheld for mountain scenes. Bottom panel: resting-state condition,
10 in which the participants viewed a fixation cross. Please see the Methods section for further
11 details about each scanning condition.
12

13 Prediction performance is highest in the Yale youth sample using task data

14 We first assessed which scanning condition resulted in the highest prediction
15 performance of autistic traits in the Yale youth sample. To ensure consistent amounts of data

1 across scanning conditions, we discarded frames from the end of gradCPT and resting-state runs,
2 such that the total amount of data was the same as from the Selective Social Attention task runs
3 (four minutes of data). CPM²³ was then used to assess prediction performance of ADOS scores
4 (Supplemental Figure 2) and was repeated 500 times. Head motion was controlled for during
5 CPM as before^{28,66,67}. The median performing model is represented in the text below, as well
6 as prediction ranges where appropriate; significance was assessed via permutation testing
7 (Methods).

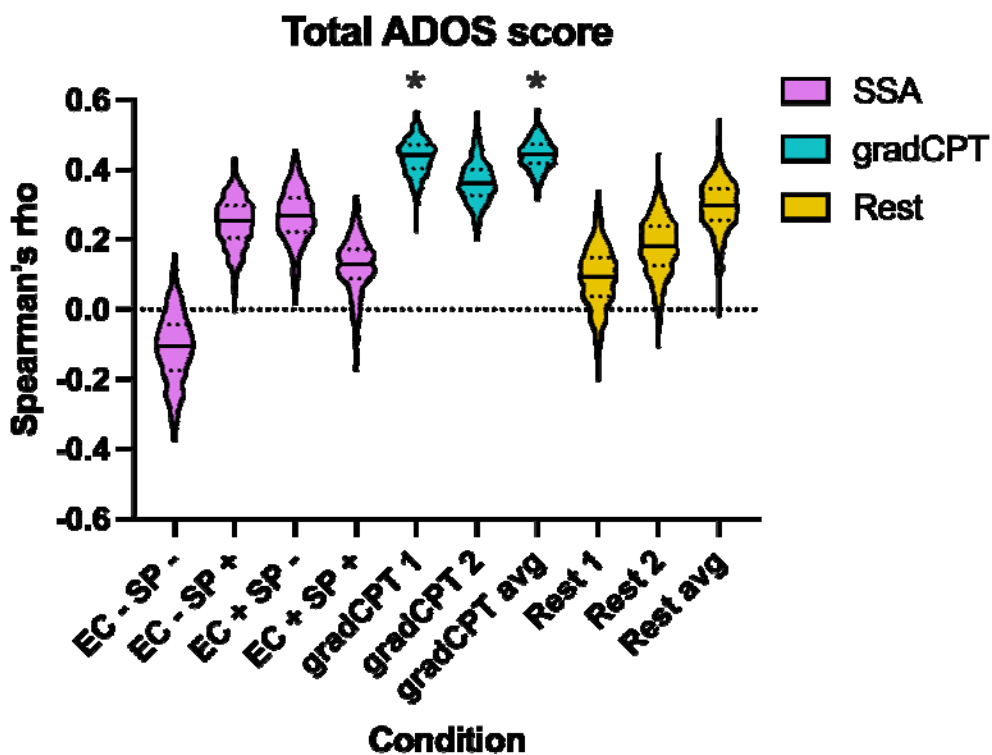
8 We found differential performance across the various task conditions (Figure 3;
9 Supplemental Table 1). For example, performance using the resting-state data was quite low
10 (rest 1, Spearman's rho = 0.093, *P*-value = 0.115; rest 2, Spearman's rho = 0.18, *P*-value =
11 0.062), and prediction performance was noted to have substantial variance (i.e., using data
12 from resting-state run 1, the minimum Spearman's rho = -0.2017, maximum Spearman's rho =
13 0.337, with 15% of the prediction performance scores below zero). Performance was also
14 quite low in the SSA condition with no eye contact and no speech (EC-SP-; Spearman's rho =
15 -0.106, *P*-value = 0.41). Surprisingly, there was large variance in prediction performance
16 scores using the SSA condition with eye contact and speech (EC+SP+; minimum Spearman's
17 rho = -0.172; maximum Spearman's rho = 0.323, with 7.2% of the prediction performance
18 scores below zero). Prediction performance was higher in the other SSA conditions, but was
19 not statistically significant after correcting for multiple comparisons (EC+SP-: Spearman's
20 rho = 0.251, *P*-value = 0.026; EC-SP+: Spearman's rho = 0.266, *P*-value = 0.017). The only
21 condition that resulted in statistically significant brain-behavior predictions was gradCPT 1
22 (Spearman's rho = 0.441, *P*-value = 0.002, corrected). See Supplemental Table 1 for statistics
23 for all CPM analyses.

1 Prediction performance has been noted to increase with increasing amounts of data⁶⁸,
2 possibly due to an increase in reliability of functional connectivity estimates⁶⁹⁻⁷¹. We tested
3 this possibility by combining data from gradCPT 1 and gradCPT 2, as well as resting-state
4 session 1 and resting-state session 2. More data led to a slight increase in prediction
5 performance using both gradCPT and rest (Figure 3), though only gradCPT prediction
6 performance was statistically significant after multiple comparisons correction (gradCPT
7 average: Spearman's rho = 0.445, P -value = 0.001, corrected; rest average: Spearman's rho =
8 0.296, P -value = 0.019).

9 To ensure results were internally consistent, we repeated the CPM analysis using a
10 multiverse approach, which assesses how results are affected by different analytical choices⁷².
11 The point of this approach is not to determine what CPM pipeline results in the highest
12 prediction performance. Instead, the goal is to assess various analytical scenarios and
13 determine how arbitrary modelling choices impact CPM performance. In the Yale youth
14 sample, we first adjusted CPM models for age, sex, and IQ. Encouragingly, we found similar
15 results to that above: gradCPT results in the highest prediction performance; the SSA task
16 with no eye contact and no speech results in the lowest (Supplemental Table 2). The other
17 SSA task conditions did not tend to result in high predictions; rest performance was also low.

18 We continued with the multiverse analysis and repeated CPM using the same pipeline
19 as above, except instead of predicting total ADOS scores, we attempted to predict the social
20 affect and the restricted and repetitive behaviors subscales of the ADOS. We observed the
21 same overall trend—gradCPT tends to result in the highest prediction performance and the
22 resting-state and SSA task with no eye contact and no speech performed the poorest
23 (Supplemental Figure 3; Supplemental Table 1). Interestingly, the SSA tasks resulted in

1 increased prediction performance of social affect scores, but predictions were not significant
2 after controlling for multiple comparisons. Prediction performance of restricted and repetitive
3 behaviors using the SSA data tended to be low. (Note that we continued with the multiverse
4 approach below when assessing generalizability; see ‘Testing generalizability of the ADOS
5 network’ in the Methods for a full description of all parameters tested in the multiverse analysis.)
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9 Figure 3. CPM prediction performance across different scanning conditions for total ADOS
10 scores. The scan condition is shown on the x-axis; on the y-axis, Spearman's rho is shown for
11 the correlation of predicted and actual ADOS scores. For each condition, the median of the
12 500 iterations is shown as a solid black line in the violin plot; quartiles, as dotted lines. The
13 Selective Social Attention task conditions are shown in purple, gradCPT in turquoise, and
14 resting-state data in yellow. Asterisk (*) indicates statistical significance after correcting for
15 multiple comparisons. ADOS, autism diagnostic observation schedule; Avg, average; EC-SP-,
16 no eye contact, no speech; EC-SP+, no eye contact, with speech; EC+SP-, eye contact, with no
17 speech; EC+SP+, eye contact, with speech; mm, millimeters; SSA, selective social attention
18 task.

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2 *External validation of predictive models—attention prediction in the adult attention sample*

3 Having determined that data derived from attention tasks are best for predicting
4 autistic traits, we next assessed generalizability of the attention predictive model. Previously,
5 we have shown it is possible to build predictive models of sustained attention in the Yale
6 youth sample and that such a model is related to autistic traits²⁸. Therefore, we assessed the
7 extent to which predictive models of autistic traits are related to sustained attention. To ensure
8 generalizability was not driven by sample-specific noise, we tested the predictive model in an
9 external dataset of individuals performing the same gradCPT task (n=25 neurotypical adults,
10 13 females, mean age = 22.8 years, st. dev. = 3.5 years)³⁶. Hereafter, we refer to this dataset as
11 the “adult attention sample” (Figure 1). The behavioral outcome of interest in this sample is
12 performance on the gradCPT, d' (sensitivity), the participant’s hit rate minus false alarm rate
13 (mean d' = 2.11, st. dev. = 0.92).

14 We determined which edges tended to contribute consistently to successful prediction
15 of ADOS phenotypes in the Yale youth sample (see Methods, ‘Testing generalizability of the
16 ADOS network’) using the model generated from average gradCPT data in the prediction of
17 total ADOS scores. The resulting model (the ‘ADOS consensus network’) was used to
18 determine if there was a relationship between predicted ADOS scores and d' scores in the
19 adult attention sample. Specifically, we used the fMRI gradCPT task data from the adult
20 attention sample to generate a predicted ADOS score. Predicted ADOS scores were then
21 compared to actual d' scores across participants to assess accuracy. We point out this differs
22 from the Yale youth sample, where we were able to compare predicted ADOS scores with

1 observed ADOS scores. In the adult attention sample, the goal was to assess the relationship
2 between the model (trained to predict ADOS) and attention (d').

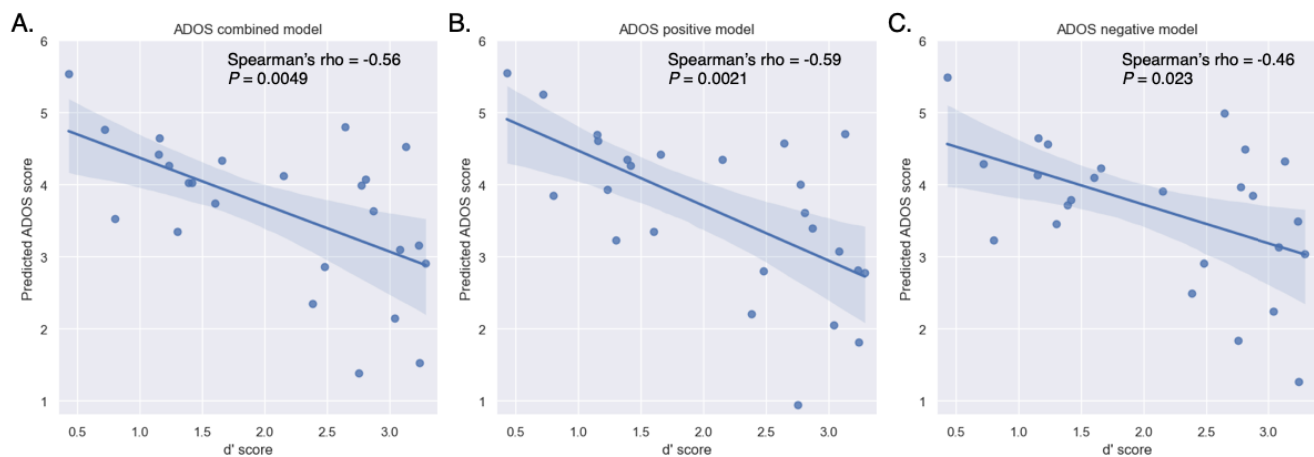
3 We observed a statistically significant relationship between predicted ADOS scores
4 and d' scores (Spearman's $\rho = -0.56$, $P = 0.0049$, corrected; Figure 4A). Specifically,
5 higher predicted ADOS scores were associated with lower d' scores, indicating poorer
6 performance on the task and implying lower sustained attention. To ensure results were
7 robust, we repeated analyses controlling for potential confounds; predictions remained high
8 when adjusting for participant head motion (Spearman's $\rho = -0.56$, $P = 0.0043$),
9 participant sex (Spearman's $\rho = -0.49$, $P = 0.0164$), and participant age (Spearman's
10 $\rho = -0.55$, $P = 0.0066$). In addition, we also assessed the relationship between predicted
11 ADOS scores and d' scores using only the ADOS positive network and then only the ADOS
12 negative network. We observed a statistically significant negative correlation in the ADOS
13 positive model (Spearman's $\rho = -0.59$, $P = 0.0021$, corrected; Figure 4B) and in the ADOS
14 negative model (Spearman's $\rho = -0.46$, $P = 0.023$, corrected; Figure 4C).

15 We also calculated combined network strength in the consensus networks and computed
16 correlations (Spearman) with d' in the adult attention sample. A statistically significant
17 relationship was observed between ADOS network strength and d' score (Spearman's $\rho = -$
18 0.58 , $P = 0.002$, corrected; Supplemental Figure 4A). Specifically, higher network strength in
19 the ADOS network is associated with a lower d' score, indicating poorer performance on the
20 task. In addition, a statistically significant negative correlation was also observed in the
21 ADOS positive model (Spearman's $\rho = -0.62$, $P = 0.001$, corrected; Supplemental Figure
22 4B) and a positive correlation in the ADOS negative model (Spearman's $\rho = 0.50$, $P =$

1 0.011, corrected; Supplemental Figure 4C), confirming that connectivity strength in the
2 consensus networks aligns with d' in the expected directions.

3 Lastly, we altered the stringency of how often an edge had to be included in the ADOS
4 consensus model (Methods). We observed consistent results across a range of thresholds
5 (Supplemental Table 3), increasing confidence that there is a relationship between ADOS
6 network strength and d' scores. In sum, these results suggest that the predictive model of
7 autistic traits captures variance related to sustained attention.

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10 Figure 4. Generalization of the ADOS consensus network in the adult attention sample. A.
11 Results using the combined network model. B. Results using the positive-association network
12 model. C. Results using the negative-association network model. Predicted ADOS scores are
13 indicated on the y-axis; d' scores, on the x-axis. Higher predicted ADOS scores are associated
14 with lower d' scores, indicating poorer performance on the task and implying lower sustained
15 attention. A regression line and 95% confidence interval are shown. ADOS, autism diagnostic
16 observation schedule; P = P -value.

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19 External validation of predictive models—social responsiveness prediction in ABIDE

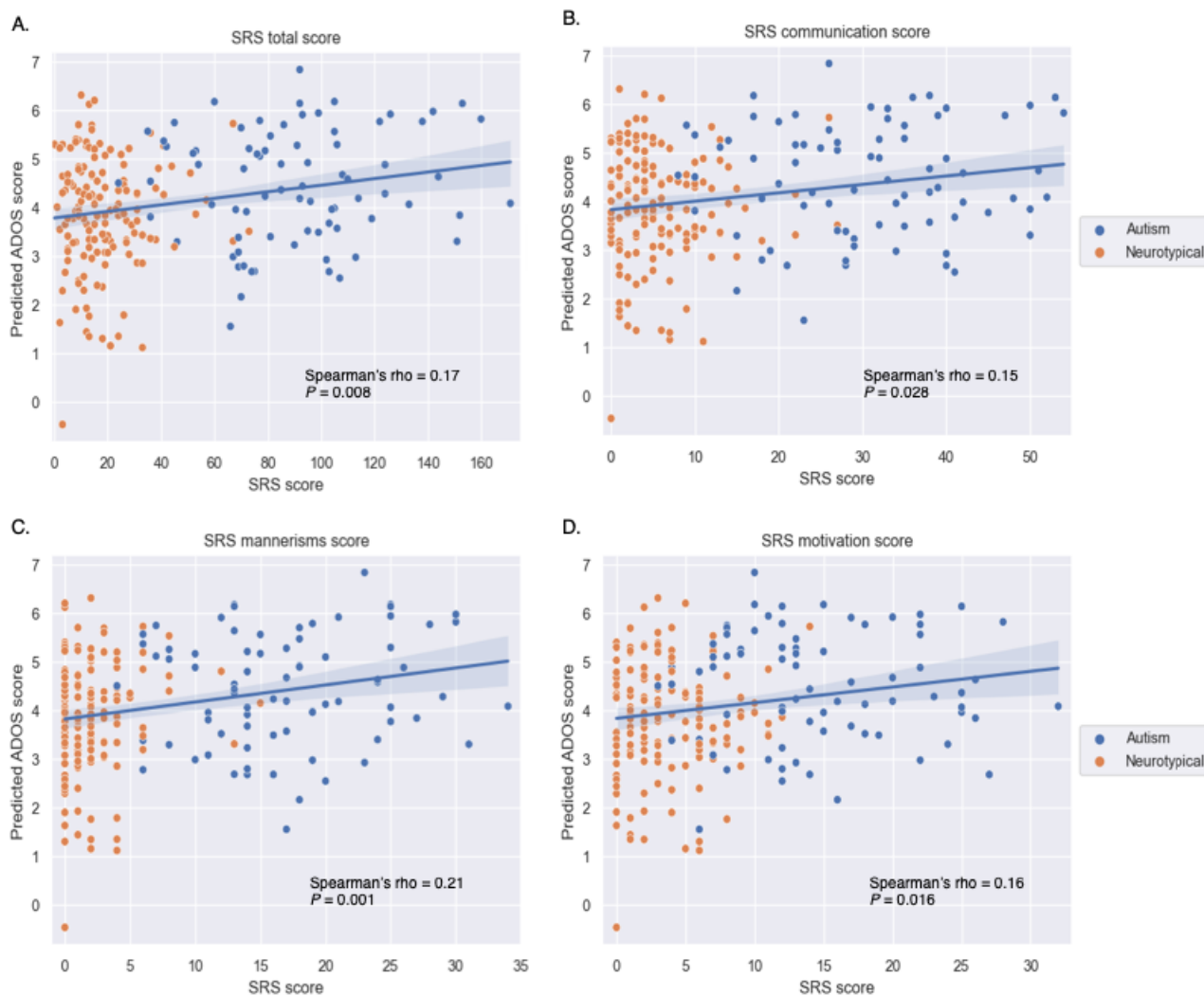
20 After finding we could successfully predict attention scores, we set out to determine if
21 the predictive model from the Yale youth sample generalized to predict social responsiveness
22 in a large sample of participants from ABIDE (n=229, 65 females; mean age = 10.45 years, st.

1 dev. = 1.8 years; mean IQ = 113.7, st. dev. = 15.1)^{73,74} described previously²⁴. We used the same
2 approach as in the adult attention sample to assess generalizability. Specifically, we used the
3 resting-state data from ABIDE and applied the ADOS consensus model to predict social
4 responsiveness scale (SRS) scores⁷⁵ across participants (Methods). As with the other test of
5 generalizability above, predicted ADOS scores were then compared to actual SRS scores to
6 assess accuracy.

7 We observed successful prediction of all SRS scales tested (Figure 5). In particular,
8 the model generalized to predict SRS total scores (Spearman's $\rho = 0.17$, $P = 0.008$,
9 corrected, Figure 5A), as well as SRS subscales quantifying communication (Spearman's
10 $\rho = 0.15$, $P = 0.028$, corrected, Figure 5B), mannerisms (Spearman's $\rho = 0.21$,
11 $P = 0.001$, corrected, Figure 5C), and motivation (Spearman's $\rho = 0.16$, $P = 0.016$,
12 corrected, Figure 5D). We also tested prediction of each SRS scale after adjusting for
13 participant age, sex, and head motion; predictions were essentially unchanged, further
14 supporting that the ADOS model is capturing variance related to the SRS scales
15 (Supplemental Table 4).

16 As above, we altered how often an edge had to be included in the ADOS CPM and
17 retested predictions. In every case, we observed similar predictions across various thresholds
18 for all SRS scales (Supplemental Table 5). Taken together, these data indicate the ADOS
19 model from the Yale youth sample generalizes to predict aspects of sociality in ABIDE.

1



2 Figure 5. Generalization of the ADOS consensus network to ABIDE. A. SRS total score
3 results. B. SRS communication score results. C. SRS mannerism score results. D. SRS
4 motivation score results. For all plots, actual SRS scores from each subscale are indicated on
5 the x-axis; predicted scores, on the y-axis. A regression line and 95% confidence interval are
6 shown. ADOS, autism diagnostic observation schedule; $P = P$ -value; SRS, social
7 responsive scale.

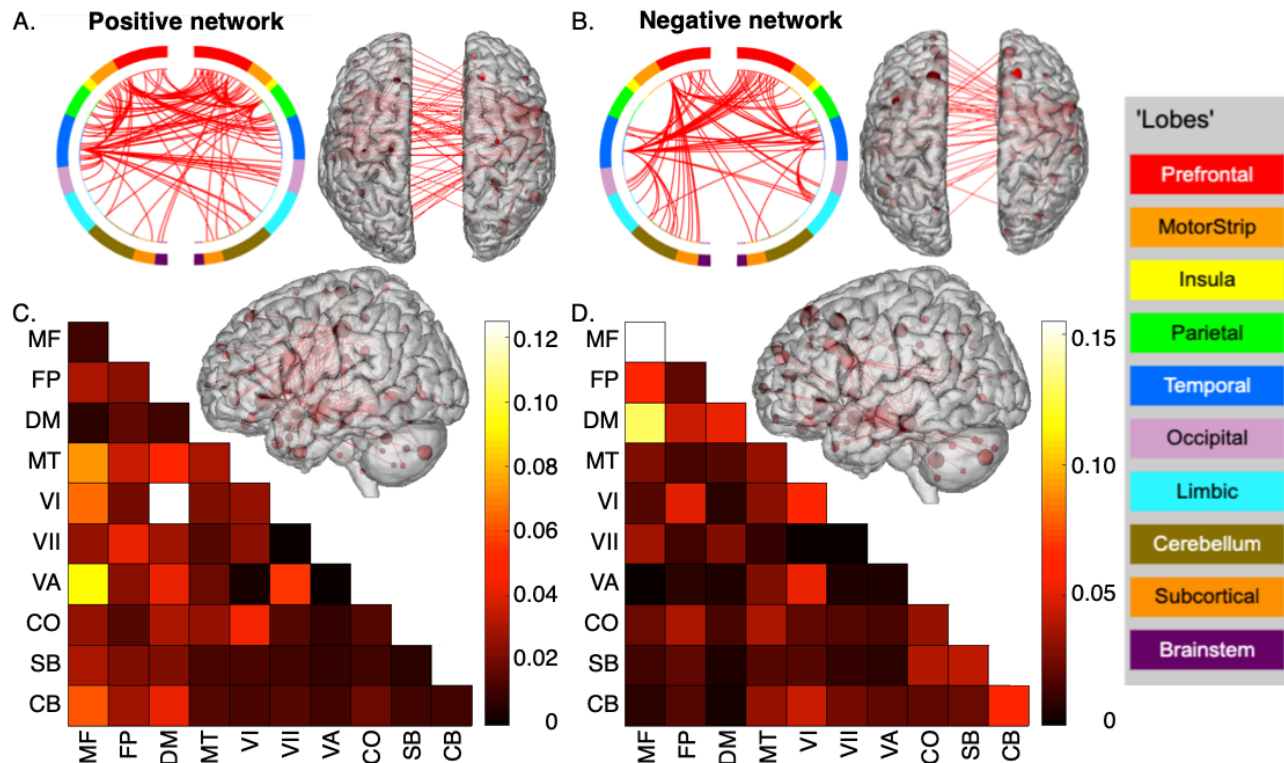
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9 Neuroanatomy of predictive edges

10 Finally, we visualized brain connections in the ADOS consensus model. The network
11 comprised 2,014 total edges (1,001 edges in the positive-association and 1,013 edges in the
12 negative-association network), approximately 5.6% of the connectome. Edges across the brain

1 were represented in the model, constituting a complex, distributed network (Figure 6A-B). In
2 particular, connections within and between heteromodal association networks were found to
3 contain the highest fraction of edges (Figure 6C-D; note that results have been corrected for
4 differing network size)²⁸. For instance, the top three network pairs containing the greatest
5 proportion of edges in the positive-association network involved medial frontal, frontoparietal, or
6 default mode networks. In the negative-association network, the top three network pairs involved
7 connections within and between medial frontal, frontoparietal, or default mode networks (e.g., in
8 this case, the top network pair comprised connections within the medial frontal network; the next
9 highest network comprised connections between the medial frontal and frontoparietal networks;
10 and the third highest network connected the medial frontal and default mode networks). In
11 addition, 704/1001 of the edges in the positive-association network and 535/1013 of the edges
12 connected to medial frontal, frontoparietal, or default mode networks. We performed further
13 visualizations using slightly different thresholding techniques; these analyses again showed
14 that association networks were important in the ADOS consensus model (Supplemental
15 Figure 5).
16

1



2 Figure 6. Neuroanatomy of ADOS consensus network. A. The positive-association network.
 3 B. The negative-association network. For both A and B: a circle plot is shown in the upper left.
 4 The top of the circle represents anterior; the bottom, posterior. The left half of the circle plot
 5 corresponds to the left hemisphere of the brain. A legend indicating the approximate anatomic
 6 'lobe' is shown to the left. The same edges are plotted in the glass brains as lines connecting
 7 different nodes (red circles); in these visualizations, nodes are sized according to degree, the
 8 number of edges connected to that node. To aid in visualization, we have thresholded the
 9 matrices to only show nodes with a degree threshold > 25. C. Matrix of the positive-association
 10 network. D. Matrix of the negative-association network. For both C and D: The proportion of
 11 edges in a given network pair is shown; data have been corrected to account for differing
 12 network size. MF, medial frontal; FP, frontoparietal; DM, default mode; MT, motor; VI,
 13 visual I; VII, visual II; VA, visual association; CO, cingulo-opercular; SB, subcortical; CB,
 14 cerebellum.
 15

16 Discussion

17 We determined that using functional connectivity calculated from data acquired during
 18 gradCPT resulted in the prediction of autistic traits and generalized to independent samples to
 19 predict attention and social phenotypes in neurotypical participants and those with autism.

1 Altogether, results highlight the potential of using in-scanner tasks, particularly those demanding
2 sustained attention, to more accurately determine brain-behavior relationships in clinical
3 samples.

4 There is a rich history of using tasks to probe the cognitive architecture of autism⁷⁶⁻⁸¹.
5 Nevertheless, most fMRI brain-behavior prediction studies in autism that use machine learning
6 techniques have typically relied on resting-state data (see⁴ for a recent review). Our results
7 suggest that by optimizing the brain state under which data are acquired through task
8 engagement⁸², more accurate brain-behavior relationships can be studied²⁹. Improved brain-
9 behavior mapping increases the potential clinical utility of neuroimaging approaches⁸³ and might
10 help obtain a more accurate picture of brain circuits underlying the complex phenotypic
11 landscape of autism. Tasks also offer the advantage of improving the reliability of task-engaged
12 functional connections⁸⁴. More generally, the results obtained here are in line with other work in
13 neurotypical populations indicating that predictions of phenotypes improve when using task as
14 opposed to resting-state data^{29,33,34,36,41,85,86}. We note that resting-state studies still retain utility,
15 particularly in terms of ease of data collection and their ability to facilitate the collation of large
16 datasets across centers.

17 Our work adds to the growing literature suggesting an important link between autism and
18 attention, at both neurobiological and phenotypic levels. Previous studies^{24,47,87,88} have indicated
19 that complex models spanning numerous functional networks are important for attention in
20 autism, particularly in higher order resting-state networks, such as the default mode network
21 (recently reviewed in⁸⁹). Hence, the ADOS consensus model continues to highlight the role of
22 the default mode network in mediating attention related to autistic traits. In addition, attention
23 has been posited as playing a key role in the central behavioral manifestations of autism⁹⁰.

1 Broadly considered, attention is the means by which information is selectively perceived. It
2 makes sense that some of the core features of autism—restricted and repetitive behaviors and
3 social abilities—depend intimately on a process governing how external stimuli gain access to an
4 individual’s internal world. Indeed, the co-occurrence of autism and ADHD symptoms has long
5 been acknowledged^{49-51,91}.

6 It is perhaps surprising that the SSA clips did not result in higher prediction performance.
7 One explanation is that the SSA clips resembled resting-state⁹², in that they were passive
8 experiences in which participants could essentially attend to whatever they wanted^{55,56}. It has
9 been noted that the unconstrained nature of the resting-state is suboptimal for probing certain
10 aspects of brain-behavior relationships²⁹. Similarly, it is also perhaps surprising that the gradCPT
11 data resulted in the highest prediction performance. Beyond attention, the highly structured,
12 rules-based design of gradCPT may effectively highlight variations in networks linked to autistic
13 traits, given the rules-based tendencies observed in autism⁹³.

14 In addition, it must be noted that the SSA task and resting-state conditions might have
15 underperformed with respect to prediction performance as they came later in the study (i.e.
16 following gradCPT) and participants were possibly fatigued. Nevertheless, previous work has
17 shown that arousal does not appear to drive differences in predictions across different scanning
18 conditions and that increased prediction performance seems to be due to cognitive differences
19 driven by the task⁴¹. Future work could more fully investigate the role of arousal in brain-
20 behavioral relationships in autism, while accounting for the challenging realities of scanning
21 youth with neurodevelopmental conditions. (See Supplemental Methods for more about task
22 design choices in the current study.)

1 These findings underscore the importance of considering both practical and conceptual
2 aspects of task design—both the study population and the nuts and bolts of collecting high
3 quality data must be considered when planning an fMRI study⁹⁴. Further, other populations that
4 are difficult to study and/or tend to exhibit significant head motion, like those with
5 schizophrenia⁹⁵ or bipolar disorder⁹⁶, could have study designs optimized from both conceptual
6 and practical standpoints. In some cases, demanding tasks requiring participants to be actively
7 engaged might be desired. In other cases, more passive designs, like age-appropriate, naturalistic
8 movie clips^{97,98}, might be better suited. In yet other cases, resting-state data may be collected and
9 meaningfully linked to behavior^{99,100}.

10 In this work, we attempted to balance a ‘deep’ approach, which involves collecting many
11 scans from the same subject¹⁰¹, with a ‘broad’ approach, which involves collecting data from
12 many subjects^{102,103}. Hence, the data allowed us to compare the conditions across subjects,
13 though this necessarily limited our sample size. Additionally, acquiring high-quality data from
14 youth with autism is often time-intensive. In our experience, it is necessary to conduct a mock
15 scan for at least an hour to adequately prepare a participant for the scanning environment⁶⁰. The
16 time commitment is on par with that reported by other groups in youth with neurodiverse
17 conditions^{104,105}.

18 In our view, investing such time to acquire smaller samples is still necessary for the field.
19 We contend that in the age of big data, it is essential to continue exploring brain-behavior
20 associations in samples that might not contain thousands of subjects, but comprise unique
21 scanning conditions. Such an approach allows the field to better determine which scans to
22 include in big data endeavors and facilitates the exploration of questions that may be difficult to
23 address in large-scale studies. Further, replicable and generalizable findings can still be

1 determined by using robust methods¹⁰⁶⁻¹⁰⁸. Collecting small, unique samples also facilitates
2 testing across diverse experimental conditions, thereby enhancing generalizability¹⁰⁹. Future
3 work could address if findings observed here hold when sample sizes are larger.

4 A few final items warrant discussion. Participant IQ in the Yale youth sample and
5 ABIDE are fairly high. More research should be conducted using participants with a broad range
6 of IQ scores to determine which scanning conditions are optimal for prediction performance. As
7 with other autism samples, the dataset contained mainly males; the importance of sex-based
8 differences in brain circuitry¹¹⁰⁻¹¹² and behavioral phenotypes¹¹³ relevant for autism is
9 increasingly well-described. Finally, the current work focused on prediction of traits in an
10 adolescent dataset. Future studies could assess task design and prediction performance in much
11 younger samples, such as toddlers and young children. Such efforts aim to optimize the detection
12 of brain-behavior relationships at earlier developmental stages, ultimately providing better
13 support for individuals with autism and their families.

14

15 **Conclusions**

16 We have shown in a preliminary study that sustained attention tasks, such as gradCPT,
17 can enhance the prediction of autistic traits. Such an approach leads to a robust marker that
18 generalizes to predict attention and social phenotypes in independent samples. Our findings
19 highlight the need to further investigate optimal brain states for modeling phenotypes in autism
20 and related conditions.

21

22 **Methods**

23 *Description of datasets*

1 We used three datasets in this work (Figure 1). The first dataset, the Yale youth sample,
2 comprised 63 subjects from a sample described previously (mean age = 11.7 years, st. dev. = 2.8
3 years; 29 females; mean IQ = 107.8, st. dev. = 15.1)^{28,60}. Twenty of the participants had autism;
4 11 other participants had a neurodevelopmental condition (five with ADHD, two with anxiety
5 disorder, and four were classified as belonging to the broader autism phenotype)⁶¹. Participants
6 were scanned on a 3T Siemens Prisma System. See Supplementary Material for full exclusion
7 criteria and imaging parameters. Autism symptoms were scored using the Autism Diagnostic
8 Observation Schedule-2 (ADOS-2)⁶² and were ascertained by trained clinical psychologists;
9 calibrated severity scores were used in the present work for the social affect subscale (mean =
10 3.2, st. dev. = 2.9), the restricted and repetitive behavior subscale (mean = 4.0, st. dev. 3.3), and
11 the ADOS total score (mean = 3.1, st. dev. = 3.1). This sample was used to conduct CPM,
12 compare how scanning condition impacted performance, and generate a consensus model.

13 A second dataset of neurotypical adults, the adult attention sample (n=25, 13 females,
14 mean age = 22.8 years, st. dev. = 3.5 years) was used as a validation dataset and is described
15 elsewhere³⁶. Participants were scanned on a 3T Siemens Trio TIM system. This sample was used
16 to determine if the consensus model generalized to predict attention.

17 A third dataset of individuals with and without autism (n=229, 65 females; mean age =
18 10.45 years, st. dev. = 1.8 years; mean IQ = 113.7, st. dev. = 15.1) comprising data from
19 ABIDE^{73,74} was used as an additional validation dataset; processing of these data is described
20 elsewhere²⁴. SRS⁷⁵ scores were used from ABIDE and included the following scales: SRS total
21 scores (mean = 42.4, st. dev. = 40.2); SRS communication (mean = 13.8, st. dev. = 14.2); SRS
22 motivation (mean = 7.3, st. dev. = 6.9); SRS mannerisms (mean = 7.1, st. dev. = 8.5). Seventy-
23 seven of the participants had autism. SRS was chosen due to the low numbers of subjects with

1 ADOS scores (when using the exclusion criteria described in²⁴), along with the additional quality
2 control exclusion criteria we performed (i.e., there were 229 subjects with SRS data, compared to
3 only 33 with ADOS; see Supplemental Methods). This sample was used to determine if the
4 consensus model generalized to predict SRS scores.

5 All datasets were collected in accordance with the institutional review board or research
6 ethics committee at each site. Where appropriate, informed consent was obtained from the
7 parents or guardians of participants. Written assent was obtained from children aged 13–17
8 years; verbal assent was obtained from participants under the age of 13 years.

9
10 *Preprocessing of functional imaging data*

11 A standard preprocessing approach was used that has been described elsewhere^{33,63-65}.
12 Preprocessing steps were performed using BioImage Suite¹¹⁴ unless otherwise noted, and
13 included: skull stripping the 3D magnetization prepared rapid gradient echo images using
14 optiBET¹¹⁵ and performing linear and non-linear transformations to warp a 268-node functional
15 atlas¹¹⁶ from Montreal Neurological Institute space to single subject space. Functional images
16 were motion-corrected using SPM8 (<https://www.fil.ion.ucl.ac.uk/spm/software/spm8/>).
17 Covariates of no interest were regressed from the data, including linear, quadratic, and cubic
18 drift, a 24-parameter model of motion¹¹⁷, mean cerebrospinal fluid signal, mean white matter
19 signal, and the global signal. Data were temporally smoothed with a zero-mean unit-variance
20 low-pass Gaussian filter (approximate cutoff frequency of 0.12 Hz). Visual inspections were
21 performed after skull-stripping, non-linear, and linear registrations to ensure there were no errors
22 in processing. Head motion was calculated as described previously⁶⁰ (see Supplemental Methods
23 for additional motion control considerations, as well as Supplemental Figure 6). To ensure

1 consistent amounts of data across scanning conditions, we discarded frames from the end of the
2 gradCPT and resting-state runs, such that the total amount of data was the same as from the SSA
3 task runs (four minutes of data).

4 Connectomes were generated using a 268-node atlas²². For each subject, the mean time-
5 course of each region of interest (“node” in graph theory) was computed, and the Pearson
6 correlation coefficient was computed between each pair of nodes to achieve a symmetric 268 x
7 268 matrix of correlation values representing “edges” (connections between nodes) in graph
8 theory. The Pearson correlation coefficients were then transformed to z -scores via a Fisher
9 transformation, and only the upper triangle of the matrix was considered, yielding 35,778 unique
10 edges.

11

12 *Scanning conditions in the Yale Youth Sample*

13 *1) Scanning condition one: the free-viewing selective social attention task*

14 Participants completed a novel version of a free-viewing selective social attention (SSA)
15 task^{55,58} in which an actress is presented at the center of the screen and is surrounded by objects
16 in corners of the screen (Figure 2). Four types of clips were used in which the presence of speech
17 (SP) and eye contact (EC) were manipulated. The first condition included clips in which the
18 person smiled and made eye contact with the camera while speaking in full sentences (e.g.,
19 “Have you ever seen a monkey? Monkeys eat bananas, swing in trees, and chase each other.”;
20 this was designated as the EC+SP+ condition). The second condition included a direct gaze
21 condition with no speech (EC+SP-), in which the person smiled directly at the viewer while
22 remaining silent. The third condition consisted of the person looking down at the table while
23 speaking in full sentences (EC-SP+). The fourth condition consisted of the person looking down

1 at the table and not speaking (EC-SP-). Each clip lasted two minutes and was shown twice over
2 four runs, such that eight clips were shown total. To allow successful scene transitions in
3 between sentences, the direct gaze and speech condition lasted 2 minutes and 8 seconds. The
4 speech with no eye contact condition lasted 2 minutes and 6 seconds. In between clips during
5 each run, a white fixation cross on a black background was shown for 15 seconds. Clip order was
6 counterbalanced across participants (see Supplemental Materials for more about the
7 counterbalancing of clips, as well as study design considerations of the Yale youth sample). Clip
8 conditions were concatenated across runs, such that each resulting connectivity matrix comprised
9 four minutes of data from a single scanning condition. Both gradCPT and the SSA task were
10 presented using Psychtoolbox (version: 3.0.14; <http://psychtoolbox.org/>; MATLAB version
11 R2018a) on a Lenovo IdeaPad 720S computer, with Ubuntu 16.04 LTS installed.

13 *2) Scanning condition two: testing gradual onset continuous performance task (gradCPT)*

14 The gradual onset continuous performance task (gradCPT; Figure 2) has been described
15 previously^{36,53,54}. The gradCPT tests sustained attention and inhibition, producing a range of
16 performance scores across neurotypical^{53,54} and neurodiverse populations²⁸. Participants viewed
17 grayscale pictures of cities and mountains presented at the center of the screen, with images
18 gradually transitioning from one to the next every 1,000 ms. Subjects were instructed to respond
19 with a button press for city scenes and to withhold button presses for mountain scenes. City
20 scenes occurred randomly 90% of the time. Performance was calculated using d' (sensitivity),
21 the participant's hit rate minus false alarm rate. The task took 5 minutes to complete; participants
22 completed the task twice. Note that because of differences in task timing between gradCPT, the
23 selective social attention task, and resting-state, we trimmed the gradCPT and resting-state data

1 to include 4 minutes of data per scan (to match the selective social task time length of 4
2 minutes).

3 Subjects in the adult attention sample also performed gradCPT; the same parameters were
4 used as above, except scene transitions took 800 ms.

5

6 *3) Scanning condition three: resting-state data*

7 Resting-state data were also obtained. Subjects were instructed to keep their eyes open,
8 relax, and think of nothing in particular while they viewed a white fixation cross on a black
9 screen. Each scan lasted five minutes and was repeated twice per participant.

10 Resting-state data were also obtained in the ABIDE sample as described previously^{73,74}.

11

12 *Connectome-based predictive modelling*

13 CPM²³ (Supplemental Figure 1) was used to predict ADOS scores from functional
14 connectivity data in the Yale youth sample. Briefly, using 10-fold cross-validation, connectivity
15 matrices from a given scan condition and ADOS scores were split into an independent training
16 set including subjects from 9 folds and a test set including the left-out fold. Linear regression
17 was used to relate edge strength to ADOS score in the training set. Edges most strongly
18 associated with ADOS scores were selected (feature selection threshold of $P = 0.05$) for both a
19 ‘positive network’ (in which increased connectivity was associated with higher ADOS scores)
20 and a ‘negative network’ (in which increased connectivity was associated with lower ADOS
21 scores). We used partial correlation to control for mean participant head motion at the feature
22 selection step^{28,66,67}. Mean network strength was computed in both the positive and negative

1 networks, and the difference between these network strengths was computed ('combined
2 network strength'), as in previous work³³:

3
4 Positive network strength_s = $\frac{1}{b} (\sum_{i,j} c_{i,j} m^+_{i,j})$; $b = \frac{i(j-1)}{2}$

5 Negative network strength_s = $\frac{1}{b} (\sum_{i,j} c_{i,j} m^-_{i,j})$; $b = \frac{i(j-1)}{2}$

6 Combined network strength_s = Positive network strength_s – negative network strength_s

7
8 where c is the connectivity matrix for subject s and m^+ and m^- are binary matrices indexing the
9 edges (i, j) that survived the feature selection threshold for the positive-association and negative-
10 association networks, respectively.

11 A linear model was then calculated relating combined network strength to ADOS scores
12 in the training set. In the last step, combined network strength was computed for the test set, and
13 the model was applied to generate ADOS predictions for these unseen participants.

14 Model performance was assessed as reported previously⁶⁷ by comparing the similarity
15 between predicted and observed ADOS scores using both Spearman's correlation (to avoid
16 distribution assumptions)¹¹⁸. We performed 500 iterations of a given CPM analysis and selected
17 the median-performing model; we report this in the main text when discussing model
18 performance. To calculate significance, we randomly shuffled participant labels and attempted to
19 predict ADOS scores. We repeated this 500 times and calculated the number of times a permuted
20 predictive accuracy was greater than the median of the unpermuted predictions to achieve a non-
21 parametric P -value:

22
23
$$P = (\#\text{(rho}_{\text{null}} \geq \text{rho}_{\text{median}})) / 500$$

1
2 where $\#(\rho_{\text{null}} \geq \rho_{\text{median}})$ indicates the number of permuted predictions numerically
3 greater than or equal to the median of the unpermuted predictions⁶⁷. We used the Benjamini–
4 Hochberg method¹¹⁹ to correct for multiple comparisons, correcting for ten tests in the Yale
5 youth sample (two for gradCPT, four for SSA, two for resting-state, one for gradCPT average,
6 and one for resting-state average), three tests in the adult attention sample, and four tests in
7 ABIDE.

8
9 *Testing generalizability of the ADOS network*

10 To determine if the ADOS networks from the Yale youth sample generalized to external
11 datasets (the adult attention sample and ABIDE), we defined a consensus positive-association
12 network and consensus negative-association network as edges that appear in at least 6/10 folds in
13 300/500 iterations of CPM. This process resulted in 1,001 edges in the positive-association
14 network and 1,013 edges in the negative-association network; hereafter, we refer to the
15 collection of edges in the positive and negative networks as the ‘ADOS consensus network.’ We
16 note the size of the ADOS consensus network is consistent with other CPM networks that have
17 generalized^{36,120,121}. To ensure generalizability results were robust, we tested summary networks
18 of varying sizes (from liberal cases where an edge appeared in at least 1/10 folds and 50/500
19 iterations, to more stringent thresholds where an edge must appear in 10/10 folds and 500/500
20 iterations, moving in intervals of 1 fold and 50 iterations for each summary network).

21 To determine if the network predicted autistic traits, we then used the combined network
22 strength in the ADOS consensus network and computed model coefficients across the Yale youth
23 sample, as conducted previously^{36,66,122}. Model coefficients and the network masks were

1 subsequently applied to the ABIDE sample to predict SRS scores. Model performance was
2 determined by comparing the similarity between predicted and observed behavioral scores using
3 Spearman's correlation. We used the same approach to determine if the network predicted d'
4 scores.

5 To further assess generalizability, we repeated testing if the ADOS network predicts d'
6 and SRS using a multiverse approach. A multiverse analysis assesses how results are affected
7 by different analytical choices⁷². Specifically, we tested if the ADOS positive and negative
8 networks generalized; we adjusted models for IQ, age, and sex; and, as mentioned above, we
9 tested a range of consensus network sizes. Also, we calculated combined network strength in
10 the consensus networks and computed correlations (Spearman) with d' in the adult attention
11 sample. We performed this analysis because one could argue that in a sample of neurotypical
12 participants, it is perhaps clinically meaningless to predict ADOS scores. We point out the goal
13 of a multiverse approach is not to determine what pipeline results in the highest prediction
14 performance. Instead, the point is to assess various analytical scenarios and determine how
15 different modelling choices impact generalization. As such, we do not perform multiple
16 comparisons correction when assessing these results.

17 For completeness' sake, we include the additional multiverse analyses performed in
18 the Yale youth sample in this section. In this dataset, we adjusted CPM models for sex, age,
19 and IQ; we also used CPM to predict social affect and restricted and repetitive behavior
20 scores. Additionally, we assessed how altering the feature selection threshold impacted CPM.
21 We observed a 0.01 feature selection threshold resulted in similar prediction performance
22 using gradCPT data (data not shown), in line with previous work^{28,85,122}.

23

1 Code and data availability

2 Preprocessing was carried out using freely available software:

3 (<https://medicine.yale.edu/bioimaging/suite/>). CPM code is freely available here:

4 (<https://github.com/YaleMRRC/CPM>). The functional parcellation is available here:

5 (https://www.nitrc.org/frs/?group_id=51). ABIDE data are available here:

6 (https://fcon_1000.projects.nitrc.org/indi/abide/). All other data or materials are available from

7 the authors upon request.

8

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18

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