

Relationship between cortical glutamatergic metabolite levels and hippocampal activity in schizotypy

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To the Editors:

The development of psychotic symptoms has been associated with elevated hippocampal regional cerebral blood flow (rCBF) and glutamatergic metabolite dysfunction (Lieberman et al., 2018). Preclinical evidence suggests that hippocampal hyperactivity may arise from glutamatergic dysfunction, associated with a reduction in GABAergic inhibition or hypofunction of the N-methyl D-aspartate glutamate receptor (Abbott and Bustillo, 2006). However, whether this mechanism translates to humans remains unclear.

The continuum model of psychosis proposes a dimensional continuity between subclinical psychotic-like experiences in healthy individuals (termed schizotypy) and psychotic symptoms in patients with schizophrenia spectrum disorders (Nelson, et al., 2013). With a large body of evidence supporting shared genetic, environmental, neurobiological and cognitive-emotional factors between them (Nelson, et al., 2013), the schizotypy framework enables the investigation of neurobiological mechanisms involved in psychotic-like experiences in healthy individuals, without potential confounders of neuroimaging studies in schizophrenia samples (Millman, 2018).

Previous work from our group identified higher hippocampal rCBF in individuals with high schizotypy (HS, Modinos et al., 2018a), supporting the notion that this might be a pivotal characteristic of the extended psychosis phenotype. Previous proton magnetic

resonance spectroscopy ($^1\text{H-MRS}$) studies reported increased glutamatergic metabolite levels in the ACC in clinical high-risk (CHR, Merritt et al., 2016) and genetic high-risk individuals (Wang et al., 2020). While we did not find evidence of altered ACC glutamate levels in HS (Modinos et al., 2017), the nature of the association between rCBF increases and ACC glutamate levels in schizotypy remains to be examined. Our study sought to address this issue by combining $^1\text{H-MRS}$ and arterial spin labeling (ASL) to test the hypothesis that individuals with HS would show a negative relationship between ACC glutamatergic metabolite levels and hippocampal rCBF relative to individuals with low schizotypy (LS), based on previous evidence of a positive correlation between ACC GABA levels and hippocampal rCBF in individuals at CHR (Modinos et al. 2018b).

The study was approved through the King's College London (KCL) Research Ethics Committee. All participants gave written informed consent to the study protocol. Twenty-one healthy individuals with HS and 22 with LS were enrolled based on their scores on the unusual experiences (UE) subscale of the Oxford and Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason et al., 2005). Individuals with UE scores ≥ 7 were recruited in the HS group, and individuals with $\text{UE} < 2$ in the LS group.

Both $^1\text{H-MRS}$ and ASL scans were acquired during the same session on a Discovery MR750 3T system at KCL. The full procedure is described in detail in the Supplementary Material.

Individual glutamate or Glx values were entered as regressors in two separate voxel-wise ANCOVAs, to analyze group differences in the relationship between glutamate (or Glx) and hippocampal rCBF in HS compared to LS individuals. We used small volume correction for region-of-interest analysis, with pre-defined anatomical masks of the bilateral hippocampus and the ACC. The ANCOVAs controlled for age, sex, cigarettes, caffeine, cannabis use and mean global rCBF. Effects were considered significant after voxel-wise family-wise error correction of $p < 0.05$. Finally, a third voxel-wise ANCOVA was specified to analyze group differences in the relationship between rCBF and schizotypy severity, using the O-LIFE total score as regressor.

As expected by the study design, the O-LIFE total scores differed between the two groups. There were no significant group differences in cigarettes, caffeine or cannabis use (all $p > 0.05$, Table S1).

We identified a significant Group x ACC glutamate x rCBF interaction ($p_{FWE} = 0.03$), which was driven by a negative association in HS individuals ($p_{FWE} = 0.02$) which was absent in LS (Figure 1A). A negative association between ACC Glx and hippocampal rCBF was also identified in the HS sample ($p_{FWE} = 0.01$) (Figure 1B). Finally, we observed a significant Group x ACC rCBF x O-LIFE total score interaction ($p_{FWE} = 0.04$), driven by a negative association in the HS group ($p_{FWE} = 0.002$) which was different from the LS group (Figure 1C).

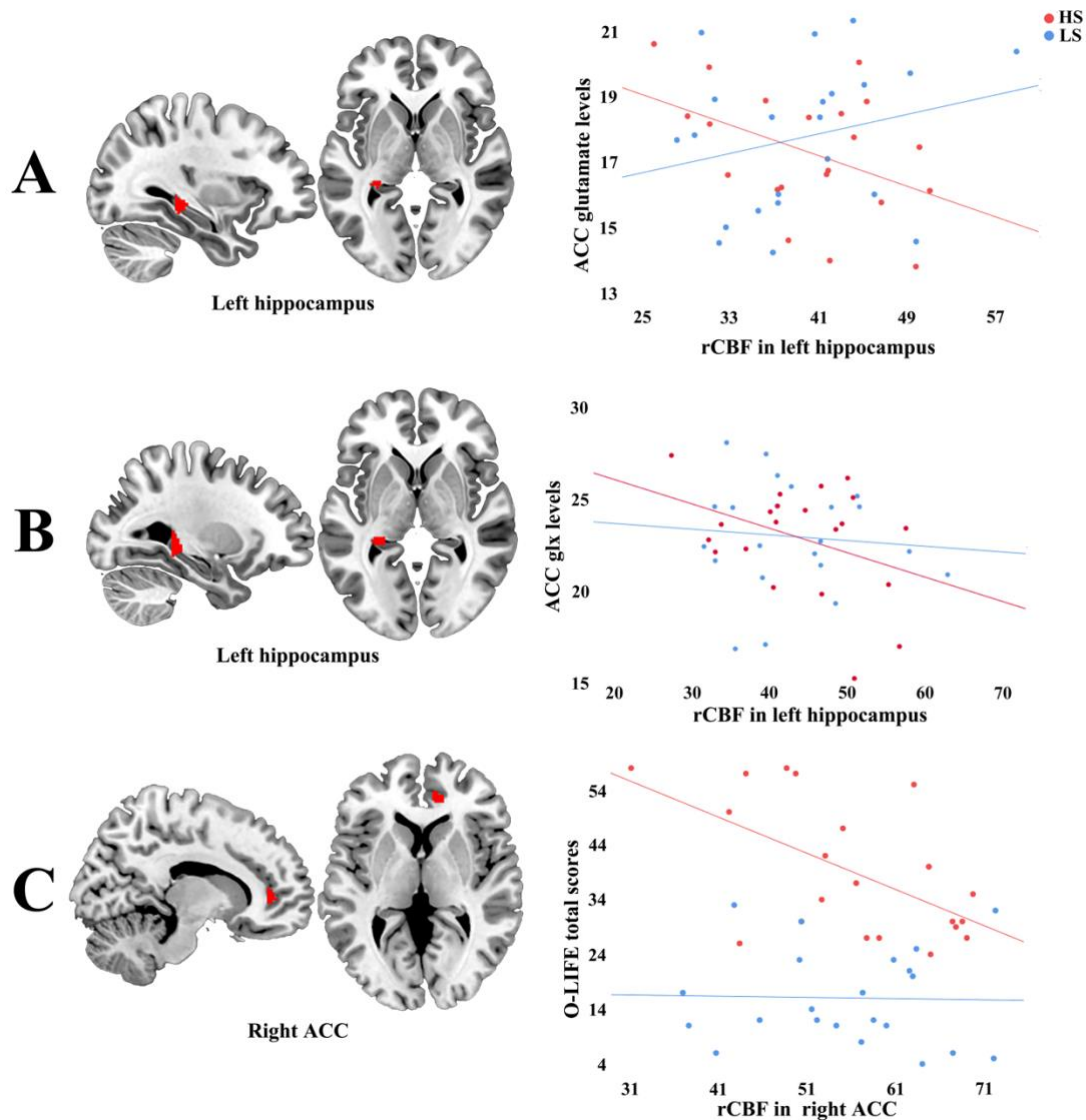


Figure 1. (A) ACC Glutamate and hippocampal rCBF associations by group. Left, group interaction in left hippocampus overlaid on standard brain template. Right, scatterplot showing significantly different regression slopes between participants with high schizotypy (HS) vs. participants with low schizotypy (LS) (xyz: -32, -32, -4; k=45; $t=3.64$, $p_{FWE}=0.03$; and individuals with HS showed a negative association between ACC glutamate levels and hippocampal rCBF; xyz: -32, -32, -4; k=82; $t=3.97$, $p_{FWE}=0.02$). (B) ACC Glx and hippocampal rCBF associations by group. Left, group interaction in left hippocampus overlaid on standard brain template. Right, scatterplot showing trend-level significance for different regression slopes between participants with HS and with LS (xyz: -30, -34, 0; k=53; $t=3.30$, $p_{FWE}=0.07$; and individuals with HS showed a negative association between ACC Glx levels and hippocampal rCBF; xyz: -28, -34, 0; k=53; $t=4.02$, $p_{FWE}=0.01$). (C) O-LIFE total scores and ACC rCBF associations by group. Left, group interaction in right ACC overlaid on standard brain template. Right, scatterplot showing significantly different regression slopes between participants with HS vs. LS (xyz: 12, 42, 0; k=53; $t=3.59$, $p_{FWE}=0.04$; and individuals with HS showed a negative association between rCBF in the ACC and O-LIFE total

scores; xyz: 10, 54, 10; k=161; t=4.95, pFWE=0.002).

Our main finding was that glutamate and Glx levels in the ACC were negatively associated with hippocampal rCBF in individuals with HS. ACC glutamate or Glx levels did not differ significantly between the high and low schizotypy groups in our previous studies on this sample (Modinos et al., 2017; Modinos et al., 2018b), but hippocampal rCBF was increased in HS (Modinos et al. 2018a). Within the broader continuum of psychosis, increased hippocampal rCBF was also found in CHR individuals and patients with schizophrenia (Schobel et al., 2013; Allen et al., 2018). Our findings suggest that such hippocampal dysfunction may be partially related to cortical glutamatergic dysfunction (Lieberman et al. 2018) in the context of schizotypy.

The observed negative association between hippocampal rCBF and ACC glutamate/Glx levels may suggest a bottom-up process by which hippocampal hyperperfusion disrupts prefrontal function in the context of psychotic-like experiences, as a feed-forward process (Kraguljac et al., 2017). Prior research indicated that high scores on positive schizotypy scales and rCBF deficits in the prefrontal cortex reflect the biological-genetic vulnerability to schizophrenia (de Zwarte et al., 2019). An alternative explanation may be that these findings reflect a level of resilience to a genetic- or environment-related liability for psychiatric outcomes, enabling psychiatrically resilient high schizotypes to effectively compensate.

Our observed interaction effects were located within the posterior part of the

hippocampus. Prior ASL research in CHR individuals (Allen et al., 2018) reported rCBF increases in the anterior hippocampus, as well as our own previous study in HS individuals (Modinos et al. 2018a). Structural effects in anterior versus posterior hippocampus have been postulated to play a distinct role in early psychosis and schizotypy (McHugo et al., 2018). Future studies assessing interactions between hippocampal rCBF and glutamatergic metabolite levels across different stages of the psychosis continuum and within hippocampal subfields, including CHR and first-episode psychosis patients, are warranted to expand on the potential functional segregation of these effects. Furthermore, a limitation of our study is that the sample size was relatively small.

The present study suggests that levels of cortical glutamatergic metabolites are associated with hippocampal rCBF in high schizotypy. These results expand our understanding of the role of hippocampal dysfunction in the extended psychosis spectrum, and may also indicate potential neurobiological mechanisms of resilience.

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Contributions

Dr. Wang has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, wrote the first draft of the manuscript. Dr. Egerton, Dr. McMullen, Ms. McLaughlin, Dr. Kumari, Dr. Lythgoe, Dr. Barker, Dr. Williams, Dr. Zelaya managed the data collection and helped for data analysis and manuscript revision. Dr. Modinos designed the study, obtained funding, and conducted critical revision of the manuscript for important intellectual content. All authors contributed to and have approved the final manuscript.

Conflict of interest

GJB received honoraria for teaching from General Electric Healthcare at the time of this study. The other authors declare no competing financial interests.

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