

Glutamate, contextual insensitivity and disorganised speech in first-episode schizophrenia: A 7-Tesla MRS study



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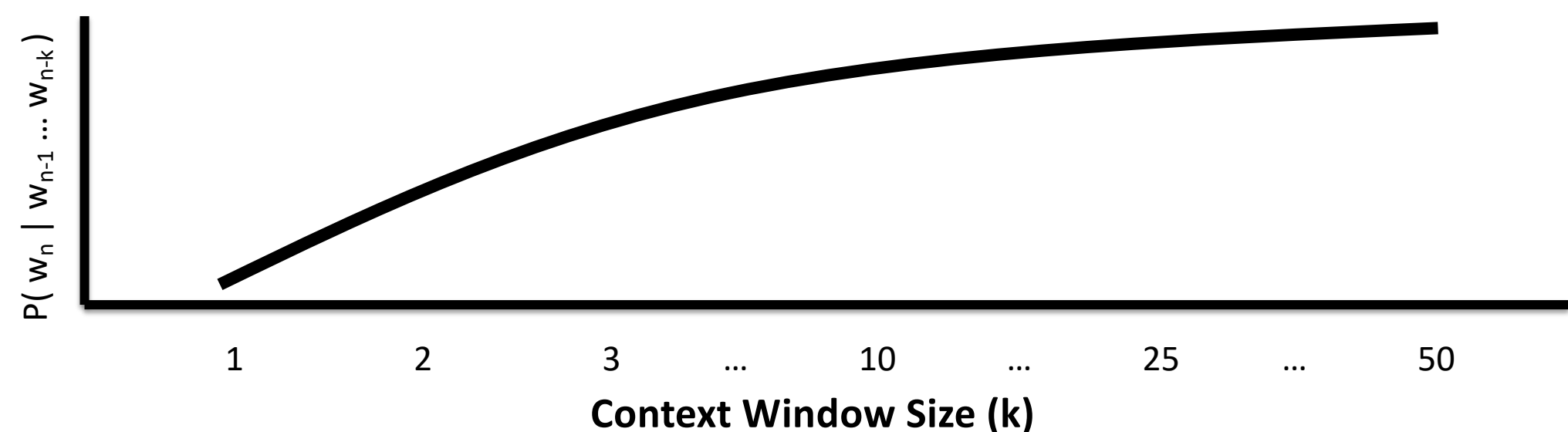
Background

- Context processing is the foundation of language comprehension and production. Linguistic context means the preceding information in a discourse that affects the processing of an incoming word. In a more neurocentric term, it was described as “any information that is used to modulate the strength with which a pyramidal cell ... transmits the information to which it is selectively sensitive.”¹
- Patients with schizophrenia presented deficits in context processing, characterized by a diminished use of preceding linguistic information to modulate the processing of incoming words. This deficit is part of the symptom domain **thought disorganization**, one of the most prominent feature in early-stage schizophrenia. However, **the neural basis of context processing deficit in schizophrenia remains poorly understood**.
- Glutamate, the major excitatory neurotransmitter in the brain, has long been proposed as an important molecule in the pathophysiology of schizophrenia².
- Genetic variants that disrupt glutamatergic pathways are associated with an increased risk of schizophrenia.
- Neuroimaging studies have also found reduced glutamate levels in frontal regions in established schizophrenia, especially the anterior cingulate cortex.

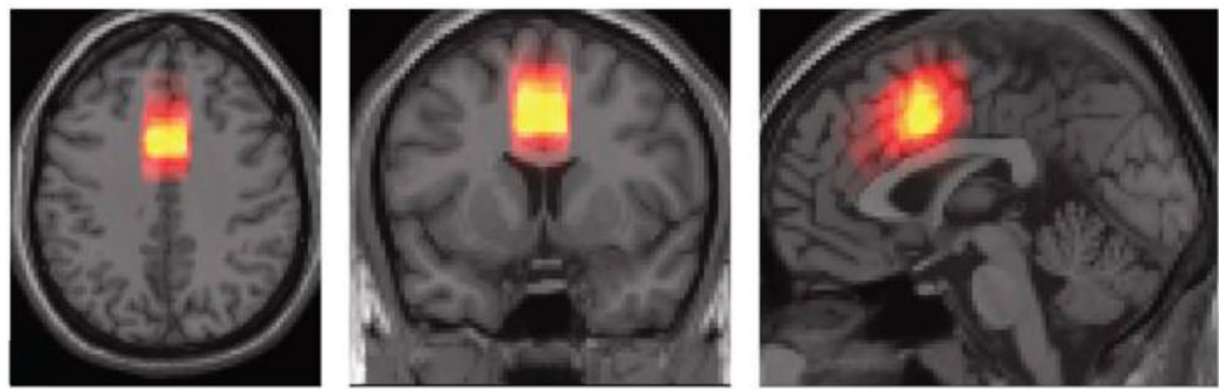
We hypothesized that glutamate in the dorsal anterior cingulate cortex may underlie the deficits in context processing in schizophrenia. We investigated their relationship in untreated patients **with first-episode psychosis**.

Methods

- To quantify context processing deficit, we computed **contextual sensitivity** of each participant, which measures how much a word is influenced by previous linguistic context. It is defined as the slope of lexical probability vs. context window size (1-50 preceding words). Lexical probability is computed by GPT-3, defined as how predictable a word is based on its preceding words (Sharpe et al., 2024)³.



- Magnetic resonance spectroscopy (MRS) noninvasively detects the metabolite (glutamate) concentration. We used a 7T head-only MRI scanner and placed a 2.0 × 2.0 × 2.0 cm (8 cm³) voxel in the bilateral dorsal anterior cingulate cortex (dACC) (Pan et al., 2021)⁴.



- Table of participant inclusion. Patients and healthy controls don't significantly differ in age, sex, or parental socioeconomic status.

Variables	Healthy controls	First-episode psychosis
N	33	39
Age	21.70 (3.32)	22.41 (4.53)
Sex	22 M, 11 F	33 M, 6 F
Parental Socioeconomic status	3.21 (1.39)	3.67 (1.24)
Lifetime antipsychotic exposure	NA	All <= 14 days

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Results

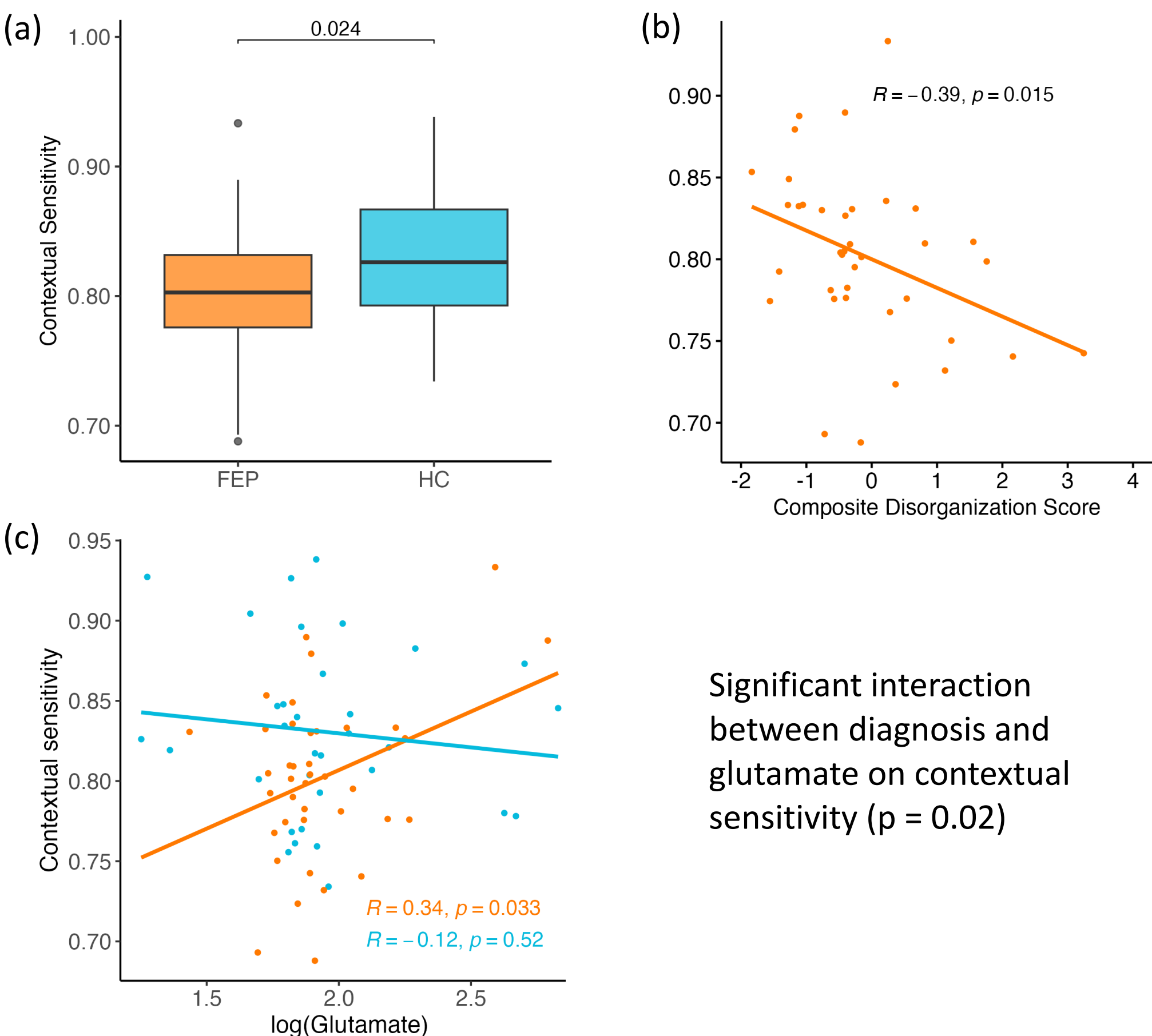


Figure: (a) Contextual sensitivity is lower in FEP (mean = 0.80, SD = 0.052) than HC (mean = 0.83, SD = 0.054). (b) Contextual sensitivity grows worse with more severe disorganization symptom (the composite score is derived from four clinical and language variables using factor analysis). (c) Patients with psychosis are more likely to have low contextual sensitivity when their glutamate concentration is low.

Variables controlled for	Stats of contextual sensitivity
Other clinical variables: TLI disorganization, TLI impoverishment, SOFAS, PANSS-8 total	$p = 0.043, \beta = 0.40$
Semantics/syntax variables: Analytic Thinking Index, a connective factor, semantic similarity, type-token ratio, givenness, overall syntactic complexity	$p = 0.047, \beta = 0.39$
Lexical variables (word types): Linguistic, Cognitive, Affect, Time, Perception	$p = 0.013, \beta = 0.45$

Table: Glutamate continues to correlate with contextual sensitivity after controlling for three sets of clinical and linguistic variables from our previous studies, and does not correlate with other variables.

Discussion

- Contextual sensitivity, an easily obtained speech measurement, is related to dACC glutamate level. It could potentially serve as a biomarker to assess disorganization symptom in early stage of schizophrenia, and detect and predict illness outcomes.
- Our finding that the glutamatergic dysfunction in schizophrenia varies with the severity of contextual insensitivity supports the previous argument that glutamate underlies disorganization symptoms in schizophrenia.

References

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