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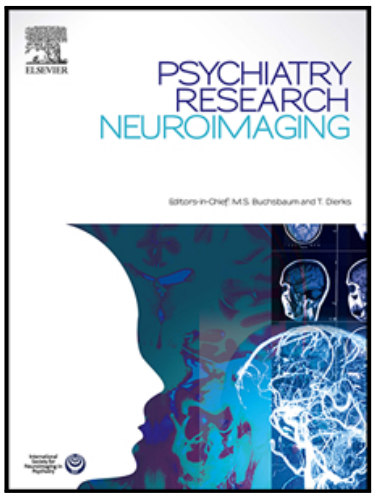

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Highlights:

- Schizophrenia patients show reduced hippocampal subfield volumes and memory deficits.
- Left CA1 volume is positively associated with recall performance in schizophrenia.
- Thematic recall correlates with left CA1, CA3, and CA4/DG volumes in schizophrenia.
- Findings highlight hippocampal subfield involvement in memory deficits in schizophrenia.
- Results may inform targeted interventions for memory impairment in schizophrenia.

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Hippocampal Subfield Volumes and Memory Deficits in Schizophrenia

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Abstract

Background: Schizophrenia is a debilitating disorder commonly associated with significant cognitive impairment, particularly in memory. Reduced gray matter volume in various brain regions, including hippocampus and its subfields, is also well-documented in individuals with schizophrenia (SZH). However, few studies have investigated how memory deficits relate to hippocampal subfield volume loss. **Methods:** In this study, we examined hippocampal subfield volumes and their associations with immediate and delayed memory performance (using the WMS-III battery), comparing 57 individuals with SZH to 32 well-matched controls. **Results:** Compared to controls, SZH exhibited lower memory performance, and lower hippocampal volumes, particularly in the left hippocampus and parasubiculum, CA1 subfields specifically. Both Immediate and Delayed Free Recall memory performance was seen to be positively correlated with left CA1 volume in SZH only, and not in controls. Positive associations were also observed between Thematic Recall scores and volumes in the left CA1, CA3, and CA4/DG subfields in SZH only, but only at an uncorrected threshold. **Conclusion:** These findings support the notion that hippocampal volumetric alteration contributes to memory impairment in SZH. In particular, findings point to the left CA1 subfield as being particularly important in this regard, informing potential targeted intervention strategies to address memory impairment and functional recovery in SZH.

Keywords: immediate recall, delayed recall, thematic recall, schizophrenia, cognition, MRI, brain volume

1. Introduction

Schizophrenia is a serious mental illness affecting approximately 1% of the global population (Velligan and Rao, 2023); it profoundly impacts the well-being and functional capacity of those affected (Harvey and Strassnig, 2012), and the associated economic costs are significant (Ride et al., 2020). Most individuals with schizophrenia (SZH) suffer persistent cognitive impairments which are a major contributor to long-term difficulties in social and occupational function (Bowie and Harvey, 2006):

these are largely unresponsive to pharmacological therapy (Tripathi et al., 2018) and cognitive training is not always effective (Best et al., 2019). Despite decades of research, we still lack knowledge regarding the neuropathology underlying symptoms and cognitive impairment.

A progressive reduction in Gray Matter Volume (GMV), predominantly observed in frontal and temporal brain regions (Jiang et al., 2018; Vita et al., 2012), has been reliably reported in SZH. Amongst these, hippocampal structural alterations have become a topic of considerable research interest, with accumulating and converging evidence suggesting that hippocampal subfield neuropathology might be an important mechanism underlying schizophrenia disease progression and symptomology. The hippocampus is a highly connected "hub" brain region, with particularly high network centrality and vulnerability to dysfunction. Hippocampal structural abnormalities have been consistently demonstrated across schizophrenia disease stages. Amongst all subcortical regions, it shows the largest magnitude of volume deficits when compared to controls (van Erp et al., 2016), these have been associated with symptom severity and cognitive dysfunction (Hu et al., 2020). The hippocampus comprises various anatomically and functionally distinct subfields, including the dentate gyrus, Cornu Ammonis (CA) regions of the hippocampus proper, and the subiculum. Various models have posited glutamate dysregulation as a pathogenic driver in psychosis, proposing that dysregulation of CA1 glutamate neurotransmission triggers CA1 hypermetabolism and atrophy due to glutamate-mediated neurotoxicity (Schobel et al., 2013; Small et al., 2011). Subsequently, dysfunction of gamma-aminobutyric acid (GABA)-ergic interneurons is thought to drive hyper-excitation of the hippocampal trisynaptic circuit, leading to a propagation of atrophy across other subfields. Such models are supported by evidence from various laboratory and human neuroimaging studies (Provenzano et al., 2020). The dentate molecular layer might also be important in this cascade, as revealed by post-mortem studies (Toro and Deakin, 2005). This propagation of atrophy across subfields is theorised to be a major contributor to both symptomology and cognitive impairment, particularly learning and memory (Small et al., 2011). Hippocampal subfield reduction has been fairly consistently identified in neuroimaging studies, with volume reductions most prominent in CA1 and DG/CA4, as well as CA2/3, and subiculum; studies tended to find these reductions to be either bilateral or left lateralised (Small et al., 2011). While the majority of studies have been in antipsychotic-treated long-term ill patients, studies in high-risk and first episode groups (McHugo et al., 2024) tend to support the idea that CA1 may play a critical role in prodromal/early psychosis. Some studies have provided evidence linking illness duration to more extensive hippocampal subfield deficits: in CA1 (Ho et al., 2017), CA2−3 (Kawano et al., 2015; Ota et al., 2017), and DG/CA4 (Kawano et al., 2015), consistent with the propagation hypothesis outlined above.

Fewer studies have examined correlations between subfield volumes, symptoms, and cognition, with only a handful of relevant studies in SZH. Regarding links to symptom severity, findings are heterogeneous, some studies find no significant correlations (McHugo et al., 2024), others point to links with negative symptoms (Lang et al., 2022), others to positive symptoms (Mathew et al., 2014). Regarding links to cognition, Wannan et al. (2019) found (in both chronic and recent-onset SZH), relationships between visuospatial associative memory performance and volumes in the CA4/dentate gyrus that were only present in the patient. Vargas et al. found associations in CA1, CA4/DG, and subicular regions, for visual learning, verbal learning, and working memory domains, but correlations in healthy controls were not assessed. No medication effects were found for any of the subregions (Vargas et al., 2018). Other relevant studies have limitations too, for example, Haukvik et al. (2015), despite finding widespread CA volume reduction in SZH, restricted their correlation analyses to the subiculum only (and found none); Yasuda et al. (2022) found SZH-specific associations with right CA1 in particular, but only used a composite cognitive score, and their sample size was small (N=21). A

meta-analysis by Antoniades et al. included 755 SZH and 914 healthy controls: in SZH, left and right hippocampal volume positively correlated with immediate and delayed verbal recall, no relationships were found in the HCs, but subfields were not assessed (Antoniades et al., 2018).

Thus, there is at present only limited work on the significance of subfield abnormalities in SZH, in relation to cognitive dysfunction and symptom severity, and the lack of a control group in some studies means it is uncertain whether relationships are specific to patients. Leveraging the advanced parcellation methods available within the FreeSurfer package, we investigated subfield-specific links to immediate and delayed memory performance, contrasting SZH with controls. In SZH, we also interrogated subfield volumetric relationships with symptom severity and medication dosage, to again clarify a limited and heterogeneous literature regarding these.

2. Methods

2.1 Participants

The sample included 57 SZH (16 females (biological sex at birth), aged between 21 and 49, mean age 37.21, see Table 1), and 32 age and sex-matched healthy controls (CON) (10 females, aged between 20 and 65, mean age 33.19, see Table 1). The study sample overlaps with those reported previously (Premkumar et al., 2018; Premkumar et al., 2009; Premkumar et al., 2015). The exclusion criteria for both groups consisted of the following: motion-related or other artefacts on the T1 images, any neurological conditions, head injuries resulting in a loss of consciousness, prior exposure to the current neuropsychological assessments, and substance abuse; for SZH, having an additional Axis I disorder diagnosis; for controls, having a personal history of DSM-IV Axis I and II disorders or a family history of psychosis. This was assessed using SCID-I (First and Gibbon, 2004) and Structured Clinical Interview for DSM-IV Axis II Disorders Research Version (SCID-II) (First and Gibbon, 2004). Schizophrenia was diagnosed by an experienced psychiatrist using the SCID-I. The evaluation of symptoms was conducted using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Patients were receiving typical and/or atypical antipsychotics, either in oral form or through depot injections; the mean chlorpromazine equivalent dosage was 453.4 (standard deviation = 300.2), range was 100 to 1600 mg per day (reliable medication information not available for 5 patients). The study procedures received approval from the ethics committee at the Institute of Psychiatry and Maudsley Hospital. Additionally, all participants provided written consent after being informed about the study procedures and were compensated for their time and travel expenses.

Table 1. Demographic and clinical characteristics of the sample

	All Subjects (N=89)	**Healthy Controls (N=32)**	**SZH (N=57)**	***p***
Age, M (SD)	35.76 (9.53)	33.19 (11.43)	37.21 (8.02)	0.055[a]
Female (N, %)	26 (27.4%)	10 (31.3%)	16 (25.4%)	0.355[b]
Education (years) (SD)	14.37 (2.72)	15.34 (2.62)	13.82 (2.65)	0.011[a]
Current IQ (WASI) (Mean/SD)	109.00 (20.1)	120.09 (13.86)	103.35 (20.38)	<0.001[a]
Predicted IQ (NART) (Mean/SD)	110.23 (9.83)	114.62 (8.47)	107.83 (9.77)	0.002
Medication (Chlorpromazine equivalents mg/day) (SD)			453.40 (300.23)	N/A

PANSS (7 items) positive symptoms (mean) (SD)	16.49 (4.87)	N/A
PANSS (16 items) general psychopathology (mean) (SD)	32.75 (6.75)	N/A
PANSS (7 items) negative symptoms (mean) (SD)	17.97 (5.01)	N/A
PANNS Total (mean, SD)	67.21 (13.98)	N/A

Abbreviations. SZH, Schizophrenia; SD, standard deviation; PANSS, Positive and Negative Syndrome Scale; N/A, Not Applicable

[a] Independent sample *t*-test, [b] Pearson Chi-Square

2.2. MRI Acquisition and processing

T1-weighted structural images (TR = 18 ms, TI = 450 ms, TE = 5.1 ms, flip angle = 20°, voxel matrix: 256 × 256 × 128) were acquired in the axial plane with 1.5 mm contiguous slices using a 1.5 Tesla GE NV/i MR Signa System (General Electric, Milwaukee, Wisconsin), at the Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London.

Brain volumes were calculated using the standard recon-all pipeline in FreeSurfer 6.0.0 (http://surfer.nmr.mgh.harvard.edu), from which the ICV measure was derived. We visually reviewed the accuracy of the derived white and pial surfaces, the segmentation, and the skull-stripping: no manual edits were required. Hippocampal subfield volumes were calculated using FreeSurfer's automated hippocampal and amygdala segmentation algorithm (included with the development version of FreeSurfer 6.0) which uses a probabilistic atlas built with ultra-high resolution MRI data to segment the hippocampal substructures and nuclei of the amygdala (Iglesias et al., 2015). For each hemisphere, the volumes of the whole hippocampus as well as 8 hippocampal subfields were extracted: CA1, CA3, CA4, subiculum, parasubiculum, parasubiculum, hippocampal tail and molecular layer of the hippocampus. These volumes were checked for outliers; none were found.

For the correlation analyses, we only included hippocampal subfields implicated by previous research in SZH, indicating possible relationships with memory performance, these were: (all bilateral) CA1, CA3, CA4/DG and subiculum (8 regions in total).

2.4. Logical Memory Measures

The WMS-III Logical Memory (LM) subtest, including both immediate and 30-minute delayed recall trials, was administered following standard guidelines (Wechsler, 1997). In the immediate recall phase, the examiner reads Story A aloud once, after which the participant recounts as much information as possible. Story B is read twice, with the participant providing a recall response after each reading. The examiner records both the number of freely recalled details and broader thematic units. Participants are informed that they will need to recall the stories later. After a 30-minute interval filled with other tasks, delayed recall is assessed. The participants first attempt to recall Story A, followed by Story B. If no recall occurs, a standard prompt is given. The examiner again records the recall and thematic unit scores. Finally, a recognition memory test is conducted, where the participants answer 15 yes/no questions about each story, and the recognition scores are documented.

2.5. Statistical Analysis

We conducted statistical analyses using IBM SPSS Statistics 28.0. For demographic variables, group comparisons were made using independent sample t-tests for age and education, and a $\chi 2$ test for sex distribution. We used analysis of covariance (ANCOVA) to test for group differences in each of the hippocampal subfield volumes, with ICV, age, sex and years of education as covariates. ANCOVAs also used to test group differences in logical memory domains with age, sex, and education as covariates.

We also performed partial correlations to test the relationship between symptom severity and hippocampal subfields in patients, controlling for age, sex, education, and ICV. Finally, we run partial correlation analyses to test the relationship between medication (chlorpromazine equivalents) and hippocampal subfield volumes in patients, controlling for age, sex, years of education and ICV. To test the correlation between subfield volumes and logical memory measures, a series of partial correlation analyses were conducted separately for SZH and controls, controlling for ICV, education, sex, and age. The significance of the difference between the correlation coefficients for controls and SZH was assessed using the Fisher r-to-z transformation (http://vassarstats.net/rdiff.html). Corrections for multiple comparisons were performed using a false discovery rate (FDR) with the Benjamini- Hochberg method (Benjamini and Hochberg, 1995), and the significance level was set at 0.05.

3. Results

3.1. Participant characteristics

Summary demographic data are presented in Table 1. There were no statistically significant differences between the SZH and healthy control groups in terms of age and sex (all p values > 0.05), but controls had a significantly higher level of education (M = 15.34, SD = 2.62) compared to SZH (M = 13.82, SD = 2.65, p = 0.011). Controls scored higher than SZH on both the WASI, which measures current IQ (M = 120.09, SD = 13.86) and on premorbid IQ as measured by the NART (M = 103.35, SD = 20.38).

3.2. Logical Memory measures

Means and standard deviation scores for all logical memory scores are reported in Table 2. SZH, compared to controls, had significantly lower performance on all measures, and all results remained significant after FDR corrections (FDR corrected p<.05).

Table 2 Memory Performance differences (age, sex, and years of education as covariates)

	CON		SZH		Group Differences		
Logical Memory Domains	Mean	SD	Mean	SD	F	$P_{unadjusted}$	P_{FDR}
Free Recall Immediate	42.37	12.1	27.57	10.6	24.438**	0.000004	<.001
Free Recall Delay	26.48	9.3	16.05	6.6	25.566**	0.000003	<.001
Thematic Immediate Recall	18.62	2.73	15.91	4.50	5.154**	0.026	0.035
Thematic Delay	13.96	10.1	9.80	3.1	4.518**	0.037	0.037
*Unadjusted p<.05 ** FDR corrected P<.05							

3.3. Hippocampal Subfield Volume Differences between SZH and Controls

We found reduced GMVs in SZH, in left CA1 (p_{FDR}=.009), left CA3 (p_{FDR}=.021), left CA4/DG (p_{FDR}=.021), left molecular layer (p_{FDR}=.009), left Parasubiculum (p_{FDR}=.021), and left total hippocampus (p_{FDR}=.021), after FDR correction for multiple comparisons (Table 3). Uncorrected, there were also reduced volumes in SZH evident in bilateral hippocampal tail (unadjusted right: p=.039, unadjusted left: p=.049), right parasubiculum (unadjusted p=.010), right CA1 (unadjusted p=.012), and right total hippocampus (unadjusted p=.050).

Table 3 Hippocampal subfield differences (ICV, age, sex, and education as a covariate)

Left Hemisphere	CON	SZH	Group Differences			**Right Hemisphere**	CON	SZH	Group Differences		
Subfield	Mean	Mean	F	$P_{unadjusted}$	P_{FDR}	Subfield	Mean	Mean	F	$P_{unadjusted}$	P_{FDR}
Hippocampal Tail	567.81	533.00	3.98*	0.049	0.063	Hippocampal Tail	580.75	542.79	4.42*	0.039	0.094
Subiculum	448.70	433.52	1.99	0.162	0.162	Subiculum	436.63	429.47	0.24	0.623	0.623
Presubiculum	311.70	294.03	2.56	0.114	0.128	Presubiculum	295.31	285.49	0.26	0.613	0.623
Parasubiculum	69.76	62.01	6.49**	0.013	0.021	Parasubiculum	67.86	61.00	6.93*	0.010	0.054
CA1	698.95	644.16	11.23**	0.001	0.009	CA1	716.20	669.54	6.59*	0.012	0.054
CA3	237.88	220.09	6.256**	0.014	0.021	CA3	248.08	239.67	0.710	0.402	0.517
CA4/DG	585.57	549.25	6.967**	0.010	0.021	CA4/DG	596.80	574.72	1.773	0.187	0.281
Molecular Layer	600.63	561.17	10.19**	0.002	0.009	Molecular Layer	605.66	577.09	3.875	0.052	0.094
Total Left Hippocampus	3673.3	3447.2	7.503**	0.008	0.021	Total Right Hippocampus	3702.2	3527.5	3.961*	0.050	0.094

*Unadjusted p<.05
** FDR corrected P<.05

3.4. Correlations between Memory Performance and Hippocampal Subfield Volumes

Partial correlation analyses were conducted to test the relationship between the memory measures and hippocampal subfield volumes, controlling for ICV, education, sex, and age.

Free Recall - Immediate: After FDR correction, Free Recall Immediate scores in SZH positively correlated with volume in left CA1 (r=.378, p_{FDR}=.042, see Figure 1). Fisher's Z test indicated that the correlation coefficients for left CA1 were significantly different between SZH and controls. Uncorrected, there was also a positive correlation between free recall immediate scores and volume in left CA4/DG (r=.290, unadjusted p=.037), but although no significant associations were seen in healthy

controls, the correlation coefficients for left CA4/DG were not significantly different between SZH and controls (Supplementary Table 1).

Thematic Recall - Immediate: In SZH, there were (uncorrected) positive relationships between thematic recall immediate scores and volume in left CA1 (r=.315, unadjusted p=.023), left CA3 (r=.273, unadjusted p=.050), and left CA4/DG (r=.327, unadjusted p=.018). However, these relationships did not survive FDR correction. No associations were seen in healthy controls, but Fisher's Z test indicated that the correlation coefficients for left CA1 were not significantly different between SZH and controls (Supplementary Table 2).

Free Recall - Delayed: In SZH, Free Recall Delay scores positively correlated with volume in left CA1 (r=.307, unadjusted p=.027), but this did not survive FDR correction. No associations were seen in healthy controls. Fisher's Z test indicated that the correlation coefficient for left CA1 was significantly different between SZH and controls (Supplementary Table 3).

Thematic Recall - Delayed: No associations were observed (Supplementary Table 4).

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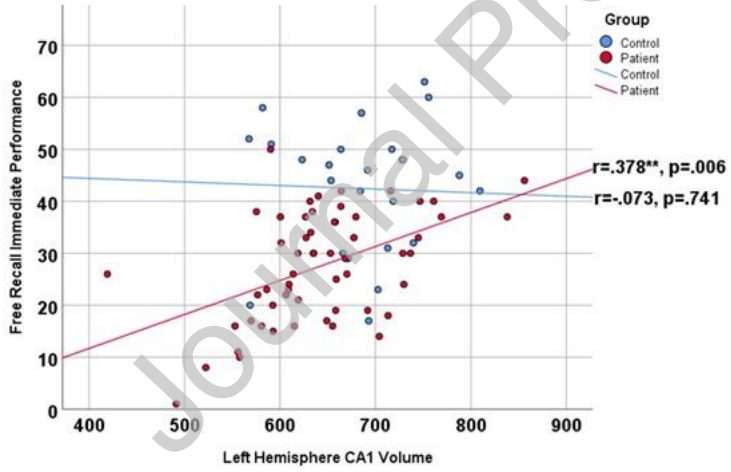

Figure 1. The association between left CA1 volume and Immediate Free Recall Memory performance, by group.

3.5. Correlations between symptom severity and Hippocampal Subfield Volumes

In SZH, partial correlation analyses interrogated relationships between PANSS scores and hippocampal subfield volumes, controlling for ICV, education, sex, and age.

PANSS Positive Symptoms: Uncorrected, there were significant negative correlations between positive symptoms and volume in left CA1 (r=-.359, unadjusted p=.008) and left CA3 (r=-.285, unadjusted

p=.039) (Supplementary Table 5). Adjusted, the left CA1 relationship was at trend (r=-.359, p_{FDR} = 0.064).

PANSS Negative Symptoms: There were no correlations between negative symptom severity and volumes in any hippocampal subfields.

PANSS Total: Uncorrected, there was a significant negative correlation between total symptom severity scores and left CA3 (r=-.276, unadjusted p=.045) (Supplementary Table 5).

3.6. Correlations between Medication (Chlorpromazine equivalent) and Hippocampal Subfield Volumes

In SZH, partial correlation analyses were conducted to test the relationship between medication dose (chlorpromazine equivalent) and volumes in hippocampal subfields (controlling for age, sex, education, and ICV). Uncorrected, there was a negative correlation between right hippocampal tail and CPZ equivalent (r=-.329, unadjusted p=.022) which did not survive FDR correction (p_{FDR} = 0.176), see Supplementary Table 6.

3.7. Correlations between duration of illness and Hippocampal Subfield Volumes

In SZH, partial correlation analyses were conducted to test the relationship between duration of illness and volumes in hippocampal subfields (controlling for age, sex, education, and ICV). Uncorrected, there were negative correlations between duration of illness and left hippocampal tail (r=-.337, unadjusted p=.014), left subiculum (r=-.381, unadjusted p=.005), left presubiculum (r=-.347, unadjusted p=.011), see Supplementary Table 7. However, these relationships did not survive FDR correction. No associations were observed in right hemisphere.

4. Discussion

The present study aimed to elucidate the associations between specific hippocampal subfield volumes and memory performance in SZH. We employed the well-used logical memory subtest from the Wechsler battery. Consistent with previous research, we found that SZH demonstrated poorer memory performance compared to healthy controls on all memory measures (Achim et al., 2007; Di Giorgio et al., 2013; Fung et al., 2023; Hori et al., 2012; Lui et al., 2018; Matsui et al., 2007; Tan et al., 2024).

Impaired logical memory potentially represents an endophenotypic marker of schizophrenia (Callicott et al., 2005; Hori et al., 2012), with many studies showing poorer logical memory performance on both immediate and delayed tasks in unaffected parents, siblings and offspring of SZH (Liang et al., 2016) (de la Serna et al., 2011; de la Serna et al., 2010) (Wang et al., 2010). Memory is one of the most affected cognitive domains in both FEP and chronic SZH (Chan et al., 2023). Moreover, longitudinal studies suggest that while improvements in other cognitive domains (e.g. attention, executive function, and processing speed) are possible, pharmacological treatments have limited efficacy in improving logical memory (Chan et al., 2023; Goff et al., 2008). While cognitive remediation therapies show some potential (Choi et al., 2017; Fernandez-Gonzalo et al., 2015), it is important to understand the neural

basis of memory deficits in psychosis so as to develop intervention strategies, various possibilities for targeting the hippocampus have been put forward (Knight et al., 2022). These could benefit functional recovery: better logical memory performance has been associated with improved functional outcomes (Zaragoza Domingo et al., 2015), and social functioning (Xiang et al., 2010); memory system dysfunction might also contribute to delusion formation in psychosis (Zadbood et al., 2025).

Likewise, hippocampal volume reduction is considered a hallmark of SZH (Roeske et al., 2021); some studies have found reductions in unaffected relatives also (Ho and Magnotta, 2010; Seidman et al., 1999; Seidman et al., 2002; Van Erp et al., 2002). Here, consistent with previous work, we observed reduced hippocampal gray matter volumes in SZH compared to controls, most prominent in left hippocampus (particularly CA1, CA3, CA4/DG, molecular layer, parasubiculum); differences in right hippocampus were also observed but did not survive FDR correction. This aligns with frameworks positing an important role for CA1 neuropathology that then propagates to other subfields (Schobel et al., 2013; Small et al., 2011), alongside evidence highlighting reduced left hippocampal volumes as a possible vulnerability marker for psychosis (Radulescu et al., 2014; Seidman et al., 2002). Some studies implicate left CA1 in particular, showing a correlation between the rate of volume reduction in left CA1, and the rate of worsening of symptoms (Ho et al., 2017), and findings in FEP suggesting that smaller left CA1 volume might predict medication response (Lang et al., 2022).

Consistent with these studies highlighting left CA1 as an important subregion, we found that Immediate Free Recall performance positively correlated with left CA1 volume in SZH only (left CA4/DG volume also correlated, but this did not survive multiple comparisons correction). Hippocampal volume, specifically on the left, was earlier found to be associated with a stronger response to CBT for psychosis (Premkumar et al., 2009), and the current findings suggest that CA1 might be particularly important in this context given that better memory performance has also been reported to facilitate responsiveness to CBT for psychosis (Penadés et al., 2010). On Delayed Free Recall, a positive correlation with volume in left CA1 was also seen in SZH only, although this did not survive multiple comparisons correction. Crucially, the correlation coefficients for all these relationships were significantly different to controls, suggesting that they are specific and unique to patients. For Thematic Immediate Recall, correlations were present in SZH for left CA1, CA3 and CA4/DG, although these did not survive multiple comparisons correction (and did not show correlation coefficients significantly different to controls). Although little previous work exists, findings accord with previous studies that have identified subfield volumetric associations with cognitive performance that are potentially unique to SZH. Wannan et al. (2019) reported SZH-specific relationships between visuospatial associative memory performance and volumes in the CA4/dentate gyrus in both chronic and recent-onset SZH. Vargas et al. (2018) found associations between right CA1, CA4/DG, and bilateral subicular regions with visual learning, verbal learning, and working memory in SZH; in their ultra-high-risk (UHR) group, they also found links with left CA1 and subicular volumes, but they did not contrast with healthy controls. In a sample spanning schizophrenia, schizoaffective disorder and psychotic bipolar disorder, left CA1, CA2/3, CA4/DG, and subiculum volumes positively correlated with BACS list-learning score; these were absent in controls (Mathew et al., 2014). Notably, no medication effects were observed for any hippocampal subregions in these studies. Considering the role of CA1 in the consolidation and retrieval of information (Bartsch et al., 2011), the dysfunction or structural abnormalities of this subfield could negatively affect logical memory in SZH. Yasuda et al. (2022) found SZH-specific associations with right CA1 volume but used a composite cognitive score, limiting the interpretation; their study was also constrained by a small sample size (N = 21). In studies where subfields were not assessed, Ehrlich et al. (2012) found that left hippocampal volume correlated positively with logical memory performance (immediate story recall) in SZH but not in healthy controls, and a meta-analysis by Antoniades et al. (2018) found that total, left,

and right hippocampal volumes positively correlated with both immediate and delayed recall in SZH, but not in healthy individuals.

Regarding relationships between hippocampal volumes and symptom severity, right CA1 and left CA3 did show (uncorrected) negative associations with PANSS-positive symptom severity, and the right CA1 correlation was significant at the trend level after multiple comparison adjustments. Findings in the literature are mixed, with some studies not finding relationships (McHugo et al., 2024), but others identifying relationships with positive symptoms in particular (Mathew et al., 2014). Likewise, we found no significant relationships between hippocampal volumes and medication dose. As summarised in the review by Hu et al. (2020), most studies fail to find associations, but interestingly there is one study that found left hippocampal tail volume to negatively correlate with the duration of medication use in SZH (Sasabayashi et al., 2021); we found some evidence of (uncorrected) negative relations between hippocampal tail volumes and medication dosage, no other correlations were seen even without multiple comparisons correction. This suggests that hippocampal subfields are largely unaffected by medication dosage, despite suggestions that a higher antipsychotic dosage could be neuroprotective (Koolschijn et al., 2010).

A key strength of this study lies in its thorough characterisation of associations with hippocampal subfield volumes in SZH versus a healthy control group, offering a comprehensive analysis of the significance of these in SZH, which is largely lacking in the literature. The use of a well-established memory task that differentiates immediate and delayed recall is another strength. However, some limitations must be acknowledged. First, the cross-sectional design means we cannot infer any causal relationships in the data: longitudinal studies are required to establish these. Also, it would be useful to include potential confounding factors, such as lifestyle variables (e.g., physical activity, substance use) and environmental influences.

In sum, findings contribute to the limited literature around hippocampal subfield volumetric alterations in SZH and help elucidate their role in relation to memory impairment. Findings highlight left CA1 in particular as a potentially important subregion; associations were observed with cognitive performance that were unique to the patient group. Memory is one of the most affected cognitive domains in both FEP and chronic SZH (Chan et al., 2023) and unlike some other cognitive domains, shows very limited improvements with pharmacological therapy (Chan et al., 2023; Goff et al., 2008). Better logical memory performance has been associated with improved functional outcomes (Zaragoza Domingo et al., 2015) and social functioning (Xiang et al., 2010). Thus, the current study provides important insights into the neural basis of memory deficits in psychosis, which could help guide targeted and effective intervention strategies that will benefit functional recovery.

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Declarations of interest

The authors declare no competing interests.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Author contributions

Conceptualization; E.A., S.E., V.K. Data curation; V.K. Formal analysis; E.A., S.E., V.K. Funding acquisition; V.K. Writing - original draft; E.A., S.E, V.K. and Writing - review & editing; E.A., S.E., V.K.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Declaration of interests

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☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Veena Kumari reports financial support was provided by Welcome Trust. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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