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RESEARCH ARTICLE

Specialization of anterior and posterior hippocampal functional connectivity differs in autism

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Abstract

Structural and functional differences in the hippocampus have been related to the episodic memory and social impairments observed in autism spectrum disorder (ASD). In neurotypical individuals, hippocampal–cortical functional connectivity systematically varies between anterior and posterior hippocampus, with changes observed during typical development. It remains unknown whether this specialization of anterior–posterior hippocampal connectivity is disrupted in ASD, and whether age-related differences in this specialization exist in ASD. We examined connectivity of the anterior and posterior hippocampus in an ASD ($N = 139$) and non-autistic comparison group ($N = 133$) aged 5–21 using resting-state functional magnetic resonance imaging (MRI) data from the Healthy Brain Network (HBN). Consistent with previous results, we observed lower connectivity between the whole hippocampus and medial prefrontal cortex in ASD. Moreover, preferential connectivity of the posterior relative to the anterior hippocampus for memory-sensitive regions in posterior parietal cortex was reduced in ASD, demonstrating a weaker anterior–posterior specialization of hippocampal–cortical connectivity. Finally, connectivity between the posterior hippocampus and precuneus negatively correlated with age in the ASD group but remained stable in the comparison group, suggesting an altered developmental specialization. Together, these differences in hippocampal–cortical connectivity may help us understand the neurobiological basis of the memory and social impairments found in ASD.

Lay Summary

The brain's hippocampus is an important structure for memory, learning, and social interaction. Research has shown differences in the structure and function of the hippocampus in autism. We investigated the anterior–posterior specialization of the hippocampus; whereby the front and back portions of the hippocampus display unique patterns of coordinated activity with the rest of the brain. This specialization matures during child development and is related to memory performance. Based on previous work, we hypothesized that hippocampal specialization would differ in those diagnosed with autism. Using magnetic resonance imaging, we measured the coordinated activity of the hippocampus with the rest of the brain in autistic and non-autistic children and young adults. We identified several brain regions displaying different hippocampal specialization between autistic and non-autistic participants. Many of these regions are known to be

involved in memory processes. Interestingly, only the autistic group showed age-related differences in specialization. This suggests that distinct developmental patterns of hippocampal specialization exist in autistic and non-autistic children. These findings help us understand how the hippocampus functions differently in autism and may give insight into differences in memory and social behavior.

KEYWORDS
autism spectrum disorder (ASD), anterior/posterior, development, episodic memory, hippocampus, hippocampus, longitudinal axis, medial prefrontal cortex, resting-state functional connectivity

INTRODUCTION

Measures of functional connectivity, which are derived by regionally correlating tissue oxygenation levels estimated through fMRI (functional magnetic resonance imaging), are amongst the neuroimaging measures with the highest sensitivity to autism spectrum disorder diagnoses (ASD; Hull et al., 2017; Traut et al., 2022). Recent work examining resting-state and task-based functional connectivity in ASD has reported atypical patterns in the hippocampus (Cooper et al., 2017; Liu et al., 2023): a medial temporal lobe structure crucial for learning and memory, and recently linked to social functioning (Banker et al., 2021; Montagrin et al., 2018; Tao et al., 2022; Tavares et al., 2015). Compared to neurotypical controls, ASD participants show hippocampal hypo-connectivity with lateral prefrontal regions during episodic memory retrieval (Cooper et al., 2017), and hyper-connectivity with the fusiform gyrus and default mode regions at rest (Liu et al., 2023). Work in ASD rodent models has also found alterations in hippocampal connectivity: in *POGZ*-deficient mice (a high confidence ASD gene), electrophysiological measures of functional connectivity between the ventral hippocampus and medial prefrontal cortex are disrupted (Cunniff et al., 2020). These findings have been taken to suggest the cognitive-behavioral phenotype observed in ASD, which often includes episodic memory and social cognitive processing impairments, may be partially attributable to differences in hippocampal–cortical functional connectivity (Banker et al., 2021; Tao et al., 2022).

In neurotypical samples, hippocampal–cortical functional connectivity is non-uniform across the hippocampus, differing primarily along its longitudinal axis, from anterior to posterior (Grady, 2020; Vogel et al., 2020; Vos de Wael et al., 2018; Warren et al., 2021). Specifically, the anterior hippocampus shows greater connectivity with the anterior temporal lobe and ventromedial prefrontal cortex, while the posterior hippocampus shows greater connectivity with posterior parietal cortex and medial occipitotemporal cortex (Grady, 2020; Vogel et al., 2020; Vos de Wael et al., 2018), a highly-replicated pattern also found in anatomical connectivity (i.e., synaptic; Dalton et al., 2022). There is also evidence that anterior–posterior differentiation of the hippocampus emerges in neurotypical development throughout mid- to late-childhood in both macro- and microstructural properties (Langnes et al., 2020; Plachti et al., 2023; Solar et al., 2021), as well as memory-related functional connectivity and activation (DeMaster & Ghetti, 2013; Tang et al., 2020). Preliminary evidence suggests that this developmental specialization is functionally relevant: anterior–posterior differences in hippocampal connectivity during a task-free state (i.e., movie watching) have been shown to relate with performance on episodic memory tasks in children (Geng et al., 2019).

Converging lines of evidence lead us to suspect that this specialization of functional connectivity between anterior and posterior hippocampus is disrupted in ASD. First, ASD risk genes, as identified through genome-wide association studies, are differentially expressed in the anterior and posterior hippocampus (Ayhan et al., 2021). Second, episodic memory performance, which is related with anterior–posterior differences in task-free functional connectivity (Geng et al., 2019), is lower in those with ASD (meta-analytic effect size: $g = -0.54$; Griffin et al., 2022). Third, the relationship between anterior–hippocampal functional connectivity and episodic memory performance (but not *posterior*–hippocampal functional connectivity) differs in ASD and controls (Hashimoto et al., 2021).

Despite this indirect evidence suggesting the specialization of anterior–posterior hippocampal functional connectivity may be impacted in ASD, no study has directly tested this hypothesis. Furthermore, it remains unknown whether the age-related differences in this specialization during child development are altered in ASD. Here we examine: (1) how resting-state functional connectivity of the anterior and posterior hippocampus differ in a large sample of children and young adults with ASD diagnoses ($N = 139$) and no diagnoses ($N = 133$), and (2) whether the relationship between this anterior–posterior specialization and age differs between the two groups. Finally, motivated by findings, which suggest differences in anterior–posterior specialization are both related to episodic memory performance and disrupted in ASD, we tested for spatial overlap between regions, which show differential specialization in ASD and regions that show increased BOLD response during episodic memory tasks (determined meta-analytically).

Ultimately, understanding these differences may help us uncover the neurobiological factors underlying the

episodic memory and socio-cognitive processing difficulties observed in ASD (Banker et al., 2021).

METHODS

Participants

Resting-state fMRI data were obtained from the Child Mind Institute's Healthy Brain Network biobank (HBN), a large-scale open-source dataset of participants diagnosed with a broad range of psychopathologies (Alexander et al., 2017). We acquired data from all releases available at the time of writing (releases: 1.1, 2.1, 3, 4, 5, 6, 7, 8, and 9 [http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/sharing_neuro.html]). We analyzed a subset of the participants from these releases that had completed two resting-state fMRI scans, and had either a formal ASD diagnosis (ASD group), or no diagnoses (TD group). This resulted in a total of 441 participants (257 ASD, 184 comparison). Ethics approval for the HBN was acquired from the Chesapeake Institutional Review Board (IRB), and our group obtained a data usage agreement via (cmidatausage@childmind.org). General inclusion/exclusion criteria for the HBN are described extensively elsewhere (Alexander et al., 2017). In brief, participants were excluded if they: lacked fluency in English, had cognitive or behavioral deficits that interfered with their participation, or had medical issues that might have affected their neuroimaging data. Participants in the ASD group were diagnosed using the Autism Diagnostic Interview–Revised (ADI-R) and Autism Diagnostic Observation Schedule 2nd Edition (ADOS-2). The IQ of participants between the ages of 6 and 17 was scored using the Wechsler Intelligence Scale for Children (WISC-V; Wechsler, 2003); the IQ of participants aged 18 and over was scored using the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008); the IQ of participants under the age of 6 (or who were suspected to have an IQ below 70) was scored with the Kaufman Brief Intelligence Test (KBIT; Kaufman, 1990). Socioeconomic status (SES) was measured through the Barratt Simplified Measure of Social Status. The comparison group did not have any psychiatric or neurological diagnoses.

Of these 441 participants, 152 participants were removed due to fMRI motion artifacts (as assessed during motion quality control, discussed below; 102 of the subjects removed belonged to the ASD group, while 50 belonged to the TD group), and an additional 17 participants were removed for missing information related to age and/or sex. This resulted in a total of 272 participants (139 ASD, 133 TD group; both groups aged 5–21), with demographic information for these participants shown in Table 1. It should be noted that 20 of these participants were missing information related to SES; 46 were missing information related to IQ (18 in the ASD group; 28 in the TD group), and 9 were missing information related to SES.

TABLE 1 Participants' demographic characteristics.

Variable	ASD	TD
Sample size		
Total	139	133
CBIC site ***	63	27
RU site	56	59
SI site ***	20	47
Age*	12.19 ± 3.95	11.23 ± 3.52
Sex (M/F) ***	109/30	71/62
SES ($N = 263$)	47.95 ± 14.06	50.72 ± 13.02
SRS (N = 250)		
Total *T*-scores***	70 ± 11.11	49.08 ± 8.64
KBIT (N = 10)		
IQ	89.6 ± 12.46	105.8 ± 16.99
WISC (N = 203)		
FSIQ***	96.20 ± 20.79	107.58 ± 15.36
VSI*	99.57 ± 20.39	104.57 ± 14.99
VCI***	100.38 ± 20.05	109.66 ± 15.08
FRI**	98.98 ± 18.93	106.48 ± 15.54
PSI***	88.79 ± 18.35	104.41 ± 15.78
WMI**	95.52 ± 18.95	102.54 ± 16.78
WAIS (N = 13)		
FSIQ	98.00 ± 14.32	98.00 ± 22.87
VCI	35.80 ± 6.81	33.67 ± 13.43
WMI	15.70 ± 3.65	16.67 ± 6.51
PSI	16.70 ± 6.77	20.33 ± 0.58
PRI	29.40 ± 10.17	26.33 ± 13.58

Note: Mean ± SD reported. Significance assessed through independent samples t-tests or chi-squared tests.
Abbreviations: CBIC, CitiGroup Cornell Brain Imaging Center; FRI, Fluid reasoning index; FSIQ, Full-scale intelligence quotient; KBIT, Kaufman Brief Intelligence Test; PRI, Perceptual reasoning index; PSI, Processing speed index; RU, Rutgers University; SES, Socioeconomic status; SI, Staten island; SRS, Social responsiveness scale; VCI, verbal comprehension index; VSI, visual spatial index; WAIS: Wechsler adult intelligence scale; WISC, Wechsler intelligence scale for children; WMI, working memory index.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

MRI acquisition and preprocessing

Imaging data from the HBN were acquired from three different sites: Staten Island (SI), Rutgers University Brain Imaging Center (RU) and CitiGroup Cornell Brain Imaging Center (CBIC). At the CBIC and RU sites, resting-state fMRI images were acquired with a 3 T scanner, repetition time (TR) of 800 ms, echo time (TE) of 30 ms, 375 volumes, resolution of 2.4 × 2.4 × 2.4 mm, flip angle of 31, slice number of 60 and multi-band

acceleration of 6. At the SI site, resting-state fMRI images were acquired with a 1.5 T scanner, TR of 1450 ms, TE of 40 ms, 420 volumes, resolution of 2.5 × 2.5 × 2.5 mm, flip angle of 55, slice number of 54 and multi-band acceleration of 3. All participants included in the current study had two 5-min resting-state scans.

Resting-state fMRI were preprocessed in spm12, using a standard pipeline in the CONN toolbox (version 12.b, Whitfield-Gabrieli & Castanon, 2012), which included realignment, outlier detection, indirect segmentation, normalization, and smoothing (6 mm Gaussian kernel). Outlier scans were identified using the conservative setting in ART (Artifact Detection Tools; RRID: SCR_005994, Nieto-Castanon, 2020; RRID: SCR_009550), which defines outliers as images in which average intensity deviated more than three standard deviations from the mean intensity or composite head movement exceeding 0.5 mm from the previous image. In addition, potential confounding effects from physiological and other spurious sources of noise were estimated and regressed from the fMRI time series. Confounds included noise components from white matter and cerebrospinal fluid areas (aCompCor; Behzadi et al. 2007; Chai et al., 2012), estimated subject-motion parameters, and identified outlier scans (Satterthwaite et al. 2013). Following preprocessing, participants were removed if more than half the volumes in their time-series (~200 volumes) were labeled as outliers by CONN. This resulted in the removal of 152 participants (102 ASD, 50 comparison group).

Functional connectivity analyses

All functional connectivity analyses were implemented in *CONN*. For each participant, we derived whole-brain functional connectivity maps for four regions of interest (ROIs: left anterior hippocampus, left posterior hippocampus, right anterior hippocampus, right posterior hippocampus; see Figure 2a), which were based on the Olsen, Amaral, and Palombo (OAP) protocol (Olsen et al., 2009; Yushkevich et al., 2015). To derive these maps, BOLD time-series from all voxels within a ROI were extracted, and the average correlation (Pearson's r) between the time-series of these voxels and the time-series of a given voxel in the brain was taken. Correlations were then transformed to Fisher's z-scores. Clusters were identified via random field theory, with a voxel-threshold of $p < 0.001$ and a family-wise error rate corrected cluster-threshold of FWE-$p < 0.05$.

For analyses comparing groups, age, sex, and site were included as covariates, as each of these differed significantly between our ASD and comparison group (see Table 1). All analyses were conducted averaging across left and right hemisphere ROIs. Surface views, when shown, are projected onto a cortical surface derived from the ICBM MNI 2009b nonlinear asymmetric template (Whitfield-Gabrieli & Nieto-Castanon, 2012).

Whole hippocampal connectivity

First, we tested for clusters where the whole hippocampal connectivity, averaged across anterior–posterior regions, differed significantly between the ASD and comparison groups. Based on previous work, we expected this initial analysis to identify ASD-related differences in functional connectivity across the hippocampus as a whole, independent of position along the longitudinal axis (Cooper et al., 2017; Liu et al., 2023). This allowed us to test whether our measures of hippocampal connectivity are in line with what we expect based on previous literature (despite a different sample, preprocessing procedure, scanner hardware, and in some instances, task), thereby increasing our confidence in the generalizability of our primary analyses focused on anterior–posterior specialization.

Anterior–posterior hippocampal connectivity differentiation

Then, to address our first research question, we identified clusters where functional connectivity differed significantly between the anterior and posterior hippocampus. We first conducted this analysis for the ASD and comparison groups separately. These within-group analyses allowed us to compare the anterior–posterior specialization of hippocampal connectivity for each group with prior work conducted in those without formal ASD diagnoses (Grady, 2020; Vogel et al., 2020; Vos de Wael et al., 2018). Next, we directly tested our hypothesis of altered anterior–posterior specialization in ASD, by identifying clusters where this anterior–posterior specialization of connectivity significantly differed between our ASD and comparison groups. This was done using a 2 × 2 mixed ANCOVA with group as the between-subject factor and anterior/posterior as the within-subject factor. Analyses comparing our ASD and TD group included age, sex, and site as covariates.

These analyses are averaged across right and left hemispheres. However, this relies on the assumption that anterior–posterior specialization is consistent for both right and left hippocampus in our ASD and comparison groups. To test whether this is the case, we visually inspected anterior–posterior specialization for right and left hippocampus independently (see Figure S1). Right and left hippocampus showed very similar effects. Thus, all subsequent analyses are averaged across hemispheres.

These univariate analyses tested whether distinct cortical regions show differential anterior–posterior

hippocampal connectivity in our ASD and comparison group. To help contextualize these results, we report two post-hoc descriptive analyses. First, to facilitate our interpretation of these spatially distributed effects, we assessed the extent to which they correlated with one another, across participants, via a principal component analysis (PCA, $X = [\text{Participant-by-Cluster}]$ matrix). This allowed us to condense the dominant pattern of anterior–posterior specialization differences in ASD into a single latent variable with higher interpretability. Second, we quantified the spatial overlap that these significant clusters showed with known regions that exhibit activation during episodic memory tasks. Such memory-related regions were defined as those in the 'episodic memory' term mask available on *NeuroSynth* (https://neurosynth.org/), which was created through a meta-analytic synthesis of the results from 332 studies.

Finally, we tested whether the anterior–posterior specialization of hippocampal connectivity related with measures of intelligence and/or social responsiveness. Specifically, we examined the Pearson correlation between the strength of each effect and participants' scores on measures of verbal/non-verbal IQ and social responsiveness. These were indexed via the Verbal comprehension, Working memory, and Full-scale IQ scores on the Wechsler Intelligence Scale for Children (WISC; Wechsler, 2003), as well as total scores on the Social Responsiveness Scale (SRS-2; Constantino et al., 2003). The false-discovery rate of these tests was controlled at $p < 0.05$ (Benjamini & Hochberg, 1995). These analyses were motivated by findings suggesting the strength of anterior–posterior specialization in children may account for performance gains on episodic memory tasks. While we lacked direct measures of episodic memory performance (which were only available for 11 participants within the current sample), these general measures of cognitive ability partially contribute to, and tend to be highly correlated with, performance on episodic memory tasks. The contribution of the hippocampus to working memory specifically is known to be particularly prominent in early childhood (Finn et al., 2010).

Age-related differences in the anterior and posterior hippocampal connectivity

To address our second research question, we assessed whether the anterior–posterior specialization of hippocampal connectivity differed with age in ASD and/or our comparison group, and if so, whether these age-related differences would significantly differ between the two groups. To test this, we conducted multiple regressions testing for an effect of age while controlling for the effect of sex and site. In line with our age-invariant analyses, this was first conducted for our ASD and comparison group separately. Then, we directly tested whether any anterior–posterior specialization age-effects differed significantly between the two groups. These analyses directly test for an age effect of anterior > posterior connectivity, with negative values suggesting greater posterior-hippocampal connectivity relative to anterior-hippocampal connectivity with age (and vice versa for negative values). However, it is possible that such effects are driven by either age-related *increases* in posterior hippocampal connectivity, or alternatively, age-related *decreases* in anterior hippocampal connectivity. To disentangle these possibilities, we conducted post-hoc analyses to test the effect of age, focusing on the anterior and posterior hippocampus separately.

Community involvement statement

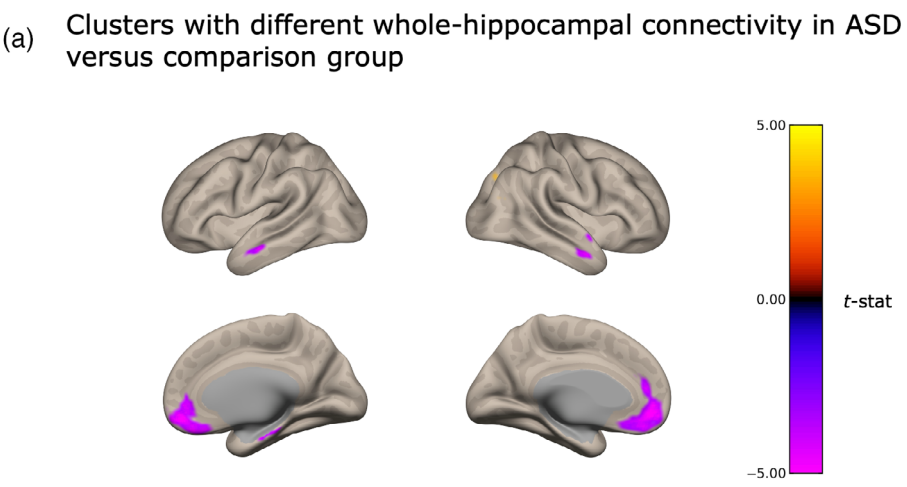
Family members of those with autism were involved in all aspects of the current study, including: development of the research questions and hypotheses, study design, implementation, and interpretation of the findings.

RESULTS

With regard to the whole hippocampal connectivity, we identified four clusters with lower functional connectivity in the ASD group relative to the comparison group (Figure 1), located in the medial prefrontal cortex (mPFC; 11, 648 mm^3), bilateral middle temporal gyrus (right-hemisphere: 1, 936 mm^3, left-hemisphere: 896 mm^3), and brainstem (4, 232 mm^3). We also identified one cluster with which the ASD group showed greater hippocampal connectivity in the right lateral occipital cortex (1, 272 mm^3).

Next, we examined the anterior–posterior specialization of hippocampal functional connectivity in both our ASD and comparison group. The anterior and posterior seeds used in these analyses are shown in Figure 2a. The clusters with significantly different anterior versus posterior connectivity in each group (projected onto the cortical surface) are shown in Figure 2b. In both groups, the posterior hippocampus was more connected than the anterior hippocampus to posterior parietal and posterior midline regions, including the medial occipitotemporal cortex and lingual gyrus. The anterior hippocampus was more connected than the posterior hippocampus to bilateral anterior temporal cortex, the frontal poles, and in the pre- and postcentral gyri. These patterns are similar to previous reported results from non-autistic adults. For a qualitative comparison of these maps with prior work in non-autistic adults, the reader is referred to Figure 5a in Vogel et al. (2020).

We then tested for clusters that showed significant group differences in anterior/posterior hippocampal connectivity specialization. We identified seven clusters, described in Table 2, in which the ASD group showed a



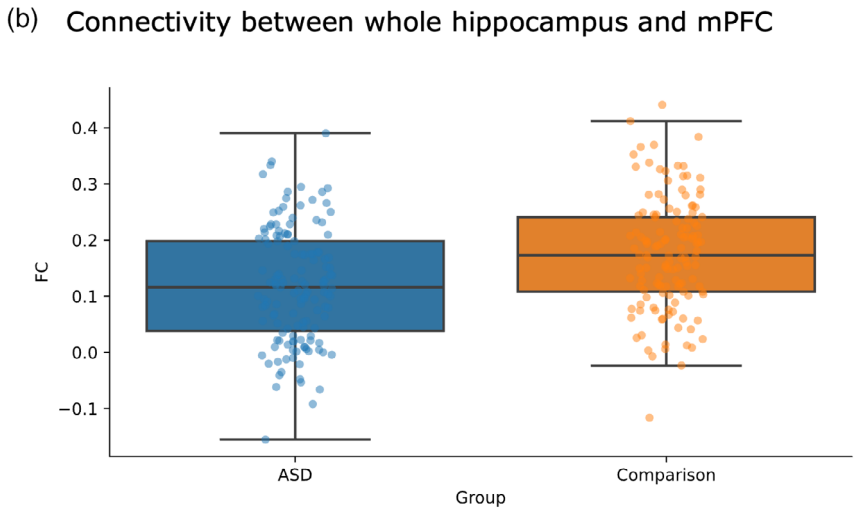


FIGURE 1 Hypo-connectivity between the hippocampus and medial prefrontal cortex in ASD. (a) Cluster of voxels in the medial prefrontal cortex with significantly different hippocampal connectivity in ASD relative to the comparison group. Voxels are colored by *t*-statistic. Results are presented for the whole hippocampus, averaged across anterior and posterior seeds. (b) Box plot illustrating the size of the effect across participants (center box-line: median, outer box-lines: first/third quartiles, outside lines: minimum/maximum values within the 1.5-times the interquartile range).

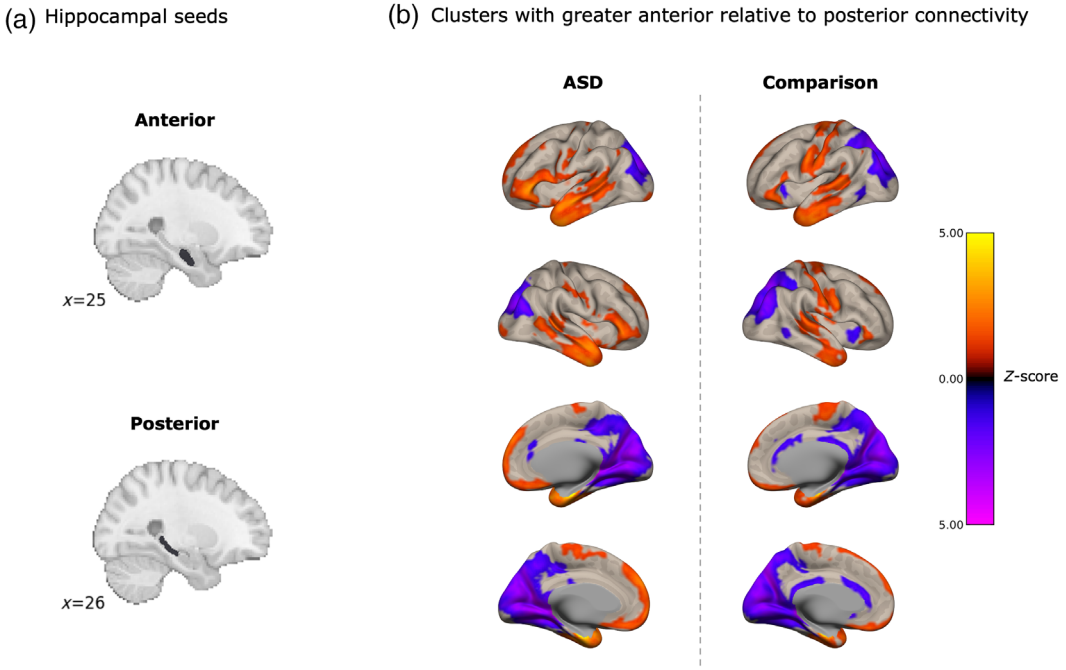


FIGURE 2 Anterior–posterior specialization of hippocampal connectivity in the ASD and comparison groups (a) Anterior and posterior hippocampus seeds used in analyses. (b) Clusters of voxels with significantly different anterior relative to posterior functional connectivity, projected onto the cortical surface, for both the ASD and comparison group.

TABLE 2 Clusters with significantly different anterior relative to posterior functional connectivity between groups (ASD > Comparison).

Cluster (x, y, z)	Main composition	Cluster size	FWE-*p* value
+34 − 68 + 46	Right angular gyrus	3000 mm^3	4.4e-5
+58 − 54 − 04	Right middle temporal gyrus	2616 mm^3	7.8e-5
+52 − 02 − 18	Right middle temporal gyrus	2328 mm^3	1.4e-4
−22 − 64 + 56	Left superior parietal gyrus	1448 mm^3	2.9e-3
−42 − 12 − 26	Left uncus	1144 mm^3	8.6e-3
−28 − 70 + 42	Left inferior parietal cortex	816 mm^3	3.1e-2
+38 − 22 − 20	Right parahippocampal gyrus	800 mm^3	3.1e-2

higher value for anterior minus posterior hippocampal connectivity compared to the comparison group. No clusters showed the opposite group difference pattern. Of these seven clusters, four spatially overlapped with regions that are associated with episodic memory (as determined by the 'episodic memory' mask from NeuroSynth). These were located in the: right angular gyrus, left superior parietal gyrus, left inferior parietal cortex, and the right parahippocampal gyrus. Each of these clusters, in MNI-152 space, are shown in Figure 3, along with boxplots visualizing the size of the effects. The group difference was driven by the ASD group having lower posterior versus anterior hippocampal connectivity in the parietal regions compared to the comparison group. We then conducted a principal component analysis to assess the extent to which these effects related to one another and to facilitate interpretation of the results. The first principal component accounted for 51.6% of the variance in the [Participant-by-Cluster] matrix, with each effect loading positively onto the component, demonstrating more than half of the variance in these seven effects could be accounted for by a single latent variable. Loadings of each cluster onto the first principal component, as well as the projection of participant scores onto this component, can be seen in Figure 4. Scores on this latent variable (PC1, Figure 4a) are a weighted combination of the effects in Figure 4c; thus, participants with higher scores (over-represented in the ASD group) tend to exhibit greater anterior > posterior hippocampal connectivity across all seven clusters.

We correlated the strength of each effect with the measure of social responsiveness (SRS-Total) and measures of verbal/non-verbal IQ (WISC-FSIQ, WISC-WMI, WISC-VCI) in those diagnosed with ASD. There were no significant correlations when controlling for the false-discovery rate at $p < 0.05$. One correlation was significant without correction for multiple comparisons (WISC-WMI and right_middle_temporal_gyrus_1: $r\,(104) = 0.24$, $p = 0.015$).

Age-related analyses

Next, we tested for clusters where the anterior–posterior specialization of hippocampal connectivity differed with age. We first conducted these analyses in the ASD and comparison groups separately. In the ASD group, we identified five spatially distributed clusters, which exhibited an increased anterior–posterior specialization with age (i.e., anterior > posterior as age increased), including clusters in the parahippocampal gyrus, superior temporal gyrus, putamen, and thalamus (Figure 5, Table S1). We also identified seven smaller clusters (all <3928 mm^3), which exhibited a decreased anterior–posterior specialization with age, located in the cerebellum, brainstem, lingual gyrus, and middle frontal gyrus (Table S1). In the comparison group, there were no clusters that showed an age effect.

To better understand the anterior–posterior specialization in ASD, we separately tested for age-related differences in posterior-hippocampal connectivity and anterior-hippocampal connectivity in the ASD group. Connectivity between the posterior hippocampus and the posterior midline regions of the precuneus, lingual gyrus, the parahippocampal gyrus and left inferior frontal gyrus was negatively correlated with age (Figure 6a). There were no age-related differences in anterior hippocampal connectivity. This would suggest that in ASD, age-related differences in anterior–posterior specialization are driven by the posterior hippocampus. However, it is not clear from this analysis whether such age-related differences in posterior-hippocampal connectivity are specific to ASD. To address this, we tested for clusters where age-related differences in posterior-hippocampal connectivity (which we observed in ASD) differed significantly from the comparison group (Figure 6a). To facilitate interpretation of these group-difference results, we present age-related differences in the posterior hippocampal connectivity of both ASD and controls in Figure 6a. It should be reiterated, however, that controls did not show age-related differences in anterior–posterior connectivity.

We identified a small cluster in the left precuneus (1384 mm^3, FWE-$p = 0.0027$) with, which our ASD group showed a significantly greater age-effect than controls (Figure 6b). The comparison group showed stable anterior-versus-posterior connectivity with this cluster with age, whereas the ASD group showed a decrease in anterior-versus-posterior connectivity with this cluster with age.

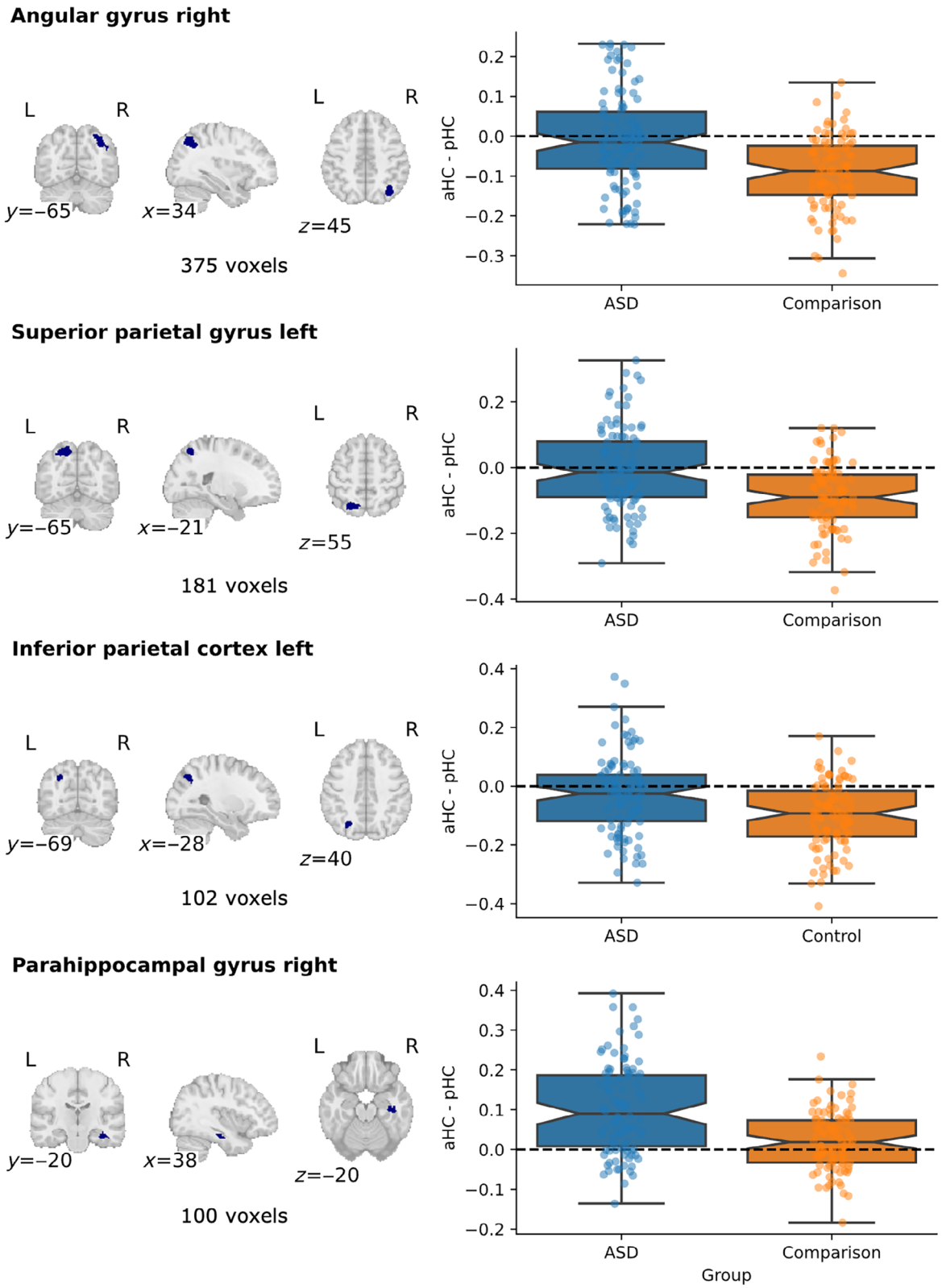


FIGURE 3 Differences in anterior–posterior specialization in ASD are spatially distributed On the left of each; clusters of voxels that exhibited significantly different anterior–posterior specialization in the ASD versus comparison group, within MNI-152 space. On the right; boxplots showing the distribution of differences in anterior–posterior specialization across participants. Results are presented for the 4/7 clusters, which exhibited spatial overlap with the episodic memory mask in Figure 4d.

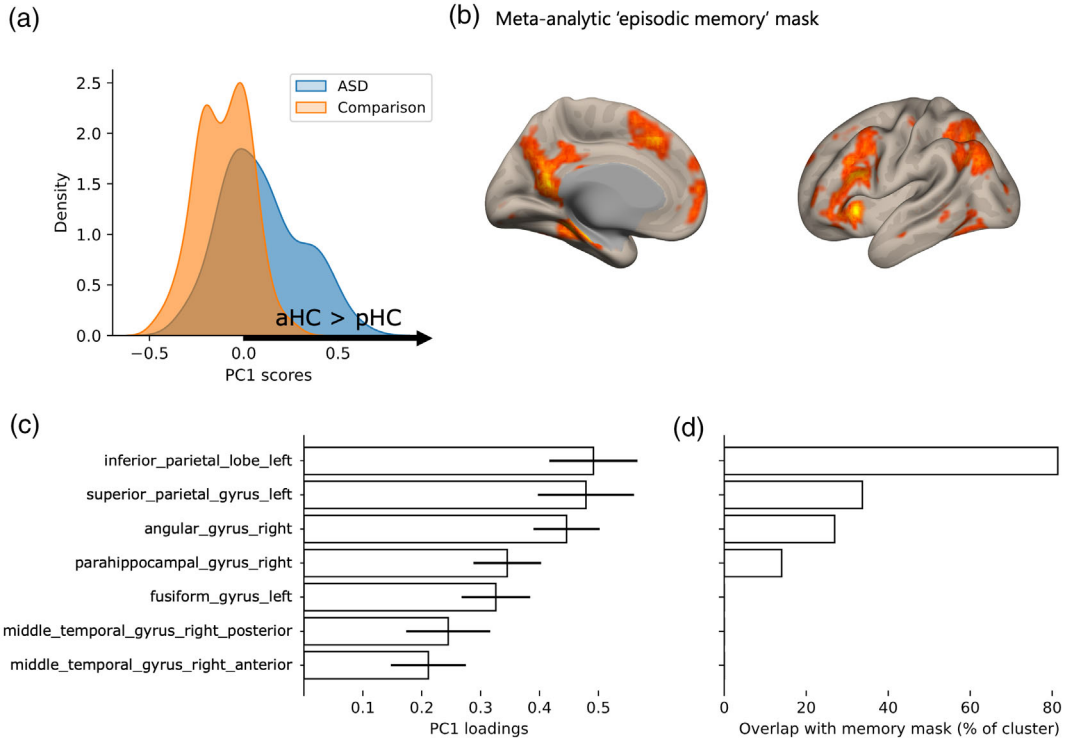


FIGURE 4 Regions that show different anterior–posterior specialization in ASD are related and show spatial overlap with memory-sensitive cortex (a) Kernel density plots showing the distribution of scores from the principal component analysis, which reduced the functional connectivity within regions that show different anterior-versus-posterior connectivity in ASD into a single latent variable (PCA conducted on the matrix: [Rows: participants; Columns: 7 clusters with different anterior–posterior connectivity in ASD]). Results are presented for the ASD and comparison groups. (b) Regions, which tend to activate during episodic memory tasks, determined through a meta-analytic approach (https://neurosynth.org/analyses/terms/episodic%20memory/). (c) Bar plot showing the loadings of each cluster onto the first principal component. All clusters positively loaded onto PC1; positive scores on this latent variable thereby reflect greater anterior relative to posterior hippocampal connectivity. Error bars reflect the bootstrapped standard error (estimated via 1000 bootstrapped samples). (d) Bar plot showing the amount of spatial overlap between each cluster and the episodic memory mask.

DISCUSSION

The aim of the current study was to investigate whether the resting-state functional connectivity of the anterior and posterior hippocampus, as well as the relationship between these patterns of connectivity and age, differ in participants with and without ASD diagnoses. This investigation was motivated by two lines of evidence. First, the episodic memory and socio-cognitive processing impairments observed in ASD have been partially attributed to differences in hippocampal function (Banker et al., 2021; Tao et al., 2022). Second, performance gains on episodic memory tasks throughout child development have been specifically related to the anterior–posterior specialization of hippocampal connectivity (Geng et al., 2019).

To address these aims, we first tested whether the functional connectivity of the whole hippocampus, including both anterior and posterior hippocampus, differed in those with and without ASD diagnoses. We found reductions in functional connectivity between the hippocampus and medial prefrontal cortex (mPFC), bilaterally, in those diagnosed with ASD relative to our comparison group. This finding replicates previous observations in ASD both at rest and during episodic retrieval (Cooper et al., 2017; Gotts et al., 2012; Hogeveen et al., 2020; Kennedy et al., 2006). Functional connectivity between the hippocampus and mPFC reliably increases during episodic memory retrieval tasks, and the magnitude of this connectivity correlates with memory accuracy and the number of stimuli encoding repetitions (King et al., 2015; Robin et al., 2015; Zeithamova et al., 2012). This interaction is thought to be important in integrating contextual details, social relevance, inferential memory, and schemas (as reviewed by Preston & Eichenbaum, 2013; Ritchey & Cooper, 2020). Thus, the decreased hippocampal-mPFC connectivity observed in ASD may relate to impaired integration of episodic memories, therefore contributing to impaired recall identified in the disorder meta-analytically (Ben Shalom, 2009; Griffin et al., 2022).

Next, we tested whether the anterior–posterior specialization of hippocampal connectivity differs in those with and without ASD diagnoses. In non-autistic adults, the anterior and posterior hippocampus preferentially connect with distinct cortical systems (Vogel et al., 2020).

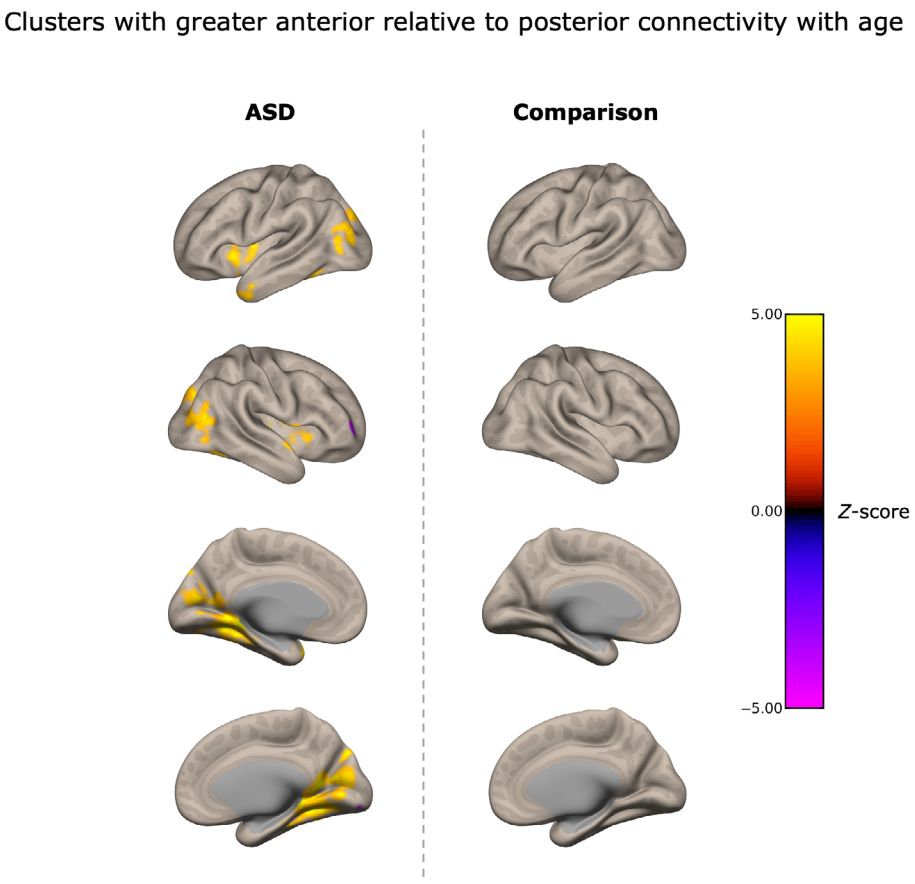


FIGURE 5 Age-related differences in anterior–posterior specialization observed in ASD Clusters of voxels where anterior–posterior specialization showed a significant relationship with age, projected onto the cortical surface. No clusters were present in the comparison group.

In non-autistic children, this specialization emerges with development alongside increases in episodic memory performance (Geng et al., 2019; Hashimoto et al., 2021). We hypothesized that this specialization would differ in children diagnosed with ASD. When inspecting our ASD and comparison group separately, we found that both groups, in general, exhibited similar patterns of connectivity as non-autistic children and adults (Blankenship et al., 2017; Vogel et al., 2020). Indeed, independent of ASD diagnosis, anterior hippocampus exhibited preferential connectivity with anterior temporal lobe and ventromedial PFC, while posterior hippocampus exhibited preferential connectivity with the posterior and medial parietal and medial occipitotemporal regions.

Despite these similarities, however, direct comparison between our ASD and comparison group revealed a set of spatially distributed regions with which ASD showed different anterior relative to posterior hippocampal connectivity, in support of our hypothesis. Post hoc analyses revealed that these spatially distributed regions correlated across participants, and can thus be interpreted as a general shift towards increased anterior relative to posterior hippocampal connectivity in ASD. Interestingly, a subset of these regions showed spatial overlap with cortical regions sensitive to episodic memory, as determined meta-analytically through *NeuroSynth* (Yarkoni et al., 2011). These included the left inferior parietal cortex, superior parietal gyrus, angular gyrus, and parahippocampal gyrus. We lack the ability to directly test whether these effects related with episodic memory in the current study, as measures of episodic memory performance were only available in 11 participants within the current sample. However, extant evidence suggests this may be the case. First, Liu et al. (2023) demonstrated intrinsic hyper-connectivity between the anterior hippocampus and mPFC, cingulate cortex, supramarginal gyrus, fusiform, thalamus, and cerebellum to be predictive of general memory impairment in 8- to 12-year-old children with ASD. Second, Hashimoto et al. (2021) showed that anterior hippocampal connectivity in 7- to 16-year-old typically developing children was positively correlated with recognition memory success, whereas posterior hippocampal connectivity in children with ASD had a negative correlation with memory. Together, these findings indicate that children with ASD have altered specialization, namely an increased anterior relative to posterior connectivity, compared to typically developing children and that these differences show some overlap with memory-related regions.

Finally, we tested whether this anterior–posterior specialization of hippocampal connectivity correlated with differences in age, and whether these age-related differences differed between children with and without ASD. With age, our ASD group primarily showed differential

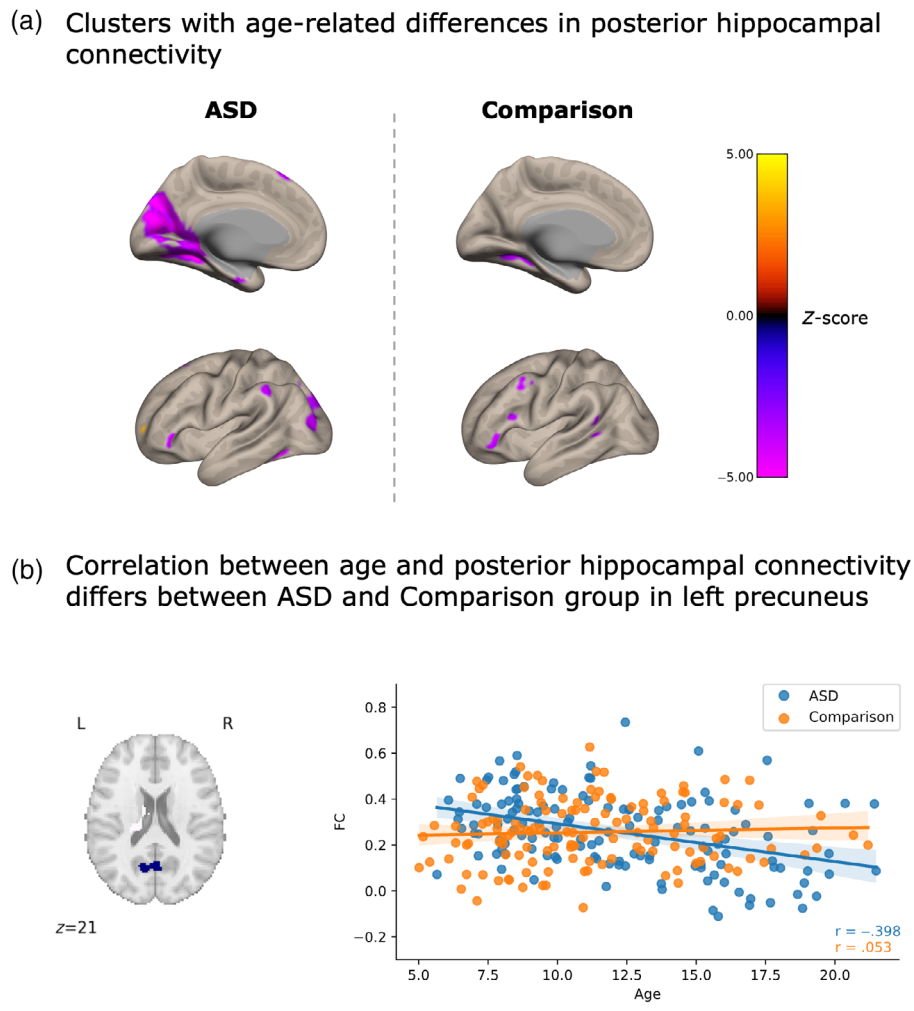


FIGURE 6 Age-related differences in anterior–posterior specialization in ASD are driven by decreases in posterior hippocampal connectivity (a) Clusters of voxels with, which the posterior hippocampus differentially connected with age, projected onto the cortical surface. Results are shown for both the ASD and comparison group separately. (b) On the left; clusters of voxels within the left precuneus where the age-effect shown in panel *A* differed significantly between the ASD and comparison group, in MNI-152 space. On the right; a scatterplot showing the strength of this left-precuneus effect in both ASD and comparison groups. Shaded error bars reflect 95% confidence intervals.

anterior–posterior hippocampal connectivity with the posterior medial regions including the posterior cingulate cortex (PCC), precuneus, lingual gyrus, the parahippocampal gyrus, and the inferior frontal gyrus. This was driven by age-related decreases in functional connectivity between the posterior hippocampus and these posterior medial regions. No such effects existed in the comparison group. Direct comparison of our two groups revealed an age-related decrease in posterior hippocampal connectivity with the left precuneus significantly dependent on ASD diagnosis. These results suggest that throughout this developmental period, the anterior–posterior specialization of hippocampal connectivity across the cortex is relatively stable in non-autistic children. This would also indicate that the anterior–posterior specialization of hippocampal connectivity may follow a different developmental trajectory in ASD. Interestingly, some previous work has shown an increased anterior–posterior specialization of the hippocampus from ages 4 to 8, both at rest and during a memory encoding task (Geng et al., 2019), as well as age effects in anterior–posterior hippocampal specialization from age 8 to 25 during a memory encoding task (Tang et al., 2020). These results suggest that anterior–posterior hippocampal specialization, as detectable by intrinsic functional connectivity, may mature between age 4 to 8 in non-autistic children, and was therefore not detected in our older sample, but that developmental effects of specialization may be evident in mid- to late-childhood when the hippocampus is engaged in functionally relevant tasks such as memory encoding.

Limitations and future directions

The current study is strengthened by the relatively large sample size and stringent quality control. However, there are some limitations that should be noted. First, ASD is a highly heterogeneous disorder, and the majority of ASD participants in the Healthy Brain Network were diagnosed with at least one comorbidity (most prominently ADHD). Since the current sample lacks sufficient size to tease apart this heterogeneity, it is possible that the current results are specific to a certain ASD phenotype or associated with comorbidities. Future efforts subtyping ASD may help address this limitation (Hong et al., 2020). Third, we estimated the maturational

trajectories of hippocampal–cortical connectivity cross-sectionally. Some work investigating the structural development of the hippocampus suggests these trajectories vary considerably from those estimated longitudinally (Keresztes et al., 2022). This should be kept in mind when interpreting age-related differences in posterior–hippocampal connectivity in ASD as a distinct maturational trajectory. Fourth, our sample is predominantly male (~3.6:1 male to female ratio). While this is generally representative of the ~3:1 male to female ratio found in autism (Loomes et al., 2017), the extent to which these results extend to the female presentation of ASD is less clear.

Finally, a potential limitation of the study is that resting-state fMRI data were collected across three different scanners, each with unique field strengths and acquisition parameters. Moreover, certain participant characteristics varied by site: one-way ANOVAs testing whether our behavioral measures significantly differed by site revealed significant site-differences in SRS-total scores (after correcting for the False Discovery rate at $p < 0.05$). However, the inclusion of site as a covariate in all analyses is a widely used method to account for the confounding effect of these site-differences on group-differences. Indeed, the patterns of resting-state hippocampal connectivity, which we observed replicated those found in prior literature.

It is also worth noting that the current study utilized fMRI data acquired during a resting-state, as opposed to a task. The decision to conduct the analysis using resting-state fMRI was guided by several considerations. First, it is more feasible to acquire good quality resting-state data from young and vulnerable populations compared to task-based data. Second, the use of resting-state data facilitates comparison with the large body of prior work examining functional connectivity differences between ASD and controls (for review, see: Lau et al., 2019). Third, functional connectivity profiles of the anterior and posterior hippocampus at rest are highly similar to those observed during encoding (Raud et al., 2023). However, task-based data may be better able to tease apart the neural mechanisms that contribute to episodic memory deficits observed in ASD. This therefore represents an important direction for future research.

Conclusion

Overall, the current study demonstrates differences in the anterior–posterior specialization of hippocampal–cortical connectivity in ASD, and suggests these differences may be associated with a different maturational trajectory of posterior-hippocampal connectivity in ASD. Ultimately, understanding these differences may help us better understand the neurobiological factors underlying the episodic memory and socio-cognitive processing differences observed in ASD.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Child Mind Institute at http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/About.html. These data were derived from the following resources available in the public domain—Healthy Brain Network Biobank, http://fcon_1000.projects.nitrc.org/indi/cmi_healthy_brain_network/About.html.

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