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REVIEW ARTICLE

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Hippocampal subregion abnormalities in schizophrenia: A systematic review of structural and physiological imaging studies

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Abstract

Aim: The hippocampus is considered a key region in schizophrenia pathophysiology, but the nature of hippocampal subregion abnormalities and how they contribute to disease expression remain to be fully determined. This study reviews findings from schizophrenia hippocampal subregion volumetric and physiological imaging studies published within the last decade.

Methods: The PubMed database was searched for publications on hippocampal subregion volume and physiology abnormalities in schizophrenia and their findings were reviewed.

Results: The main replicated findings include smaller CA1 volumes and CA1 hyperactivation in schizophrenia, which may be predictive of conversion in individuals at clinical high risk of psychosis, smaller CA1 and CA4/DG volumes in first-episode schizophrenia, and more widespread smaller hippocampal subregion volumes with longer duration of illness. Several studies have reported relationships between hippocampal subregion volumes and declarative memory or symptom severity.

Conclusions: Together these studies provide support for hippocampal formation circuitry models of schizophrenia. These initial findings must be taken with caution as the scientific community is actively working on hippocampal subregion method improvement and validation. Further improvements in our understanding of the nature of hippocampal formation subregion involvement in schizophrenia will require the collection of structural and physiological imaging data at submillimeter voxel resolution, standardization and agreement of atlases, adequate control for possible confounding factors, and multi-method validation of findings. Despite the need for cautionary interpretation of the initial findings, we believe that improved localization of hippocampal subregion abnormalities in schizophrenia holds promise for the identification of disease contributing mechanisms.

KEYWORDS
CA1, dentate gyrus, hippocampus, psychosis, subfield

1 | INTRODUCTION

The hippocampus, which plays a key role in emotion, stress, and declarative memory, has long been considered a key region in the pathophysiology of schizophrenia[1–3] and findings such as smaller hippocampal volume,[4–6] lower episodic memory performance,[7,8] and hippocampal physiological abnormalities[9–11] are well established in individuals with schizophrenia when compared to controls. These abnormalities are also observed in relatives of individuals with schizophrenia,[12–15] suggesting possible genetic influences. The illness stage at which these abnormalities arise has not been fully clarified, but research suggests that lower whole hippocampal volume is present at psychosis onset but may not predate the illness.[16] Most schizophrenia-related brain imaging studies published to date, however, have focused on the overall hippocampus, or the anterior and posterior hippocampus[17,18] based on the view that the anterior hippocampus serves anxiety-related and the posterior hippocampus serves spatial navigation and memory-related behaviors.[19] The hippocampal formation, however, is comprised of several subregions, including the dentate gyrus (DG), cornu ammonis (CA) 1-4, the subiculum (pre-, para-, and pro), and the entorhinal cortex (EC). The EC provides input to the hippocampus and connects via the perforant pathway to the DG, which connects via the mossy fiber pathway to CA3, which connects via the schaffer collateral pathway to CA1. These regions form the trisynaptic pathway. CA1 projects to the subiculum, which is the major hippocampal output region of the hippocampus. Both CA1 and subiculum also have bidirectional connections with the EC [for review, see[20]].

Several models of hippocampal formation circuitry pathology in schizophrenia have been proposed.[20–25] Benes[21] suggested that schizophrenia is associated with GABAergic dysfunction in areas CA2/3 of the trisynaptic pathway. Lisman and Grace[22] hypothesized a hyperdopaminergic state in schizophrenia due to an abnormally functioning loop connecting the subiculum to the ventral tegmental area; they suggest that this may result in a mismatch between lowered cortical input to CA1, representing sensory reality, and CA3 input to CA1, representing predicted information. Behrendt[23] hypothesized that increased CA3 excitability may produce hallucinations. Tamminga et al[24] model posits a primary deficit in the DG with reduced input to CA3 and predicts that individuals with schizophrenia show a deficit in DG-dependent pattern separation, required for the formation of nonoverlapping memory representations, and an increase in CA3/CA1-dependent pattern completion, required for associate retrieval based on partial information; two processes critically important for the formation and retrieval of declarative episodic memories that may play a role in generating psychotic symptoms including hallucinations and delusions. Small and colleagues' 2013 model posits a primary deficit in the hippocampal CA1 region, thought to be involved in the integration of multiple sources of input.[20] Taken together, these models suggest primary involvement of different hippocampal subregions in schizophrenia pathophysiology. Here, we review structural and physiological studies of hippocampal subregions that may provide evidence for or against these schizophrenia hippocampal formation circuitry models by addressing questions such as: (a) what subregions are affected; (b) at what illness stage age are they affected; (c) how are they influenced by genetic and environmental factors; (d) are they unique to schizophrenia; (e) are they associated with cognitive performance, and (f) are they associated with symptoms?

2 | METHODS

We searched the PubMed database using the terms "hippocampal subfield[s]" OR "hippocampal subregion[s]" AND "schizophrenia" OR "psychosis," as well as "cornu ammonis," "CA1," "CA2," "CA3," "CA4," "dentate gyrus," "DG," "molecular layer," "ML," or "subiculum" AND "schizophrenia" AND "volume" OR "fMRI." We combined the search results, removed duplicates, and manually reviewed titles and abstracts from 1373 manuscripts published after 2008—when the first automated method for hippocampal subfield volume estimation was published[26]—inclusive and prior to November 9, 2017 (Figure 1). We excluded any manuscripts based on shape methods based on primary interest in hippocampal subregion volume and physiology findings and because shape findings are difficult to summarize. We identified 13 relevant structural imaging publications[27–39] (Table 1), and 3 relevant physiological imaging publications[40–42] (Table 2).

3 | RESULTS

3.1 | Structural abnormalities in hippocampal subregions in schizophrenia

Several high-resolution automated and manual methods have been developed to compute hippocampal formation subregion or subfield volumes.[43–45] Van Leemput et al[26,46] first published method and atlas implemented in FreeSurfer morphometry package versions prior to 6.0,[47,48] segments the hippocampus into CA4/DG, CA2/3, CA1, subiculum, presubiculum, fimbria, posterior hippocampus, and hippocampal-fissure regions based on a high-resolution T1-weighted image. More recently, Iglesias et al[49] published an updated method and ex vivo atlas that is implemented in FreeSurfer 6.0, which segments the hippocampus into granule cell-molecular layer-dentate gyrus (GC-ML-DG), CA3, CA4, subiculum, presubiculum, parasubiculum, alveus, fimbria, hippocampal-amygdaloid transition region (HATA), and hippocampal tail regions. The atlas was updated because it was noted that the earlier atlas underestimated the volume of CA1 and that subregions were segmented along the entire longitudinal axis of the hippocampus, suggesting that additional rigor in atlas creation was warranted.[50]

Most schizophrenia imaging studies using FreeSurfer to estimate hippocampal subregion volumes published to date have employed the first method and atlas.[27,28,30–34] Three FreeSurfer studies have used the second method with the updated hippocampal subregion

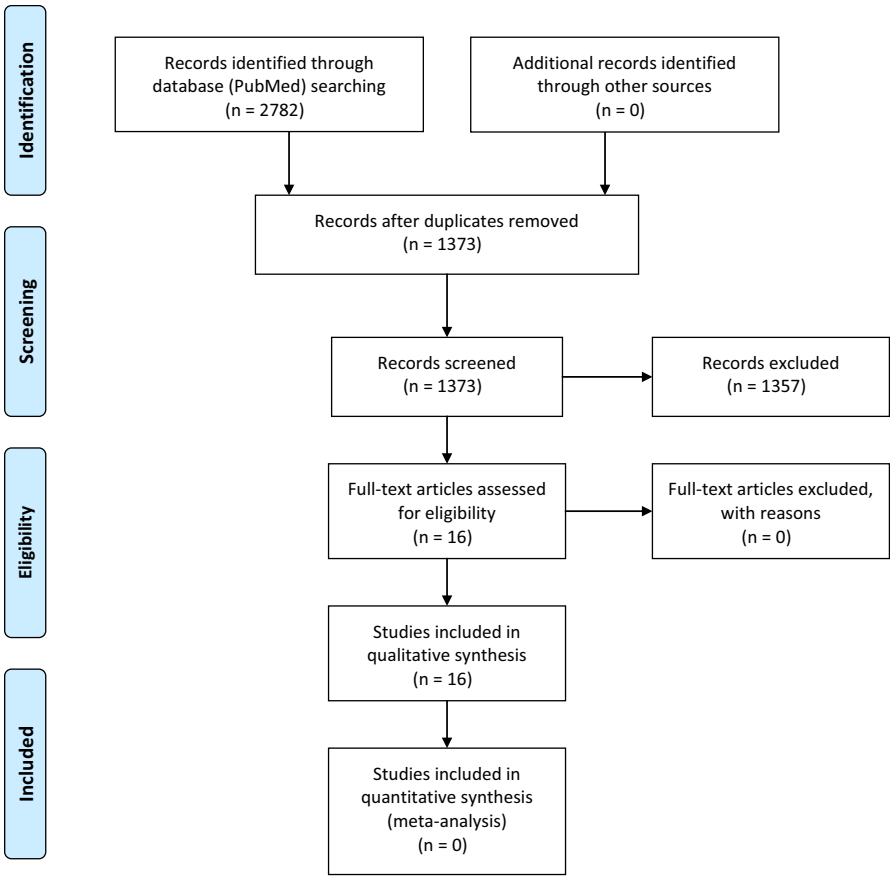

FIGURE 1 Study selection flow diagram

segmentation atlas run on top of the FreeSurfer 5.3 whole hippocampal segmentation.[35,36,39]

Another method, Automated Segmentation of Hippocampal Subfields (ASHS),[51,52] requires a high-resolution coronal T2-weighted image in addition to a high-resolution T1-weighted image. Its initial atlas segmented the hippocampus into CA1-3, DG, EC, and parahippocampal gyrus. Several additional atlases are provided with the software and researchers can also build their own based on manual tracings (http://picsl.upenn.edu/software/ashs). This method has only been employed by a single schizophrenia study published to date.[30] Finally, two studies performed manual tracings to compare hippocampal formation subregion volumes between individuals with schizophrenia or at clinical high-risk and healthy controls,[37,41] and one study rated granule cell layer contrast (visibility) based on high-resolution brain scans acquired at 7T between individuals with schizophrenia and healthy controls.[29]

The first study of hippocampal subregion volumes in schizophrenia by Kühn et al[27] found a negative correlation between bilateral CA2/3 and CA1 volumes and positive symptoms in 21 subjects with schizophrenia with a mean duration of illness of 7.8 years. In contrast, negative symptoms were not found to be associated with CA subfield volumes. This study provides initial suggestive evidence for an association between CA2-3/CA1 and positive symptoms in schizophrenia. The study was conducted in predominantly medicated patients (19/21 on atypical antipsychotics) and did not compare subfield volumes between patients with schizophrenia and healthy controls.

Francis and colleagues (2013) found lower bilateral subicular volumes in 46 offspring of parents with schizophrenia (familial high-risk subjects) compared with 29 healthy volunteers.[27,28] They also reported significant positive correlations between left and right subicular volumes and Wechsler Memory Scale immediate recall and learning slope measures of declarative memory in the offspring of parents with schizophrenia but not in the healthy controls. Importantly, among the familial high-risk subjects, 27 of 46 had a diagnosis of major depressive disorder (MDD) and 9 of 46 had a diagnosis of anxiety disorder (AD) relative to 2 of 30 for each of these two diagnoses in the control group. Hippocampal subregion volumes between familial high-risk subjects with MDD, AD, and without DSM-IV diagnoses were not compared, leaving the possibility that the observed lower subicular volumes between the offspring of parents with schizophrenia and healthy control groups could be predominantly driven by the subjects with MDD/AD diagnoses. In addition, parental socioeconomic status was significantly higher in the offspring compared with the healthy control group and was not controlled for. Finally, a reference suggests that a FLASH sequence with a resolution of $1.17 \times 1.17 \times 8$ mm[53] was used and it is not clear whether that is sufficient for accurate hippocampal subregion segmentation.

Mathew et al[30] published the first study comparing hippocampal subregion volumes between individuals with schizophrenia (mean

TABLE 1 Schizophrenia hippocampal subregion volume studies

Author	Year	Group (N)	Study design	Segmentation method	Tesla	CA1	CA2/3[a] CA3[b]	CA4/DG[a] CA4[b] DG[c]	preSUB	SUB	ML-GC-DG	ML	TAIL	HIP
Kühn et al[27]	2012	SCZ (21)	CSD	FS[a]	3T									
Schobel et al[41]	2013	CHR-C (10) CHR-NC (15) HC (25)	LD	Manual tracings	1.5T	T↓				T↓				T↓
Francis et al[28]	2013	FHR (45) LRC (29)	CSD	FS5.0[a]	3T					L/R				
Mathew et al[30]	2014	SCZ (219) HC (337)	CSD	FS5.1[a]		L/R	L/R	L/R	L/R	L/R				L/R
Haukvik et al[32]	2015	SCZ (210) HC (300)	CSD	FS5.2[a]	1.5T	R	L/R	L/R	L/R	L/R				L/R
Kawano et al[31]	2015	FES (19) HC (15)	LD	FS5.1[a]	1.5T		L	L, L↓						
		SCS (6) HC (15)	CSD				L	L						L
		CS (9) HC (15)	CSD				L	L						L
Hýža et al[33]	2016	FES (58) HC (58)	CSD	FS5.2[a]	1.5T	L[d]								
Papiol et al[38]	2017	SCZ (20) HC (23)	CSD	FS5.3[a]	3T			L[e]						
Ho et al[36]	2017	SCZ (155)[f] HC (79)	LD	FS5.3[b]	3T	L								
		SCZ (34)[g] HC (41)				L/R↓	R↓				L/R↓	R↓		
		SCZ (46)[h] HC (46)				L/R	L/R	L/R		L/R	L/R	L/R	L/R	
Ho et al[35]	2017	UHR-NR (52) UHR-R (41) HC (54)	LD	FS5.3[b]	3T	L/R↓	R↓[i]							R↓
Baglivo et al[39]	2017	FEP (58) HC (76)	CSD	FS5.3[b]	3T	L/R	L	L/R			L/R	L		
Ota et al[34]	2017	SCZ (20) HC (35)	CSD	ASHS	3T	T		T						T
Rhindress et al[37]	2017	FES (29) HC (29)	LD	Manual tracings	3T			T↓		T↑				

↓/↑, longitudinal decrease/increase; ASHS, Automated Segmentation of Hippocampal Subfields; CSD, cross-sectional design; CA, Cornu Ammonis; CHR-C, clinical high risk for psychosis converters; CHR-NC, clinical high risk for psychosis non-converters; CS, chronic schizophrenia; DG, dentate gyrus; FEP, first-episode psychosis; FES, first-episode schizophrenia; FHR, familial high risk; HC, healthy control; FS, FreeSurfer; HIP, whole hippocampus; L, left; LD, longitudinal design; LRC, low genetic risk (no family history); ML-GC-DG, molecular layer-granule cell layer-dentate gyrus; ML, molecular layer; preSUB, presubiculum; R, right; SCS, subchronic schizophrenia; SCZ, schizophrenia; SUB, subiculum; UHR-NR, ultra high risk of psychosis who remained at risk/converted to psychosis; UHR-R, ultra high risk of psychosis who subsequently remitted; T, total (left and right hemisphere combined).

[a]Van Leemput et al (2008) atlas[21,41]

[b]Iglesias et al (2015) atlas[44]

[c]ASHS Atlas[46,47]

[d]Enlarged.

[e]High PRS associated with less CA4/DG SCZ when performing exercise.

[f]Data set 1 with mean duration of illness of 7 y.

[g]Data set 1 follow-up subsample.

[h]Data set 2 with mean duration of illness of 18 y.

[i]CA3 decrease was not significant when statistically controlling for antidepressant/benzodiazepine treatment.

duration of illness 15.67 years) and healthy controls. They found lower bilateral CA1, CA2/3, CA4/DG, presubiculum, and subiculum volumes in 219 individuals with schizophrenia compared to 337 controls. Similar effects were observed in individuals with schizoaffective disorder (n = 142), though individuals with bipolar disorder (n = 188) only showed significantly lower bilateral CA2/3, left

TABLE 2 Schizophrenia hippocampal physiology studies

Author	Year	Group (N)	Study design	Method	Hyperactivity
Schobel et al[40]	2009	SCZ (18) HC (18)	CSD	CBV	CA1
		CHR-C (11) CHR-NC (7)			T CA1, L CA1
Schobel et al[41]	2013	CHR-C (10) CHR-NC (15) HC (25)	LD	CBV	CA1; subiculum↑
Talati et al[42]	2014	SCZ (15) HC (15)	CSD	CBV	CA1[a]

↓/↑, longitudinal decrease/increase; CA, Cornu Ammonis; CBV, cerebral blood volume; CHR-C, clinical high risk of psychosis converters; CHR-NC, clinical high risk of psychosis non-converters; CSD, cross-sectional design; HC, healthy control; L, left; LD, longitudinal design; R, right; SCZ, schizophrenia; T, total (left and right hemisphere combined).
[a]Marginally significant effect (P = 0.06).

presubiculum, and right CA4/DG and subiculum volumes and overall smaller effect sizes than the other two groups. Unfortunately, despite known and noted lack of hippocampal volume[54] and other gray matter deficiencies[55] in lithium-treated individuals with bipolar disorder, the authors did not report findings and effect sizes for lithium-treated (n = 53) and non-lithium-treated (n = 135) bipolar disorder subjects separately. They further found that the volumes of the bilateral subiculum and the left presubiculum were negatively correlated with positive symptom severity, that the right subiculum negatively correlated with delusion item ratings, and that left CA2/3, CA4/DG, presubiculum, and subiculum volumes negatively correlated with hallucination item ratings. In schizophrenia, bilateral CA1, CA2/3, CA4/DG, presubiculum, and subiculum showed significant positive correlations with the BACS (Brief Assessment of Cognition in Schizophrenia[56]) composite cognitive score. Left CA1, CA2/3, CA4/DG, and subiculum also showed significant positive correlations with the BACS list learning score; a verbal declarative memory measure.[30] No significant correlations were observed in the healthy controls. Together, these findings suggest that multiple hippocampal subregion volumes may be affected in schizophrenia and schizoaffective disorder, with possibly the strongest effects in CA2/3, CA4/DG and the subiculum, and that they are associated with higher positive symptom severity and lower declarative memory performance. The study did not examine possible relationships between hippocampal subregion volumes and duration of illness.

A study by Haukvik et al[32] compared 210 individuals with schizophrenia spectrum disorders (mean duration of illness 8.2 years), 192 individuals with bipolar spectrum disorders (mean duration of illness 7.8 years), and 300 healthy controls. They found lower bilateral CA2/3, CA4/DG, presubiculum, and subiculum, as well as right CA1 volumes in individuals with schizophrenia when compared to controls. Similar effects, except for no differences in presubiculum volume, were observed in individuals with bipolar disorder when compared to healthy controls; though bilateral subiculum and right presubiculum volumes appeared significantly lower in individuals with schizophrenia compared to individuals with bipolar disorder. Furthermore, subiculum volume was positively correlated with verbal memory performance (free and cued recall) in the bipolar and control but not schizophrenia subjects. Finally, subiculum volume was negatively associated with negative symptom severity in individuals with schizophrenia. An additional analysis controlling for total hippocampal volume only found larger CA1 volume in individuals with schizophrenia compared to controls. This finding suggests a lack of anatomical specificity in hippocampal subregion volume deficiencies, possibly with CA1 being the least affected in individuals with schizophrenia; though it is also possible that the subregion segmentations were predominantly driven by template priors and therefore highly correlated with total hippocampal volume. It is further noted that the CA1 volume estimates must be interpreted with caution because they are likely underestimated by the method. The findings further suggest that subicular outflow regions may be more affected in schizophrenia when compared to bipolar disorder.

Kawano et al[31] conducted the first assessment of hippocampal subregion volume abnormalities in first-episode psychosis. In a 6-month longitudinal follow-up study, they compared hippocampal subregion volumes between individuals with first-episode (n = 19; first contact for psychosis treatment and <1 month of treatment), sub-chronic (n = 6; 6 months < illness duration <5 years), or chronic schizophrenia (n = 9; illness duration > 5 years) and fifteen healthy controls. They found lower left CA2/3 and CA4/DG volumes in the first-episode, sub-chronic, and chronic schizophrenia groups compared to controls with effect sizes scaling with disease chronicity and strongest for the CA4/DG. Moreover, they found a steeper rate of decline in CA4/DG in first-episode patients (n = 10) compared with healthy controls (n = 12). In addition, they found that left CA2/3 and CA4/DG volumes were negatively correlated with duration of illness and negative symptom severity. While this study has a relatively small sample size, its findings suggests that CA2/3 and CA4/DG volume deficiencies may be present at illness onset and may progress with illness duration.

Hýža et al,[33] in a 4-year longitudinal study found enlarged left CA1 volume in 58 individuals with first-episode schizophrenia (with a mean duration of untreated psychosis of 7.23 months; 38 with follow-up clinical data) when compared to 58 healthy controls. They also found a trend-level negative correlation between duration of untreated psychosis and CA2/3 volume and a positive correlation between right CA1 volume and positive symptom severity. The findings from this study, in particular enlarged CA1 and the positive correlation between CA1 volume and positive symptom severity are hard to interpret. The authors provide no table of raw mean subregion volumes that can be examined to see if volume estimates are in line with those found in other reports. The manuscript depicts a normalized CA1 volume but does not provide the denominator region. Hence, the larger CA1 volume could suggest that CA1 volume was less affected than that of the denominator region used in the normalization. It is also unclear whether the patient and control groups were matched for demographic variables such as parental socioeconomic status or education level.

In a 3-month follow-up study, Papiol et al[38] assessed changes in hippocampal subregion volumes in 20 multi-episode schizophrenia patients (mean number of hospitalization of 4.2) and 23 healthy controls who performed aerobic exercise with cognitive remediation training compared to 21 multi-episode schizophrenia patients who performed table soccer (control intervention) with cognitive remediation training. They found that a higher schizophrenia genetic risk burden (assessed based on a Psychiatric Genomics Consortium derived polygenic risk score [PRS][57]) was associated with less volume increase or decrease in DG/CA4 volume during the intervention in the patients who performed aerobic exercise with cognitive remediation training but not in the two control groups. These findings provide initial evidence for a gene-environment interaction effect on DG plasticity in schizophrenia but must be regarded with caution as they warrant replication in a larger sample.

Ho et al[35,36] conducted the first study using FreeSurfer with the new ex vivo hippocampal subregion atlas. They assessed 155 individuals with schizophrenia—with a mean duration of illness of 7 years—along with 79 healthy comparisons subjects (study 1), as well as 46 individuals with schizophrenia—with a mean duration of illness of 18 years—along with 46 healthy comparisons subjects (study 2); follow-up scans were available from 34 individuals with schizophrenia (mean of 4.52 years apart) and 41 healthy comparison (mean of 5.26 years apart) subjects from study 1. Compared with controls, they reported significantly smaller left CA1 volume in schizophrenia in study 1, and more widespread lower volume in bilateral ML_GC_DG (reported as GCL), CA1, CA3, CA4, ML, subiculum, and tail regions in schizophrenia in study 2. In a secondary analysis of a study 1 subsample, they found smaller bilateral CA1 and right ML_GC_DG volumes in patients within their first 5 years of illness (n = 53) compared to controls (n = 61). The analysis of the follow-up sample showed smaller CA1 volumes at baseline and significant reductions over time in bilateral CA1 and ML_GC_DG, and right ML and CA3 volumes. However, in addition to a longer duration of illness, sample 2 also had a higher daily dose of antipsychotic medication and higher symptom severity. While they found no significant relationships between hippocampal subregion volumes and medication dose or symptom severity, they found that CA1 volumes were negatively associated with duration of illness. Moreover, in the longitudinal sample, rate of reduction in hippocampal subregion volumes correlated with overall worsening of general symptom severity; more specifically, rate of reduction in left CA1 volume correlated with rate of worsening of negative symptom severity. They concluded that in the early phases of illness, individuals with schizophrenia show lower CA1 volumes and that during the course of the illness, this focal atrophy extends to other hippocampal subregions including the CA3 and ML_GC_DG regions. Further, hippocampal subregion volumes decline with longer duration of illness and worsening of symptoms. This study has several strengths, it uses the updated and more accurate hippocampal subregion template, it includes short- and long duration of illness samples, and longitudinal data from a subsample. The authors list a rate of change of hippocampal subregion volume loss of 2%-6% per year. This rate of change seems rather high as when assuming linearity, after 5 years of illness, patients would have lost 10%-30% of their hippocampal volumes which is more than the mean reported in most studies to date.

More recently, Baglivo et al[39] reported lower bilateral CA1, CA4, and ML_GC_DG, and lower left CA3 and ML volumes comparing 58 individuals with first-episode psychosis and 76 healthy controls using FreeSurfer's new ex vivo atlas. No significant correlations with clinical variables were observed.

In a second longitudinal study, Ho et al[35] assessed hippocampal subregion volumes using the same method in 93 individuals at ultra high risk (UHR) of psychosis (12 UHR who converted to clinical psychosis, 40 whose symptoms persisted, and 41 whose symptoms remitted) and 54 healthy controls at baseline, 1-year, and 2-year follow-up, or at time of conversion. They found greater decline in CA1 volume in UHR subjects whose symptoms persisted or who converted to psychosis than in those whose symptoms remitted and healthy controls. Moreover, rate of reduction in CA1 volume but not any other sub region was associated with overall increased symptom severity. Among all the other hippocampal subregions, only the right CA3 showed a steeper reduction in UHR subjects who did not remit when compared to controls though this effect was no longer significant when antidepressant and benzodiazepine medication treatment were statistically controlled for. Additionally, UHR subjects were never treated with antipsychotic or mood stabilizers and did not have histories of substance abuse suggesting disease-related rather than comorbid or treatment-related effects on the changes in CA1 volumes. This study replicates the earlier finding of a steeper rate of change for hippocampal subregion volumes, specifically in CA1, in CHR subjects.[36] Together with their prior report, these findings provide compelling evidence for primary involvement of CA1 early in schizophrenia pathogenesis.

To date, the only study that has assessed hippocampal subregion volumes using ASHS[51,52] has been reported by Ota and colleagues (2017). They assess 20 individuals with schizophrenia, 36 with major depressive disorder (MDD), and 35 healthy volunteers with high-resolution T1-weighted and high-resolution T2-weighted scans (perpendicular to the longitudinal axis of the hippocampus). They found lower CA1 volumes in schizophrenia compared to control subjects, and lower DG volumes in schizophrenia compared to control and unmedicated MDD subjects. This study makes an important contribution by replicating CA1 and DG volume abnormalities in an independent sample using a different and well-regarded hippocampal subregion segmentation method.

The first study that performed manual tracings of hippocampal subregion volumes assessed individuals at clinical high risk (CHR) of psychosis[41] and will be addressed in the physiology section of the review. A second study that performed manual tracings of hippocampal subregions, by Rhindress et al,[37] found that DG/CA4 volume decreased while subiculum volume increased in a sample of 29 individuals with first-episode psychosis, treated for 12-weeks with either risperidone or aripiprazole, relative to 29 healthy volunteers in a double-blind randomized clinical trial. Interestingly, percent DG/CA4 of total hippocampus volume change showed a quadratic

relationship with chlorpromazine equivalent dose, perhaps suggesting that the DG/CA4 decreases were predominantly present in individuals with the lowest and the highest treatment doses. While the larger reductions in DG/CA4 volume in first-episode psychosis subjects compared to controls are interesting, it is unclear to what extent they are due to the antipsychotic treatment or part of the normal course of the illness.

Finally, the first ultra high-resolution structural imaging study performed at 7T with a voxel size of 0.238 × 0.238 × 1.5 mm (20% gap) found lower mean dentate gyrus granule cell layer integrity (visibility) when comparing scans from 16 individuals with schizophrenia (mean duration of illness of 20 years) with 15 age- and gender-matched controls.[29] This study is unique and suggests additional avenues to pursue using high-field, high-resolution, imaging of hippocampal subregions.

3.2 | Physiological abnormalities in hippocampal subregions in schizophrenia

With regard to physiological abnormalities, three studies have reported on hippocampal subregion cerebral blood volume in schizophrenia during rest.[40–42] Using a gadolinium-enabled cerebral blood flow (CBV) mapping technique, Schobel et al[40] measured EC, DG, CA3, CA1, and subiculum CBV in 18 individuals with schizophrenia or schizoaffective disorder (mean duration of illness 10.5 years) and 18 demographically similar controls. They also assessed regional CBV in 18 individuals at CHR for psychosis, of which 7 converted to a schizophrenia spectrum disorders after a 2-year follow-up. They found higher CA1 CBV in the individuals with schizophrenia or schizoaffective disorder when compared to the healthy volunteers. They also found higher CA1 CBV in the CHR subjects who converted vs those who did not. Moreover, CA1 CBV was positively correlated with symptom severity in the combined clinical subject group (schizophrenia and CHR), with the strongest association with delusional symptom severity; CA1 CBV was also positively associated with delusion severity within each clinical group. Within the CHR group, CA1 CBV was also positively associated with total negative symptom, social dysfunction, and avolition severity. Finally, only 1 out of 7 CHR converters received antipsychotic medication making it unlikely that the observed higher CA1 CBV was due to effects of antipsychotic treatment. This study's major strength is that it shows higher CA1 CBV in schizophrenia with a replication in an independent sample of individuals at CHR for psychosis.

In a second study, using the same technique, Schobel et al[41] measured EC, DG, CA3, CA1, and subiculum CBV and hippocampal subregion volumes in 25 individuals at CHR for psychosis at baseline and 20 of the same subjects during follow-up with a mean interscan interval of 2.4 years. During follow-up, 10 of the 25 subjects developed a psychotic disorder. At baseline, CHR subjects who developed a psychotic disorder had higher bilateral mean CA1 CBV when compared to subject who did not. When each hemisphere was considered separately, higher left but not right hemisphere CA1 CBV was found. At follow-up, CHR subjects who developed psychosis showed CBV increases in the subiculum only, while CA1 CBV did not increase beyond the elevation observed at baseline. Moreover, left hemisphere CA1 CBV predicted time to psychosis in a Cox regression analysis; this was found even when known symptom-based predictors were included in the statistical model. Morphological analyses also showed significant loss of whole hippocampal volume, in particular CA1 and subiculum volumes, at follow-up, compared to baseline, in CHR converters compared to non-converters. This study found no effect of antipsychotic treatment on the regional hippocampal CBV or morphology. They further found that a larger increase in left anterior CA1 CBV was associated with a larger decrease in hippocampal volume at follow-up. Further, a shape analysis showed that a posterior to anterior gradient in CA1 hyperactivity was associated with a posterior to anterior gradient in CA1 volume loss. Of note, the authors showed that acute injection of ketamine in mice resulted in a significant increase in CA1 and subiculum but not EC, CA3, and DG CBV, findings that mimic the observation in the UHR converters. This study suggests that high left anterior CA1 CBV spreads to the subiculum after illness onset. Importantly, the reported translational work in mice provides a mechanistic link between high CA1 CBV, the presence of extracellular glutamate, and hippocampal volume loss. It must be noted that, while the findings are compelling, this study does not represent a fully independent replication of Schobel et al[40] findings in subjects at CHR for psychosis as 18/25 CHR subjects overlapped with the prior study. Further, it has been noted by Talati et al[42] that the higher CA1 CBV findings were based on only a single slice of left anterior CA1 averaged across both hemispheres. This report, however, makes a unique a contribution to the research literature with the inclusion of longitudinal data, and it importantly provides a stellar example of how the integration of rodent work can further our understanding of mechanisms underlying human brain imaging findings.

Talati et al[42] conducted a gadolinium-enhanced, T1-weighted, steady state brain mapping study comparing 15 individuals with schizophrenia or schizoaffective disorder (mean duration of illness of 8.47 years) with 15 demographically similar controls. They found lower CA1 than CA2/3 CBV in controls but similar CA1 and CA2/3 CBV in individuals with schizophrenia or schizoaffective disorder. Between group comparisons showed marginally higher CA1 CBV in the patients compared to the controls ($P = 0.06$; Cohen's $d = 0.63$). Anterior CA1 CBV did not correlate significantly with symptom severity. This study provides a partial replication by an independent group of the higher CA1 CBV reported in the first two studies, though did not replicate previously observed associations with symptom severity.

4 | DISCUSSION

This study reviews hippocampal subregion volume and physiology findings to assess the status of the field with regard to the following

questions: (a) what subregions are affected; (b) at what illness stage are they affected; (c) how are they influenced by genetic and environmental factors; (d) are they unique to schizophrenia; (e) are they associated with cognitive performance, and (f) are they associated with symptoms?

Twelve studies, comprising 15 samples—including 1 familial high risk, 2 clinical high risk, and 4 first-episode—examined schizophrenia-associated hippocampal subregion volume deficiencies. Overall, the subregions that show the most prominent volume alteration in schizophrenia are CA1,[30,32,34,35,39,41] CA2/3,[30–32,34–36,39] DG/CA4,[30–32,34–36,39] and subiculum.[28,30,32,36] The two longitudinal clinical high-risk studies published to date replicate larger decreases in CA1 volume in those who convert to psychosis when compared with those who do not and healthy controls[35,41]; one shows an additional decrease in CA2/3 and the other in subiculum volumes.[35] In addition, in all but two studies,[31,33] the more chronic schizophrenia samples[30,32,34,36] showed more hippocampal subregion deficiencies than the first-episode schizophrenia samples,[31,37,39] and all[31,36,37] but one longitudinal study[33] found further volume decline in subregion volumes after illness onset.

Three studies, comprising 4 samples (3 independent)—including 2 chronic schizophrenia and 1 clinical high risk for psychosis—reported high CA1 CBV in schizophrenia[40,42] or in CHR converters compared to controls.[40,41] Importantly, high CA1 CBV was associated with overall hippocampal and CA1 volume loss and initial evidence of an underlying mechanism involving extracellular glutamate was reported on.[41]

Together, these findings indicate that the deficits in the DG-CA3-CA1-subiculum circuit may contribute to the emergence of psychosis, though the degree of alteration and contribution for each of these regions to psychosis may depend on the stage of illness. The findings of fewer regional deficiencies in clinical high risk and first-episode schizophrenia subjects compared to chronic schizophrenia subjects, with the most evidence for early replicated CA1 volume deficiency[36,41] and high CA1 CBV[40,41] during the prodromal phase and in addition replicated CA4/DG volume deficiency at first-episode,[31,37,39] suggest that regional hippocampal volume deficiencies may be larger than total hippocampal volume deficiencies. This interpretation fits well with the observation that overall hippocampal volume deficits were found not present prior to illness onset, to emerge in first-episode schizophrenia, and to be clearly present in chronic schizophrenia.[16]

With regard to genetic and environmental influences, only a single study in individuals at familial high risk for schizophrenia showed smaller subiculum volumes in high- vs low-risk subjects.[28] An additional study found that higher schizophrenia polygenic risk scores predicted less volume increase or possibly volume decrease in CA4/DG volume in an exercise trial.[38] No further family or genetic association studies examining hippocampal subregions in schizophrenia have been reported on, though hippocampal subregion volumes were shown to be heritable in healthy individuals.[58,59]

Two studies compared hippocampal subregion volumes between schizophrenia and bipolar disorder,[30,32] with one reporting less,[30] and the other reporting similar hippocampal subregion volume deficiencies in bipolar disorder compared to schizophrenia.[32] The later study found that presubiculum and subiculum volumes were more affected in schizophrenia.[32] Another study found lower CA1 volumes in schizophrenia compared to controls subjects, and lower DG volumes in schizophrenia compared to control and unmedicated subjects with major depressive disorder.[34] Clearly, these findings warrant replication. Cross-disorder comparisons are critically important to determine whether any of the observed hippocampal subregion anomalies are disease-specific or generic to multiple psychiatric disorders and perhaps due to common underlying risk factor such as stress.[21] Based on our literature review, no cross-disorder studies of hippocampal subregion physiology have been conducted.

With regard to contributions of hippocampal subregions to declarative memory deficiencies observed in schizophrenia, one study reported a significant positive correlation between subiculum volume and declarative memory performance in familial high-risk subjects,[28] while another found significant positive correlations between CA1, CA2/3, CA4/DG and subiculum volumes and episodic memory performance in individuals with schizophrenia.[28,30] While encouraging in suggesting potential differential involvement of subregion abnormalities in observed declarative memory performance abnormalities in schizophrenia, these findings are by no means conclusive and require further investigation.

Several studies have shown significant correlations between CA1 and CA2/3 volumes[27,30] and one study between presubiculum and subiculum volumes and positive symptom severity.[30] Additionally, three studies found a relationship between hippocampal subregion volumes and negative symptoms but each with a different region, namely subiculum,[32] CA2/3 and CA4/DG,[31,34] or CA2.[31] Finally, CA1 CBV has been found to be associated with overall, positive, and negative symptom severity[40] though these findings were not replicated in a more recent report.[42]

In sum, the structural and physiological imaging studies of hippocampal subregion abnormalities in schizophrenia published to date provide the most consistent evidence for the involvement of CA1 early on in the disease process. These findings support Small and colleagues (2011) model[20,29] of hippocampal subregion dysfunction in schizophrenia. However, ultra high-resolution structural imaging at 7T has provided initial in-vivo evidence for lower dentate gyrus granule cell layer integrity in schizophrenia,[20] and lower CA4/DG or GC-ML-DG or DG volumes have been replicated and shown to be present in individuals with first-episode schizophrenia,[31,37] and may be unique to schizophrenia when compared major depressive disorder,[30] also providing relatively strong support from volumetric studies for Tamminga and colleagues' (2010) model of hippocampal subregion dysfunction in schizophrenia.[24,25] The observations of lower pre/subiculum volumes in schizophrenia when compared to bipolar disorder[32,41] and the presence of subiculum hyperactivation after psychosis onset[41] provide some initial in-vivo imaging evidence for subiculum involvement in schizophrenia in support of the Lisman and Grace's[22] model. Two studies have shown significant negative associations between CA2/3 volumes and positive symptoms[27,30]

and with one specifically lending some, albeit as of yet weak, support for CA3 involvement in hallucinations.[23]

Post-mortem studies have shown numerous pathophysiological abnormalities that may underlie hippocampal formation (HF) circuitry volumetric and physiological abnormalities in schizophrenia. For example, immature dentate granule cells[60] and lower dentate gyrus neural stem cell proliferation have been observed in schizophrenia.[61] These findings may support Tamminga and colleagues model[24] of hypoglutamatergic activity in the dentate gyrus and may fit with findings of diminished mossy fiber projections to CA3 in individuals with schizophrenia compared to controls.[62] In addition, several studies suggest that schizophrenia is associated with a lower number of interneurons, possibly resulting in disinhibition of hippocampal pyramidal cells in CA2/3 and CA1.[63,64] These findings support the Benes,[21] Behrendt,[23] and Small et al[20] models. A lower number of interneurons may in part account for the high CA1 CBV observed in schizophrenia as translational work in rodents has shown that high CA1 CBV is associated with a hyperglutamatergic state.[41] Finally, evidence for lower subicular spine density, dendritic branching, and dendritic density in schizophrenia compared to controls[65–67] supports the Lisman and Grace model[22]; though contrary findings exist.[68]

Several limitations of the studies reported to date must be noted. First, the volumetric studies predominantly used FreeSurfer versions prior to version 6.0 which included a substandard anatomical template.[50] Second, none of the published HF subregion studies do date set out to test different HF circuitry models. For example, testing for differential involvement of any of the subregions requires a multivariate statistical model that takes into account scalar differences between the regional volumes and includes a group by region interaction term in the statistical model. Third, all reported studies to date employ univariate statistical models to compare volumes and no studies have been designed to identify patient subgroups that may be relevant to different prognosis, treatment response, or symptom profiles. Finally, only a single study statistically controlled for total hippocampal volume to assess regional specificity and no studies examined differences in lateralit. This review also has several limitations. First, given that the total number of studies reporting on HF subregion volumes and physiology is rather small, the review is limited to qualitative report of their findings. Second, this qualitative review does not include hippocampal shape studies whose findings are challenging to review and considered beyond the scope of the current report.

This review suggests several future directions to advance the aforementioned six questions about HF subregion abnormalities in schizophrenia. First, any new morphometry study should include scans at submillimeter resolution; at least in the plane perpendicular to the longitudinal axis of the hippocampus. Second, associations between HF subregion volumes and clinical symptom and cognitive performance scores, which tend to be weak, may benefit from meta- or mega-analyses such as those performed by the Enhancing NeuroImaging Genetics Analysis through Meta-Analysis (ENIGMA) Schizophrenia Working Group[5,69] and the Cognitive Genetics Collaborative Research Organization (COCORO)[6] in order to achieve the sample sizes needed for robust findings. Finally, the field as a whole would benefit from additional physiological studies as few have been conducted to date.

The area of hippocampal subregion imaging in schizophrenia is still in its infancy, and we must caution against overinterpretation of the findings published to date for several reasons. First, the CA1 is the largest hippocampal subregion and given that these studies are at the cutting edge of what current imaging technology can provide, it may be easier to detect effects in large compared to small regions. Second, it is not clear whether our current image resolution is sufficient to assess all relevant anatomical variation.[70] Third, there are major differences in the methods employed by studies and the field is still working toward a consensus of best practices.[43–45] Fourth, observations in downstream regions may be a consequence of abnormalities in less easily observable (eg, smaller) upstream regions. Finally, possible confounding factors in imaging must be carefully considered.[71] Nevertheless, continued advances in neuroimaging data collection methods and image processing techniques are starting to enable in-vivo investigations of hippocampal subregion abnormalities in schizophrenia, and hold promise for a deeper understanding of hippocampal circuitry involvement in schizophrenia.

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CONFLICT OF INTEREST

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