Functional and structural changes of the hippocampal and amygdala subregions in autism throughout development

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Abstract

Autism spectrum disorder (ASD) is characterized by deficits in social communication and interaction, in addition to restrictive and repetitive patterns in behaviour. It is also common for individuals with ASD to exhibit other impairments such as deficits in language, executive function, working memory (WM) and episodic memory. Two important brain regions, namely the hippocampus and amygdala, have been linked to these memory deficits in ASD. However, the structural and functional changes occurring in the hippocampus and amygdala in ASD throughout development are poorly understood. In addition, previous studies have focused on whole hippocampal and amygdala rather than investigating the subfields and nuclei of these brain regions in ASD. Given the differences in histological characteristics, connectivity, and function between hippocampal subfields/divisions and amygdala nuclei, it's important to study these individual subregions in order to have a more comprehensive understanding of the structural and functional connectivity changes occurring in ASD. AIM 1 of this thesis was to investigate the resting-state functional connectivity of the anterior and posterior divisions of the hippocampus in ASD at various ages (5-21). AIM 2 of this thesis was to investigate the volumetric changes of hippocampal subfields and amygdala nuclei in ASD at various ages (5-21). Structural and functional Magnetic Resonance Imaging (MRI) data was obtained from the Healthy Brain Network, a large-scale open-source dataset. The resting-state functional MRI data of autistic (n = 156) and neurotypical (n = 133) participants were included in the functional connectivity analysis of the anterior and posterior hippocampus. The T1-weighted MRI scans of autistic (n = 135) and neurotypical (n = 87) participants underwent hippocampal and amygdala segmentation for volumetric analyses. We found that both the anterior and posterior hippocampus showed decreased connectivity with the medial prefrontal cortex (MPFC) in the ASD group compared to the typically developing (TD)

group. We also observed decreased interhemispheric functional connectivity between the right anterior hippocampus and the left posterior hippocampus and parahippocampal cortex (PHC) in individuals with ASD. In addition, the connectivity between the posterior hippocampus and the precuneus decreased with age in the ASD group but remained stable with age in the TD group. After conducting a mixed linear model with age, sex and intelligence quotient (IQ) as fixed effects and the sites of data collection as a random effect, we found significantly larger volumes of the left cornu ammonis (CA) 3 body, molecular layer (ML) of the hippocampal body and CA4 body in the ASD group relative to the TD group before correcting for multiple comparisons. After false discovery rate (FDR) correction, no significant group differences for amygdala nucleus and hippocampal subfield volumes were observed. Partial least squares correlations (PLSC) were then applied to examine the relationship between subfield/nucleus volumes and behavioural measures. We observed a positive relationship between several hippocampal subfields and amygdala nuclei with age in the ASD group, but no age effect was found in the TD group. In addition, a positive relationship of several hippocampal subfields and amygdala nuclei with WM and IQ was found in neurotypical individuals whereas this relationship was absent in individuals with ASD. This exploratory study provides evidence that the developmental trajectories of amygdala nuclei and hippocampal subfields differ between groups. Weaker functional connectivity between the hippocampus and the MPFC, a region implicated in both episodic memory and social cognition, may contribute to behavioural abnormalities in ASD. These findings may help us better understand the pathophysiology and the neuroanatomical underpinnings of memory impairments in ASD.

Résumé

Les troubles du spectre autistique (TSA) se caractérisent par des déficits de communication et d'interaction sociales, ainsi que par des comportements restrictifs et répétitifs. Il est également fréquent que les personnes atteintes de TSA présentent d'autres déficiences, notamment au niveau du langage, des fonctions exécutives, de la mémoire de travail et de la mémoire épisodique. Deux régions importantes du cerveau, l'hippocampe et l'amygdale, ont été associées à ces déficits de mémoire dans les TSA. Toutefois, les changements structurels et fonctionnels qui se produisent dans l'hippocampe et l'amygdale au cours du développement des TSA sont mal compris. En outre, les études antérieures ont porté sur l'ensemble de l'hippocampe et de l'amygdale plutôt que sur les sous-champs et les noyaux de ces régions cérébrales dans les TSA. Étant donné les différences de caractéristiques histologiques, de connectivité et de fonction entre les sous-champs/divisions de l'hippocampe et les noyaux de l'amygdale, il est important d'étudier ces sous-régions individuelles afin d'avoir une compréhension plus complète des changements structurelles et fonctionnelles qui se produisent dans les TSA. Le premier objectif de cette thèse était d'étudier la connectivité fonctionnelle au repos des divisions antérieures et postérieures de l'hippocampe dans les TSA à différents âges (5-21 ans). Le deuxième objectif de cette thèse était d'étudier les changements volumétriques des sous-champs de l'hippocampe et des noyaux de l'amygdale dans les TSA à différents âges (5-21 ans). Les données d'imagerie par résonance magnétique (IRM) structurelles et fonctionnelles ont été obtenues du Healthy Brain Network, un ensemble de données à grande échelle en libre accès. Les données d'IRM fonctionnelle au repos des participants autistes (n = 156) et neurotypiques (n = 133) ont été incluses dans l'analyse de la connectivité fonctionnelle de l'hippocampe antérieur et postérieur. Les scans d'IRM pondérés en T1 des participants autistes (n = 135) et neurotypiques (n = 87) ont été soumis à une segmentation de l'hippocampe et de

l'amygdale pour les analyses volumétriques. Les mesures volumétriques de ces sous-champs et noyaux ont ensuite été extraites pour chaque participant et comparées entre groupes. Nous avons constaté que l'hippocampe antérieur et postérieur présentait une connectivité réduite avec le cortex préfrontal médian (CPFM) dans le groupe des TSA par rapport au groupe des personnes au développement typique (DT). Nous avons également observé une diminution de la connectivité fonctionnelle interhémisphérique entre l'hippocampe antérieur droit et l'hippocampe postérieur gauche et le cortex parahippocampique (PHC) gauche chez les personnes atteintes de TSA. De plus, la connectivité entre l'hippocampe postérieur et le précuneus diminuait avec l'âge dans le groupe TSA mais restait stable avec l'âge dans le groupe DT. Après avoir effectué un modèle linéaire à effets mixtes, avec l'âge, le sexe et le quotient intellectuel (QI) comme effets fixes et les sites de collecte des données comme effet aléatoire, nous avons trouvé des volumes significativement plus larges du corps de la cornu ammonis (CA) 3, de la couche moléculaire (ML) du corps de l'hippocampe et du corps de la CA4 gauche dans le groupe TSA par rapport au groupe DT avant la correction du taux de fausse découverte (FDR). Après correction du FDR, aucune différence significative entre les groupes n'a été observée pour les volumes de sous-régions. La méthode de corrélations des moindres carrés partiels (PLSC) a ensuite été appliquée pour examiner la relation entre les volumes de sous-champs/nucléus et des mesures comportementales. Nous avons observé une relation positive entre plusieurs sous-champs hippocampiques et noyaux amygdaliens avec l'âge dans le groupe TSA, mais aucun effet de l'âge n'a été trouvé dans le groupe DT. De plus, une relation positive entre plusieurs sous-champs hippocampiques et noyaux amygdaliens avec la mémoire de travail et le QI a été observée chez les personnes neurotypiques, alors que cette relation était absente chez les personnes atteintes de TSA. Cette étude exploratoire fournit des preuves que les trajectoires de développement des noyaux amygdaliens et des sous-

champs hippocampiques diffèrent selon les groupes. Une connectivité fonctionnelle plus faible entre l'hippocampe et le CPFM, une région impliquée dans la mémoire épisodique et la cognition sociale, pourrait contribuer aux anomalies comportementales des TSA. Ces résultats pourraient nous aider à mieux comprendre la physiopathologie et les fondements neuroanatomiques des troubles de la mémoire dans les TSA.

List of abbreviations

AAA	Anterior amygdaloid area
ABN	Accessory basal nucleus
ADIR	Autism Diagnostic Interview – Revised
ADOS-2	Autism Diagnostic Observation Schedule 2nd Edition
ANCOVA	Analysis of Covariance
ASD	Autism spectrum disorder
AT	Anterior temporal
CA	Cornu ammonis
CATA	Cortico-amygdaloid transition area
CBIC	CitiGroup Cornell Brain Imaging Center
CobrALab	Computational Brain Anatomy Laboratory
CVLT-C	California Verbal Learning Test-Children's Version
DG	Dentate gyrus
DG body	Granule cell layer of the body of the dentate gyrus
DG head	Granule cell layer of the head of the dentate gyrus
DMN	Default mode network
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
HATA	Hippocampus amygdala transition area
HBHL	Healthy Brains Healthy Lives
HBN	Healthy Brain Network
ICV	Intracranial volume
IPN	Integrated Program in Neuroscience
IQ	Intelligence quotient
LH	Left hemisphere
MAGeTbrain	Multiple Automatically Generated Templates Brain Segmentation Algorithm
ML body	Molecular layer of the hippocampal body
ML head	Molecular layer of the hippocampal head
MPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
NIH	National Institute of Health
OAP	Olsen, Amaral, Palombo protocol
PCC	Posterior cingulate cortex
PHC	Parahippocampal cortex
PLN	Paralaminar nucleus
PLSC	Partial least squares correlations
PM	Posterior medial
PRC	Perirhinal cortex
RH	Right hemisphere
ROI	Regions of interest
RU	Rutgers University Brain Imaging Center
SCQ	Social communication questionnaire
SI	Staten Island

SPM	Statistical Parametric Mapping
TACC	Transforming Autism Care Consortium
TD	Typically developing
WM	Working memory
WMS	Wechsler Memory Scale
WRAML	Wide Range Assessment of Memory and Learning

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Contributions of authors

As lead author of this original and independent thesis, I conducted the preprocessing, quality assessments and analyses of the neuroimaging data. I interpreted the findings, generated the figures and wrote the thesis. Xu Elsie Yan accessed and downloaded the HBN imaging data. Romke Hannema provided CONN toolbox training and a script for extracting the first-level analysis connectivity results. Shirley Zhang assisted with the quality assessments of the structural T1-weighted images by being the second rater. Raihaan Patel shared the PLSC script and taught me the PLSC analysis. Elise Barbeau provided input regarding the statistical analyses performed. Dr. Xiaoqian Chai designed the master's project, developed the research questions and supervised the project.

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1 Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder currently estimated to affect 1 in every 66 Canadian children. This disorder is characterized by deficits in social communication and interaction, in addition to restrictive and repetitive patterns in behaviour. The social communication and interaction domain involves difficulties in using and interpreting non-verbal signals (i.e., hand gestures, eye contact and facial expressions) (Papagiannopoulou et al., 2014; Caruana et al., 2018), engaging in conversation (Wagner et al., 2019) and developing and maintaining relationships with others (Baron-Cohen, Leslie and Frith, 1985). Symptoms related to the restricted and repetitive behaviour domain include having narrow interests, performing repetitive movements such as rocking or spinning, developing specific routines and being hyper- or hypo-reactive to sensory modalities (Faras, Al Ateeqi and Tidmarsh, 2010). The manifestation of these symptoms and their severity differs from person to person in the autism community. It is also common for individuals with ASD to exhibit other impairments such as deficits in language, executive function and memory. Studies that assessed language abilities in ASD observed syntactic delays (Pierce and Bartolucci, 1977) as well as grammatical (Roberts, Rice and Tager-Flusberg, 2004), pragmatic (Kissine, 2012), vocabulary (Hudry *et al.*, 2010) and semantic impairments (Haebig, Kaushanskaya and Ellis Weismer, 2015). Researchers investigating executive functions in ASD reported difficulties with switching between mental states or tasks (Kimhi *et al.*, 2014), inhibition and suppression of information that may interfere with the task objective at hand (Roelofs *et al.*, 2015) and planning (Kimhi *et al.*, 2014) . Individuals with ASD were also found to have impaired memory functions.

1.1 Memory types

There are several different types of memory, some of which are fleeting (sensory and short-term memory), and others are lasting (long-term memory). Sensory memory is the brief storage of information received from the five senses (i.e., sight, hearing, taste, smell, touch). This type of memory typically lasts up to a few seconds. Short-term memory, with a duration of seconds to minutes, encompasses working memory (WM). WM allows the brain to hold and update a small quantity of information for a short period of time while doing a task or making a decision (e.g., retaining a person's address in mind while setting up the GPS). Long-term memory, on the other hand, can store much larger amounts of information for a potentially unlimited duration. Long-term memory is subdivided into both implicit and explicit memory types. Implicit memory, also known as non-declarative memory, involves memories that are unconsciously and effortlessly recalled whereas explicit memory, also known as declarative memory, involves memories that must be consciously recalled. Implicit memory includes procedural memory which involves completing certain tasks automatically by remembering a sequence of events or movements (e.g., riding a bike). Explicit memory encompasses both semantic and episodic memory. Semantic memory involves remembering decontextualized factual information (e.g., the city where you were born) whereas episodic memory involves recalling personal experiences that occur in daily life (e.g., a vacation with family). More specifically, episodic memory is concerned with the context of a particular time, place or event that one experiences.

1.2 Memory impairments in ASD identified by standardized tests

Standardized neuropsychology tests have been conducted to assess memory in individuals with ASD. The Wechsler Memory Scale-III (WMS-III) was administered to adults with ASD between the ages of 16 and 53 (Williams, Goldstein and Minshew, 2005). This clinical memory test

revealed no deficits in immediate and delayed memory for word pairs and stories as well as no deficits in verbal WM in the autistic participants. However, the individuals with ASD were impaired in immediate and delayed recall of faces and of family scenes and in spatial WM. Consistent with the deficits identified in Williams *et al.*'s study, older autistic adults, who were administered the WMS-IV, were found to have poorer performance in visual memory (Tse *et al.*, 2019).

Neuropsychology measures have also been designed to evaluate memory processes at an earlier developmental stage. The Wide Range Assessment of Memory and Learning (WRAML), a parallel instrument to the WMS–III, found that children and adolescents aged 8 to 16 with ASD performed poorly on complex visual memory, complex verbal memory and spatial WM tasks (Williams, Goldstein and Minshew, 2006). No deficits were identified in the ASD group regarding associative learning ability, verbal WM and recognition memory. Another study assessed strategic learning and memory performance in autistic children and adolescents aged 12 to 18 through the California Verbal Learning Test-Children's Version (CVLT-C) (Solomon *et al.*, 2016). Utilization of memory strategies was found to be reduced in the ASD group.

The results of the previously discussed standardized tests have identified specific memory processes impaired in ASD. To further understanding of the memory profile in ASD, experimental memory tests have been designed and conducted.

1.3 Memory impairments in ASD identified by experimental memory tests

A characteristic pattern of memory performance, where WM and episodic memory are disproportionally impaired, has been revealed in individuals with ASD through experimental memory tests. A meta-analysis summarizing previous findings on WM in ASD found that individuals with ASD exhibited impairments in specifically spatial and verbal WM where spatial

WM was more severely affected (Wang *et al.*, 2017). Individuals with ASD have higher error rates and decreased accuracy in comparison with their neurotypical counterparts when conducting WM tasks (Habib *et al.*, 2019). Moreover, WM deficits worsen in individuals with ASD as task difficulty increases such as having to encode and recall a larger amount of information or more complex information (Landa and Goldberg, 2005). The findings of these studies suggest that the WM impairments observed in ASD vary depending on the task being performed and the difficulty level of the task at hand.

Along with WM deficits, episodic memory was reported to be diminished in individuals with ASD while semantic memory was reported to be intact (Desaunay *et al.*, 2020). Impaired episodic memory has been observed in not only adults but also in children with ASD as early as 6 years of age (Naito, Hotta and Toichi, 2020). When asked to recollect personally experienced events, individuals with ASD provide less specific and fewer accurate descriptions of these autobiographical events (Bowler, Gardiner and Grice, 2000; Bowler, Gaigg and Gardiner, 2008; Lind and Bowler, 2010; Lind, Bowler and Raber, 2014). Another study found that participants with ASD had a decreased sense of presence in their remembered events as well as lower memory saliency and spatial coherence scores in comparison with the neurotypical participants (Lind *et al.*, 2014). These reduced spatial coherence scores suggest that autistic individuals have more fragmented and less coherent recollections of past personally experienced events.

In addition, specific components of episodic memory are affected in ASD. Relational memory, source memory and item memory are different memory systems that support episodic memory (Eichenbaum and Cohen, 2004; C *et al.*, 2006). Relational memory is the ability to remember associations between items or between items and their contexts. Source memory is the ability to recall the origin of a memory and contextual aspects surrounding this memory (i.e., time

and place). Item memory, on the other hand, is the ability to recognize previously encountered information and the features of this information. Several studies have investigated these processes in ASD. Deficits in relational memory were identified in individuals with ASD (Gaigg, Gardiner and Bowler, 2008). The encoding of item-specific information on the other hand, such as the physical or conceptual features of an item, appeared to be preserved in ASD (Gaigg, Gardiner and Bowler, 2008). When undergoing a change detection memory test that assesses the reconstruction of visual scenes, individuals with ASD had a reduced ability to identify item and spatial changes in the scenes (Cooper *et al.*, 2015). This finding suggests, in contradiction with the Gaigg *et al.* study, impaired item and source memory in ASD. In sum, specific processes involved in episodic memory are compromised in autistic individuals.

Taken together, the results of these studies suggest selective deficits in WM and episodic memory which may be related to changes in the brain structures supporting these memory types.

1.4 Brain structures supporting working memory

WM is supported by a broad network of brain regions. An important brain region that has been associated with this memory type is the prefrontal cortex (Robertson, 2002; Yaple, Stevens and Arsalidou, 2019). Across many studies, the prefrontal cortex was reported to be active during the WM n-back task where study participants must judge whether each stimulus matches a stimulus that appeared n trials before (Yaple, Stevens and Arsalidou, 2019). The prefrontal cortex also contributes to the encoding of spatial WM, along with the hippocampus (Spellman *et al.*, 2015). In addition to the hippocampus' role in spatial WM, the hippocampus was revealed to maintain novel information during a delayed-recognition WM task (Ranganath and D'Esposito, 2001). Another brain region reported to be involved in active maintenance is the amygdala (LoPresti *et al.*, 2008). More specifically, the amygdala maintains and binds information related to social cues

(i.e. identity and emotion) during WM tasks (LoPresti *et al.*, 2008). Furthermore, the posterior parietal cortex, was found to play a role in selective attention during WM tasks (Kang *et al.*, 2020).

1.5 Brain structures and networks supporting episodic memory

Much research has been conducted to determine the underlying brain systems of episodic memory. Although previous studies on episodic memory have focused on the medial temporal lobe (MTL), recent human neuroimaging studies have taken a more network-based approach. These network-based studies suggest that episodic memory relies on large-scale neural networks rather than the MTL alone (Jeong, Chung and Kim, 2015). One prominent large-scale memory network suggested to play a role in episodic memory is the default mode network (DMN), an interconnected group of brain regions activated during wakeful rest (Raichle *et al.*, 2001). Consistent areas compromising the DMN include the posterior cingulate cortex (PCC), medial prefrontal cortex (MPFC), parietal cortex, hippocampus, parahippocampal cortex (PHC), retrosplenial cortex, temporal pole, middle temporal gyrus and amygdala (Raichle *et al.*, 2001; Alves *et al.*, 2019). Brain regions within the DMN have been found to support episodic memory (Wagner *et al.*, 2005; Eichenbaum, 2017). The prefrontal cortex, for example, contributes to episodic memory by selecting memories that will be retrieved and suppressing competing memories that are context-inappropriate (Eichenbaum, 2017). The parietal cortex is critical for recollecting episodic details (Wagner *et al.*, 2005). Moreover, the amygdala plays a key role in our ability to remember personally experienced events that were emotionally arousing by binding the emotion felt with the contextual information of the event (Yonelinas and Ritchey, 2015).

Other suggested episodic memory networks include the posterior-medial (PM) and anterior-temporal (AT) networks of the PMAT framework which have some overlap with brain regions found within the DMN (Ritchey, Libby and Ranganath, 2015). The PM network includes

the PHC, retrosplenial cortex, PCC, angular gyrus, precuneus, anterior thalamus, presubiculum, mammillary bodies and MPFC. The AT network, on the other hand, includes the perirhinal cortex (PRC), anterior ventral temporal cortex, amygdala and lateral orbitofrontal cortex. In this framework, the hippocampus is believed to serve as a relay between the PM and AT networks during the formation of episodic memories. It has been suggested that the anterior division of the hippocampus communicates with the AT network and the posterior division with the PM network (Ritchey, Libby and Ranganath, 2015). There is ample evidence supporting not only this difference in functional connectivity between the anterior and posterior hippocampus (Kahn *et al.*, 2008; Libby *et al.*, 2012; Maass *et al.*, 2015) but also the difference in functionality between these divisions (Poppenk *et al.*, 2013).

1.6 Anterior and posterior hippocampus functional specializations

The differential role of the anterior and posterior hippocampus in memory has long been established. In 1998, Moser and Moser proposed that episodic memory was supported by the posterior region of the hippocampus alone based on animal studies. In that same year, Lepage et al. suggested a new theory where the anterior hippocampus is activated by memory encoding while the posterior hippocampus is activated by memory retrieval (Lepage, Habib and Tulving, 1998). However, many theories have since been proposed. It has been suggested that the posterior hippocampus is preferentially involved in recalling spatial information of a familiar environment whereas the anterior hippocampus is involved in recalling the episodic details of said environment (Hirshhorn *et al.*, 2012). Another study correlated the volume of the posterior hippocampus with source memory (Poppenk and Moscovitch, 2011). Consistent with Poppenk and Moscovitch's study, more grey matter volume within the posterior hippocampus and less grey matter volume

within the anterior hippocampus predicted better performance on source memory tasks in young neurotypical adults (Snytte *et al.*, 2020).

In summary, the anterior and posterior hippocampus have distinct functions with regards to memory. The differences in functional specializations of the anterior and posterior hippocampus may derive from their differential connectivity with other brain regions and/or subfield composition given that hippocampal subfields also differ in function (Poppenk *et al.*, 2013).

1.7 Distinct functions of hippocampal subfields

An emerging body of literature has reported the involvement of distinct hippocampal subfields in specific memory processes. Research involving animal models has helped elucidate the specific functions of the cornu ammonis (CA) 1, CA3 and dendate gyrus (DG) of the hippocampus. By studying rats with selective lesions to the temporoammonic axons (which project from the the entorhinal projection to the hippocampal area CA1), the CA1 was revealed to play a role in intermediate and long-term memory but not short-term memory (Remodes and Schuman, 2004). Vago, Bevan and Kesner arrived at the same conclusion, in 2007, when observing the impact of lesioning the CA1 subfield in rats on memory. Research on rats and mice also found that the CA1 supports the encoding of spatial information in WM (Spellman *et al.*, 2015). The CA3, on the other hand, was found to be involved in processes that support episodic memory. Evidence from a study conducting voltage imaging in rat hippocampal slices supports the role of the CA3 in pattern completion where memories are recalled from partial or incomplete information (Jackson, 2013). The CA3, alongside the DG, was also found to contribute to pattern separation, the process of making patterns of neuronal activity representing similar experiences more distinct (JK *et al.*, 2007). Minimizing this overlap prevents confusion between similar memories.

Lesion studies in humans have also made important advancements in determining the functionality of hippocampal subfields. A study investigating individuals with a focal lesion to the CA1 highlighted the role of this subfield in the retrieval of recent (less than a month) and remote episodic memories (Bartsch *et al.*, 2011). In this study, the ability to retrieve detailed episodic memories from up to 40 years in the past was impaired in these individuals. Another lesion study, where participants had focal bilateral damage to their CA3 hippocampal subfield, concluded that the CA3 contributes to the retrieval of recent and remote episodic memories as well (Miller *et al.*, 2020).

By using neuroimaging techniques, the role of the CA3 and DG in echoic memory, a type of sensory memory where you store auditory information, has been elucidated. More specifically, these subfields were found to support immediate auditory recall (Mueller *et al.*, 2011). Moreover, the subiculum and presubiculum were discovered to be involved in our ability to recall verbal information after a delay (Lim *et al.*, 2013). Similarly to hippocampal subfields, amygdala nuclei were found to have distinct functions.

1.8 Distinct functions of amygdala nuclei

The different functions of amygdala nuclei have been determined through research conducted on animal models. In rats, the central nucleus was found to play a role in the acquisition of conditioned taste aversion which consists of avoiding foods that have been associated with illness (Yamamoto, 2007). The central nucleus was also shown to be critical for fear conditioning, a behavioral paradigm where an aversive fear-eliciting stimulus (e.g., a painful shock) is paired with a neutral object, location or event (Ressler and Maren, 2019). Likewise, the lateral and basal nuclei are involved in fear conditioning, but their role depends on the aversive association being made. The basal nucleus processes context-conditioned stimulation information where the context is the

neutral entity that is paired with the aversive stimulus (Canteras and Swanson, 1992; Maren and Fanselow, 1995; Koo, Han and Kim, 2004). The lateral nucleus, on the other hand, receives auditory-conditioned stimulation information where an auditory stimulus is the neutral event that is associated with the aversive stimulus (Romanski and LeDoux, 1992; Doron and Ledoux, 1999; Koo, Han and Kim, 2004). Consistent with this finding, the lateral nucleus was suggested to play a role in the formation and consolidation of auditory fear memories (Yang and Wang, 2017). Furthermore, a study conducted on male hamsters suggests that the medial nucleus of the amygdala processes olfactory sensory information critical to the hamster's sexual behavior (Lehman, Winans and Powers, 1980). Similar results were replicated in a study conducted on male and female mice where the medial nucleus mediated mating behavior (Lima *et al.*, 2018).

Taken together, it's clear that hippocampal subregions (i.e., anterior/posterior divisions and subfields) and amygdala nuclei have distinct functions. Given this finding and the advance neuroimaging techniques available, these subregions should be studied as separate entities.

1.9 Hippocampal subregions and amygdala nuclei in ASD

Hippocampal subregions and amygdala nuclei have been investigated in various disorders and diseases such as Alzheimer's disease (de Flores, La Joie and Chételat, 2015), depression (Gryglewski *et al.*, 2019; Kraus *et al.*, 2019; Tannous *et al.*, 2020), bipolar disorder (Hartberg *et al.*, 2015; Haukvik *et al.*, 2018; Janiri *et al.*, 2019; Barth *et al.*, 2021), schizophrenia (Haukvik *et al.*, 2018; Tesli *et al.*, 2020), post-traumatic stress disorder (Hayes *et al.*, 2017; Postel *et al.*, 2019; Morey *et al.*, 2020; Ousdal *et al.*, 2020) and panic disorder (Asami *et al.*, 2018; Takaishi *et al.*, 2020). However, to our knowledge, no studies have investigated the changes occurring in amygdala nuclei in ASD and very few studies have investigated hippocampal subregions in this disorder. The few studies that have studied hippocampal subregions only focused on the structural

changes occurring in certain subfields and age groups. One study investigating the amygdala and hippocampal subfields in ASD conducted a volume-based analysis on infants approximately 24 months of age at risk of developing ASD (Li *et al.*, 2019). The volume-based analysis revealed that the amygdala and the CA1–3 merged subfield of the hippocampus were enlarged in infants at risk of ASD. No volume differences were identified in the CA4/DG subfield and the subiculum between the ASD and TD group. In this study, the CA1, CA2 and CA3 hippocampal subfields were combined to form the CA1-3 merged subfield and, the CA4 and DG were merged to form the CA4/DG subfield. A volume-based analysis was therefore only conducted for these merged subfields and not for the individual hippocampal subfields nor for amygdala nuclei. There are also other hippocampal subfields that have been identified whose volumes were not measured in this study. In addition, the sample size of this study was small for the group of infants at risk of ASD (n = 60) in comparison with the sample size of neurotypical infants (n = 211). Future studies conducted on the amygdala nuclei and hippocampal subfields should have larger sample sizes in order to generalize the findings to the autism population. Furthermore, this study investigated structural changes in the hippocampal subfields in infants specifically, very early in development. The volume of hippocampal subfields has been shown to change throughout development in neurotypical individuals from 4 to 22 years of age (Krogsrud *et al.*, 2014). The volumes of the CA1, CA2-3, CA4-DG, presubiculum, subiculum and fimbria were shown to increase until the age of 13 to 15 years, followed by little to no change from adolescence to adulthood. The volume of hippocampal fissure, on the other hand, was found to decreased with age. With these findings in mind, it would be important to conduct a volume-based analysis of the amygdala nuclei and hippocampal subfields in different age groups throughout development to better understand the structural changes occurring in ASD. In summary, further research is needed to better understand

the structural changes occurring during development in the hippocampal subfields and amygdala nuclei in ASD in larger samples of children. In addition, given the functional specialization along the longitudinal axis of the hippocampus, it is important to investigate the functional connectivity of hippocampal subregions in ASD. This has yet to be done.

1.10 Objectives and hypotheses

The amygdala and the hippocampus have been linked to the WM and episodic memory deficits observed in ASD. However, no study has directly examined the association of WM and episodic memory performance with the amygdala or hippocampus in autistic individuals. In addition, the structural and functional changes occurring in the amygdala and hippocampus throughout development in ASD are still unclear. Studying these brain structures will provide us with a better understanding of the pathophysiology and the neuroanatomical underpinnings of memory deficits in ASD.

The first aim of this current study was therefore to investigate the resting-state functional connectivity of the anterior and posterior hippocampus in ASD at various ages (5-21). We hypothesized that the functional connectivity between the anterior and posterior segments of the hippocampus and cortical regions supporting WM and episodic memory will be altered in ASD. Given the differential role of the anterior and the posterior hippocampus in memory and their differential connectivity, functional changes in these hippocampal subdivisions may be linked to the memory deficits observed in ASD. To test this hypothesis, we conducted a seed-based analysis of the resting-state functional MRI (fMRI) data of autistic and neurotypical participants aged 5 to 21 from the Healthy Brain Network (HBN). We assessed the functional connectivity between the anterior and posterior hippocampus and the rest of the brain. Effects of age were explored.

The second aim of this current study was to investigate the volumetric changes of hippocampal subfields and amygdala nuclei in ASD at various ages (5-21) cross-sectionally. We hypothesized that the volume of the hippocampal CA1 and CA3 subfields and the basal amygdala nucleus will differ between the ASD and the typically developing (TD) groups. Given the distinct roles of the CA1 in WM and episodic memory, the CA3 subfield in episodic memory and of the basal nucleus in processing contextual information, we believe structural abnormalities in these subfields and this nucleus may be associated with the episodic memory impairments in ASD. To assess the structural changes in these brain regions, we obtained the T1-weighted structural MRIs of autistic and neurotypical participants aged 5 to 21 from the HBN and segmented their hippocampus and amygdala. We then extracted volume measurements for these subfields and nuclei and conducted a volume-based analyses. The volumes of the hippocampal subfields and amygdala nuclei were compared between the ASD and TD groups. Effects of age, sex and intelligence quotient (IQ) were explored.

2 Methods

2.1 Participants

The participants included in this study were children and adolescents (ages 5-21 years) recruited for the Child Mind Institute HBN (Alexander *et al.*, 2017). The HBN is an ongoing initiative that accrued a large-scale open-source dataset of participants diagnosed with a broad range of psychopathologies. The participants in this dataset underwent phenotypic assessments and brain imaging measurements. All participants were fluent in English. Participants were excluded from HBN's dataset if they had cognitive or behavioural deficits that would interfere with their participation or if they had medical issues that could impact their brain-related data.

In our study, we focused on the autistic and neurotypical participants that underwent MRI scanning. The brain imaging data was collected from three different sites in New York City: Staten Island (SI), Rutgers University Brain Imaging Center (RU) and CitiGroup Cornell Brain Imaging Center (CBIC). We included the participant data from all three sites in the resting-state fMRI analysis, leaving us with 156 autistic and 133 neurotypical participants after motion quality control (Table 1). However, we did not include the participant data from the Staten Island site for the structural analysis due to its poor T1 resolution (1.0 x 1.0 x 1.0 mm) in comparison with the higher resolution of the Rutgers University and CitiGroup Cornell Brain Imaging Centers (0.8 x 0.8 x 0.8 mm). This left us with 135 autistic and 87 neurotypical participants after motion and segmentation quality control (Table 2).

Variable	ASD group	TD group
Sample size (n)	156	133
CBIC site (n)	75	27
RU site (n)	61	59
SI site (n)	20	47
Age (mean)	10.60 (SD = 3.74)	10.26 (SD = 3.42)
Sex	123 males (33 females)	68 males (65 females)
IQ (average)	94.20	107.25

Table 1. Demographic information of participants included in the resting-state fMRI analysis.

Variable	ASD group	TD group
Sample size (n)	135	87
CBIC site (n)	78	36
RU site (n)	57	51
Age (mean)	10.59 (SD = 4.1)	10.22 (SD = 3.2)
Sex	108 males (27 females)	46 males (41 females)
IQ (mean)	94.24	107.21

Table 2. Demographic information of participants included in the structural MRI analysis.

2.2 Phenotypic assessments

The autistic participants were diagnosed using the Autism Diagnostic Interview – Revised (ADI-R) and Autism Diagnostic Observation Schedule 2nd Edition (ADOS-2). The ADIR is a reliable and standardized interview conducted by a practitioner with the caregivers of the individual being evaluated for ASD to obtain the developmental history of this individual. The ADOS-2 is a semi-structured, standardized assessment that measures communication, social interaction, play/imagination, and restricted and/or repetitive behaviors. WM was assessed with the National Institute of Health (NIH) toolbox List Sorting Test where a series of items, presented visually and auditorily, must be recalled, sequenced by size and sorted into categories. Another NIH toolbox task was used to assess episodic memory, more specifically the NIH toolbox Picture Sequence Memory task. This task requires participants to remember and reproduce the order of a sequence of pictured objects and activities that were presented on a computer screen. The Picture Sequence Memory scores, however, have not been released yet by the HBN. In this study, we therefore focused on the WM task given the availability of these scores. Additional phenotypic assessments

were conducted by the HBN and considered in our analyses including demographic (i.e., age and sex) and cognitive (ie. Wechsler Intelligence Scale).

2.3 Resting-state fMRI parameters

Images of participants from the RU and CBIC (3T scanner, TR = 800 ms, TE = 30 ms, resolution = 2.4 x 2.4 x 2.4 mm, flip angle = 31, slices = 60, multi-band acceleration = 6) and from the SI site (1.5T scanner, TR = 1450 ms, TE = 40 ms, resolution = 2.5 x 2.5 x 2.5 mm, flip angle = 55, slices =54, multi-band acceleration = 3) were acquired.

2.4 Resting-state fMRI data preprocessing

The resting-state fMRI data underwent preprocessing through Statistical Parametric Mapping (SPM, version 12). The first preprocessing step, the realignment step, involves adjusting for head movement between slices. The outlier detection step then identifies any unusual images or data values in the time series, based on head motion parameters (composite frame-wise displacement >0.5mm) and global intensity (standard deviation (SD) of the session mean >3). Following this step, the fMRI data is segmented into grey matter, white matter and cerebrospinal fluid tissue classes during indirect normalization. The fMRI data is also aligned and warped into a standard space based on the transformation matrix formed during the segmentation. Finally, the smoothing step averages data points with their neighbours in order to suppress spatial noise and enhance the signal to noise ratio. The 6 mm smoothing kernel was used for this step. After the SPM preprocessing was complete, we conducted quality control on the preprocessed images to evaluate the influence of noise sources such as head-motion.

2.5 Quality control of preprocessed resting-state fMRI data

Participants were excluded if their number of outliers was larger than half of the number of timepoints in their time series (~ 200 timepoints). In addition, the connectivity maps of participants with a maximum head motion greater than 3mm were visually inspected and participants with very noisy maps were excluded. Overall, 152 participants were excluded after quality control.

2.6 Seed-based connectivity analyses

After the quality control was complete, the CONN toolbox (version 12.b), an imaging software for the computation, display, and analysis of resting-state fMRI data was used to examine at the connectivity between regions of interest (ROIs). The ROIs studied were the anterior and posterior hippocampal segments generated by the Signy Sheldon lab based on the Olsen, Amaral, Palombo (OAP) protocol (Olsen *et al.*, 2009; Amaral *et al.*, 2015). BOLD timeseries from all voxels within the ROIs were extracted and Pearson's correlation coefficients were computed between the timeseries of the voxels in the ROI seed and the timeseries of all other voxels in the brain. This produces first-level correlation maps between each ROI and every voxel or location in the brain. Following this step, the Pearson correlations were transformed to Fisher's Z scores. Running second-level analyses in CONN toolbox then allowed us to make group-level comparisons. A one-way analysis of covariance (ANCOVA) was conducted to assess connectivity differences between the ASD and TD groups while controlling for covariates such as age, sex, IQ and site. The number of outliers was not included as a covariate in the ANCOVA since the outliers did not significantly differ between groups (p-value > 0.05). In addition, a one-way ANCOVA was applied to compare age regressions between the ASD and TD groups and determine the effect of age on ROI connectivity within these groups. To determine the ROI connectivity differences between groups, cluster-based inferences were made through Random Field Theory Parametric. This approach

identifies clusters within the brain that differ in connectivity with the ROIs between groups. Clusters must surpass set voxel and cluster thresholds. We applied a threshold of voxel-level $p<0.001$ p-uncorrected, $p<0.05$ cluster-level FDR-corrected to all results unless otherwise specified.

2.7 Structural imaging parameters

Participants recruited from RU and the CBIC were scanned in the Siemens 3T Trim Trio and Siemens 3T Prisma, respectively. T1-weighted images were acquired for these participants (TR = 2500 ms, TE = 3.15 ms, resolution = 0.8 x 0.8 x 0.8 mm, flip angle = 8, 224 slices).

2.8 Quality control of structural images

Before preprocessing the structural images, quality control of the T1-weighted images was conducted based on the Motion Quality Control Manual of the Computational Brain Anatomy Laboratory (CobrALab) at the Douglas Institute (CoBrALab, 2019). Participants given a rating of 2 or below, with limited blurring and ringing, were included. Participants with severe blurring or ringing, assigned ratings of 3 or 4, were excluded. However, participants with a rating of 3, where the ringing in the cortex did not reach the hippocampus and amygdala, were included. Quality control was conducted by two raters to increase reliability. The structural images also underwent quality control following the FreeSurfer preprocessing and segmentation to ensure the hippocampal subfield and amygdala nucleus boundaries were accurate. Participants with inaccurate boundaries were excluded. Overall, 174 participants were excluded after quality control.

2.9 Structural image processing & segmentation

To accomplish the automated segmentation of hippocampal subfields and amygdala nuclei, the FreeSurfer software (version 6) was used. More specifically, the "Segmentation of hippocampal subfields and nuclei of the amygdala (cross-sectional and longitudinal)" module was used (Iglesias *et al.*, 2015; Saygin *et al.*, 2017). The T1-weighted structural images of participants first underwent preprocessing. The FreeSurfer preprocessing steps involve downsampling, intensity bias normalization, skull stripping, subcortical parcellation (labelling), white matter segmentation, surface inflation, spherical mapping and cortical parcellation (labelling). The downsampling step allows for the storage and transmission requirements of the images to be decreased by reducing spatial resolution. The images then undergo intensity bias normalization which removes the bias caused by the coils. Once this step is complete, the skull stripping step removes all non-brain such as the skull, eyes, neck and dura. FreeSurfer then labels all the subcortical structures, the white matter, the grey matter, the cerebellum and the cortex based on volume. The white matter is also segmented. Following this step, the pial surface of the brain is extracted and inflated into a 3D surface, allowing the subject's brain to be aligned to the reference spherical atlas. Lastly, FreeSurfer parcellates a cortical surface based on the reference atlas and assigns a neuroanatomical label to each location on the cortical surface. Once the participant's images underwent the preprocessing steps, hippocampal and amygdala atlases were applied to the participant's brain. The high-resolution hippocampal atlas includes 18 hippocampal subfields (parasubiculum, presubiculum head, presubiculum body, subiculum head, subiculum body, CA1 head, CA1 body, CA3 head, CA3 body, CA4 head, CA4 body, granule cell layer of the head of the dentate gyrus (DG head), granule cell layer of the body of the dentate gyrus (DG body), molecular layer of the hippocampal head (ML head), molecular layer of the hippocampal body (ML body), hippocampus

amygdala transition area (HATA), fimbria and hippocampal fissure) and 3 merged labels (the hippocampal head, body and tail). The amygdala atlas includes 9 nuclei of the amygdala (accessory basal nucleus (ABN), anterior amygdaloid area (AAA), basal nucleus, central nucleus, cortical nucleus, cortico-amygdaloid transition area (CATA), lateral nucleus, medial nucleus and paralaminar nucleus (PLN)). The volume of each subfield and nucleus was extracted after the previously described quality control to conduct a volume-based analysis.

2.10 Volume-based analyses

A mixed linear model was first conducted to determine whether subfield or nucleus volumes differed between the ASD and TD groups. The lme4 package in R (version 4.0.2) was used.

```
lmer(volume ~ group + age + sex + IQ + (1|site), data = df)
```

Group, age, sex and IQ were included as fixed effects and site as a random effect. The intraclass correlation coefficient of site was calculated for each subfield and nucleus. When the random effect was found to be very close to zero, site was removed from the model and a simple linear model was conducted. This model was conducted for both raw and intracranial volume (ICV)-corrected subfields and nuclei. The ICV correction involved dividing each raw hippocampal subfield and amygdala nucleus volume by the participant's ICV to account for inter-individual variability in brain morphology (Mathalon *et al.*, 1993). FDR was conducted to correct for multiple comparisons.

In addition to the univariate mixed linear models, we also conducted a multivariate analysis, partial-least-squares correlation (PLSC), to relate behavioral/demographic measures (age, IQ, sex, working memory) with brain volumetric measures. This multivariate correlational analysis allows us to investigate the relationship between multiple behavioural variables and the

subfield/nucleus volumes at once. In the context of neuroimaging studies, PLSC is often used to assess the relationship between brain activity and behaviour (Krishnan et al., 2011). Brain and behavioural data are stored in matrices. By means of a permutation test, PLSC identifies statistically significant latent variables that represents the association between the brain and behaviour data matrices. Bootstrap tests are used to evaluate the contribution of each brain and behavioural variable to a given statistically significant latent variable. The relationship between brain and behavioural variables that reliably contribute to a given latent variable can then be assessed. In this study, we ran the PLSC analysis in MATLAB (version R2019b) with the PLS software (version 6.15) provided by the Rotman Research Institute. The brain data matrix contained the volume measurements of the LH and RH amygdala nuclei and hippocampal subfields for each participant. The behavioural data matrix included the group, age, sex, WM scores and IQ of each participant. PLSC was conducted with data from both the ASD and TD groups to assess group effects and for each group separately to compare the brain-behaviour patterns between groups. A threshold of $p<0.05$ was used to assess whether the correlations represented by a given LV were statistically different from noise. A bootstrap ratio threshold of 2.58, analogous to a p-value of 0.01, was used to assess the contribution of each brain and behavioural variable to a given latent variable.

3 Results

3.1 Hippocampal functional connectivity analysis results

Decreased resting-state functional connectivity of the right hemisphere (RH) anterior hippocampus with the MPFC was found in the ASD group compared to the TD group (Figure 1a). The RH anterior hippocampus also had decreased connectivity with the left hemisphere (LH) posterior hippocampus and parahippocampal cortex (PHC) (Figure 1b). The LH anterior hippocampus, RH

posterior hippocampus and LH posterior hippocampus also had decreased connectivity with the MPFC in the ASD group relative to the TD group. In addition, connectivity differences of the anterior and posterior hippocampus with other brain clusters such as the middle temporal gyrus and superior frontal gyrus were observed between the ASD and TD groups (Tables 3 and 4; Figure 4). Further, we found a group-by-age interaction in the functional connectivity between the posterior hippocampus and the precuneus (Figure 2; voxel threshold $p<0.005$ p-uncorrected, cluster threshold $p<0.05$ FDR-corrected), which decreased with age in the ASD group but remained stable in the TD group (Figure 3; ASD: $r^2= 0.192$, $p<0.0001$, TD: $r^2=0.022$, $p=0.087$).

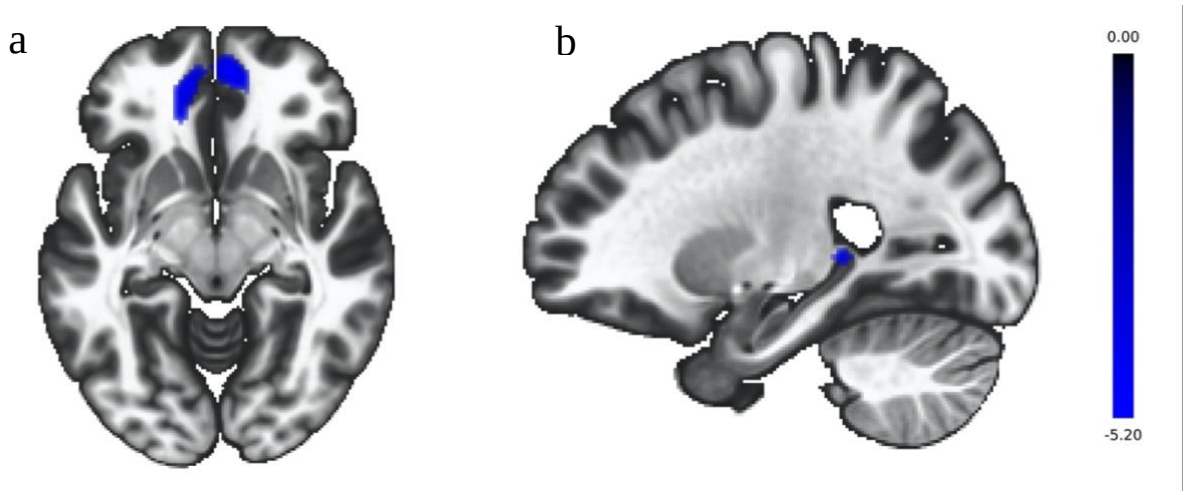

Figure 1. Brain regions that showed lower connectivity with the RH anterior hippocampus in ASD compared to TD. The MPFC can be observed in 1a (axial view) and the LH posterior hippocampus/PHC in 1b (sagittal view). A one-way ANCOVA was conducted with group as between-subjects contrast and age, sex, IQ and site as covariates (voxel threshold $p<0.001$ p-uncorrected, cluster threshold $p<0.05$ FDR-corrected). The color bar represents the strength of the t-statistic with the blue colour indicating lower connectivity in ASD compared to TD.

Figure 2. The functional connectivity between the posterior hippocampus (average between LH and RH) and the precuneus showed different age effects in ASD and TD. A one-way ANCOVA was conducted where the age-connectivity regression was compared between groups (voxel threshold $p<0.005$ p-uncorrected, cluster threshold $p<0.05$ FDR-corrected). A sagittal view of the brain is shown.

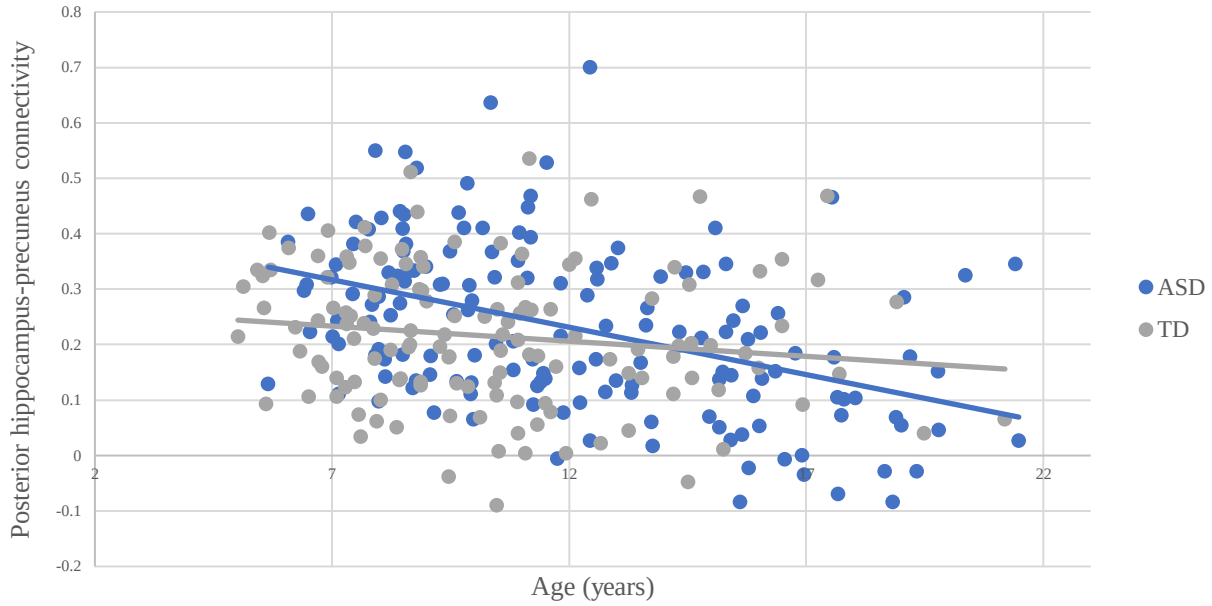

Figure 3. Developmental trajectory of the functional connectivity between the posterior hippocampus and precuneus in the ASD and TD groups. Fisher's Z scores were extracted from the precuneus cluster shown in Figure 2. The Fisher's Z scores of the LH and RH posterior hippocampus were averaged.

ROI	Clusters (x, y, z)	Main composition	Cluster size	Z score
LH anterior hippocampus	+02 +32 -24	MPFC	257	4.21
	+04 -18 -42	Pons	252	5.56
	-10 +40 -16	MPFC	164	-3.12
	+60 -02 -26	Middle temporal gyrus	109	4.15
LH posterior hippocampus	-04 +32 -14	MPFC	1332	4.90
	+56 -04 -22	Middle temporal gyrus	195	4.75
RH anterior hippocampus	+02 +58 -16	MPFC	755	5.07
	+04 -16 -42	Pons	182	4.95
	-30 -38 -04	LH posterior hippocampus/PHC	90	4.56
RH posterior hippocampus	-10 +50 -06	MPFC	1430	5.46
	+08 -16 -42	Pons	227	5.45

Table 3. Brain regions that showed lower connectivity with the anterior and posterior hippocampus in ASD compared to TD. A one-way ANCOVA was conducted with group as between-subjects contrast and age, sex, IQ and site as covariates. Included in the table are the coordinates, main composition, size and Z scores of clusters that passed the voxel ($p<0.001$) p-uncorrected and cluster ($p<0.05$) FDR-corrected thresholds.

ROI	Clusters (x, y, z)	Main composition	Cluster size	Z score
LH anterior hippocampus	+56 -54 +08	Middle temporal gyrus	144	4.49
	+28 +56 +30	Superior frontal gyrus	79	3.86
LH posterior hippocampus	+32 -70 +26	Middle occipital gyrus	206	4.27
	+34 +56 +26	Middle frontal gyrus	110	4.84
	-30 -68 +20	Lateral occipital cortex	96	4.50
RH anterior hippocampus	+58 -58 +02	Middle temporal gyrus	185	4.43
	+42 -10 -12	Superior temporal gyrus	106	4.65
RH posterior hippocampus	+34 -62 +16	Lateral occipital cortex	156	4.67

Table 4. Brain regions that showed higher connectivity with the anterior and posterior hippocampus in ASD compared to TD. A one-way ANCOVA was conducted with group as between-subjects contrast and age, sex, IQ and site as covariates. Included in the table are the

coordinates, main composition, size and Z scores of clusters that passed the voxel ($p<0.001$) p-uncorrected and cluster ($p<0.05$) FDR-corrected thresholds.

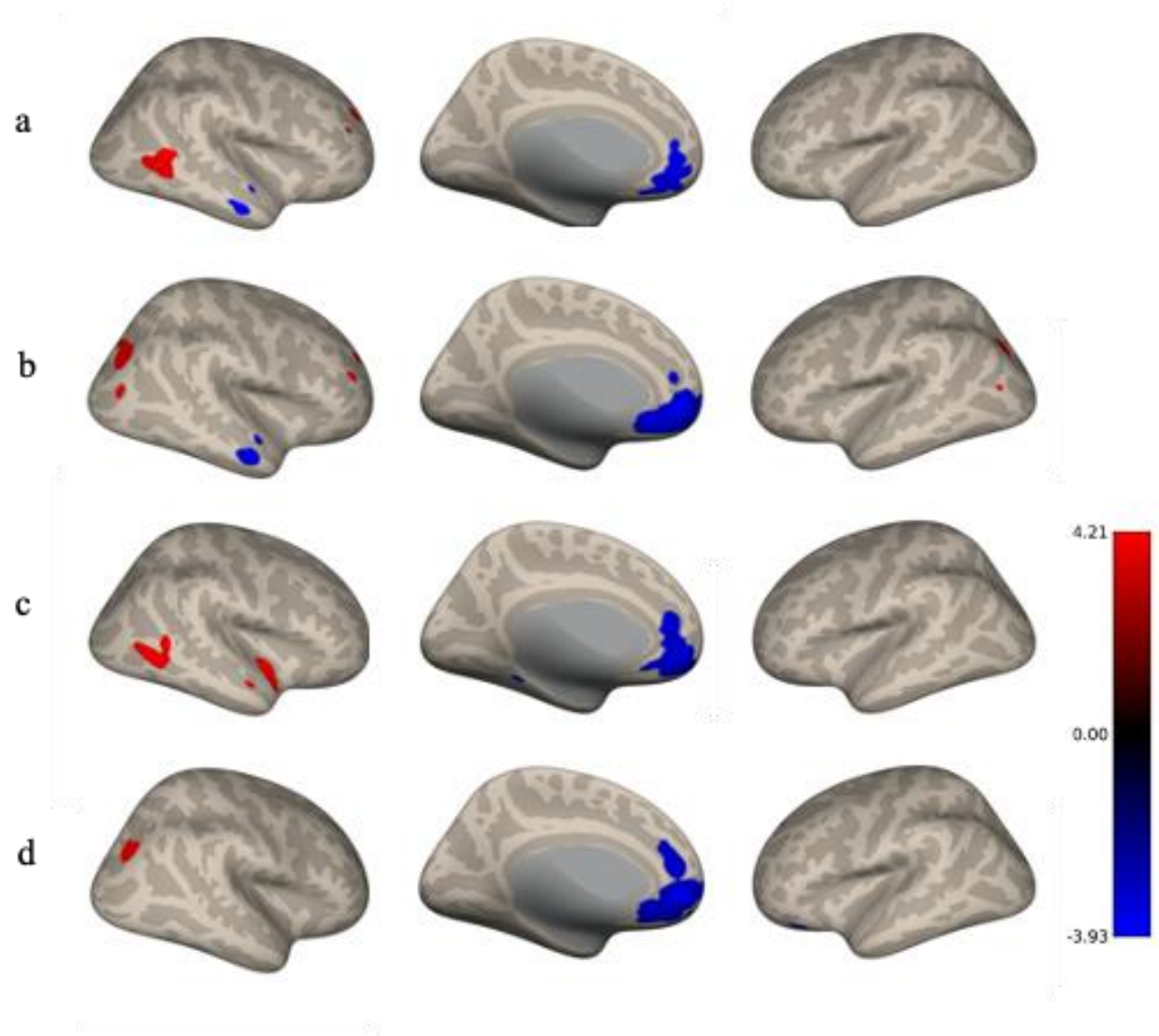

Figure 4. Functional connectivity differences of all four hippocampal seeds in ASD compared to TD. The LH anterior hippocampus can be observed in 4a, LH posterior hippocampus in 4b, RH anterior hippocampus in 4c and RH posterior hippocampus in 4d. A one-way ANCOVA was conducted with group as between-subjects contrast and age, sex, IQ and site as covariates (voxel threshold $p<0.001$ p-uncorrected, cluster threshold $p<0.05$ FDR-corrected). The color bar

represents the strength of the t-statistic with the blue colour indicating lower connectivity in ASD compared to TD and the red colour indicating higher connectivity in ASD compared to TD. Right, left medial and left views of the brain are shown.

3.3 Hippocampal and amygdala volume analysis: mixed linear model results

Before FDR correction, the volumes of the LH CA3 body, CA4 body and ML body were significantly different ($p<0.05$) between groups. These volumes were bigger in the ASD group relative to the TD group. However, after correcting for multiple comparisons, no significant differences ($p>0.05$) in LH and RH hippocampal subfield and amygdala nucleus volumes were observed between the ASD and TD groups. These findings were consistent for both raw (Tables 5, 6, 7, 8) and ICV-corrected volumes (Tables 9, 10, 11, 12). Age, sex and IQ effects were observed for several subfields and nuclei. To compare the effects of age, sex and IQ between groups, a PLSC analysis with these behavioural variables was conducted.

Region	Group		Age		Sex		IQ	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
ABN	5.4643	0.3382	3.2191	0.0002	-7.7971	0.1795	0.1973	0.1424
AAA	-0.1179	0.9262	0.49390	0.0101	-1.1588	0.3711	0.0492	0.1021
Basal nucleus	3.1077	0.7228	4.7503	0.0004	-23.765	0.0082	0.2590	0.2099
Central nucleus	-0.9807	0.4930	0.19238	0.3680	-0.7466	0.6080	0.0392	0.2450
Cortical nucleus	0.7724	0.3317	0.22724	0.0556	-0.3603	0.6569	0.0339	0.0699
CATA	5.1802	0.1940	2.53996	3.07e-5	-3.4662	0.3920	0.0822	0.3810
Lateral nucleus	14.596	0.2569	5.6619	0.0036	-36.866	0.0053	0.4343	0.1522
Medial nucleus	0.1574	0.8685	0.16776	0.2355	-0.3661	0.7059	0.0425	0.0573
PLN	0.2403	0.8160	0.54262	0.0005	-3.7118	0.0005	0.0293	0.2290
Whole amygdala	29.029	0.3826	17.8131	0.0004	-79.020	0.0202	1.1728	0.1347

Table 5. Mixed linear model parameters of fixed effects for raw volumes of the LH amygdala nuclei and whole amygdala. The estimate regression beta coefficients and their significance levels before FDR correction are included.

Region	Group		Age		Sex		IQ	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
CA1 body	6.3484	0.0725	0.3973	0.4503	-4.7634	0.1842	0.1284	0.1222
CA1 head	-0.9683	0.9301	5.7170	0.0007	-26.138	0.0208	0.4783	0.0670
CA3 body	5.2021	**0.0269**	0.7438	0.0341	1.01667	0.6685	0.0470	0.3927
CA3 head	-1.7778	0.5732	1.7475	0.0003	-5.68011	0.0781	-0.0169	0.8197
CA4 body	4.9702	**0.0403**	0.7961	0.0281	-2.8731	0.2418	0.0952	0.0946
CA4 head	-0.9929	0.7309	1.6441	0.0002	-5.9893	0.0425	0.0349	0.6080
DG body	5.0397	0.0649	0.8730	0.0327	-3.9653	0.1524	0.1245	0.0527
DG head	-1.8513	0.6029	2.1588	7.18e-5	-6.9410	0.0563	0.0409	0.6257
HATA	1.3190	0.4100	0.9510	9.58e-5	-0.2904	0.8580	0.0190	0.6130
Fimbria	-2.2679	0.4444	0.7781	0.0802	-11.911	0.0001	0.0757	0.2785
Fissure	4.8988	0.2265	0.9457	0.1181	-3.7380	0.3642	0.1777	0.0626
ML body	9.7989	**0.0189**	1.4189	0.0228	-4.9454	0.2410	0.2319	0.0182
ML head	-0.1836	0.9782	3.4813	0.0006	-15.365	0.0253	0.3032	0.0562
Parasubiculum	-1.4267	0.4254	0.2470	0.3560	-5.7193	0.0019	0.0945	0.0257
Presubiculum body	1.0024	0.8398	0.7992	0.2817	-6.4469	0.2022	0.1996	0.0886
Presubiculum head	1.8052	0.5825	1.0198	0.0388	-8.8217	0.0089	0.2089	0.0074
Subiculum body	9.6953	0.0646	1.7577	0.0253	-7.8255	0.1418	0.3349	0.0070
Subiculum head	0.8745	0.8588	1.2885	0.0806	-7.0412	0.1600	0.3247	0.0055
Head	-3.2876	0.9231	18.252	0.0004	-81.877	0.0190	1.4866	0.0651
Body	39.789	0.0608	7.5639	0.0174	-41.714	0.0533	1.2372	0.0136
Tail	22.823	0.0605	3.0876	0.0890	-13.195	0.2843	0.3171	0.2663
Whole hippocampus	59.324	0.3308	28.904	0.0017	-136.79	0.0283	3.0410	0.0351

Table 6. Mixed linear model parameters of fixed effects for raw volumes of the LH hippocampal subfields, merged subfields and whole hippocampus. The estimate regression beta coefficients and their significance levels before FDR correction are included.

3.4 Subfield/nucleus volumes-behaviour PLSC results

Permutation testing revealed a single statistically significant ($p<0.01$) latent variable for each of the PLSC analyses conducted.

3.4.1 PLSC analysis of both the ASD and TD groups

The statistically significant latent variable ($p<0.0001$) produced in the PLSC analysis of both the ASD and TD groups represents the relationship between behavioural variables and the amygdala nucleus and hippocampal subfield volumes of both groups. This latent variable accounted for 80.05% of the variance explained. Consistent with the mixed linear model results, no difference in nucleus and subfield volumes was observed between groups (Figure 5). To better understand the brain-behaviour patterns within each group, we conducted PLSC for each group separately and obtained a significant latent variable for each group's PLSC analysis.

3.4.2 PLSC analysis of the ASD group

The statistically significant latent variable ($p<0.0001$) produced in the PLSC analysis of the ASD group represents the relationship between behavioural variables and the amygdala nucleus and hippocampal subfield volumes within this group. This latent variable accounted for 84.78% of the variance explained. The subfields and nuclei that contributed to this latent variable include the LH hippocampal fissure, LH fimbria, LH CA1 body, LH and RH thalamus, LH and RH PLN, LH and RH latent nucleus, LH and RH CATA, LH and RH cortical nucleus, LH and RH central nucleus, LH and RH basal nucleus, LH and RH AAA, LH and RH ABN, LH and RH subiculum body, LH and RH presubiculum head, LH and RH ML head, LH and RH ML body, LH and RH HATA, LH and RH DG head, LH and RH DG body, LH and RH CA4 head, LH and RH CA4 body, LH and RH CA3 head, LH and RH CA3 body, LH and RH CA1 head, RH putamen, RH medial nucleus

and, RH subiculum head (Figure 7). The correlating behavioural variables included sex and age (Figure 6). A positive relationship between nucleus/subfield volumes and age was observed whereas a negative relationship was observed with sex in the ASD group.

3.4.3 PLSC analysis of the TD group

The statistically significant latent variable ($p<0.001$) produced in the PLSC analysis of the TD group represents the relationship between behavioural variables and volumes of amygdala nuclei and hippocampal subfields within this group. This latent variable accounted for 81.27% of the variance explained. The subfields and nuclei that contributed to this latent variable include the LH CATA, LH central nucleus, LH presubiculum head, LH parasubiculum, LH ML body, LH DG head, LH CA4 body, LH CA1 body, LH and RH thalamus, LH and RH putamen, LH and RH PLN, LH and RH lateral nucleus, LH and RH basal nucleus, LH and RH AAA, LH and RH ABN, LH and RH subiculum head, LH and RH ML head, LH and RH fimbria, LH and RH DG body and, LH and RH CA1 head (Figure 9). The correlating behavioural variables included WM and IQ (Figure 8). A positive relationship between nucleus/subfield volumes and WM and IQ was observed in the TD group.

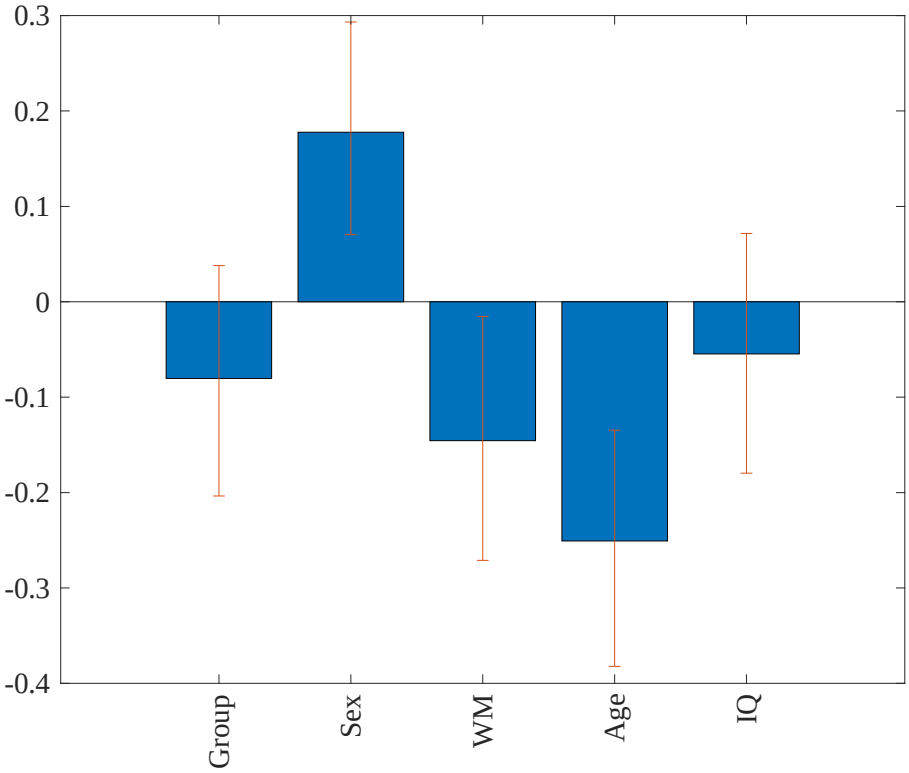

Figure 5. The behavioural pattern of the latent variable from the PLSC analysis with both the ASD and TD groups. The y-axis designates correlation within the latent variable and the x-axis designates the behavioural variables. The error bars denote the 95% confidence interval.

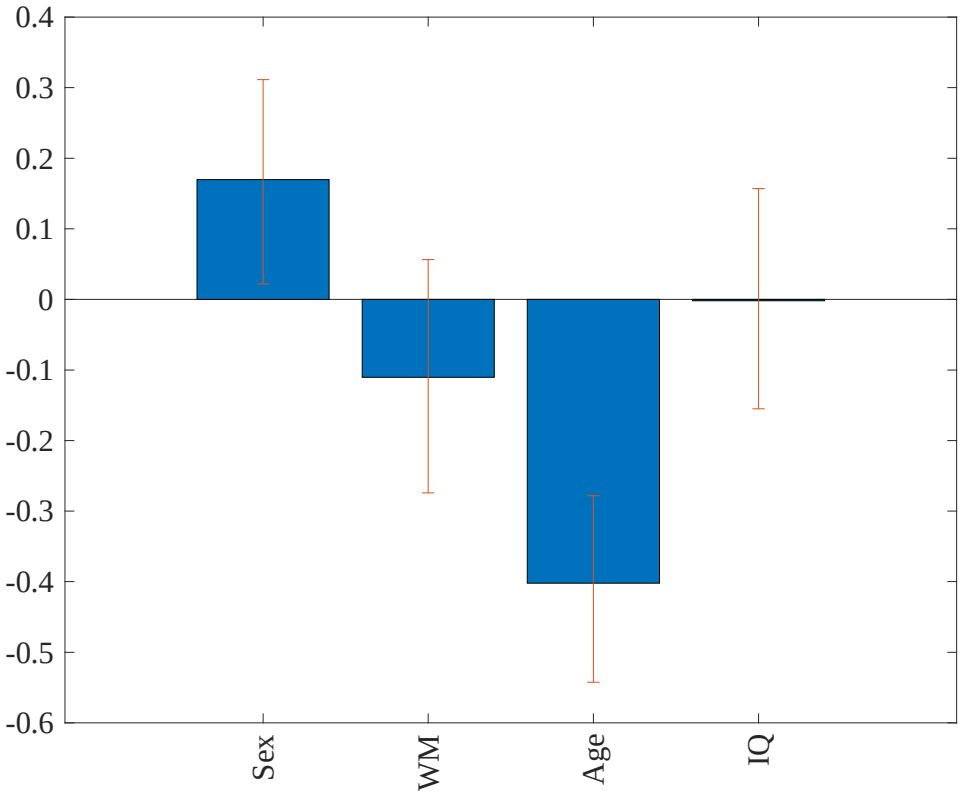

Figure 6. The behavioural pattern of the latent variable from the PLSC analysis with the ASD group. The y-axis designates correlation within the latent variable and the x-axis designates the behavioural variables. The error bars denote the 95% confidence interval.

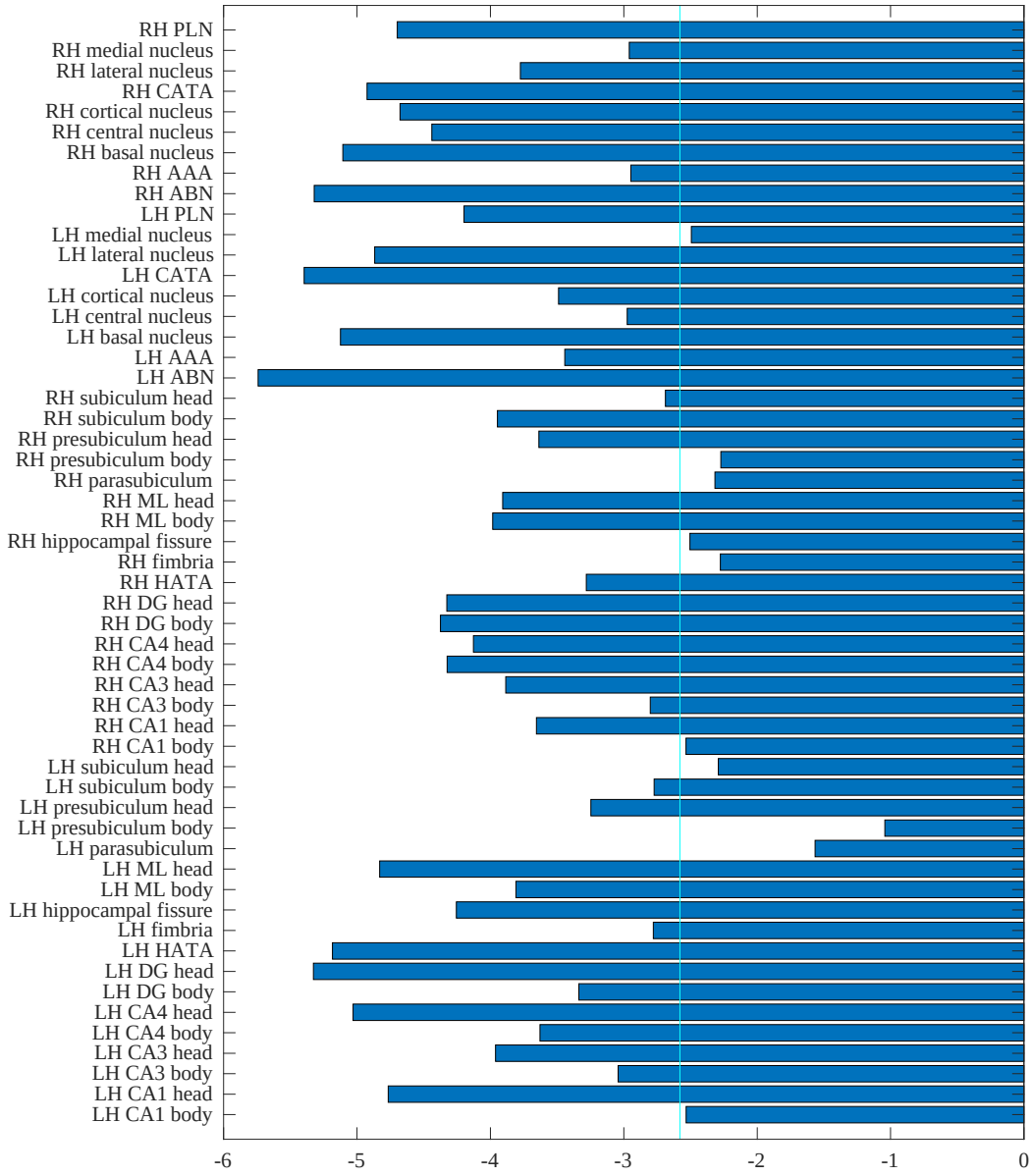

Figure 7. The brain pattern of the latent variable from the PLSC analysis with the ASD group. The y-axis designates the nuclei/subfields and the x-axis designates the bootstrap ratio. The blue line denotes the bootstrap ratio threshold of 2.58.

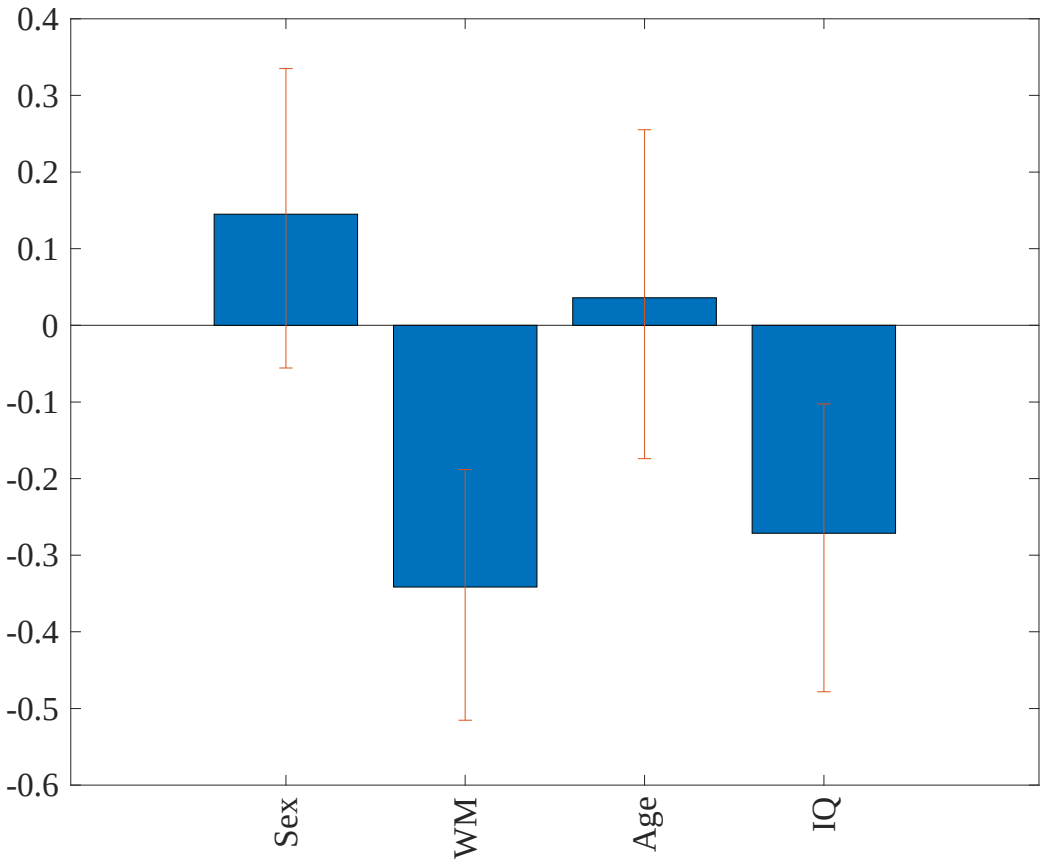

Figure 8. The behavioural pattern of the latent variable from the PLSC analysis with the TD group. The y-axis designates correlation within the latent variable and the x-axis designates the behavioural variables. The error bars denote the 95% confidence interval.

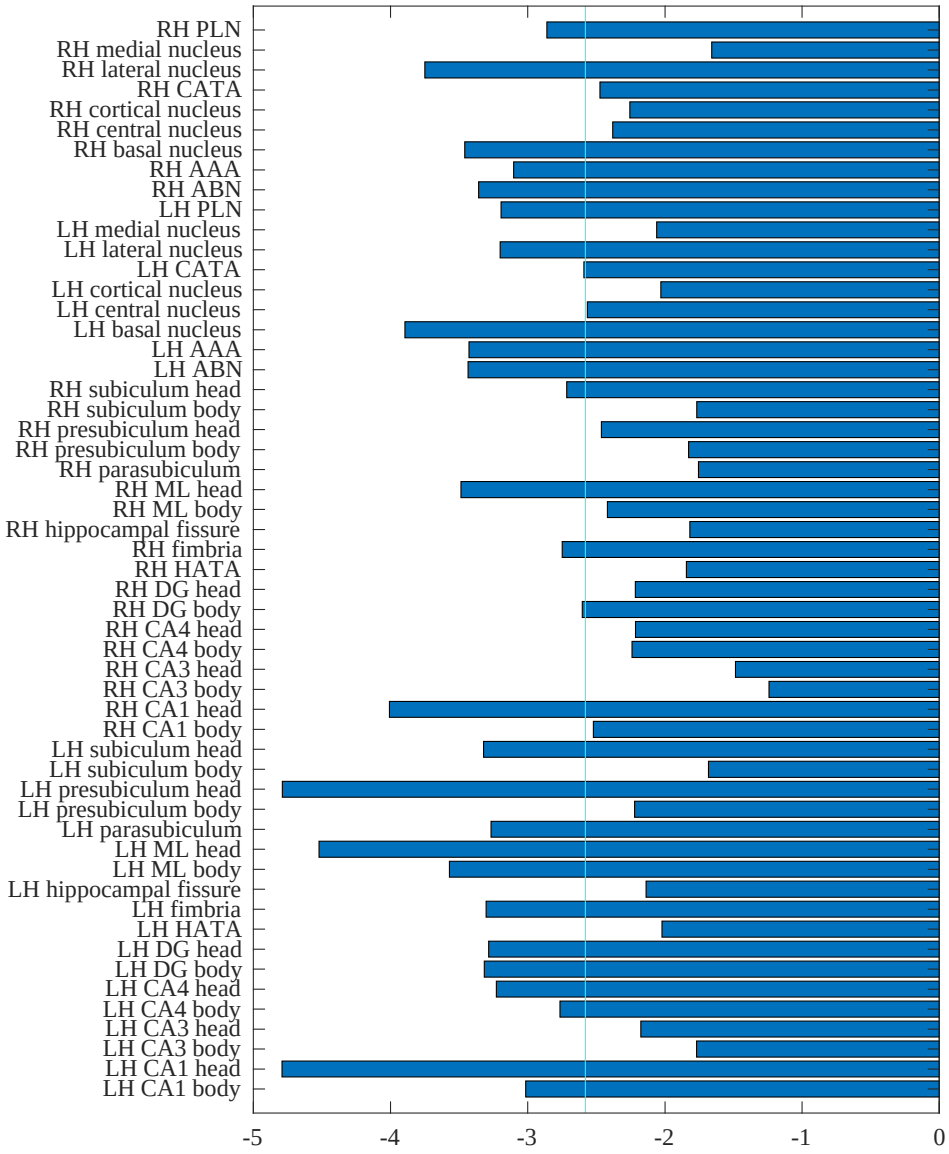

Figure 9. The brain pattern of the latent variable from the PLSC analysis with the TD group. The y-axis designates the nuclei/subfields and the x-axis designates the bootstrap ratio. The blue line denotes the bootstrap ratio threshold of 2.58, analogous to a p-value of 0.01.

4 Discussion

4.1 Alterations in the functional connectivity of the anterior and posterior hippocampus in ASD

The first aim of the current study was to investigate the resting-state functional connectivity of the anterior and posterior hippocampus at various ages (5-21) in ASD. Resting-state fMRI data of autistic and neurotypical participants was obtained from the HBN. A seed-based analysis of this resting-state fMRI data was conducted in CONN toolbox to assess the functional connectivity of the anterior and posterior hippocampus with the rest of the brain.

We found altered functional connectivity of the anterior and posterior hippocampus with the MPFC, a region implicated in both episodic memory and social cognition, in ASD. Our results indicate decreased connectivity of the left and right anterior and posterior hippocampus with the MPFC of the posterior medial (PM) episodic memory network (Ritchey, Libby and Ranganath, 2015) in the ASD group relative to the TD group. This finding is in agreement with other studies who investigated the functional connectivity of episodic memory networks in ASD (Cooper *et al.*, 2017; Hogeveen *et al.*, 2020). Cooper *et al.* (2017) found reductions in functional connectivity between the hippocampus and frontal regions, including the fronto-parietal network and the MPFC, during episodic memory retrieval in ASD. Hogeveen *et al.* (2020) investigated the functional connectivity between the MTL (comprised of the bilateral perirhinal cortex, bilateral PHC and bilateral head, body, and tail of the hippocampus) and PM network during a relational encoding and recollection task in ASD. During the relational encoding task, the ASD group exhibited reduced connectivity between MTL and PM network regions, including the MPFC, compared to the TD group (Hogeveen *et al.*, 2020). In line with these task-based fMRI results, reduced connectivity of the MPFC was reported in autistic individuals during resting state (Kennedy and Courchesne, 2008). Decreased connectivity of the hippocampus with the MPFC

may contribute to the episodic memory and theory of mind deficits observed in ASD given the involvement of the MPFC in these cognitive processes. There is robust evidence supporting the role of MPFC in episodic memory (Spreng, Mar and Kim, 2009; Kveraga *et al.*, 2011; Benoit and Schacter, 2015; Sekeres, Winocur and Moscovitch, 2018). Greater activation of the MPFC was observed during this memory type (Benoit and Schacter, 2015). In addition, the MPFC was found to be involved in the processing of contextual information pertaining to episodic memories (Kveraga *et al.*, 2011; Sekeres, Winocur and Moscovitch, 2018). Another study, investigating the MPFC in episodic memory and theory of mind, found increased activity and engagement of the MPFC in both these cognitive processes (Spreng, Mar and Kim, 2009). Theory of mind is the social and cognitive ability of ascribing mental states to ourselves and others, which is impaired in individuals with ASD (Baron-Cohen, Leslie and Frith, 1985). One of the key brain regions supporting this social-cognitive ability is the MPFC (Carrington and Bailey, 2009). Activation of the MPFC during theory of mind has been reported across many studies (Gallagher *et al.*, 2000; Spence *et al.*, 2001; Lee *et al.*, 2002; Ganis *et al.*, 2003; Kozel *et al.*, 2004; Gobbini *et al.*, 2007). In light of the MPFC's involvement in both episodic memory and theory of mind, reduced connectivity of the hippocampus with the MPFC may contribute to memory and social deficits in ASD.

Additionally, we observed reduced connectivity of the right anterior hippocampus with the left posterior hippocampus and PHC in ASD relative to the TD group. To our knowledge, no other studies have reported decreased interhemispheric connectivity between the left and right hippocampus in ASD. However, intrinsic hippocampal connectivity was found to be positively correlated with performance on an episodic memory task in TD individuals (Wang *et al.*, 2010). The reduced interhemispheric connectivity of the hippocampus, observed in the current study, may

therefore contribute to episodic memory impairments in ASD. The decreased connectivity between the hippocampus and PHC in ASD has, on the other hand, been observed in a study conducted by Hogeveen (2020), although the laterality of the connectivity differed. Hogeveen *et al.* (2020) found decreased connectivity between the left hippocampus and right PHC in individuals with ASD during an episodic memory task (Hogeveen *et al.*, 2020). PHC functional connectivity in ASD has been found to be altered when compared to TD, with mixed results. The PHC was found to have decreased connectivity with the PCC in ASD (Weng *et al.*, 2010). Increased connectivity of the retrosplenial cortex and PCC with the PHC was observed at rest in autistic children aged 7 to 12 years (Lynch *et al.*, 2013). Weng *et al.* (2010) and Lynch *et al.* (2013) did not report reduced connectivity between the PHC and hippocampus. Nonetheless, the reduced connectivity of the hippocampus with the PHC observed in the current study may contribute to the memory impairments in ASD, as the PHC is a core node in the episodic memory network. The PHC was found to play a role in the recollection of source memory but not item memory (Davachi, Mitchell and Wagner, 2003; Diana, Yonelinas and Ranganath, 2010). In addition, the PHC was activated during the retrieval of autobiographical memories (Svoboda, McKinnon and Levine, 2006; Cabeza and St Jacques, 2007). Given the role of the PHC in episodic memory, this brain region has been included in different neurobiological models of memory. In the PMAT framework, the PHC is one of the brain regions comprising the PM episodic memory network (Ritchey, Libby and Ranganath, 2015). In other memory frameworks, it has been suggested that the hippocampus creates episodic memories by binding information from the PHC and PRC (Eichenbaum, Yonelinas and Ranganath, 2007; Montaldi and Mayes, 2010). Taken together, reduced connectivity of the right anterior hippocampus with the left posterior hippocampus and PHC may be related to the episodic memory deficits in ASD.

Furthermore, functional connectivity between the posterior hippocampus and precuneus decreased with age in the ASD group but remained stable in the TD group. To our knowledge, other studies investigating resting-state functional connectivity throughout development in ASD did not include the hippocampus as a ROI. The current study is therefore the first to report a negative relationship between hippocampus-precuneus connectivity and age in ASD. This finding suggests distinct developmental trajectories of functional connectivity in ASD.

4.2 Volumetric changes of hippocampal subfields and amygdala nuclei in ASD

The second aim of the current study was to investigate the volumetric changes of hippocampal subfields and amygdala nuclei in ASD at various ages (5-21) cross-sectionally. To assess the structural changes in these brain regions, we obtained the T1-weighted structural MRIs of autistic and neurotypical participants aged 5 to 21 from the HBN. We segmented their hippocampus and amygdala using FreeSurfer. We then the extracted the volume measurements of the subfields and nuclei and conducted volume-based analyses.

The mixed linear model revealed statistically significant group differences in the volumes of the left CA3 body, CA4 body and ML body subfields before FDR correction. More specifically, the left CA3 body, CA4 body and ML body were significantly larger in the ASD group compared to the TD group. To our knowledge, no studies have investigated amygdala nuclei in ASD and only one study has explored hippocampal subfields in ASD. Li *et al.* (2019) studied the CA1, CA3, subiculum and CA4/DG hippocampal subfields in infants at risk of ASD. Li *et al.* (2019) reported overgrowth of the CA1, CA3 and subiculum in infants at risk of ASD but did not report group differences with regards to the CA4/DG volume. Our findings, before FDR correction, are consistent with group differences in CA3 volume and no group differences in DG. On the other hand, we did observe group differences in CA4 volume and did not observe overgrowth of the

CA1 and subiculum. Direct comparisons between the current study's and Li's findings may be difficult, however, as Li *et al.* (2019) relied on a longitudinal sample of infants at risk of ASD aged 6 to 24 months whereas we relied on a cross-sectional sample of individuals aged 5-21 with a formal diagnosis of ASD. Nonetheless, overgrowth of the CA3 may contribute to memory impairments in ASD. It has been suggested that the CA3 plays a vital role in the retrieval of long-term episodic memories (Miller *et al.*, 2020). In congruence with Miller's study, remote autobiographical memories were detected in the CA3 (Bonnici, Chadwick and Maguire, 2013). Given the role of the CA3 in episodic memory, increased volume of this subfield may be related to the episodic memory deficits observed in autistic individuals. Our finding of the enlarged CA3 in ASD, although did not survive multiple comparison correction, warrants further investigation.

After FDR correction, no statistically significant group differences in hippocampal subfield and amygdala nucleus volumes were observed in the mixed linear model. These findings are in agreement with studies that did not find volume changes in the whole amygdala and hippocampus in ASD (Piven *et al.*, 1998; Haznedar *et al.*, 2000; Barnea-Goraly *et al.*, 2014). In line with these mixed linear model results, the PLSC with both the ASD and TD groups revealed no significant group differences in the volume of the hippocampal subfields and amygdala nuclei. In addition, the mixed linear model revealed age, sex and IQ effects for several subfields and nuclei. To determine whether these effects were driven by the TD group or ASD group, we conducted PLSC analyses for each group. The PLSC analyses conducted for each group revealed differences in the effects of behavioural variables between the ASD and TD groups. The volumes of most subfields and nuclei were found to be correlated with age and sex within the ASD group whereas this relationship with age and sex was absent in the TD group. A positive relationship between subfields and nuclei volume and age in ASD is in congruence with the positive linear

developmental trajectories of the amygdala, CA1, CA3, subiculum and CA4/DG observed in the Li *et al.* (2019) study. Within the TD group, the volumes of subfields and nuclei did not significantly change with age. Consistent with these findings, Tamnes *et al.* (2018) reported no development of the hippocampal fissure and HATA in a longitudinal sample of TD participants aged 8–26 years. However, Tamnes *et al.* (2018) observed linear age-related volume decreases in the parasubiculum, presubiculum, CA3, CA4 and DG and nonlinear age-related volume increases in the CA1, ML and fimbria of TD participants. The development of hippocampal subfields was also investigate in a cross-sectional sample of TD individuals aged 4 to 22 years by Krogsrud *et al.* (2014). Krogsrud found nonlinear volume increases in the CA1, CA3, CA4/DG, presubiculum, subiculum and fimbria until ages 13-15, followed by little age-related volume. As for the hippocampal fissure, the volume of this subfield was found to decrease linearly with age (Krogsrud *et al.*, 2014). Inconsistent findings between the Tamnes *et al.* (2018) study, Krogsrud *et al.* (2014) study and current study may be attributable to differences in hippocampal subfield boundaries, research design (i.e., longitudinal vs cross-sectional) and the age distribution of the samples. Nevertheless, these results suggest differential developmental trajectory patterns of hippocampal subfields and amygdala nuclei between the ASD and TD groups. These age-related differences in hippocampal subfields development between groups may be related to memory impairments observed in ASD. Riggins *et al.* (2018) suggested that protracted development of hippocampal subfields may contribute to better memory during childhood. Within the hippocampal head, a larger CA1 subfield was associated with improved source memory in young children whereas a smaller CA1 subfield contributed to better memory performance in older children (Riggins *et al.*, 2018). Within the hippocampal body, a smaller CA1 but larger CA2-4/DG was related to better performance on a source memory task in both younger and older children (Riggins *et al.*, 2018).

The non-protracted developmental trajectory of the ASD group, where subfield volumes increase with age, may therefore contribute to episodic memory deficits.

Furthermore, the volumes of several hippocampal subfields and amygdala nuclei had a positive relationship with WM and IQ in the TD group but this relationship was absent in the ASD group. To our knowledge, no studies have investigated amygdala nuclei with regards to WM and IQ but the whole amygdala has been associated with these cognitive measures (Schaefer *et al.*, 2006; Rice *et al.*, 2014; Oren *et al.*, 2017). Increased event-related amygdala activity was found to predict faster response times during the WM n-back task in healthy participants, with accuracy remaining unaffected (Schaefer *et al.*, 2006). The amygdala was also found to be engaged during the emotional n-back WM task, where both WM load and emotional valence are manipulated (Oren *et al.*, 2017). Additionally, the volume of the amygdala has been positively correlated with IQ performance in TD children (Rice *et al.*, 2014). Taken together, relationship of the amygdala with WM and IQ identified by the previously discussed studies is consistent with our findings regarding subregions of the amygdala in TD participants. As for the relationship of hippocampal subfields with WM and IQ, few studies have investigated subfields in relation to these cognitive measures. One of the studies that did investigate the relationship between hippocampal subfields and WM suggests that the CA1 and subiculum play a role in maintaining representations of stimuli with overlapping features during working memory in healthy individuals aged 19-31 (Newmark *et al.*, 2013). The DG was also found to be activated during working memory tasks in rhesus monkeys (Friedman and Goldman-Rakic, 1988). The findings from the Newmark *et al.* (2013) and Friedman and Goldman-Rakic (1988) studies agree with our PLSC results where the LH and RH CA1, DG and subiculum head were positively correlated with WM scores. Inconsistent with our results, the CA3 has been associated with spatial working memory in rats (Gilbert and Kesner,

2006) whereas the current study's CA3 head and body volumes had no association with WM in the PLSC. In addition, the volumes of the DG and CA regions have been negatively correlated with IQ measured by the WAIS in healthy adults (Amat *et al.*, 2008) which is not congruence with the current study's findings. Given the discrepancies and the lack of research regarding the relationship of hippocampal subfields and amygdala nuclei with WM and IQ, future research is needed in this field. However, the absent relationship of subfields and nuclei with WM in the ASD group may be related to the WM deficits observed in autistic individuals.

5 Limitations

The previously discussed findings should be interpreted in the context of several limitations. First, the cross-sectional design of the study limits our understanding of the relationship between age and hippocampal subfield and amygdala nucleus volumes in ASD. The age-volume relationship, revealed by the PLSC, may reflect age differences in volume rather than volume changes with age. A longitudinal study design would be more optimal for studying subfield and nuclei development. In addition, it was not feasible to assess the shape and surface area of hippocampal subfields and amygdala nuclei on account of the current study's timeline. These neurodevelopment measures, combined with the volume measure, would allow us to have a more comprehensive understanding of the structural changes occurring in ASD. It also was not feasible, given the study's timeframe and large MRI data set, to manually trace the hippocampal subfields and amygdala nuclei which is the is the gold standard for hippocampal and amygdala segmentation. The FreeSurfer software, an automated segmentation tool, may therefore have overestimate or underestimated the boundaries of the hippocampus and amygdala. Further, the sex distribution of our sample did not permit for the analysis of sex effects on the volumes of subfields and nuclei. We did not have enough female participants to conduct meaningful analyses. Lastly, we did not have access to the

episodic memory scores assessed by the HBN through the NIH toolbox Picture Sequence Memory task. The scores were either missing or have not been made available yet. Given the role of certain hippocampal subfields and amygdala nuclei in episodic memory, investigating the relationship between subfield/nucleus volumes and this memory type may allow us to better understand the episodic memory deficits in ASD.

6 Conclusion

In conclusion, the findings of the current study suggest that functional connectivity and structural changes are occurring in hippocampal and amygdala subregions of individuals with ASD. The weaker functional connectivity between the hippocampus and the MPFC may contribute to behavioural impairments in ASD. The decreased interhemispheric hippocampal connectivity as well as the reduced connectivity of hippocampal subdivisions with other PM network regions, namely the PHC and precuneus, may be related to the episodic memory deficits in ASD. An enlarged left CA3 body in individuals with ASD may also contribute to episodic memory impairments. Lastly, the non-protracted developmental trajectories of subfields and nuclei in ASD may contribute to poor memory performance in ASD. Taken together, these findings may help us better understand the pathophysiology and the neuroanatomical underpinnings of memory impairments in ASD.

7 Supplementary materials

Region	Group		Age		Sex		IQ	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
ABN	1.3636	0.8200	4.0644	1.01e-5	-10.638	0.0821	0.1637	0.2467
AAA	0.3104	0.8422	0.7014	0.0029	-2.5261	0.1125	0.0540	0.1427
Basal nucleus	-3.3485	0.7094	5.5987	4.65e-5	-27.673	0.0028	0.2150	0.3099
Central nucleus	0.1997	0.8920	0.5860	0.0083	-0.5621	0.7072	0.0524	0.1318
Cortical nucleus	0.4412	0.5723	0.3772	0.0014	-1.0222	0.2006	0.0174	0.3422
CATA	-0.7297	0.8600	2.5407	6.21e-5	-4.5488	0.2820	0.0485	0.6190
Lateral nucleus	5.3996	0.6744	5.1346	0.0081	-43.045	0.0012	0.3449	0.2550
Medial nucleus	0.3167	0.7351	0.2355	0.0915	-0.2765	0.7723	0.0175	0.4241
PLN	-0.6702	0.5232	0.5709	0.0003	-3.7774	0.0005	0.0209	0.3969
Whole	3.8939	0.9085	19.828	0.0001	-94.854	0.0065	0.9402	0.2395

Table 7. Mixed linear model parameters of fixed effects for raw volumes of the RH amygdala nuclei and whole amygdala. The estimate regression beta coefficients and their significance levels before FDR correction are included.

Region	Group		Age		Sex		IQ	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
CA1 body	5.0448	0.1334	1.1620	0.0210	-4.8429	0.1568	0.1405	0.0757
CA1 head	3.4421	0.7683	5.6838	0.0013	-19.612	0.1001	0.3651	0.1853
CA3 body	2.5101	0.3384	0.7804	0.0474	-2.6078	0.3281	0.0263	0.6697
CA3 head	0.2738	0.9310	1.9734	4.18e-5	-7.4687	0.0214	0.0320	0.6656
CA4 body	2.4269	0.2996	0.9284	0.0085	-3.8644	0.1051	0.0263	0.6323
CA4 head	-0.2359	0.9336	1.7094	7.76e-5	-6.5095	0.0247	0.0336	0.6141
DG body	2.5706	0.3043	0.9703	0.0101	-4.8821	0.0560	0.0403	0.4936
DG head	-0.7102	0.8434	2.2887	3.25e-5	-7.4404	0.0431	0.0383	0.6506
HATA	1.3914	0.4299	0.8853	0.0009	0.7363	0.6820	0.0182	0.6594
Fimbria	5.2021	0.0269	0.7438	0.0341	1.0167	0.6685	0.0470	0.3927
Fissure	1.0052	0.8010	0.6991	0.2400	-4.2086	0.3020	0.1096	0.2430
ML body	4.9984	0.2299	1.6796	0.0074	-9.7380	0.0221	0.1198	0.2213
ML head	2.3392	0.7324	3.7875	0.0003	-12.608	0.0712	0.2222	0.1687
Parasubiculum	-3.0118	0.1032	0.4411	0.1102	-3.3922	0.0713	0.0361	0.4054
Presubiculum body	-1.9409	0.6333	0.74039	0.2242	-7.0881	0.0879	0.1180	0.2187
Presubiculum head	-0.6059	0.8442	1.3673	0.0034	-6.0351	0.0555	0.1281	0.0789
Subiculum body	6.7852	0.1561	1.6152	0.0242	-12.000	0.0143	0.0970	0.3874
Subiculum head	1.9064	0.6874	2.0910	0.0035	-4.8586	0.3142	0.2245	0.0450
Head	4.1602	0.9047	20.209	0.0001	-66.380	0.0616	1.0921	0.1829
Body	23.687	0.2349	8.1736	0.0065	-57.726	0.0048	0.6454	0.1694
Tail	17.219	0.1751	3.6244	0.0568	-21.229	0.1006	0.3383	0.2573
Whole	45.066	0.4584	32.007	0.0005	-145.34	0.0195	2.0760	0.1476

Table 8. Mixed linear model parameters of fixed effects for raw volumes of the RH hippocampal subfields, merged subfields and whole hippocampus. The estimate regression beta coefficients and their significance levels before FDR correction are included.

Region	Group		Age		Sex		IQ	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
ABN	2.81e-6	0.4048	1.52e-6	0.0029	8.00e-6	0.0206	3.17e-8	0.6894
AAA	-4.64e-7	0.6133	1.92e-7	0.1732	2.25e-6	0.0268	8.84e-9	0.6819
Basal nucleus	-4.18e-9	0.9993	2.05e-6	0.0063	5.73e-6	0.2572	-1.05e-8	0.9283
Central nucleus	-1.01e-6	0.3236	-1.89e-8	0.9016	1.73e-6	0.0972	9.05e-9	0.7068
Cortical nucleus	5.04e-7	0.4000	7.07e-8	0.4260	9.79e-7	0.1210	1.47e-8	0.2990
CATA	3.17e-6	0.1814	1.31e-6	0.0003	7.50e-6	0.0021	-2.65e-8	0.6341
Lateral nucleus	8.45e-6	0.2417	1.88e-6	0.0826	6.82e-6	0.3523	-3.55e-9	0.9833
Medial nucleus	3.91e-8	0.9575	4.46e-8	0.6837	7.84e-7	0.3050	2.37e-8	0.1815
PLN	-5.99e-8	0.9233	2.38e-7	0.0112	-1.13e-7	0.8579	-9.1e-10	0.9507
Whole	1.38e-5	0.4426	7.30e-6	0.0070	3.32e-5	0.0693	4.96e-8	0.9063

Table 9. Mixed linear model parameters of fixed effects for ICV-corrected volumes of the LH amygdala nuclei and whole amygdala. The estimate regression beta coefficients and their significance levels before FDR correction are included.

Region	Group		Age		Sex		IQ	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
CA1 body	4.30e-6	0.1050	-1.89e-7	0.6330	2.72e-6	0.314	4.40e-8	0.4810
CA1 head	-3.70e-6	0.5527	2.53e-6	0.0072	8.64e-6	0.1738	1.27e-7	0.3888
CA3 body	3.64e-6	0.0358	2.80e-7	0.2779	4.91e-6	0.0056	3.74e-9	0.9267
CA3 head	-2.49e-6	0.2326	9.15e-7	0.0037	2.27e-6	0.2837	-6.97e-8	0.1565
CA4 body	3.31e-6	0.0471	1.99e-7	0.4213	3.88e-6	0.0224	2.48e-8	0.5263
CA4 head	-1.57e-6	0.3764	8.14e-7	0.0021	2.04e-6	0.2592	-3.02e-8	0.4679
DG body	3.35e-6	0.0666	1.90e-7	0.4856	3.96e-6	0.0334	3.93e-8	0.3616
DG head	-2.66e-6	0.2170	1.12e-6	0.0006	3.03e-6	0.1664	-4.03e-8	0.4273
HATA	8.83e-7	0.4320	5.54e-7	0.0034	2.85e-6	0.0205	-8.30e-9	0.7508
Fimbria	-1.88e-6	0.3207	2.30e-7	0.4166	-4.46e-6	0.0214	1.39e-8	0.7558
Fissure	3.44e-6	0.2610	2.28e-7	0.6160	3.83e-6	0.2190	6.30e-8	0.3790
ML body	6.35e-6	0.0227	2.81e-7	0.4971	8.19e-6	0.0040	7.68e-8	0.2389
ML head	-1.91e-6	0.6151	1.48e-6	0.0095	6.51e-6	0.0936	7.54e-8	0.3976
Parasubiculum	-1.51e-6	0.2440	-7.17e-8	0.7100	-6.54e-7	0.6180	4.27e-8	0.1600
Presubiculum body	-3.10e-8	0.9930	2.34e-8	0.9650	4.33e-6	0.2400	6.63e-8	0.4360
Presubiculum head	5.65e-7	0.7883	2.51e-7	0.4256	1.31e-6	0.5409	9.01e-8	0.0703
Subiculum body	6.49e-6	0.0954	5.83e-7	0.3149	6.65e-6	0.0931	1.51e-7	0.0994
Subiculum head	-2.29e-7	0.9462	2.68e-7	0.5971	5.76e-6	0.0965	1.49e-7	0.0642
Head	-1.25e-5	0.5066	7.86e-6	0.0056	3.16e-5	0.0999	3.36e-7	0.4473
Body	2.55e-5	0.0570	1.60e-6	0.4232	3.02e-5	0.0275	4.20e-7	0.1824
Tail	1.56e-5	0.0759	4.54e-7	0.7278	1.93e-5	0.0308	-8.85e-9	0.9656
Whole	2.97e-5	0.3855	9.94e-6	0.0518	7.98e-5	0.0227	7.57e-7	0.3456

Table 10. Mixed linear model parameters of fixed effects for ICV-corrected volumes of LH hippocampal subfields, merged subfields and whole hippocampus. The estimate regression beta coefficients and their significance levels are included.

Region	Group		Age		Sex		IQ	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
ABN	-9.02e-7	0.8110	2.12e-6	0.0002	6.32e-6	0.1006	-1.27e-8	0.8866
AAA	-2.69e-7	0.8130	3.34e-7	0.0608	1.48e-6	0.2102	5.50e-9	0.8368
Basal nucleus	-5.1e-6	0.3386	2.65e-6	0.0010	2.10e-6	0.6985	-5.81e-8	0.6421
Central nucleus	-2.50e-7	0.8170	2.65e-7	0.1020	2.23e-6	0.0440	1.53e-8	0.5480
Cortical nucleus	1.99e-7	0.7132	1.81e-7	0.0398	6.41e-7	0.2573	-2.41e-9	0.8492
CATA	-1.72e-6	0.5180	1.27e-6	0.0013	6.35e-6	0.0192	-6.08e-8	0.3295
Lateral nucleus	1.02e-6	0.8960	1.46e-6	0.2080	3.34e-6	0.6720	-1.07e-7	0.5580
Medial nucleus	1.19e-7	0.8670	9.26e-8	0.3870	1.10e-6	0.1450	-9.4e-10	0.9550
PLN	-8.06e-7	0.2013	2.51e-7	0.0082	-2.58e-7	0.6876	-9.28e-9	0.5312
Whole	-7.98e-6	0.6808	8.62e-6	0.0033	2.36e-5	0.2313	-2.33e-7	0.6097

Table 11. Mixed linear model parameters of fixed effects for ICV-corrected volumes of the RH amygdala nuclei and whole amygdala. The estimate regression beta coefficients and their significance levels before FDR correction are included.

Region	Group		Age		Sex		IQ	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
CA1 body	3.27e-6	0.2120	4.56e-7	0.2440	3.20e-6	0.2290	3.87e-8	0.5290
CA1 head	-7.40e-7	0.9190	2.46e-6	0.0245	1.45e-5	0.0516	-3.76e-9	0.9825
CA3 body	1.54e-6	0.4440	2.89e-7	0.3320	2.43e-6	0.2340	-2.12e-8	0.6520
CA3 head	-1.23e-6	0.5783	1.11e-6	0.0010	1.41e-6	0.5293	-3.90e-8	0.4537
CA4 body	1.35e-6	0.4277	2.97e-7	0.2451	3.38e-6	0.0526	-3.19e-8	0.4262
CA4 head	-6.39e-7	0.7271	8.85e-7	0.0012	1.58e-6	0.3995	-3.40e-8	0.4278
DG body	1.46e-6	0.4175	2.74e-7	0.3086	3.40e-6	0.0642	-2.74e-8	0.5170
DG head	-1.29e-6	0.5775	1.25e-6	0.0003	2.32e-6	0.3254	-4.46e-8	0.4116
HATA	6.42e-7	0.6172	4.95e-7	0.0136	3.78e-6	0.0066	-1.55e-8	0.6058
Fimbria	2.75e-7	0.8890	-1.30e-7	0.6570	-4.71e-6	0.0190	9.05e-9	0.8450
Fissure	9.04e-8	0.9750	3.80e-9	0.9930	3.73e-6	0.2140	6.42e-9	0.9260
ML body	2.75e-6	0.3470	4.91e-7	0.260	4.62e-6	0.1200	-1.79e-8	0.7940
ML head	-3.03e-7	0.94253	1.72e-6	0.0067	9.21e-6	0.0322	-6.96e-9	0.9438
Parasubiculum	-2.79e-6	0.0458	9.70e-8	0.6398	1.19e-6	0.3998	-2.80e-9	0.9315
Presubiculum body	-1.99e-6	0.5070	3.48e-9	0.9940	3.11e-6	0.3090	1.86e-8	0.7920
Presubiculum head	-1.51e-6	0.4683	5.44e-7	0.0813	3.23e-6	0.1282	2.41e-8	0.6233
Subiculum body	5.09e-6	0.1410	4.14e-7	0.4230	2.82e-6	0.4220	-2.66e-8	0.7430
Subiculum head	3.74e-7	0.9116	9.19e-7	0.0693	7.31e-6	0.0339	6.50e-8	0.4125
Head	-7.62e-6	0.7185	9.48e-6	0.0030	4.47e-5	0.0391	-5.91e-8	0.9052
Body	1.36e-5	0.3010	2.09e-6	0.2880	1.84e-5	0.1700	-5.96e-8	0.8470
Tail	1.05e-5	0.2490	8.32e-7	0.5410	1.33e-5	0.1510	-2.24e-8	0.9170
Whole	1.54e-5	0.6742	1.24e-5	0.0249	7.79e-5	0.0378	-1.52e-7	0.8602

Table 12. Mixed linear model parameters of fixed effects for ICV-corrected volumes of RH hippocampal subfields, merged subfields and whole hippocampus. The estimate regression beta coefficients and their significance levels before FDR correction are included.

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