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Replicable Patterns of Memory Impairments in Children With Autism and Their Links to Hyperconnected Brain Circuits

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ABSTRACT

BACKGROUND: Memory impairments have profound implications for social communication and educational outcomes in children with autism spectrum disorder (ASD). However, the precise nature of memory dysfunction in children with ASD and the underlying neural circuit mechanisms remain poorly understood. The default mode network (DMN) is a brain network that is associated with memory and cognitive function, and DMN dysfunction is among the most replicable and robust brain signatures of ASD.

METHODS: We used a comprehensive battery of standardized episodic memory assessments and functional circuit analyses in 25 8- to 12-year-old children with ASD and 29 matched typically developing control children.

RESULTS: Memory performance was reduced in children with ASD compared with control children. General and face memory emerged as distinct dimensions of memory difficulties in ASD. Importantly, findings of diminished episodic memory in children with ASD were replicated in 2 independent data sets. Analysis of intrinsic functional circuits associated with the DMN revealed that general and face memory deficits were associated with distinct, hyperconnected circuits: Aberrant hippocampal connectivity predicted diminished general memory while aberrant posterior cingulate cortex connectivity predicted diminished face memory. Notably, aberrant hippocampal-posterior cingulate cortex circuitry was a common feature of diminished general and face memory in ASD.

CONCLUSIONS: Our results represent a comprehensive appraisal of episodic memory function in children with ASD and identify extensive and replicable patterns of memory reductions in children with ASD that are linked to dysfunction of distinct DMN-related circuits. These findings highlight a role for DMN dysfunction in ASD that extends beyond face memory to general memory function.

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Episodic memory function is critical for a wide range of tasks in children's lives that extend from navigating their complex social world to classroom performance (1,2). Aspects of episodic memory have been reported to be diminished in children with autism spectrum disorder (ASD) (3), which may contribute to impairments in social function (4) and academic achievement (5). Little is known regarding the specific dimensions of memory function that are impaired in children with ASD and the brain mechanisms underlying these deficits.

Early research on episodic memory in ASD suggested that affected children might have memory deficits restricted to social content, particularly memory for faces, while general memory was largely intact (6,7). However, subsequent studies have reported broader impairments in memory profiles in ASD beyond face stimuli (1,8), supporting a general memory deficit model (9) in which face and general memory deficits may represent distinct factors influencing memory performance. Our detailed review of the behavioral literature points to inconsistent findings arising from a lack of comprehensive and standardized assessments of episodic memory, limited measures of general cognitive abilities, and a wide age range of study participants (Table S1). In addition, no previous studies have examined the replicability of findings related to episodic memory dysfunction in ASD. It is unclear whether memory for faces and other stimuli constitute distinct dimensions of memory function in children with ASD, and, crucially, the underlying neural circuit bases of impairments in episodic memory remain poorly understood.

The default mode network (DMN) is a large-scale brain network that has been implicated in a wide range of cognitive deficits in ASD, including the ability to understand other people's mental states (10–12). The DMN comprises distributed and interconnected nodes encompassing the posterior cingulate cortex (PCC), medial prefrontal cortex, angular gyrus, and hippocampus. Importantly, atypical functional connectivity of the DMN is among the most replicable brain signatures of childhood ASD. This is evident not only in task-based functional magnetic brain imaging (fMRI) during theory of mind and mentalizing tasks but also in studies examining intrinsic functional connectivity (13–15).

Beyond the established role of the DMN in social cognition, nodes of this network, most notably the hippocampus, are important for episodic memory function. An extensive literature has demonstrated a critical role for the hippocampus (16–21) and its neocortical circuits (22,23) in encoding and recall of episodic memory. For example, previous research in neurotypical children has shown that intrinsic functional connectivity between the hippocampus and the lateral prefrontal, temporal, and posterior parietal cortices is correlated with episodic memory performance (24,25). In addition, the PCC, a hub node of the DMN, has also been implicated in both general (26) and social memory function (27). However, it is not known whether dysfunction of PCC and hippocampal circuits of the DMN are associated with impairments in different aspects of episodic memory, including face and general memory, in children with ASD.

Here, we address crucial gaps in our knowledge of episodic memory impairments in children with ASD and elucidate the underlying brain circuit mechanisms, with a focus on DMN circuits. First, we sought to overcome limitations of previous behavioral studies by using a comprehensive battery of standardized episodic memory assessments (Figure S1) in a well-characterized sample of 8- to 12-year-old children with ASD with normal IQ as well as IQ-, age-, and sex-matched typically developing (TD) children (Table 1). Our behavioral findings of episodic memory functions in children with ASD compared to TD children were validated in independent cohorts of participants (Table S1). We then used hierarchical clustering analysis to examine whether general and face memory constituted distinct dimensions of memory function in children with ASD. This analysis was critical for adjudicating between different theoretical models, including face-specific and general memory deficit models, which have been associated with reduced memory performance in ASD. Then, we investigated links between distinct dimensions of memory function and brain connectivity in hippocampal and PCC nodes of the DMN. We hypothesized that children with ASD would show weaker performance in both face and general memory domains than their TD peers. Based on the centrality of DMN impairments to cognitive function and clinical symptomology in ASD (13), we hypothesized a primary role for PCC and hippocampal nodes of the DMN in distinct dimensions of memory functions.

METHODS AND MATERIALS

Participants

All study protocols were approved by the Stanford University Institutional Review Board, and informed written consent was obtained from the legal guardian of each child. Fifty-four 8- to 12-year-old children (25 children with ASD and 29 matched TD children) completed the study (Table 1). The diagnosis of ASD was confirmed by an experienced clinical psychologist using the standard criteria based on the Autism Diagnostic Interview-Revised (28) and/or the Autism Diagnostic Observation Schedule (29). Details regarding inclusion criteria and demographic characteristics of study participants can be found in the Supplement Methods and Results. The number of children included was based on the availability of high-quality data for each analysis (Table S2).

Memory Assessments

To characterize children's episodic memory profile across multiple dimensions—content domain (general/face), retrieval type (recall/recognition), type of material (verbal/visual), and delay interval (short/long) (Figure S1)—subtests of the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2) (30) and the Developmental Neuropsychological Assessment, Second Edition (NEPSY-II) (31) were administered by trained assessors (Supplemental Methods).

Wide Range Assessment of Memory and Learning, Second Edition. Ten subtests were administered. We generated 5 memory subscores based on the following relevant subtests (Figure S1): 1) immediate verbal, 2) delayed verbal recall, 3) immediate visual recall, 4) delayed verbal recognition, and 5) delayed visual recognition. A composite total memory score of WRAML2 was generated by averaging the 5 memory subscores to represent general memory performance.

Developmental Neuropsychological Assessment, Second Edition. Four subtests were administered. Four memory subscores were defined by the scaled scores of these 4 subtests. A composite general memory score was generated by averaging the scaled scores of 2 design subtests. A composite face memory score was generated by averaging the scaled scores of 2 face subtests.

Behavioral Analysis

Group Differences and Interaction Between Group and Memory Dimensions in General Memory Scores (WRAML2). We used a linear mixed model to examine overall memory function in the ASD group compared to the TD group as well as the effects of retrieval type, type of material, delay interval, and their interactions with the group (ASD, TD). Here, we modeled the unbalanced design of 5 memory subscores from the WRAML2, in which only verbal recall had both immediate and delayed versions, as follows:

$$y_i = \beta_0 + b_i + \beta_1 \text{ group} + \beta_2 \text{ retrieval type} + \beta_3 \text{ type of material} + \beta_4 \text{ delay interval} + \beta_5 \text{ group} \times \text{retrieval type} + \beta_6 \text{ group} \times \text{type of material} + \beta_7 \text{ group} \times \text{delay interval} + \varepsilon_i \quad (1)$$

where y_i is the observed memory subscore for subject i and ε_i is the residual of subject i.

Group Differences and the Interaction Between Group and Memory Dimensions in General and Face Memory Scores (NEPSY-II). A 2 × 2 × 2 mixed-design analysis of variance was performed with the group as a between-subject factor and content domain and delay interval as within-subject factors, using the 4 memory subscores from the NEPSY-II.

Replication Analysis With National Institute of Mental Health Data Archive Cohort Data. Using an open-source dataset, the National Institute of Mental Health Data Archive (https://nda.nih.gov/), we identified 2 cohorts: 1) the WRAML

Table 1. Demographic, Neuropsychological, and Clinical Measures

Measure	ASD, n = 25	TD, n = 29	t/χ^2	df	Cohen's d	p
Sex, Female/Male	4/21	5/24	0.01[a]	1	0.01	.903
Age, Years	10.44 (1.29)	10.41 (1.24)	0.08	52	0.02	.940
WASI Scale (45)						
Verbal IQ	114.96 (16.00)	120.41 (15.08)	−1.29	52	−0.35	.203
Performance IQ	113.76 (16.75)	118.79 (16.56)	−1.11	52	−0.30	.273
Full Scale IQ	116.00 (16.55)	122.17 (15.99)	−1.39	52	−0.38	.170
WRAML2[b] (30)						
Immediate verbal recall	10.23 (3.12)	12.56 (2.62)	−2.89	49	−0.81	.006
Immediate visual recall	8.50 (2.61)	10.20 (2.95)	−2.17	49	−0.61	.035
Delayed verbal recall	10.38 (2.84)	12.39 (2.16)	−2.86	49	−0.80	.006
Delayed verbal recognition	10.50 (2.70)	12.04 (1.51)	−2.55	49	−0.71	.014
Delayed visual recognition	10.48 (2.62)	10.50 (2.48)	−0.03	49	−0.01	.977
Total general memory	10.02 (2.38)	11.54 (1.79)	−2.59	49	−0.73	.012
NEPSY-II[c] (31)						
Immediate design recognition	10.30 (3.14)	12.07 (3.14)	−2.00	49	−0.56	.051
Delayed design recognition	9.96 (2.90)	12.18 (3.02)	−2.66	49	−0.75	.010
Total general memory	10.13 (2.87)	12.12 (2.89)	−2.46	49	−0.69	.017
Immediate face recognition	8.43 (2.94)	11.71 (3.16)	−3.81	49	−1.07	<.001
Delayed face recognition	9.43 (3.53)	11.68 (2.68)	−2.58	49	−0.73	.013
Total face memory	8.93 (2.88)	11.70 (2.52)	−3.65	49	−1.03	<.001
ADI-R[d] (28)						
Social	18.83 (6.06)	–	–	–	–	–
Verbal	15.83 (4.90)	–	–	–	–	–
Repetitive behavior	5.21 (2.54)	–	–	–	–	–
Development	3.08 (1.59)	–	–	–	–	–
Severity scores	32.67 (8.58)	–	–	–	–	–
ADOS[e] (29)						
Social/Affect	8.00 (2.65)	–	–	–	–	–
Restricted and repetitive behavior	2.61 (1.44)	–	–	–	–	–
Severity scores	6.26 (1.79)	–	–	–	–	–
Total	10.61 (3.43)	–	–	–	–	–

Values are presented as n or mean (SD). Unless otherwise noted, t statistics were obtained.

ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; NEPSY-II, Developmental Neuropsychological Assessment, Second Edition; TD, typically developing; WASI, Wechsler Abbreviated Scale of Intelligence; WRAML2, Wide Range Assessment of Memory and Learning, Second Edition.

[a] χ^2 statistic.

[b] Missing data from 3 participants (ASD: n = 1; TD n = 2).

[c] Missing data from 3 participants (ASD: n = 2; TD n = 1).

[d] Missing data from 1 participant (ASD: n = 1).

[e] Missing data from 2 participants (ASD: n = 2).

replication cohort and 2) the NEPSY replication cohort. Details about the procedures used to generate the replication cohorts are shown in Figure S2.

Relation Between Memory Measures. Pearson's correlation coefficients were computed for pairs of WRAML2 and NEPSY-II memory subscores in each group.

Hierarchical Clustering Analysis of Memory Measures. Hierarchical clustering analysis with Euclidean distance and complete-linkage criterion (32–34) was used to investigate the relation between memory measures. The optimal number of clusters was determined on the basis of the majority vote of 19 indices of internal validity measures on the number of clusters from 1 to 8 (NbClust 3.0.1 package in R 4.1.0) (35).

General and Face Memory Reduction Scores in ASD. For each child with ASD, 2 composite memory reduction scores, relative to overall composite memory scores in the TD group, were generated. A general memory reduction score was obtained by averaging the scaled reduction scores of all general memory assessments from the WRAML2 and NEPSY-II. A face memory reduction score was obtained by averaging the scaled reduction scores of NEPSY-II for 2 face memory assessments. The scaled reduction score was calculated as follows:

$$x'_{ASD} = \frac{x_{ASD} - M_{TD}}{SD_{TD}} \quad (2)$$

Greater negative values indicated greater memory reduction relative to the TD group.

Statistical Analysis

Planned two-sample *t* tests were used to test group differences. Cohen's *d* or η_p^2 was calculated to estimate effect sizes.

Brain Imaging Analysis

Functional Connectivity Analysis. Details of fMRI data acquisition and preprocessing (36) are described in the Supplemental Methods. For each child, voxelwise whole-brain functional connectivity analysis was performed for hippocampus and PCC regions of interest (ROIs) (Figure S3). The PCC ROI (Montreal Neurological Institute coordinates: 4 −38 32) was defined using coordinates from the largest meta-analysis of fMRI studies on social cognition deficits in ASD, which encompassed 50 studies and included 675 individuals with ASD and 695 TD individuals (37). Voxels in non–gray matter areas in the PCC ROI were excluded using the Harvard-Oxford atlas as the reference. There is currently no similar meta-analysis of fMRI studies on episodic memory deficits in ASD. To define hippocampal ROIs, we first conducted a meta-analysis using Neurosynth (38), with the search term "episodic memory," which identified a large cluster in the medial temporal lobe including the hippocampus. ROIs in the left (Montreal Neurological Institute coordinates: −24 −14 −20) and right (Montreal Neurological Institute coordinates: 24 −14 −20) hemisphere were then selected based on overlap of the meta-analysis−derived cluster with hippocampus coordinates from our previous study of medial temporal lobe connectivity patterns along the long axis of the hippocampus (39). Please see the Supplemental Methods for definition of control ROIs. Two-sample *t* tests were used to examine group differences in connectivity for each ROI. Results were corrected for multiple comparisons using a height threshold of $p < .01$ and with the familywise error rate correction at $p < .01$ (cluster extent of 128 voxels) based on Monte Carlo simulations using a custom MATLAB script (version R2018b; The MathWorks, Inc.).

Multivariate Brain-Behavior Association Analysis. We used an epsilon-insensitive support vector regression (SVR) analysis with a nonlinear sigmoid kernel (40) to investigate brain-behavior associations. This supervised machine learning approach is widely used in the field and was selected for its robust performance (40–44). First, for each ROI, we identified all target brain regions that showed significant differences in connectivity between the ASD and TD groups. Connectivity values for each ROI served as the feature vector in the SVR analysis. The SVR model was trained using a leave-one-out cross-validation strategy. The predicted score for each child was generated by a model that was trained on data from all other children in the group, with the connectivity features serving as predictors and the observed memory performance serving as the predicted variable. The correlation between predicted and actual scores was then computed. Significance levels were computed using permutation testing. Bonferroni correction was used to correct for multiple comparisons ($p_{\text{corrected}} = p \times 4$ for 2 ROIs and 2 memory scores in each group). We performed additional control analysis using the matrix reasoning score of the Wechsler Abbreviated Scale of Intelligence (45) to examine the specificity of our findings with respect to memory measures.

RESULTS

General Memory Reductions in Children With ASD (WRAML2)

We first examined general memory function, assessed using the WRAML2, in children with ASD, compared to TD children. A linear mixed model on 5 memory subscores from the WRAML2 showed a significant main effect of group ($\beta = 4.86$, $p = .002$). There was no significant main effect of retrieval type, type of material, or delay interval or their interactions with group (βs < 1.25, *p*s $> .14$) (Table S3). A planned two-sample *t* test on the total general memory score from the WRAML2 revealed that children with ASD had significantly reduced scores compared with TD children ($t_{49} = -2.59$, $p = .012$, Cohen's $d = -0.73$) (Figure 1A, left). Planned *t* tests also revealed significantly lower scores in children with ASD compared to TD children on immediate and delayed verbal recall, immediate visual recall, and delayed verbal recognition subscores ($ts_{49} < -2.17$, *p*s $< .035$, Cohen's $d < -0.61$) (Figure 1A, right; Table 1) but not on delayed visual recognition ($t_{49} = -0.03$, $p = .977$; Cohen's $d = -0.01$). Together, these results provide converging evidence for weak memory function across recognition and recall, verbal and visual materials, and short and long delay intervals in children with ASD compared with their TD peers, highlighting general memory reductions in individuals with ASD.

General and Face Memory Reductions in Children With ASD (NEPSY-II)

Next, we examined general and face memory functions, assessed using the NEPSY-II, in children with ASD, compared to TD children. A mixed-design analysis of variance on four memory subscores from the NEPSY-II, with group, content domain, and delay interval, revealed a significant effect of group ($F_{1,49} = 20.22$, $p < .001$, $\eta_p^2 = 0.29$), with reduced performance in children with ASD compared to TD children. No significant main effect of content domain or delay interval or their interactions with group were observed ($Fs_{1,49} < 2.43$, *p*s $> .126$) (Table S4). In planned two-sample *t* tests on total general and face memory scores from the NEPSY-II, we observed similar patterns of reduced performance in the ASD group compared with the TD group ($ts_{49} < -2.46$, *p*s $< .017$, Cohen's *d*s < -0.69) (Figure 1B, C, left). Additional analyses confirmed reduced performance across short and long delay intervals for general and face memory in the ASD group compared with the TD group. Significantly lower scores were observed in children with ASD for all subscores (*p*s $< .05$) except for immediate design recognition (Figure 1B, C, right; Table 1). Results from the NEPSY-II extend the findings from the WRAML2 and provide additional evidence for both general and face memory reductions in children with ASD.

Replication of General and Face Memory Reductions From Independent Samples

To validate our findings of memory functions in independent samples of children with ASD, we queried the National Institute of Mental Health Data Archive dataset for WRAML2 and NEPSY-II measures, which assess general and face memory, respectively (Figure S2). The WRAML2 replication sample comprised $n_{\text{ASD}} = 22$ and $n_{\text{TD}} = 24$ participants. We observed

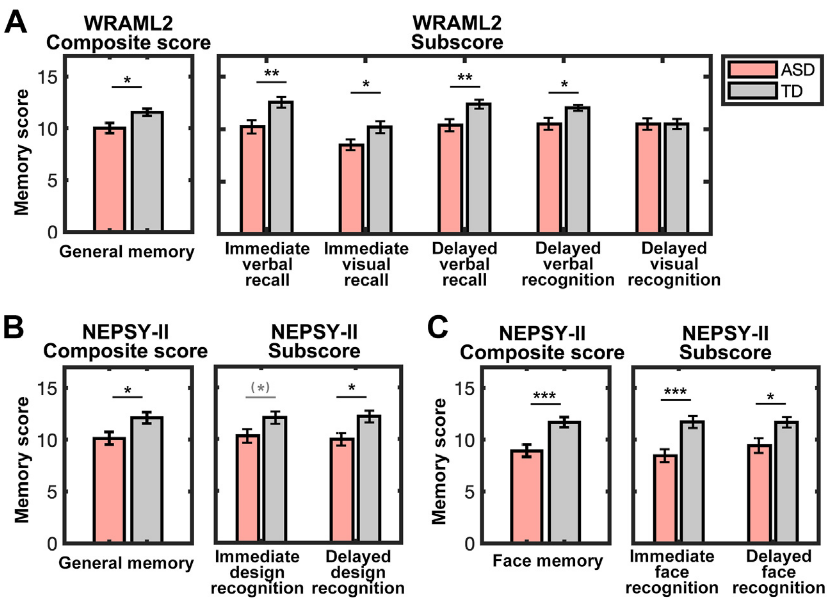

Figure 1. General and face memory deficits in children with autism spectrum disorder (ASD) relative to typically developing (TD) children. **(A)** General memory performance across multiple dimensions (also see Figure S1), as measured by the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2), was significantly lower in children with ASD than in well-matched TD children. Immediate verbal and visual recall, delayed verbal recall, and delayed verbal recognition abilities were weaker in children with ASD than in TD children. **(B)** General memory, assessed by the Developmental Neuropsychological Assessment, Second Edition (NEPSY-II), was also weaker, with significantly lower performance on delayed design recognition in children with ASD compared to TD children. **(C)** Face memory performance after both immediate and delayed intervals, measured by the NEPSY-II, was significantly lower in children with ASD. Error bars represent the standard error of the mean. ***$p < .001$, **$p < .01$, *$p < .05$, (*)$p < .10$.

significantly lower general memory scores in children with ASD than in TD children ($t_{44} = -3.08$, $p = .004$) (Figure 2A). The NEPSY-II replication sample comprised $n_{ASD} = 42$, which were compared with the TD sample from the Stanford cohort. We observed significantly reduced performance in face memory in children with ASD compared with TD children ($t_{68} = -3.49$, $p < .001$) (Figure 2B). These findings demonstrate replicable patterns of reduced scores in general and face memory abilities in children with ASD across independent datasets.

Hierarchical Relations Between General and Face Memory Measures in Children With ASD

To examine whether general and face memory constituted distinct dimensions of memory function in children with ASD,

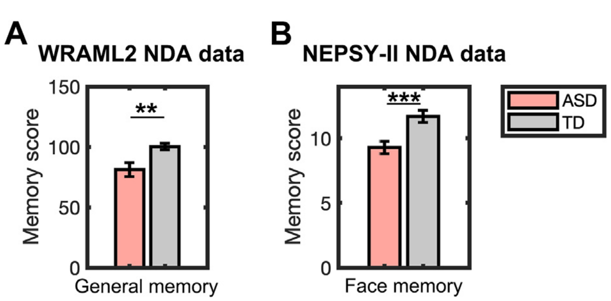

Figure 2. Replication of general and face memory deficits in children with autism spectrum disorder (ASD) from the National Institute of Mental Health Data Archive (NDA) (https://nda.nih.gov/). **(A)** General memory, assessed by the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2), was weaker in children with ASD than in typically developing (TD) children in the WRAML2 NDA replication sample ($n_{ASD} = 22$; $n_{TD} = 24$). **(B)** Face memory, measured by the Developmental Neuropsychological Assessment, Second Edition (NEPSY-II), was also weaker in children with ASD in the NEPSY-II NDA replication sample ($n_{ASD} = 42$) than in the TD sample from the Stanford cohort (no TD sample was available from the NDA for NEPSY-II measure). Error bars represent standard error of the mean. ***$p < .001$, **$p < .01$.

we first examined interrelations between general and face memory measures in children with ASD by computing a correlation matrix of all memory measures. Two distinct blocks of interrelation between memory measures emerged in the ASD group: All general memory measures were highly correlated with each other (rs $\geq$ 0.46, ps $\leq$ .031) (the purple frame in Figure 3A, top; Table S5), and the 2 face memory measures were highly correlated with each other ($r = 0.58$, $p = .005$). More importantly, the correlations between the 2 domains (i.e., general vs. face) were generally low in this group ($|rs| \leq 0.32$, ps $\geq$.146) (the orange frame in Figure 3A, top).

The correlation matrix in the TD group showed stronger associations between general and face memory measures than the ASD group. More specifically, in the TD, compared to the ASD, group, correlations between general memory measures were lower (the purple frame in Figure 3A, bottom; Table S6), while correlations between general and face memory measures were higher (the orange frame in Figure 3A, bottom; Table S6). Direct comparisons of correlation matrices of the ASD and TD groups confirmed that correlations between general memory measures were stronger in the ASD group than in the TD group ($t_{40} = 3.98$, $p < .001$, Cohen's $d = 1.23$) (Figure 3B), and correlations between general and face memory measures were lower in the ASD group than in the TD group ($t_{26} = -3.12$, $p = .004$, Cohen's $d = -1.18$) (Figure 3C). These findings suggest that distinct structures of general and face memory may underlie broadly diminished memory performance in children with ASD.

Next, we conducted a hierarchical clustering analysis that revealed a two-cluster solution, one for general memory and the other for face memory in children with ASD (Figure 3D, top; Table S7). The dendrogram produced by the hierarchical clustering showed that one cluster included all measures of general memory while another cluster included face memory measures. In contrast, clustering analysis in TD children revealed different patterns (Figure 3D, bottom; Figure S4; Table S8), which

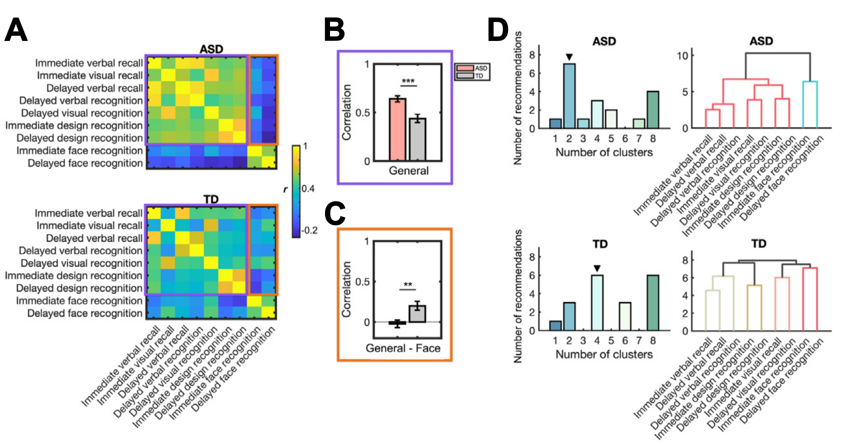

Figure 3. Stronger dissociation between general and face memory in children with autism spectrum disorder (ASD) than in typically developing (TD) children. **(A)** Correlations between memory subscores assessed by the Wide Range Assessment of Memory and Learning, Second Edition (WRAML2) and the Developmental Neuropsychological Assessment, Second Edition (NEPSY-II). Purple frames show correlations between general memory measures. Orange frames show correlations between general and face memory measures. **(B)** Compared to TD children, children with ASD showed higher correlations between general memory measures [purple frames in **(A)**]. **(C)** Compared to TD children, children with ASD showed lower correlations between general and face memory measures [orange frames in **(A)**]. **(D)** Results of hierarchical clustering analysis of memory subscores measured from the WRAML2 and NEPSY-II in each group. ▼ indicates the optimal cluster solution supported by consensus analysis (see details in Methods and Materials). Dendrogram shows clear hierarchical clustering into general and face domains in children with ASD. In TD children, no single cluster had all general memory measures (see also Supplemental Results). ***$p < .001$, **$p < .01$.

suggest four- or eight-cluster solutions. Unlike what was observed in the ASD group, no single cluster had all general memory measures in TD children (Supplemental Results).

Together, converging results suggest that general and face memory are two different underlying constructs contributing to broad memory impairments in children with ASD.

Functional Connectivity of the Hippocampus Predicts General Memory in Children With ASD

Next, we investigated the link between memory function and functional connectivity of the hippocampus in children with ASD. Compared to TD children, children with ASD showed greater functional connectivity between the left hippocampus and the posterior fusiform gyrus, thalamus, and cerebellum. Children with ASD also showed greater connectivity between the right hippocampus and the fusiform gyrus, anterior cingulate cortex, medial prefrontal cortex, supramarginal gyrus, cerebellum, and PCC (Figure 4A; Table S9). No regions showed decreased connectivity with the bilateral hippocampus in ASD compared with the TD group. Results from SVR showed that functional connectivity between the hippocampus and hyperconnected brain regions predicted general memory performance in children with ASD (correlation between predicted and observed values: r = 0.56, $p_{corrected}$ = .016) (Figure 4B). In contrast, these hippocampal connectivity features did not predict general memory performance in TD children ($p_{corrected} > .99$).

To examine whether this prediction was specific to general memory, we performed control analyses, which revealed that hippocampal connectivity features did not predict face memory in children with ASD ($p_{corrected} > .99$) or general or face memory in TD children ($p_{corrected} > .780$) (Table S10).

To further examine the specificity of our findings, we also examined children's performance on matrix reasoning from the

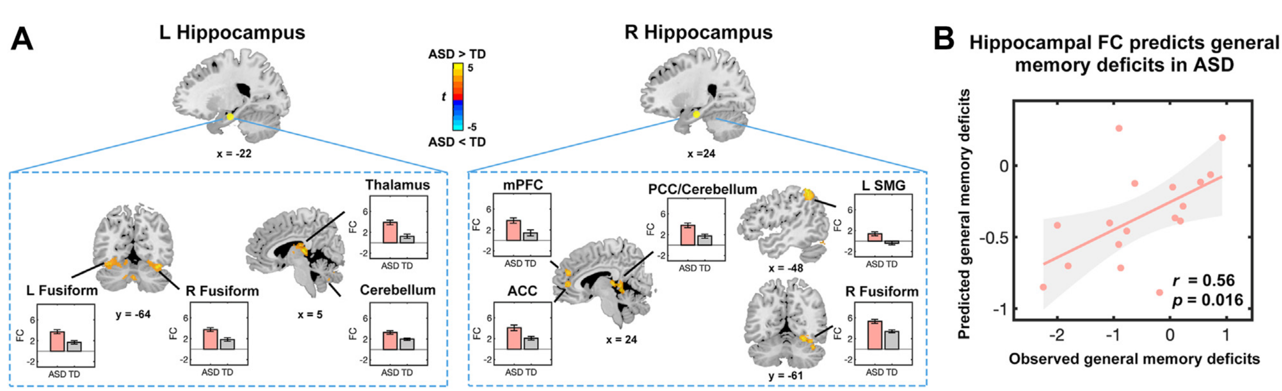

Figure 4. Aberrant hippocampal connectivity predicts general memory deficits in children with autism spectrum disorder (ASD). **(A)** Brain areas showing aberrant connectivity of the hippocampus in children with ASD (height threshold at $p < .01$, with familywise error rate correction at $p < .01$ for cluster extent). Significant hyperconnectivity in children with ASD compared to typically developing (TD) children was observed between the hippocampus and the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), supramarginal gyrus (SMG), medial prefrontal cortex (mPFC), fusiform gyrus, thalamus, and cerebellum. No brain areas showed reduced connectivity with the hippocampus in children with ASD compared to TD children. Error bars represent standard error of mean. **(B)** Support vector regression analysis revealed that aberrant connectivity of hippocampus predicts deficits in general memory in children with ASD. Each dot represents data from one child. r is the correlation between observed and predicted general memory deficits scores. p was obtained using permutation testing, and results were Bonferroni corrected for multiple comparisons across regions of interests and memory measures. FC, functional connectivity; L, left; R, right.

Wechsler Abbreviated Scale of Intelligence (45), which utilized similar visual stimuli (e.g., shapes, designs, etc.) as those used in memory tasks in the current study but without requirements for memory recall. We found that hippocampal connectivity features did not predict variance in matrix reasoning performance in children with ASD ($p > .060$).

Finally, we examined the functional connectivity of other brain regions implicated in episodic memory, including the prefrontal cortex and posterior parietal cortex (Table S11). No significant associations between connectivity features and general memory scores were observed for these brain regions in children with ASD ($ps_{corrected} > .15$) (Supplemental Results). Together, these findings identify a specific link between hyperconnected hippocampal circuits and general memory dysfunction in children with ASD.

Functional Connectivity of the PCC Predicts Face Memory in Children With ASD

Finally, we examined the link between memory function and functional connectivity of the PCC in children with ASD. Compared to TD children, children with ASD showed greater functional connectivity between the PCC and the amygdala, hippocampus, caudate, thalamus, fusiform gyrus, and middle occipital gyrus (Figure 5A; Table S12). Results from SVR analysis showed that these hyperconnected links predict face memory performance in children with ASD ($r = 0.42$, $p_{corrected} = .016$) (Figure 5B). These PCC connectivity features were not predictive of general memory performance in children with ASD ($p_{corrected} = .192$) or general or face memory in TD children ($ps_{corrected} > .99$) (Table S10). We also examined Wechsler Abbreviated Scale of Intelligence (45) matrix reasoning task performance and did not find any significant relationship with PCC connectivity features in children with ASD ($p = .301$). Furthermore, functional connectivity of other brain regions implicated in social cognition, including the fusiform face area, amygdala, and temporoparietal junction, (Table S11) did not significantly predict face memory performance scores in children with ASD ($ps_{corrected} > .99$) (Supplemental Results). Together, these findings identify a specific link between hyperconnected PCC circuits and face memory dysfunction in children with ASD.

DISCUSSION

Memory abilities and their links to functional brain circuitry are a crucial but understudied area of childhood ASD. Our survey of the existing literature revealed a lack of comprehensive assessments of general and face memory in a within-subject design, inconsistent behavioral findings, limited characterization of the underlying neural circuitry, and lack of replication (Table S1). We used a comprehensive battery of standardized memory assessments and functional circuit analyses in a well-characterized sample of children with ASD and matched TD children. We showed that children with ASD had broad, diminished performance in memory function. Critically, general and face memory reductions were identified as distinct dimensions of memory function in children with ASD, but not in TD children. Functional circuit analysis identified the nodes of the DMN that were associated with different dimensions of memory impairments in ASD: while hippocampal brain circuits predicted general memory performance, PCC circuitry predicted face memory performance. Our study represents the first comprehensive appraisal of both general and face memory function in children with ASD and identified replicable patterns of memory reductions in independent cohorts of children with ASD that are linked to dysfunction of distinct DMN circuits. The findings highlight a crucial role of the DMN in ASD that extends beyond social cognition.

Memory plays a key role in cognitive, social, and academic development (46,47). We examined both general and face memory in children with ASD compared with TD children, and we sought to determine whether they form distinct components of aberrant memory in affected children. A plausible hypothesis is that general and face memory tasks rely on shared cognitive mechanisms given the similarity of task procedures and requirements. For example, both general and face memory tasks require that participants encode and then subsequently recall or recognize specified target stimuli, with the only difference being the type of stimulus encoded. Across 2 independent cohorts, we found replicable evidence for reduced episodic memory for both faces and general stimuli in children with ASD. Our findings help resolve inconsistent findings on episodic memory in childhood ASD that have been reported in previous studies (Table S1).

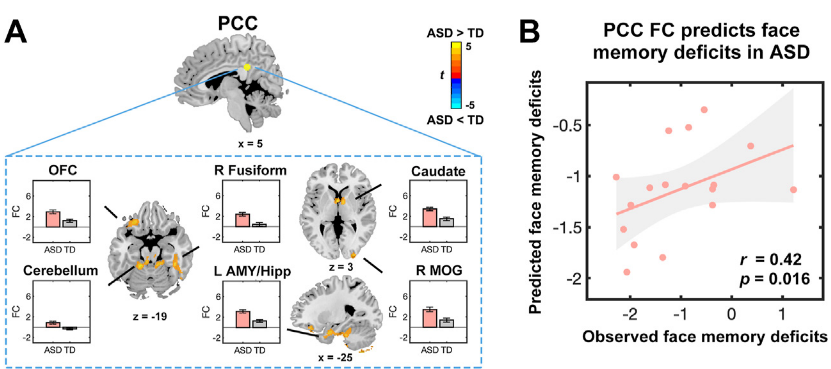

Figure 5. Aberrant posterior cingulate cortex (PCC) connectivity predicts face memory deficits in children with autism spectrum disorder (ASD). **(A)** Brain areas showing aberrant connectivity with the PCC in children with ASD (height threshold at $p < .01$, with familywise error rate correction at $p < .01$ for cluster extent). Significant hyperconnectivity in children with ASD compared with typically developing (TD) children was observed between the PCC and the orbitofrontal cortex (OFC), fusiform gyrus, amygdala (AMY), hippocampus (Hipp), caudate nucleus, and middle occipital gyrus (MOG). No brain areas showed reduced connectivity with the PCC in children with ASD compared to TD children. Error bars represent standard error of the mean. **(B)** Support vector regression analysis revealed that aberrant PCC connectivity predicts face memory deficits in children with ASD. Each dot represents the data from one child. r represents the correlation between observed and predicted face memory deficits scores. p was obtained using permutation testing, and results were Bonferroni corrected for multiple comparisons across regions of interests and memory measures. FC, functional connectivity; L, left; R, right.

Our findings are consistent with previous findings of face memory deficits in adolescents and adults with ASD (7,48). Research has consistently identified a relationship between face memory performance and autistic symptom severity in adolescents (49,50). Moreover, face memory deficits have been recognized as a core aspect of symptom profiles based on meta-analysis (51) and a potential endophenotype in ASD based on findings from a recent study in adults (52). Furthermore, our results showed that face memory was independent of IQ in children with ASD (Supplemental Results). Similarly, face memory deficits consistently identified among child and adult studies have been independent from IQ (51). These findings point to a pattern of developmentally stable deficits in episodic memory for faces in ASD, which is consistent with reports suggesting lack of improvement in face memory across development in ASD (53).

Beyond face memory, children with ASD also showed significant deficits in delayed visual recognition on NEPSY-II but not in delayed visual recognition on WRAML2. This discrepancy is likely due to different task designs in the two assessments. Although both use simple geometric designs as stimuli, the WRAML2 visual recognition subtests display one stimulus at a time and require children to make a binary response of Yes or No during the response phase, while the NEPSY-II visual recognition subtests present a series of stimuli and require children to choose one of them. The latter may impose relatively high cognitive demands on children with ASD because it requires them to suppress interference from other options. Overall, children with ASD showed both diminished recall and recognition in our study, in contrast to adults who report relatively unaffected recognition abilities (54). Further studies are needed to systematically examine the impact of task requirements on memory performance, which is critical for gaining a clearer understanding of the core memory deficits in affected children and their developmental progression (55).

Crucially, our hierarchical cluster analysis revealed that shared cognitive mechanisms underlie general and face memory abilities in TD children, who showed significant correlations between these two aspects of memory function. In contrast, children with ASD did not show a significant relationship between general and face memory abilities, which suggests that these memory components are driven by distinct cognitive mechanisms in ASD. One possible explanation for these findings is that an element of ASD symptomatology affects face memory performance that is independent from general memory abilities. For example, reduced eye contact and time spent socially interacting may be factors that contribute to specific face memory deficits in ASD (48,49). Another plausible explanation is that restricted and circumscribed interests and excessive attention to details associated with ASD may impair pattern separation for face stimuli, which tend to be more similar than other classes of visual stimuli (56,57). Together, our findings support a broad memory deficit model of ASD in which face and general memory reductions represent distinct factors influencing memory performance (9).

Next, we examined the role of PCC and hippocampus nodes of the DMN, a large-scale brain network implicated in cognitive and social dysfunction in ASD. Aberrant function of the DMN has consistently been linked to impaired social function in ASD (13,58). However, the hippocampus and PCC nodes of the DMN have also been implicated in memory function in neurotypical individuals (16–21,26,27), and it is unknown whether the integrity of these functional circuits is related to distinct dimensions of memory function in children with ASD. Our results revealed that hyperconnectivity of the hippocampus predicted general memory reductions in children with ASD. In contrast, hyperconnectivity of the PCC predicted face memory reductions in children with ASD. Notably, hippocampal-PCC circuitry was a common feature of general and face memory reductions in ASD.

Our study provides new insights into DMN dysfunction and its links to memory abilities in children with ASD. Importantly, we found that memory impairments in ASD were associated with hyperconnected, rather than hypoconnected, hippocampal and PCC circuits. This result is consistent with a growing literature highlighting the prevalence of hyperconnected brain circuitry in children with ASD, including the DMN (58–60). Previous studies have shown that functional hyperconnectivity in children with ASD is associated with increased symptom severity and elevated regional brain fluctuations (60). This hyperconnectivity is hypothesized to arise from an imbalance of neural excitation and inhibition and may explain a key component of neurophysiology in ASD (61–64). Our findings add to this evidence by suggesting that memory impairments in ASD may result from hyperconnectivity of DMN circuits, which could be similarly impacted by a similar excitation-inhibition imbalance. Moreover, hyperconnectivity in these circuits may hinder appropriate task-related modulation and cause overlap between distinct memories, thereby affecting memory abilities.

Our study sheds light on the impact of hyperconnected hippocampus circuits in episodic memory function in children with ASD. Previous research on neurotypical individuals has demonstrated that the hippocampus, in conjunction with prefrontal and parietal brain systems, is integral to the encoding and retrieval of episodic memory (22,23). Our findings are consistent with previous studies that have provided evidence for a relationship between the functional connectivity of the hippocampus and episodic memory performance across different age groups spanning childhood, adolescence, and adulthood (65–67). However, the magnitude of memory impairments and the relationship between aberrant hippocampus circuitry and memory in ASD have not been consistent across studies, likely due to differences in the developmental stage, the wide age ranges of study participants, and differences between task and resting-state fMRI connectivity. Results from the current study suggest that aberrations in the intrinsic circuitry of the hippocampus underlie general memory reductions during a developmental stage that is closer to the onset and diagnosis of ASD.

Our results also provide new information regarding a role for the PCC in memory function in children with ASD. The PCC is a primary node or hub of the DMN and has a key role in autobiographical memory and social cognitive functions (21,68), including social memory (27). Our results demonstrate that aberrant PCC circuitry is a significant predictor of face memory reductions in ASD and highlight PCC functions that extend beyond social memory to general episodic memory. These results suggest that dysfunctional PCC circuits are not only associated with deficits in social communication in ASD but also extend to a broad range of episodic memory deficits.

Individuals with ASD achieve lower levels of postsecondary education and independent living than other clinical populations (69). Our findings of distinct general and face memory dysfunction in children with ASD may have practical implications for these individuals. While many ASD interventions are focused on improving social and language function (70), a more comprehensive intervention that takes general episodic memory deficits into account may further improve cognitive function in these children. Moreover, if parents, caregivers, and teachers are aware of multiple dimensions of memory deficits in children with ASD, it may help them better understand the challenges that these children face in their daily lives and may inform their interactions to support their learning and development.

Several limitations of this study warrant consideration and suggest avenues for future work. First, larger sample sizes are needed to validate the observed memory impairments and to further characterize the heterogeneity of memory function in children with ASD. Second, our study focused on memory reductions and related neural circuits in children with ASD who do not have an intellectual disability, and it is unclear whether these mechanisms also apply to children with more severe forms of ASD. Additional research that includes a broader spectrum of autism is required to address this question. Third, while our findings demonstrate a relationship between hippocampal/PCC functional circuits and memory reductions in ASD, whether there is a causal relationship remains unclear. Further investigations with appropriate task-based fMRI studies and longitudinal designs are needed to explore the interaction between brain circuits, neural representations, and memory abilities and their developmental trajectories. Lastly, future studies should address the suitability of standardized psychological instruments for atypical populations (55), including children with autism, taking into consideration the different developmental trajectories that may impact the measurement of cognitive functioning.

Conclusions

Our study reveals that children with ASD have an array of memory reductions that affect both general and face memory and that distinct, but overlapping, DMN circuits predict performance in these two areas of memory function. Our findings identify novel neurobiological targets for memory intervention in children with ASD and point to a potentially outsized role for the DMN in neurocognitive dysfunction in affected children. More broadly, our findings provide a renewed focus on areas of impairments in ASD and further elucidate various challenges that individuals with ASD may experience as they navigate their social, educational, and professional environments.

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