Association between increased anterior cingulate glutamate and psychotic-like experiences, but not autistic traits in healthy volunteers

Klinikum rechts der Isar
Technische Universität München

Technische Universität München

Max Weber-Programm Bayern

Verena F. Demler[1], Elisabeth F. Sterner[1], Martin Wilson[2], Claus Zimmer[1] & Franziska Knolle[1,3] ✉

TUM Graduate School

[1] Department of Diagnostic and Interventional Neuroradiology, Klinikum rechts der Isar, Technical University of Munich, Germany;
[2] Centre for Human Brain Health and School of Psychology, University of Birmingham, Birmingham, UK; [3] Department of Psychiatry, University of Cambridge, Cambridge, UK; Contact: franziska.knolle@tum.de

Background

- Schizophrenia spectrum disorder and autism spectrum disorder:
  - share environmental risk factors, genetic predispositions & neuronal abnormalities [1,2]
  - show similar cognitive deficits in working memory, perspective-taking, or response inhibition [3]
- Shared abnormalities are already present in subclinical traits [4,5]
- Underlying neuronal similarities and differences could be explained by changes in the inhibitory GABAergic and the excitatory glutamatergic system [6,7]
- Only few studies explored changes of neurotransmitter concentrations associated to psychotic-like experiences (PLE) and autistic traits. [8-10]

Aims of our Study

- Investigate the interaction of glutamate (Glu) concentrations in five brain areas (ACC, left/right DLPFC, left/right putamen) and their association with autistic traits and PLE in healthy individuals.
- Hypothesis: Increased ACC Glu and decreased DLPFC/putamen Glu would relate to PLE, while reduced ACC Glu and increased putamen Glu would be linked to autistic traits

Methods

Participants and subclinical questionnaires:

- 53 healthy individuals: 26 women, aged 18-35 years
- PLE (Schizotypal Personality Questionnaire) [11]
- Autistic traits (Autism Spectrum Quotient) [12]

Figure 1: Distribution of the clinical scores

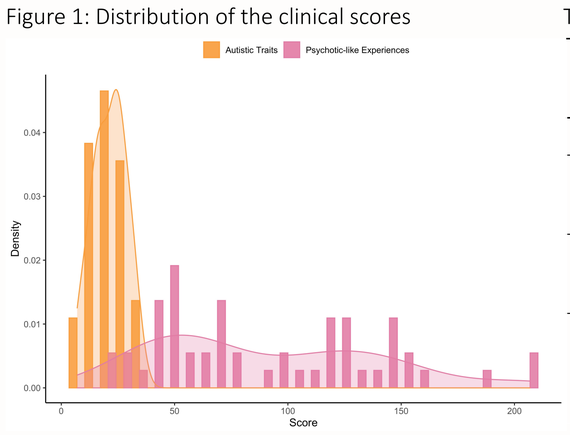


Table 1: Demographic data and clinical scores

	Female (n = 26)	Male (n = 27)	P-value[1]	W
Age	23.31 (3.54)	23.93 (4.21)	0.7266	331
SPQ: total score (/296)	97.00 (45.54)	84.26 (52.36)	0.2547	415
AQ: total score (/50)	21.65 (6.99)	20.96 (7.65)	0.7017	373

Note: Values are mean (SD); SPQ, Schizotypal Personality Questionnaire; AQ, Autism Spectrum Quotient
[1]Wilcoxon rank sum test

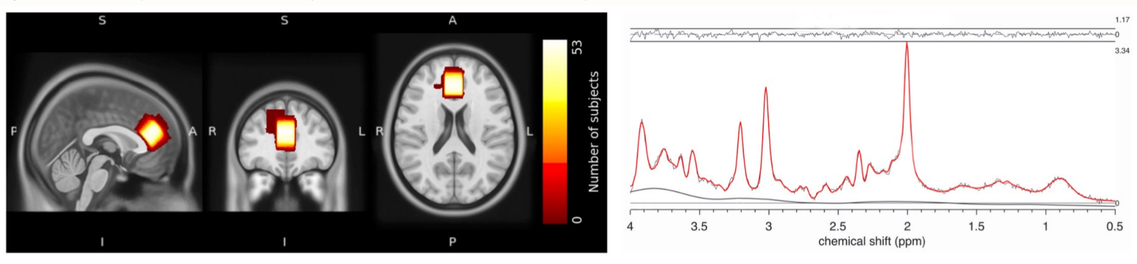
Note: Distribution of the autistic traits (AQ) and the PLE (SPQ) marked by the different colours for n=53.

Magnetic resonance spectroscopy (^{1}H-MRS):

- Glu concentrations in the anterior cingulate cortex (ACC), the left/right putamen, and left/right dorsolateral prefrontal cortex (DLPFC)
- Analysed our data in Osprey [13], using the LCModel implementation [14,15] for fitting and quantification
- Spectral exclusion criteria were:
  - Visual failure of the fitting algorithm
  - Resultant FWHM > 13 Hz in ACC and DLPFC or FWHM > 10 Hz in Putamen [16]
  - CRLB > 20% of Glu concentration

  → Levels of Glu could not be reliably estimated in the putamen

Figure 2: Voxel placement and representative fitted ^{1}H-MRS spectrum of the ACC



Note: The colours indicate the areas covered by the subjects' individually placed MRS voxels, which were standardised with SPM12, overlapped in MRIcroGL and visualised in FSLeyes.

Association between Glu and clinical scores

- Two linear regression models: Do Glu levels from the ACC, left DLPFC, and right DLPFC predict PLE or autistic traits?
- Logistic regression analyses: Can these parameters also predict high and low risk group; Median split of PLE (75) and autistic traits (22)
- Both Models have been corrected for age and sex.

Results

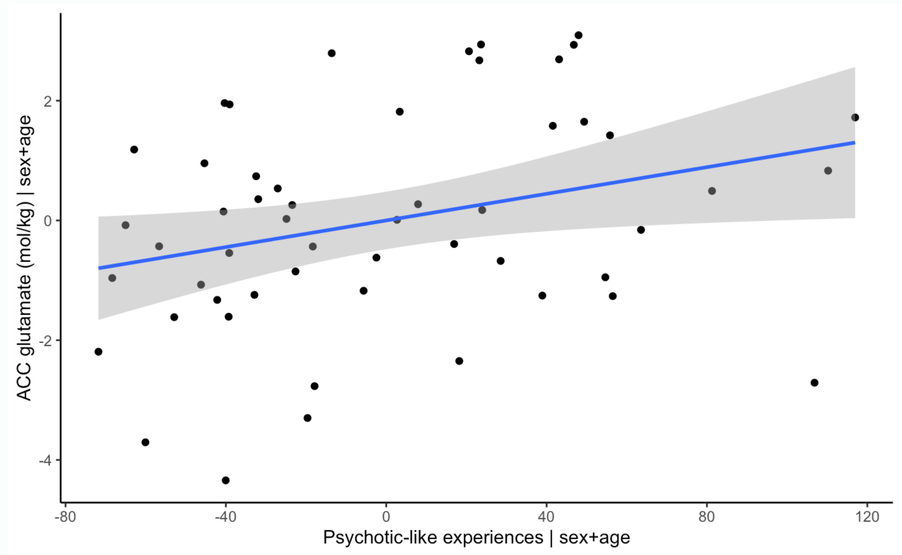
Linear Regression: PLE ~ Glu DLPFC_R + Glu DLPFC L + Glu ACC + age + sex

→ Overall regression was not significant (R2=0.15, F(5,46)=1.63, p=0.17)

→ Levels of Glu in the ACC significantly predicted PLE (β=9.72, 95% CI [2.17, 17.27], p=0.013)

→ Autistic traits were not predicted by levels of Glu

Figure 3: Visualization of association between levels of Glu in ACC and PLE, corrected for age and sex

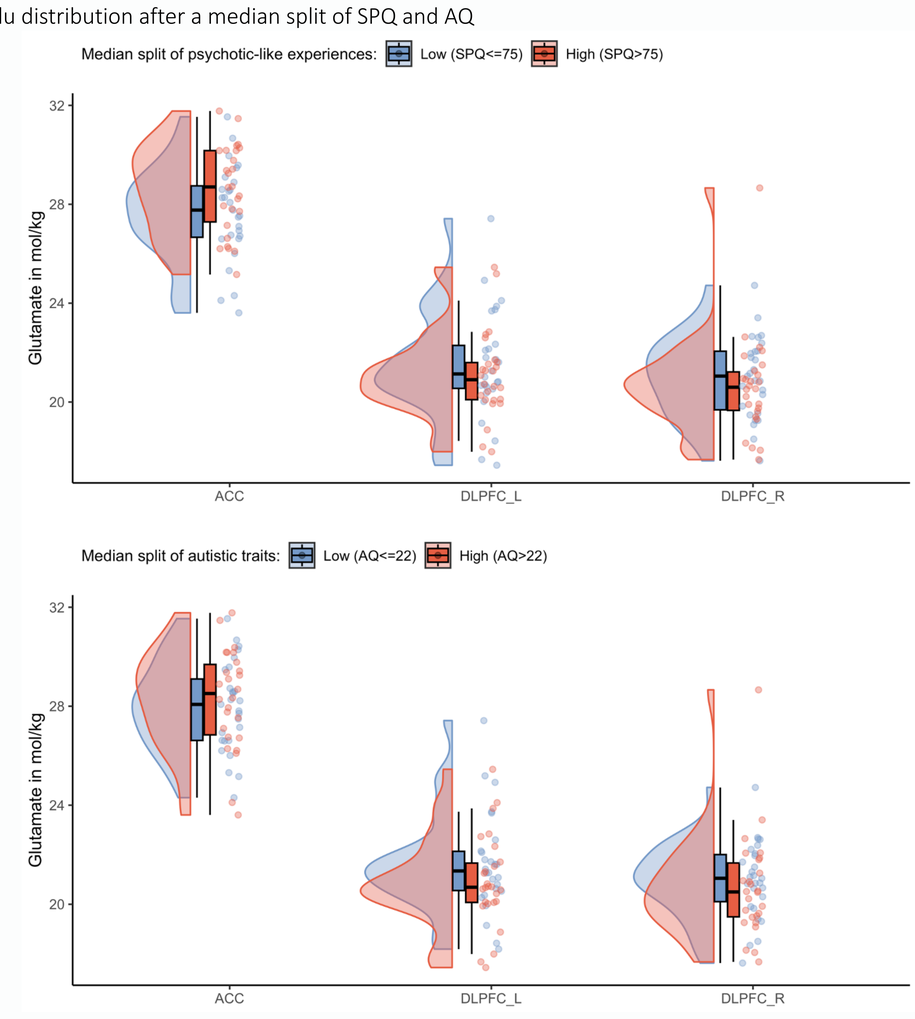


Binomial logistic regression:

PLE-group ~ Glu DLPFCR + Glu DLPFC L + Glu ACC + age + sex

→ Odds of an individual belonging to the high PLE group increased by 33.1% (β=0.49, 95% CI [0.01, 2.70], p=0.014) for a one-unit increase in ACC Glu (holding all other predictor variables constant)

Figure 4: Glu distribution after a median split of SPQ and AQ



Note: Differences of the Glu levels in the ACC, left and right DLPFC after a **(A)** Median split of PLE with a median of SPQ = 75. **(B)** Median split of autistic traits with a median of AQ = 22.

Discussion & Conclusion

- ACC Glu concentrations predicted PLE in healthy individuals
- ACC Glu concentrations contributed significantly to the determination of group status (i.e., low PLE vs high PLE) when applying a median split to the clinical data
- We did not find these results for autistic traits or Glu concentrations of DPLFC

Taken together, this study provides evidence that glutamate levels in the ACC are specifically linked to the expression of psychotic-like experiences and may be a potential candidate for identifying early-risk individuals prone to developing psychotic-like experiences.

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