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A letter to the editor: The Effects of Alcohol Use on Brain Glutamate in First Episode Psychosis

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To The Editors,

Both alcohol use and psychosis have been independently associated with changes in brain glutamate levels, but whether alcohol use impacts brain glutamate levels in people with psychosis is unknown.

Meta-analyses of proton magnetic resonance imaging (^{1}H-MRS) studies have shown that compared to healthy controls, glutamate is reduced in the medial frontal cortex (mFC)/ anterior cingulate cortex (ACC) and in the thalamus in schizophrenia (Merritt et al., 2021; Nakahara et al., 2022). However, mFC glutamate may be elevated in first episode psychosis (FEP), treatment resistance (TRS) or in greater illness severity (Merritt et al., 2021; Nakahara et al., 2022). Separate research has linked elevations in glutamate in the ACC and thalamus with alcohol use. Compared to healthy controls, individuals with alcohol dependency show elevations in ACC glutamate 24 hours into withdrawal (Hermann et al., 2012) and decreases at 9 days into abstinence before normalising within 4-5 weeks (Mon et al., 2012). Thalamic glutamate levels may also increase during acute withdrawal (Monnig et al., 2019) and these elevations may be positively related to the frequency of drinking in the last 90 days (Wiers et al., 2020). Overlapping glutamatergic pathophysiology could mean that glutamate dysfunction in schizophrenia could be exacerbated by the effects of alcohol use. We previously detected higher ACC glutamate levels in patients with TRS who had consumed alcohol in the 7 days prior to scan (McQueen et al., 2021). However, these patients had been taking antipsychotics for several years, which may also impact on glutamate or alcohol use (Green et al., 2008; Merritt et al., 2021).

We therefore examined the effects of alcohol consumption on glutamate levels in minimally-medicated FEP. We hypothesised that glutamate in the ACC and the thalamus would be higher in participants who had consumed alcohol in the last 7 days compared to those who had not. Secondly, we hypothesised that there would be a positive correlation between the number of days with alcohol use in the last 30 days and glutamate levels.

Methods

The data for this study were collected as part of the OPTiMiSE clinical trial (www.optimisetrial.eu; EudraCT: 2010-02185; clinical-trials.gov: NCT01248195). Participants were required to be 18-40 years of age with a DSM-IV diagnosis of schizophrenia, as previously described (Egerton et al., 2018; Kahn et al., 2018). Previous alcohol abuse and dependence were assessed using the MINI neuropsychiatric interview (Sheehan et al., 1998) and participants provided information about their recent alcohol consumption. Groups were defined as Alcohol+ if they had consumed alcohol in the last 7 days and Alcohol- if they had not.

^{1}H-MRS scans were acquired at 3 Tesla at 3 study sites, as previously reported (Egerton et al., 2018). Spectra were analysed using LC Model version 6.3-1L (Provencher, 1993). Glutamate values were corrected using voxel tissue composition (Glu_{corr}) (Egerton et al., 2021). To account for site effects, values were converted into Z scores before analysis. Data were analysed with independent samples t-tests, linear regression and general linear models as appropriate, statistical significance was taken at $p<0.05$.

Results

Demographic and clinical data are presented in Supplemental Table 1. ^{1}H-MRS quality measures, voxel tissue composition and metabolite levels are presented in supplemental Tables 2-5.

There was no significant difference in Glu_{corr} levels between the Alcohol+ and Alcohol- groups in the ACC ($T(52) = 0.05$, $P = 0.96$) or thalamus ($T(47) = -0.69$, $P = 0.49$) (Figure 1 Supplemental Table 5). Similarly, there was no significant group differences in the other ^{1}H-MRS metabolites (Supplemental Table 5). All comparisons remained non-significant when controlling for GM ratio, cannabis use or other substance use (Supplemental Table 6). Associations between Glu_{corr} and alcohol consumption in the last 30 days were non-significant in the ACC ($\beta = -0.032$, $P = 0.82$) and thalamus ($\beta = 0.12$, $P = 0.45$) and remained non-significant when controlling for GM ratio (ACC: ($r(51) = 0.09$, $P = 0.52$, Supplemental Appendix 1), thalamus: $r(46) = 0.111$, $P = 0.45$). Associations were also non-significant for other ^{1}H-MRS metabolites (Supplemental Table 7).

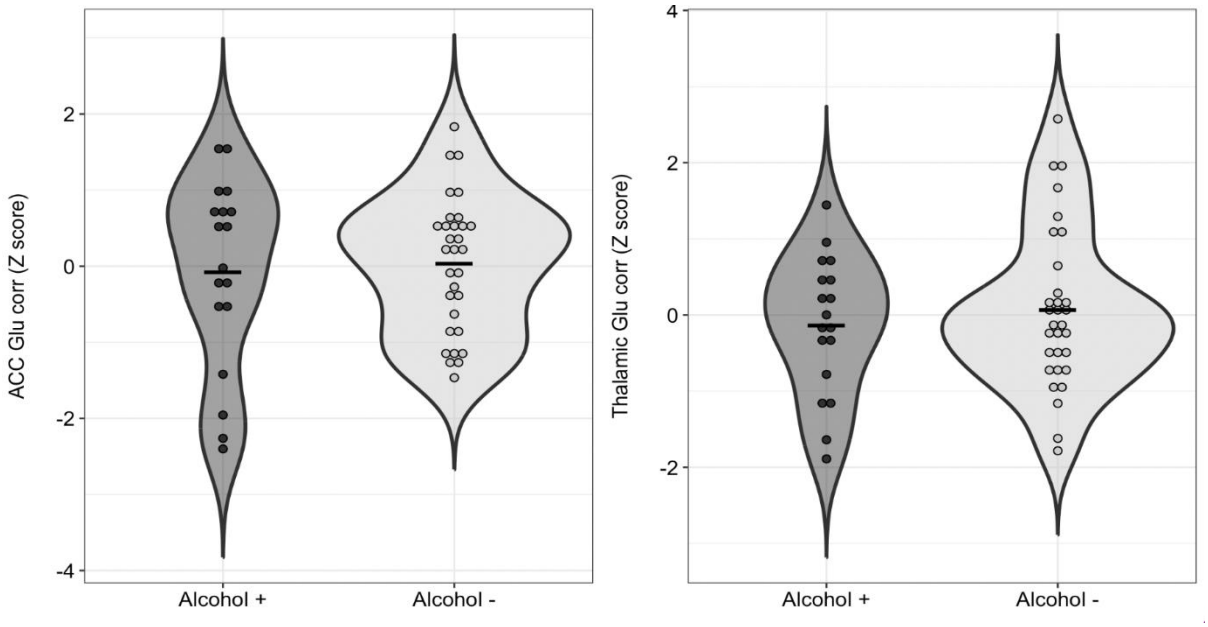

Figure 1

Glutamate (Glu_{corr}) in the ACC and thalamus in the Alcohol+ and Alcohol– groups. Glu_{corr} values are presented as Z scores, which did not differ between groups. The black bar represents the mean.

Discussion

We did not detect an effect of recent alcohol use on glutamate levels in the ACC or thalamus in individuals with minimally-medicated FEP. In relation to previous findings of glutamate elevations in patients with TRS who had consumed alcohol in the last 7 days (McQueen et al., 2021) or relating to alcohol use or withdrawal (Monnig et al., 2019; Wiers et al., 2020 (Hermann et al., 2012), it could be that glutamate mechanisms are more sensitive to the effects of alcohol in TRS compared to FEP, or that changes in glutamate are only apparent with extreme alcohol use and during the early stages of alcohol withdrawal. Some studies have found a positive correlation between glutamate levels with the severity of drinking habits (Wiers et al., 2020), whereas other studies have found negative associations (Ende et al., 2013; Prisciandro et al., 2016), these differences in findings may relate to whether patients were alcohol dependent. A further consideration is the difficulty in accurately estimating alcohol consumption via self-report.

While this study did not find any evidence that recent alcohol intake impacts on glutamate levels in the ACC or thalamus in FEP, our results provide some confidence that previous work characterising glutamate dysfunction in the ACC and thalamus in FEP are unlikely to be confounded by recent alcohol consumption (Merritt et al., 2021; Nakahara et al., 2022), although this may not be the case in later illness stages such as TRS (McQueen et al., 2021). Future studies may investigate the relationships between alcohol use and brain glutamate levels in patients with schizophrenia with and without comorbid alcohol dependency and over the course of schizophrenia.

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