



Letter to the Editor

7 T MRI reveals hippocampal structural abnormalities associated with memory intrusions in childhood-onset schizophrenia

Dale Zhou^{a,*}, Siyuan Liu^a, Xueping Zhou^a, Rebecca Berman^b, Diane Broadnax^a, Peter Gochman^a, Judith Rapoport^a, Adam Thomas^{c,d}

^a Section on Childhood Neuropsychiatric Disorders, Child Psychiatry Branch, National Institute of Mental Health, United States of America

^b Section on Cognitive Neurophysiology and Imaging, Laboratory of Neuropsychology, National Institute of Mental Health

^c Data Science and Sharing Team, Center for Multimodal Neuroimaging, National Institute of Mental Health, United States of America

^d Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

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Dear Editors,

The hippocampus exhibits striking volume reductions in schizophrenia (van Erp et al., 2016), with regionally specific changes in subfields cornu ammonis 1 to 4 (CA1-4), dentate gyrus, and subiculum (Mathew et al., 2014). Models of hippocampal function suggest an association with memory deficits in schizophrenia patients; for example, impairment of the pattern separation component of declarative memory in schizophrenia suggests dentate gyrus dysfunction (Das et al., 2014). As yet, however, there is incomplete understanding of how subfield structure contributes to these impairments. Relatedly, intrusions—a memory error where individuals mistakenly recall words from an incorrect list or never presented in any list—are associated with genetic risk for schizophrenia (Cannon et al., 2000), but hypothesized hippocampal pathophysiology remains unexplored. Childhood-onset schizophrenia, defined as onset before age 13, is a rare, possibly more homogenous, and severe form of the adult-onset disorder (Gochman et al., 2011). Our previous study of whole hippocampal structure in COS provided evidence of volume reductions in the anterior and posterior portions, suggesting differential effects on hippocampal subfields (Mattai et al., 2011). Here, we hypothesized that hippocampal reductions in COS are (1) continuous with selective reductions in reported adult-onset cases, operationalized as greater effect size; (2) associated with intrusion errors; and (3) state-/disease-based.

We investigated hippocampal subfield volume linked to short-term memory and intrusions in nationally recruited, age- and sex-matched COS patients ($n=14$; 9 female; mean age 18.4, $SD=4.0$), unaffected siblings ($n=17$; 9 female; mean age 19.3, $SD=4.4$), and

healthy controls ($n=20$; 11 female; mean age 20.0, $SD=3.8$) using 7-Tesla MRI combined with regional volumetric and voxel-wise tensor-based analyses, after excluding 8 participants with missing or poor quality data. Patients were diagnosed by two child psychiatrists with clinical interviews and exclusionary neurological/medical criteria described previously (Gochman et al., 2011). Short-term memory and intrusions were measured using the California Verbal Learning Test [CVLT]–Second Edition or Children's Version. All participants completed whole-brain T1- and limited-field-of-view T2*-imaging, which permitted multi-contrast subfield segmentation of CA1, CA2/3, CA4, the granule cell layer of the dentate gyrus (DG-GCL), molecular layer (ML), tail, and subiculum using FreeSurfer v6.0. T2*-weighted image contrast at 7T provides greater sensitivity to hippocampal tissue composition, while multiple contrasts improve subfield definition. Analysis of covariance was used to assess the effect of group on subfield volume while controlling for age, sex, and intracranial volume ($\alpha_{FDR}=0.05$). Interactions were evaluated but found non-significant. In subfields with significant effect of group, pairwise comparisons were conducted using least-squares/covariate adjusted means ($\alpha_{FWER}=0.05$). Effect size was calculated using Hedge's g , an unbiased variant of Cohen's d for smaller samples. To perform tensor-based morphometry, we created group templates incorporating population features for improved cross-subject validity using elastic image registration. Voxel-wise significance maps were generated using permutation testing of log-Jacobian fields between groups ($\alpha_{FWER}=0.05$). Subfield volumes were correlated to standardized CVLT measures. Neuroimaging details and code are online (https://github.com/agt24/cpb_d7).

Patients displayed reduced volume in laterally specific subfields. Compared to controls, patients had smaller left CA1, right CA1, and right tail ($P<0.05$; see Table 1). Compared to siblings, patients had smaller right DG-GCL, right CA4, Left CA1, right CA1, right tail, and left subiculum ($P<0.05$). In addition, tensor-based morphometry revealed clusters of deformation in COS patients' right DG-GCL

* Corresponding author at: Child Psychiatry Branch, National Institute of Mental Health, 4th floor, room N246, Bldg 10, Clinical Center, 10 Center Dr, Bethesda, MD 20814, United States of America.

Email address: dale.zhou@nih.gov (D. Zhou)

Table 1
Hippocampal subfield volume in childhood-onset schizophrenia versus siblings and controls.

Subfields	COS	Healthy Sibling	Control	Group Effect	COS vs SIB	COS vs HC	COS vs SIB	COS vs HC	S-DFR	Intrusions
Adjusted Mean Volume (SE) mm ³				F-value (p)	d (p)	Voxels deformed (p) ^c		rho (p)	rho (p)	
Left GCL	238.11 (6.19)	258.21 (5.48)	250.37 (5.05)	3.04 (0.09)	0.65 (0.05) ^b	0.33 (0.29)	–	–	0.51 (1.0)	–0.80 (0.03) ^d
Right GCL	234.17 (7.41)	263.51 (6.56)	255.88 (6.05)	4.72 (0.04) ^a	0.77 (0.01) ^b	0.61 (0.07)	143 (0.03)	26 (0.05)	0.76 (0.06)	–0.53 (1.0)
Left CA4	199.55 (5.08)	212.44 (4.49)	207.07 (4.14)	1.85 (0.21)	0.52 (0.14)	0.24 (0.49)	–	–	0.53 (1.0)	–0.81 (0.02) ^d
Right CA4	195.76 (5.96)	220.99 (5.27)	213.60 (4.86)	5.32 (0.04) ^a	0.85 (0.01) ^b	0.66 (0.06)	–	–	0.77 (0.05) ^d	–0.50 (1.0)
Left CA2/3	173.33 (5.53)	173.37 (4.89)	167.01 (4.51)	0.59 (0.65)	0.03 (1.00)	0.31 (0.65)	–	–	0.30 (1.0)	–0.64 (0.46)
Right CA2/3	169.66 (7.07)	194.21 (6.25)	183.56 (5.76)	3.47 (0.07)	0.76 (0.03) ^b	0.42 (0.29)	–	–	0.56 (0.72)	–0.18 (1.0)
Left CA1	546.32 (15.69)	606.72 (13.88)	595.79 (12.80)	4.69 (0.04) ^a	0.69 (0.02) ^b	0.66 (0.05) ^b	–	–	0.46 (1.0)	–0.77 (0.05) ^d
Right CA1	543.80 (17.24)	610.76 (15.25)	607.56 (14.06)	5.35 (0.04) ^a	0.69 (0.01) ^b	0.73 (0.02) ^b	–	–	0.53 (1.0)	–0.47 (1.0)
Left ML	515.69 (15.22)	529.63 (13.45)	518.94 (12.40)	0.28 (0.76)	0.21 (0.77)	0.04 (0.99)	–	–	0.45 (1.0)	–0.64 (0.46)
Right ML	515.64 (18.28)	533.73 (16.16)	518.72 (14.90)	0.35 (0.76)	0.21 (0.74)	0.04 (0.99)	–	–	0.51 (1.0)	–0.63 (0.46)
Left tail	444.51 (17.17)	495.93 (15.19)	476.59 (14.00)	2.59 (0.12)	0.68 (0.07)	0.34 (0.33)	–	–	0.01 (1.0)	–0.60 (0.57)
Right tail	406.21 (19.19)	498.60 (16.97)	468.08 (15.65)	6.78 (0.04) ^a	0.97 (0.002) ^b	0.78 (0.04) ^b	10,800 (0.01)	–	0.03 (1.0)	–0.51 (1.0)
Left Sub	352.45 (12.94)	401.73 (11.44)	386.40 (10.55)	4.27 (0.05) ^a	0.81 (0.02) ^b	0.72 (0.12)	–	–	0.48 (1.0)	–0.31 (1.0)
Right Sub	350.35 (11.74)	382.76 (10.38)	389.40 (9.57)	3.59 (0.07)	0.58 (0.10)	0.71 (0.04) ^b	–	–	0.64 (0.46)	–0.42 (1.0)

Disrupted volumes were observed in right DG-GCL, right CA4, bilateral CA1, right tail, and left subiculum. Significantly different subfield volumes were observed in group comparisons, calculated using Hedge's *g* (an unbiased form of Cohen's *d* for small sample sizes) with unadjusted means and pooled standard deviations. Deformation localized to voxels in the right granule cell layer and tail in childhood-onset schizophrenia patients versus their healthy siblings, and in the right granule cell layer versus controls. The tail includes posterior portions of CA1-4 and DG-GCL. Siblings did not differ from controls. Impaired episodic verbal memory was associated with reduced right CA4 volume, with a trending relationship for right DG-GCL volume. Increased rate of intrusions was associated with reduced left DG-GCL, left CA4, and left CA1 volumes. COS=childhood-onset schizophrenia; SIB=unaffected sibling; HC=healthy control; SE=standard error; d=effect size; GCL=dentate gyrus granule cell layer; CA=cornu ammonis; ML=molecular layer; Sub=subiculum; S-DFR=short-delayed free recall.

^a Significant (corrected $P < 0.05$) following Benjamini-Hochberg correction for false discovery rate.

^b Significant (corrected $P < 0.05$) following Tukey method for family-wise error rate.

^c Significant (corrected $P < 0.05$) following family-wise error correction using threshold-free cluster enhancement.

^d Correlations were considered significant (corrected $P < 0.05$) following Holm-Bonferroni correction

compared to controls; and in the right DG-GCL and right tail versus siblings ($P < 0.05$). Subfield structure did not differ between siblings and controls. In patients, right CA4 volume positively correlated with short delayed free recall scaled scores ($P < 0.05$). Intrusions negatively correlated with left DG-GCL volume, left CA4, and left CA1 volume ($P < 0.05$).

These findings parallel previous evidence linking subfield volume to cognitive impairment associated with schizophrenia, and are consistent with the hypothesized state-/disease-based link between hippocampal pathophysiology, intrusions, and psychosis (Cannon et al., 2000; Mathew et al., 2014). Human and animal studies support the dentate gyrus as a pattern separator and CA1 as a match/mismatch detector, structures which here appear vulnerable to volume reductions (Leal and Yassa, 2018). While speculative, volume reduction associated with disease-based genetic risk may contribute to dysfunctional hippocampal binding; for example, deficits in source memory (remembering information about the source of an encoded item) may result in intrusions (Brebion et al., 2009). Whereas bilateral CA1 volume reductions in COS corroborates recent reports of early and selective CA1 atrophy in adult-onset patients (Ho et al., 2017), additional lateral reductions may reflect progressive atrophy consistent with COS' more severe, continuous phenotype. Tensor-based morphometry revealed that patients had small regions of posterior deformation in right DG-GCL and tail, reflecting largely diffuse volume reduction. Though COS exhibits severe phenotypes, corresponding to higher effect sizes detectable in smaller samples (we exceeded the minimum number of subjects to detect strong effects indicated by a priori power analysis), this small sample requires caution when interpreting findings. Nevertheless, we corroborated previous reports by showing that volume reductions were continuous with adult-onset schizophrenia and introduced novel evidence of volumetric reductions in DG-GCL, CA1, and CA4 associated with memory intrusions in COS. Interestingly, clozapine, an antipsychotic drug which has shown superior efficacy in treating COS, has been demonstrated to

restore DG-GCL neurogenesis in animal models (Keilhoff et al., 2012), highlighting the potential of targeted intervention.

Contributors

Mr. Zhou, Dr. Berman, Dr. Rapoport, and Dr. Thomas designed the study and wrote the protocol. Mr. Zhou, Ms. Zhou, and Dr. Liu performed the statistical analysis. Dr. Liu, Dr. Thomas, and Dr. Rapoport provided statistical advice and assisted in data interpretation. Mr. Gochman and Ms. Broadnax managed the data and contributed to data interpretation. Mr. Zhou performed literature review, statistical analysis, data interpretation, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2018.07.023>.

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