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# Replicable patterns of memory impairments in children with autism and their links to hyperconnected brain circuits

Jin Liu<sup>1\*</sup>, Lang Chen<sup>2</sup>, Hyesang Chang<sup>1</sup>, Jeremy Rudoler<sup>1</sup>, Ahmad Belal AI-Zughoul<sup>1</sup>, Julia Boram Kang<sup>1</sup>, Daniel A. Abrams<sup>1</sup>, Vinod Menon<sup>1,3,4\*</sup>

 <sup>1</sup>Department of Psychiatry & Behavioral Sciences Stanford University School of Medicine, Stanford, CA 94305
 <sup>2</sup>Department of Psychology, Santa Clara University, Santa Clara, CA 95053
 <sup>3</sup>Department of Neurology & Neurological Sciences
 <sup>4</sup> Wu Tsai Stanford Neurosciences Institute, Stanford University School of Medicine, Stanford, CA 94305

Short Title: General and face memory deficits in children with ASD

\*Address for Correspondence:

Jin Liu, Ph.D; Vinod Menon, Ph.D. Department of Psychiatry & Behavioral Sciences 401 Quarry Rd. Stanford, CA 94305

Email: jinliu5@stanford.edu; menon@stanford.edu

#### 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 employed a comprehensive battery of standardized episodic memory assessments and functional circuit analyses in 8-12-year-old 25 children with ASD and 29 matched typically developing controls.

**RESULTS:** Memory performance was reduced in children with ASD, compared to controls. 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 two 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:** 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. Findings highlight a role for DMN dysfunction in ASD that extends beyond face memory to general memory function.

**Keywords:** Episodic memory, Autism, Default mode network, Hippocampus, Posterior cingulate cortex, Recollection and familiarity, Face memory.

#### Introduction

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 are 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 may 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, a lack of measures of general cognitive abilities, and a wide age range of study participants (**Table S1**). Additionally, no prior 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 is comprised of distributed and interconnected nodes encompassing the posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), angular gyrus (AG), and hippocampus. Importantly, atypical functional connectivity of 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 lateral prefrontal, temporal, and posterior parietal cortex 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. We first sought to overcome limitations of previous behavioral studies by employing a comprehensive battery of standardized episodic memory assessments (**Figure S1**) in a well-

characterized sample of 8–12-year-old children with ASD with normal intelligence quotient (IQ), and IQ-, age-, gender-matched typically developing (TD) children, and validating the main findings in independent cohorts of participants (**Table 1** and **Table S1**). We used hierarchical clustering analysis to examine whether general and face memory constituted distinct dimensions of memory function in children with ASD. This analysis is critical to adjudicate between different theoretical models, including face-specific and general memory deficit models, associated with reduced memory performance in ASD. We then 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 compared to 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.

#### **Materials and Methods**

#### **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 children (25 children with ASD and 29 matched TD children) aged 8 to 12 years completed the study (**Table 1**). The diagnosis of ASD was confirmed by an experienced clinical psychologist using the standard criteria based on Autism Diagnostic Interview-Revised (ADI-R) (29) and/or the Autism Diagnostic Observation Schedule (ADOS) (30). Detail inclusion criteria and demographic information can be found in **Supplementary Materials**. 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 Wide Range Assessment of Memory and Learning, Second Edition (WRAML2) (31) and A Developmental NEuroPSYchological Assessment, Second Edition (NEPSY-II) (32) were administered by trained assessors (**Supplementary Methods**).

**WRAML2**. Ten subtests were administered. We generated five memory subscores based on relevant subtests (**Figure S1**): *i*) immediate verbal; *ii*) delayed verbal recall; *iii*) immediate visual recall; *iv*) delayed verbal recognition; *v*) delayed visual recognition. A composite total memory score of WRAML2 was generated by averaging five memory subscores to represent general memory performance.

**NEPSY-II**. Four subtests were administered. Four memory subscores were defined by the scaled scores of these four subtests. A composite general memory score was generated by averaging the scaled scores of two design subtests. A composite face memory score was generated by averaging the scaled scores of two 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 as well as the effects of retrieval type, type of material, delay interval and their interactions with group. Here, we modeled the unbalanced design of five memory subscores in which only verbal recall had both immediate and delayed versions, as follows:

 $y_i = \beta_0 + b_i + \beta_1$  Group +  $\beta_2$  Retrieval Type +  $\beta_3$  Type of Material +  $\beta_4$  Delay Interval +  $\beta_5$  Group×Retrieval Type +  $\beta_6$  Group×Type of Material +  $\beta_7$  Group×Delay Interval +  $\varepsilon_i$ 

where  $y_i$  is the observed memory subscore for subject *i* and  $\varepsilon_i$  is the residual of subject *i*.

Group differences and interaction between group and memory dimensions in general and face memory scores (NEPSY-II). A 2x2x2 mixed-design ANOVA was performed with group as a between-subject factor and content domain and delay interval as within-subject factors.

**Replication analysis with NDA cohort data.** Using an open-source dataset, the National Institute of Mental Health Data Archive (NDA; <u>https://nda.nih.gov/</u>), we identified two cohorts: *i*) WRAML replication cohort, and *ii*) 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 (33-35) 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 one to eight (NbClust 3.0.1 package in R 4.1.0)(36).

*General and face memory reduction scores in ASD.* For each child with ASD, two composite memory reduction scores were generated. A general memory reduction score was obtained by averaging the scaled reduction scores of all general memory assessments from WRAML2 and NEPSY-II. A face memory reduction score was obtained by averaging the scaled reduction score scores of NEPSY-II for two faces memory assessments. The scaled reduction score was calculated as follows:

$$x_{ASD}' = \frac{x_{ASD} - M_{TD}}{SD_{TD}}$$

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  $\eta_p^2$  was calculated to estimate effect sizes.

#### Brain imaging analysis

Functional connectivity analysis. Details of fMRI data acquisition and preprocessing are described in Supplementary Methods. For each child, voxel-wise whole-brain functional connectivity analysis was performed for using hippocampus and PCC regions of interest (ROIs; Figure S3). The PCC ROI (MNI: 4-38 32) was defined using coordinates from the largest metaanalysis of fMRI studies on social cognition deficits in ASD, which encompassed 50 studies and included 675 individuals with ASD and 695 TD individuals (Patriquin et al., 2016). Voxels in non-grey 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 (Yarkoni et al., 2011), with the search term 'episodic memory', which identified a large cluster in the medial temporal lobe including the hippocampus. ROIs in the left (MNI: -24 -14-20) and right (MNI: 24-14-20) hemisphere were then selected based on overlap of the metaanalysis-derived cluster with hippocampus coordinates from our previous study of medial temporal lobe connectivity patterns along the long axis of the hippocampus (Qin et al., 2016). Please see **Supplementary Methods** for definition of control ROIs. Two sample *t*-tests examined group differences in connectivity for each ROI. Results were corrected for multiple comparisons using a height threshold of p < 0.01 and family-wise error rate correction at p < 0.010.01 (cluster extent of 128 voxels) based on Monte Carlo simulations using a custom MATLAB script.

*Multivariate brain-behavior association analysis.* We employed an epsilon-insensitive support vector regression (SVR) analysis with a non-linear sigmoid kernel (41) to investigate brainbehavior association. This supervised machine-learning approach is widely used in the field and was selected for its robust performance (41-45). First, for each ROI, we identified all target brain regions which 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 comparison ( $p_{corrected} = p \times 4$  for two regions of interest and two memory scores in each group). We performed additional control analysis using matrix reasoning score of the WASI to examine the specificity of our findings with respect to memory measures.

#### Results

#### General memory reductions in children with ASD examined using WRAML2

A linear mixed model showed a significant main effect of group ( $\beta = 4.86$ , p = 0.002). There was no significant main effect of retrieval type, type of material, or delay interval, or their interactions with group ( $\beta$ s < 1.25, ps > 0.14; **Table S3**). A planned two-sample *t*-test on total general memory score from the WRAML2 revealed that children with ASD had significantly reduced scores relative to TD children (t(49) = -2.59, p = 0.012, Cohens' 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, ps < 0.035, Cohens' d < -0.61; **Figure 1A**, **right** and **Table 1**), but not on delayed visual recognition (t(49) = -0.03, p = 0.977; Cohen's d = -0.01). Together, these results provided 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 to TD peers, highlighting general memory reductions in these individuals.

### General and face memory reductions in children with ASD examined using NEPSY-II

A mixed-design ANOVA with group, content domain, and delay interval revealed a significant effect of group (F(1, 49) = 20.22, p < 0.001,  $\eta^2_p = 0.29$ ), 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 was observed (Fs < 2.43, ps > 0.126; **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 to the TD group (ts < -2.46, ps < 0.017, Cohen's ds < -0.69; **Figure 1B&C**, **left**). Additional analyses confirmed reduced performance across short and long delay interval for general and face memory in the ASD group compared to the TD group. Significantly lower scores were observed in children with ASD for all subscores (ps < 0.05), except for immediate design recognition (**Figure 1B&C**, **right** and **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

We queried the NDA dataset for WRAML2 and NEPSY-II measures, which assess general and face memory, respectively (**Figure S2**). The WRAML2 replication sample comprised N<sub>ASD</sub> = 22 and N<sub>TD</sub> = 24 participants. We observed significant lower scores in general memory in children with ASD compared to TD children (t(44) = -3.08, p = 0.004; **Figure 2A**). The NEPSY-II replication sample comprised N<sub>ASD</sub> = 42, which were compared to the TD sample from the Stanford cohort. We observed significantly reduced performance in face memory in children with ASD compared to TD children (t(68) = -3.49, p < 0.001; **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

We first examined inter-relations 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 ( $rs \ge 0.46$ ,  $ps \le 0.031$ ; **Figure 3A**, **top**; **Table S5**), and the two face memory measures were highly correlated with each other (r = 0.58, p = 0.005). More importantly, the correlations between the two domains (i.e., general vs. face) were generally low in this group ( $|rs| \le 0.32$ ,  $ps \ge 0.146$ ; the orange frame in **Figure 3A**, **top**).

The correlation matrix in the TD group showed stronger association between general and face memory measures compared to the ASD group. Specifically, in the TD group, correlations

between general memory measures were lower ( $rs \ge 0.13$ ,  $ps \le 0.53$ ; the purple frame in **Figure 3A**, **bottom**; **Table S6**) while correlations between general and face memory measures were higher ( $|rs| \le 0.50$ ,  $ps \ge 0.009$ ; the orange frame in **Figure 3A**, **bottom**). Direct comparisons of correlation matrices of ASD and TD groups confirmed that correlations between general memory measures are stronger in the ASD group compared to the TD group (t(40) = 3.98, p < 0.001, Cohens' d = 1.23; **Figure 3B**), but the correlation between general and face memory measures was lower in the ASD group compared to the TD group (t(26) = -3.12, p = 0.004, Cohens' d = -1.18; **Figure 3C**). These findings suggest that distinct structures of general and face memory might underlie broadly diminished memory performance in children with ASD.

Next, we conducted a hierarchical clustering analysis which revealed a two-cluster solution, one for general memory and the other for face memory in children with ASD (**Figure 3D**, **top** and **Table S7**). The dendrogram produced by the hierarchical clustering suggested 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** and **Table S8**), which 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 (**Supplementary Results**).

Together, convergent results suggested general and face memory as 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

Compared to TD children, children with ASD showed greater functional connectivity between the left hippocampus and posterior fusiform gyrus, thalamus and cerebellum. Children with ASD also showed greater connectivity between the right hippocampus and fusiform gyrus, anterior cingulate cortex, medial prefrontal cortex, supramarginal gyrus, cerebellum and PCC (**Figure 4A** and **Table S9**). No regions showed decreased connectivity with the bilateral hippocampus in ASD compared to 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,  $p_{corrected} =$ 0.016; **Figure 4B**). In contrast, these hippocampal connectivity features did not predict general memory performance in TD children ( $p_{corrected} > 0.99$ ).

To examine whether this prediction is specific for general memory, we performed additional analysis which revealed that hippocampal connectivity features did not predict face memory in children with autism ( $p_{corrected} > 0.99$ ) or in TD children ( $p_{corrected} > 0.780$ ; **Table S10**). To further examine specificity of our findings, we additionally examined children's performance on matrix reasoning from the Wechsler Abbreviated Scale of Intelligence (WASI), 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 > 0.060).

Finally, we examined 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 ( $p_{s_{corrected}} > 0.15$ ; **Supplementary 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

Compared to TD children, children with ASD showed greater functional connectivity between the PCC and the amygdala, hippocampus, caudate, thalamus, fusiform, and middle occipital gyrus (**Figure 5A** and **Table S12**). Results from SVR analysis showed that these hyperconnected links predicted face memory performance in children with ASD (r = 0.42,  $p_{corrected} = 0.016$ ; **Figure 5B**). These PCC connectivity features were not predictive of general memory performance in children with ASD ( $p_{corrected} = 0.192$ ) nor were they predictive of general or face memory in TD children ( $p_{scorrected} > 0.99$ ; **Table S10**). We additionally examined WASI matrix reasoning task performance and did not find significant relation with PCC connectivity features in children with ASD (p = 0.301). 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 ( $p_{scorrected} > 0.99$ ; **Supplementary 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 extant literature revealed lack of comprehensive assessments of general and face memory in a within-subjects 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 show that children with ASD have 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 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 independent cohorts of children with ASD, and identify replicable patterns of memory reductions in children with ASD that are linked to dysfunction of distinct DMN circuits. Findings highlight a crucial role of the DMN in ASD that extends beyond social cognition.

Memory play a key role in cognitive, social, and academic development (46, 47). We examined both general and face memory in children with ASD compared to 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 two 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 reported in prior literature (**Table S1**).

Findings converge on prior 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 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, consistent with reports suggesting lack of improvement in face memory over development in ASD (53).

Beyond face memory, children with ASD also showed significant deficits on visual recognition subtests of NEPSY-II, but not in the delayed visual recognition performance on WRAML2. This discrepancy is likely due to the different task designs in the two assessments. Although both use simple geometric designs as stimuli, WRAML2 recognition subtests display one stimulus at a time and requires children to make a binary response of "Yes" or "NO" during the response phase, while NEPSY-II recognition subtests present a series of stimuli and requires children to choose one. The latter may impose relatively high cognitive demands for children with ASD, as it requires them to suppress interference from other options. Children with ASD showed both diminished recall and recognition in our study, in contrast to adults who report relatively unaffected recognition (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, 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 the 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 been consistently 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 are associated with hyperconnected, rather than hypo-connected, 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 converge on previous studies which have provided evidence for a relation 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, wide age ranges of study participants, as well as 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 closer to the onset and diagnosis of ASD.

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 post-secondary education and independent living compared to 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 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 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 participants is required to address this question. Third, while our findings demonstrate a relation between hippocampal/PCC functional circuits and memory reductions in ASD, 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 trajectory. Lastly, future studies should address the suitability of standardized psychological instruments for atypical populations (55), including children with autism, as different developmental trajectories may impact the measurement of comparable psychological abilities.

In conclusion, 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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#### **Competing interests**

The authors report no biomedical financial interests or potential conflicts of interest.

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### **Figure Legends**

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 (see also Figure S1), as measured by WRAML2, was significantly lower in children with ASD compared to well-matched TD children. Immediate verbal and visual recall, delayed verbal recall, and delayed verbal recognition abilities were weaker in children with ASD, relative to TD children. (B) General memory, assessed by 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 NEPSY-II, was significantly lower in children with ASD. Error bars represent the standard error of the mean. WRAML2, Wide Range Assessment of Memory and Learning, Second Edition; NEPSY-II, Developmental Neuropsychological Assessment, Second Edition; \*\*\* p < 0.001; \*\* p < 0.01; \* p < 0.05; (\*) p < 0.10.

Figure 2. Replication of general and face memory deficits in children with autism spectrum disorder (ASD) from NDA. (A) General memory, assessed by WRAML2, was weaker in children with ASD compared to typically developing (TD) children in the WRAML2 NDA replication sample (N<sub>ASD</sub> = 22; N<sub>TD</sub> = 24). (B) Face memory, measured by NEPSY-II, was also weaker in children with ASD in the NEPSY-II NDA replication sample (N<sub>ASD</sub> = 42) compared to TD sample from the Stanford cohort (no TD sample was available from NDA for NEPSY-II measure). Error bars represent standard error of mean. WRAML2, Wide Range Assessment of Memory and Learning, Second Edition; NEPSY-II, Developmental Neuropsychological Assessment, Second Edition; NDA, National Institute of Mental Health Data Archive (<u>https://nda.nih.gov/</u>); \*\*\* p < 0.001; \*\* p < 0.01.

Figure 3. Stronger dissociation between general and face memory in children with autism spectrum disorder (ASD) compared to typically developing (TD) children. (A) Correlations between memory subscores assessed by WRAML2 and NEPSY-II. Purple frames show correlations between general memory measures. Orange frames show correlations between general memory measures. Orange frames show correlations between general memory measures. (B) Compared to TD children, children with ASD showed higher correlations between general memory measures (purple frames in Figure 3A). (C) Children with ASD, relative to TD children, showed lower correlations between general and face memory measures (orange frames in Figure 3A). (D) Results of hierarchical clustering analysis of memory subscores measured from WRAML2 and NEPSY-II in each group.  $\checkmark$  indicates the optimal cluster solution supported by consensus analysis (see details in Methods). 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 Supplementary Results). WRAML2, Wide Range Assessment of Memory and Learning, Second Edition; NEPSY-II, Developmental Neuropsychological Assessment, Second Edition; \*\*\* p < 0.001; \*\* p < 0.01.

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 < 0.01, with family-wise error rate correction at p < 0.01 for cluster extent). Significant hyperconnectivity in children with ASD compared to typically developing (TD) children was observed between the hippocampus and

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 reveals 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.

Figure 5. Aberrant posterior cingulate cortex connectivity predicts face memory deficits in children with autism spectrum disorder (ASD). (A) Brain areas showing aberrant connectivity with the posterior cingulate cortex (PCC) in children with ASD (height threshold at p < 0.01, with family-wise error rate correction at p < 0.01 for cluster extent). Significant hyperconnectivity in children with ASD compared to typically developing (TD) children was observed between the PCC and 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 mean. (B) Support vector regression analysis reveals that aberrant PCC connectivity predicts face memory deficits in children with ASD. Each dot presents 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.

Measure	$\frac{5 \text{ on organity out}}{\text{ASD } (n = 25)}$	TD (n = 29)	$\frac{t}{\chi^2}$	df	Cohen's d	p
Gender (Male/Female)	21/4	24/5	0.01ª	1	0.01	0.903
Age	10.44 (1.29)	10.41 (1.24)	0.08	52	0.02	0.940
WASI scale						
Verbal IQ	114.96 (16.00)	120.41 (15.08)	-1.29	52	-0.35	0.203
Performance IQ	113.76 (16.75)	118.79 (16.56)	-1.11	52	-0.30	0.273
Full IQ	116.00 (16.55)	122.17 (15.99)	-1.39	52	-0.38	0.170
WRAML2 <sup>†</sup>						
Immediate verbal recall	10.23 (3.12)	12.56 (2.62)	-2.89	49	-0.81	0.006
Immediate visual recall	8.50 (2.61)	10.20 (2.95)	-2.17	49	-0.61	0.035
Delayed verbal recall	10.38 (2.84)	12.39 (2.16)	-2.86	49	-0.80	0.006
Delayed verbal recognition	10.50 (2.70)	12.04 (1.51)	-2.55	49	-0.71	0.014
Delayed visual recognition	10.48 (2.62)	10.50 (2.48)	-0.03	49	-0.01	0.977
Total general memory	10.02 (2.38)	11.54 (1.79)	-2.59	49	-0.73	0.012
NEPSY-II <sup>††</sup>						
Immediate design recognition	10.30 (3.14)	12.07 (3.14)	-2.00	49	-0.56	0.051
Delayed design recognition	9.96 (2.90)	12.18 (3.02)	-2.66	49	-0.75	0.010
Total general memory	10.13 (2.87)	12.12 (2.89)	-2.46	49	-0.69	0.017
Immediate face recognition	8.43 (2.94)	11.71 (3.16)	-3.81	49	-1.07	< 0.001
Delayed face recognition	9.43 (3.53)	11.68 (2.68)	-2.58	49	-0.73	0.013
Total face memory	8.93 (2.88)	11.70 (2.52)	-3.65	49	-1.03	< 0.001
ADI-R <sup>†††</sup>						
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 <sup>††††</sup>						
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)					

Table 1. Demographic, neuropsychological, and clinical measures

The mean (standard deviation) of measure, t or  $\chi^2$ , effect size Cohen's d and p value of two sample t-test/chi-square test are shown here. t statistics are obtained unless otherwise noted. ASD, Children with autism spectrum disorder; TD, typically developing children; IQ, Intelligence quotient; WASI, Wechsler Abbreviated Scale of Intelligence; WRAML2, Wide Range Assessment of Memory and Learning, Second Edition; NEPSY-II, Developmental Neuropsychological Assessment, Second Edition; ADI-R, Autism Diagnostic Interview-Revised (diagnostic scores); ADOS, Autism Diagnostic Observation Schedule-new algorithm.

<sup>a</sup>Chi-squared statistic.

<sup>†</sup> Missing data from 3 participants (ASD: n = 1; TD n = 2).

<sup>††</sup> Missing data from 3 participants (ASD: n = 2; TD n = 1).

<sup>†††</sup> Missing data from 1 participant (ASD: n = 1).

<sup>††††</sup> Missing data from 2 participants (ASD: n = 2).





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