Schizophrenia Research 157 (2014) 319–320

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Hippocampal and parahippocampal cortex volume predicts recollection in schizophrenia

Dear Editors,

The neural pathology of episodic memory deficits in schizophrenia is not fully understood, but regions within the medial temporal lobe (MTL) may be particularly important. The perirhinal cortex (PRC) is critical for assessing item familiarity, the parahippocampal cortex (PHC) for processing context information (i.e., time and space), and the hippocampus (HC) for binding items and contexts to support recollective, or contextual, retrieval (Eichenbaum et al., 2007). Volume reductions in the MTL have been observed in schizophrenia (e.g., Nelson et al., 1998; Sim et al., 2006) and an fMRI meta-analysis found increased PHC activity in patients relative to controls (Ragland et al., 2009). Moreover, studies examining relationships between MTL volumes and scores on standardized memory batteries reported correlations between HC volume and memory performance in patients with schizophrenia (e.g., Karnik-Henry et al., 2012), and correlations between HC and PHC volume with memory performance in siblings of patients (Karnik-Henry et al., 2012). These findings, along with evidence that schizophrenia is related to larger deficits in recollection than familiarity (Libby et al., 2013), suggest that both HC and PHC may be affected by and mediate memory deficits in schizophrenia. Nonetheless, there have not been any attempts to link MTL volume reductions in schizophrenia with recollection and familiarity.

We sought to characterize how MTL subregion volumes relate to recollection and familiarity in patients with schizophrenia by manually-tracing the HC, PRC, and PHC to estimate MTL subregion volumes, and by assessing recognition memory Receiver Operating Characteristics (ROCs) to estimate recollection and familiarity. According to an established protocol (Libby et al., 2012), left and right HC, PHC, and PRC were manually traced (ICC range: .71–.99) on each participant's high-resolution 1 mm isotropic T1 structural MPRAGE image, and subregions were analyzed as a proportion of each participants' total grey matter volume. Recognition memory confidence ratings for studied and unstudied words were collected following an fMRI encoding task (see Ragland et al., 2010). ROC analyses plotted performance as a function of confidence and fit this function with a nonlinear model to derive estimates of recollection and familiarity (Yonelinas, 1994). We examined a sample of 22 patients with schizophrenia (21 receiving medication) and 30 healthy controls. Patients exhibited mild positive, mild disorganized, and moderate negative symptom dimensions (see Barch et al., 2003), and severely impaired daily functioning. Controls were matched on age, gender, handedness, and parental education.

We first inspected MTL subregion volume differences between groups, revealing left HC ($t[50] = 2.47$, $p < .05$, Cohen's $d = .70$) and PHC ($t[50] = 2.19$, $p < .05$, Cohen's $d = .58$) volume reductions in patients relative to controls. None of the other MTL subregions significantly differed between groups (ps > .05).

We then examined whether reduced left HC and PHC volumes in patients were related to recognition memory. Recognition discriminability (*d'*) correlated with both left HC and PHC volume in patients ($rs \geq .47$, $ps < .05$), but not controls (ps > .05). A direct comparison revealed that left HC (Fisher's $Z = 1.79$, $p = .07$) and PHC (Fisher's $Z = 2.31$, $p < .05$) volumes were more strongly related to recognition performance in patients than in controls.

Finally, we assessed whether recollection and familiarity differentially correlated with left HC and PHC volume. Recollection correlated with both left HC and PHC (Fig. 1) volume in patients ($r \geq .43$, $ps < .05$), but not controls (ps > .05). The group difference between the correlations did not reach statistical significance in left HC (Fisher's $Z = 1.41$, $p = .16$), but did in left PHC (Fisher's $Z = 2.00$, $p < .05$). Familiarity, on the other hand, did not correlate with left HC or PHC volume in either patients or controls (ps > .05).

The current study is the first to examine the relationship between different MTL subregions and measures of recollection and familiarity in patients with schizophrenia. First, we observed volume reductions in left HC and PHC in patients relative to controls. We further demonstrated that left HC and PHC volumes were directly related to recollection in patients but not controls. This indicates that recollection impairments found in individuals with schizophrenia are likely related to abnormalities in HC and PHC volume. Furthermore, the lack of PRC volume differences or correlations between familiarity and PRC volume in patients (ps > .05) is consistent with evidence that familiarity is less severely impaired in schizophrenia (Libby et al., 2013). One limitation is the small sample size, and we also focused only on MTL regions known to be critical for recognition. Future larger scale studies that examine the role of regions outside the MTL will be important in further identifying structural brain differences related to specific components of encoding and retrieval in schizophrenia.

Role of funding source

This study was supported by NIH grants F31 MH096346 (Wang), RO1 MH059352 (Yonelinas), and R01 MH084895 (Ragland).

Contributors

WCW traced the MTLs, analyzed the data, and wrote the first draft. MEM traced the MTLs and conducted the literature review. JDR contributed to the interpretation of the results, designed the study, and reviewed the manuscript. APY contributed to the interpretation of the results and reviewed the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of Interest

The authors have no conflicts of interest to report.

Acknowledgments

We thank the participants and their families for participating in this research; and the staff of the UC Davis Imaging Research Center for assistance with data collection. The full manuscript is available online at: http://psychology.ucdavis.edu/labs/yonelinas.

http://dx.doi.org/10.1016/j.schres.2014.05.008

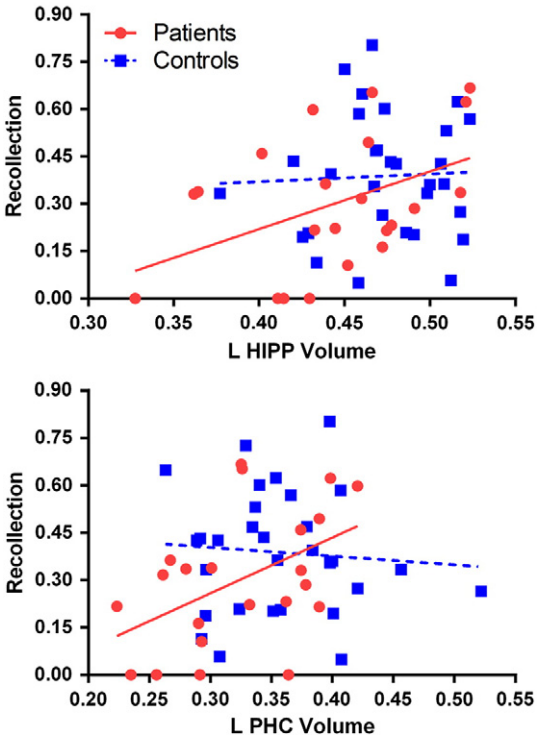

Fig. 1. Correlation between left HIPP (upper panel) and PHC (lower panel) volume and estimates of recollection in individuals with schizophrenia (red) and controls (blue). This correlation was significant in both regions for patients (ps < .05), but not controls (ps > .05). Note: MTL volumes are presented as a proportion of whole brain volume multiplied by 100.

References

Barch, D.M., Carter, C.S., MacDonald III, A.W., Braver, T.S., Cohen, J.D., 2003. Context-processing deficits in schizophrenia: Diagnostic specificity, 4-week course, and relationships to clinical symptoms. J. Abnorm. Psychol. 112 (1), 132–143.

Eichenbaum, H., Yonelinas, A.P., Ranganath, C., 2007. The medial temporal lobe and recognition memory. Ann. Rev. Neurosci. 30, 123–152.

Karnik-Henry, M.S., Wang, L., Barch, D.M., Harms, M.P., Campanella, C., Csernansky, J.G., 2012. Medial temporal lobe structure and cognition in individuals with schizophrenia and in their non-psychotic siblings. Schizophr. Res. 138 (2–3), 128–135.

Libby, L.A., Ekstrom, A.D., Ragland, J.D., Ranganath, C., 2012. Differential connectivity of perirhinal and parahippocampal cortices within human hippocampal subregions revealed by high-resolution functional imaging. J. Neurosci. 32 (19), 6550–6560.

Libby, L.A., Yonelinas, A.P., Ranganath, C., Ragland, J.D., 2013. Recollection and familiarity in schizophrenia: A quantitative review. Biol. Psychiatry 73 (10), 944–950.

Nelson, M.D., Saykin, A.J., Flashman, L.A., Riordan, H.J., 1998. Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: A meta-analytic study. Arch. Gen. Psychiatry 55 (5), 433–440.

Ragland, J.D., Laird, A.R., Ranganath, C., Blumenfeld, R.S., Gonzales, S.M., Glahn, D.C., 2009. Prefrontal activation deficits during episodic memory in schizophrenia. Am. J. Psychiatry 166 (8), 863–874.

Ragland, J.D., Ranganath, C., Ramsay, I.S., Heusser, A.C., Niendam, T.A., Yoon, J.H., Solomon, M., Carter, C.S., 2010. Effect of rule maintenance on episodic memory in schizophrenia. Biol. Psychiatry 67 (9), 154S–155S.

Sim, K., DeWitt, I., Ditman, T., Zalesak, M., Greenhouse, I., Goff, D., Weiss, A.P., Heckers, S., 2006. Hippocampal and parahippocampal volumes in schizophrenia: A structural MRI study. Schizophr. Bull. 32 (2), 332–340.

Yonelinas, A.P., 1994. Receiver-operating characteristics in recognition memory: Evidence for a dual-process model. J. Exp. Psychol. Learn. Mem. Cogn. 20 (6), 1341–1354.

Wei-Chun Wang
Center for Cognitive Neuroscience, Duke University
Corresponding author at: Duke University, LSRC Bldg Rm B254, Box 90999 Durham, NC 27708. Tel.: +1 919 668 2299.
E-mail address: ww83@duke.edu.

Maria E. Montchal
Center for Neuroscience, University of California, Davis

Andrew P. Yonelinas
Department of Psychology, University of California, Davis
Center for Mind and Brain, University of California, Davis

J. Daniel Ragland
Department of Psychiatry and Behavioral Sciences, University of California, Davis

18 February 2014