Schizophrenia Research 252 (2023) 46–47

Contents lists available at ScienceDirect

Schizophrenia Research

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

Letter to the Editor

Increased rostral medial frontal GABA+ in early psychosis is obscured by levels of negative affect

ARTICLE INFO

Keywords
Psychosis
Schizophrenia
Magnetic resonance spectroscopy
Gamma aminobutyric acid

Dysfunction of GABAergic systems has been implicated in schizophrenia and other psychosis spectrum disorders (Taylor and Tso, 2015). Using a benzodiazepine challenge in combination with fMRI, our group has demonstrated GABAergic dysfunction in schizophrenia both while patients passively viewed emotionally salient images (Taylor et al., 2014) and while performing a face processing task (Tso et al., 2015). Further, the altered blood oxygen level-dependent (BOLD) response to the benzodiazepine in schizophrenia was positively correlated with increased negative affect (NA). These emerging links between GABAergic systems, affect, and emotion processing indicate an important line of inquiry.

Here, we aimed to build upon these findings by exploring these links using Magnetic Resonance Spectroscopy (MRS). Thus far, studies of GABA concentrations in schizophrenia using MRS have reported mixed findings (Egerton et al., 2017; Nakahara et al., 2021; Simmonite et al., 2022), likely reflecting the influence of multiple factors upon GABAergic systems, such as illness stage and heterogeneous symptom presentations. To address this issue, we compared GABA+ concentrations in the rostral MFC and midline occipital cortex in patients with first episode psychosis (FEP) and individuals meeting criteria for attenuated psychosis syndrome (APS), with healthy control participants, testing the hypothesis that negative affect (NA), measured by the Psychological Stress Index (PSI9: Tso et al., 2012), would be associated with reduced GABA+ signal in the rostral MFC. Based on prior reports of increased rostral MFC GABA in early schizophrenia (Chen et al., 2017; de la Fuente-Sandoval et al., 2018; Kegeles et al., 2012), we hypothesized that GABA+ concentrations in this voxel would be increased relative to control participants, but a second process, related to affective dysregulation in the face of minor stress, would drive GABA+ levels in the opposite direction.

Study participants were 14 patients with FEP (9 men, 5 women, age = 21.64 ± 2.56), 7 individuals meeting criteria for APS (5 men, 2 women, age = 19.86 ± 3.63), and 15 demographically matched controls (10 males, 5 women, age = 21.60 ± 3.56) who were free from personal histories of psychiatric disorders or first-degree relatives with psychotic illnesses. Exclusion criteria included contraindications to MRI and history of head injury or concussions with unconsciousness lasting >5 min. Participants completed the 9-item PSI9, a validated self-report scale which measures stress sensitivity and the tendency to experience NA as a trait characteristic (Tso et al., 2012). The study and all its procedures were approved by the University of Michigan Medical School IRB.

MRS data from rostral MFC and midline occipital cortex voxels (Fig. 1A and B) were obtained using a MEGA-PRESS (Mescher et al., 1998) sequence on a 3T Phillips Ingenia system with a 32-channel head coil. Preprocessing and quantification of the edited MRS spectrum were performed using standard Gannet 3.1 processing steps (Edden et al., 2014). As the GABA signal detected at 3.00 ppm using our experimental parameters is expected to contain contributions from macromolecules and homocarnosine, we refer to it as GABA+. GABA+ concentrations were evaluated relative to the unsuppressed water signal and corrected for voxel tissue composition.

Groups differed significantly on PSI9 scores (HC_{mean} = 9.87 ± 4.09; APS_{mean} = 15.14 ± 6.07; FEP_{mean} = 19.29 ± 5.70; $F_{2,33}$ = 12.14, p < .001). Post-hoc Tukey tests revealed PSI9 scores were significantly higher in FEP compared with HC (p < .0001), but there were no differences between the APS and HC groups (p = .08), or the FEP and APS groups (p = .21). ANOVAs conducted to examine GABA+ concentrations revealed a trend toward a significant group effect in the rostral MFC (Fig. 1C; HC_{mean} = 2.16 ± 0.42; APS_{mean} = 2.04 ± 0.14; FEP_{mean} = 2.50 ± 0.53; $F_{2,28}$ = 3.04, p = .06). but no group differences in the midline occipital cortex (Fig. 1D; HC_{mean} = 3.24 ± 0.40; APS_{mean} = 3.43 ± 0.51; FEP_{mean} = 3.24 ± 0.41; $F_{2,32}$ = 0.49, p = .62). When PSI9 was included in the model to adjust for group differences in negative affect, we found a significant effect of group on rostral MFC GABA+ concentrations ($F_{2,28}$ = 4.26, p = .02). Planned comparisons revealed elevated rostral MFC GABA+ in the FEP group in comparison with the HC and APS groups (t_{27} = 2.90, p = .01). There was a trend toward elevated rostral MFC GABA+ in the APS group when compared with healthy controls (t_{27} = 2.00, p = .0548). We did not find significant group effects on occipital GABA+ ($F_{2,31}$ = 0.48, p = .62) when PSI9 was included in the model.

While limited by a modest sample size and the confound of medication, we found evidence of significantly elevated rostral MFC GABA+ in psychosis when controlling for levels of NA. When considered alongside previously published demonstrations of altered BOLD signal in response to a benzodiazepine challenge which correlate with levels of

https://doi.org/10.1016/j.schres.2022.12.017
Received 26 August 2022; Received in revised form 19 November 2022; Accepted 11 December 2022
Available online 7 January 2023

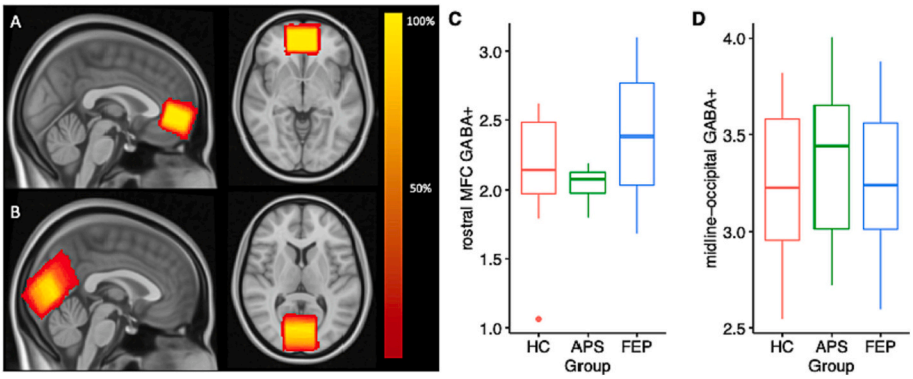

Fig. 1. Heat maps describing the spatial overlap of MRS voxels in (A) rostral MFC and (B) midline occipital cortex across all participants. Boxplots demonstrating GABA+ concentrations in (C) rostral MFC and (D) midline occipital cortex in each of the three participant groups. HC: healthy control participants, APS: attenuated psychosis syndrome; FEP: first episode psychosis. These values are uncorrected for PSI9.

NA, we suggest the presence of at least two pathological processes involving GABA in psychosis. The first is distinguished by an increase in rostral MFC GABA which occurs early in the illness and may be driven down by treatment or other factors, which has led to contradictory findings in the literature. This process may reflect a primary pathophysiological process or a compensatory response – for example, to environmental stressors. In addition, we propose a second process reflected by reduced GABA which is associated with increased negative affect and an altered BOLD response to benzodiazepine. As we note, the edited GABA signal – which we refer to as GABA+ – includes significant contributions from macromolecules and homocarnosine, a limitation which means the effect we observed could potentially be unrelated to GABA, and instead driven by other components of the signal. While more data is required to untangle these processes, and clarify GABAergic dysfunction in the psychosis spectrum, NA is a strong, transdiagnostic predictor of functional outcome, and these findings establish potential therapeutic leverage points linking GABAergic treatments, with NA as the clinical outcome.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.12.017.

References

Chen, T., Wang, Y., Zhang, J., Wang, Z., Xu, J., Li, Y., Yang, Z., Liu, D., 2017. Abnormal concentration of GABA and glutamate in the prefrontal cortex in schizophrenia.-an in vivo 1H-MRS study. Shanghai Arch. Psychiatry 29, 277–286. https://doi.org/10.11919/j.issn.1002-0829.217004.

de la Fuente-Sandoval, C., Reyes-Madrigal, F., Mao, X., León-Ortiz, P., Rodríguez-Mayoral, O., Jung-Cook, H., Solís-Vivanco, R., Graff-Guerrero, A., Shungu, D.C., 2018. Prefrontal and striatal gamma-aminobutyric acid levels and the effect of antipsychotic treatment in first-episode psychosis patients. Biol. Psychiatry 83, 475–483. https://doi.org/10.1016/j.biopsych.2017.09.028.

Edden, R.A.E., Puts, N.A.J., Harris, A.D., Barker, P.B., Evans, C.J., 2014. Gannet: a batch-processing tool for the quantitative analysis of gamma-aminobutyric acid-edited MR spectroscopy spectra. J. Magn. Reson. Imaging 40, 1445–1452. https://doi.org/10.1002/jmri.24478.

Egerton, A., Modinos, G., Ferrera, D., McGuire, P., 2017. Neuroimaging studies of GABA in schizophrenia: A systematic review with meta-analysis. Transl. Psychiatry. https://doi.org/10.1038/tp.2017.124.

Kegeles, L.S., Mao, X., Stanford, A.D., Girgis, R., Ojeil, N., Xu, X., Gil, R., Slifstein, M., Abi-Dargham, A., Lisanby, S.H., Shungu, D.C., 2012. Elevated prefrontal cortex γ-aminobutyric acid and glutamate-glutamine levels in schizophrenia measured in vivo with proton magnetic resonance spectroscopy. Arch. Gen. Psychiatry 69, 449–459. https://doi.org/10.1001/archgenpsychiatry.2011.1519.

Mescher, M., Merkle, H., Kirsch, J., Garwood, M., Gruetter, R., 1998. Simultaneous in vivo spectral editing and water suppression. NMR Biomed. 11, 266–272. https://doi.org/10.1002/(SICI)1099-1492(199810)11:6<266::AID-NBM530>3.0.CO;2-J.

Nakahara, T., Tsugawa, S., Noda, Y., Ueno, F., Honda, S., Kinjo, M., Segawa, H., Hondo, N., Mori, Y., Watanabe, H., Nakahara, K., Yoshida, K., Wada, M., Tarumi, R., Iwata, Y., Plitman, E., Moriguchi, S., de la Fuente-Sandoval, C., Uchida, H., Mimura, M., Graff-Guerrero, A., Nakajima, S., 2021. Glutamatergic and GABAergic metabolite levels in schizophrenia-spectrum disorders: a meta-analysis of 1H-magnetic resonance spectroscopy studies. Mol. Psychiatry. https://doi.org/10.1038/s41380-021-01297-6.

Simmonite, M., Steeby, C.J., Taylor, S.F., 2022. Medial frontal cortex gamma-aminobutyric acid concentrations in psychosis spectrum and mood disorders: a META-analysis of proton magnetic resonance spectroscopy studies. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2022.08.004.

Taylor, S.F., Demeter, E., Phan, K.L., Tso, I.F., Welsh, R.C., 2014. Abnormal GABAergic function and negative affect in schizophrenia. Neuropsychopharmacology 39, 1000–1008. https://doi.org/10.1038/npp.2013.300.

Taylor, S.F., Tso, I.F., 2015. GABA abnormalities in schizophrenia: a methodological review of in vivo studies. Schizophr. Res. https://doi.org/10.1016/j.schres.2014.10.011.

Tso, I.F., Fang, Y., Phan, K.L., Welsh, R.C., Taylor, S.F., 2015. Abnormal GABAergic function and face processing in schizophrenia: a pharmacologic-fMRI study. Schizophr. Res. 168, 338–344. https://doi.org/10.1016/j.schres.2015.08.022.

Tso, I.F., Grove, T.B., Taylor, S.F., 2012. Self-assessment of psychological stress in schizophrenia: preliminary evidence of reliability and validity. Psychiatry Res. 195, 39–44. https://doi.org/10.1016/j.psychres.2011.07.009.

Molly Simmonite[a,b,*], Beier Yao[c], Robert C. Welsh[d], Stephan F. Taylor[a]

[a] *Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA*

[b] *Department of Psychology, University of Michigan, Ann Arbor, MI, USA*

[c] *Department of Psychology, Michigan State University, East Lansing, MI, USA*

[d] *Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA*

[*] Corresponding author at: Department of Psychiatry, Rachel Upjohn Building, 4350 Plymouth Road, Ann Arbor, MI 48109, USA.
E-mail address: mollysimmonite@gmail.com (M. Simmonite).