



## Review article

# Neurofunctional correlates of glutamate and GABA imbalance in psychosis: A systematic review

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## ABSTRACT

Glutamatergic and GABAergic dysfunction are implicated in the pathophysiology of schizophrenia. Previous work has shown relationships between glutamate, GABA, and brain activity in healthy volunteers. We conducted a systematic review to evaluate whether these relationships are disrupted in psychosis. Primary outcomes were the relationship between metabolite levels and fMRI BOLD response in psychosis relative to healthy volunteers. 17 case-control studies met inclusion criteria (594 patients and 538 healthy volunteers). Replicated findings included that in psychosis, positive associations between ACC glutamate levels and brain activity are reduced during resting state conditions and increased during cognitive control tasks, and negative relationships between GABA and local activation in the ACC are reduced. There was evidence that antipsychotic medication may alter the relationship between glutamate levels and brain activity. Emerging literature is providing insights into disrupted relationships between neurometabolites and brain activity in psychosis. Future studies determining a link to clinical variables may develop this approach for biomarker applications, including development or targeting novel therapeutics.

## 1. Introduction

Glutamatergic dysfunction and N-methyl-D-aspartate (NMDA) receptor hypofunction is implicated in the pathophysiology of schizophrenia (Coyle, 2006; McCutcheon et al., 2020; Egerton et al., 2020). This is supported by multiple lines of evidence, including meta-analyses of proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS) studies finding regional differences in brain glutamate metabolites in individuals with psychosis compared to healthy volunteers (Merritt et al., 2016; Merritt et al., 2021; Nakahara et al., 2021). As well as observations that administration of the NMDA receptor antagonist ketamine can induce psychotomimetic effects in healthy volunteers and exacerbate symptoms in patients with schizophrenia (Beck et al., 2020; Moghaddam and Javitt, 2012; Javitt and Zukin, 1991).

Complementary research conceptualises schizophrenia as a disorder of brain functional dysconnectivity (Friston et al., 2016b). Functional magnetic resonance imaging (fMRI) studies have measured resting (Sheffield and Barch, 2016) and task-related (Mwansisya et al., 2017) activity, within or between large-scale brain networks (Friston and Frith, 1995) including the salience network (Palaniyappan and Liddle, 2012) and the default mode network (Hu et al., 2017). As the major regulators of neuronal activity, underlying pathophysiology in excitatory glutamatergic and inhibitory GABAergic activity in schizophrenia is likely to result in emergent network functional dysconnectivity. This is evidenced by studies that have shown altering excitation/inhibition balance induces measurable changes in fMRI signal, for example direct manipulation of the activity of excitatory or inhibitory neurons in rodents (Moon et al., 2021) or by pharmacological challenge in humans

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(Larsen et al., 2021).

Meta-analyses of  $^1\text{H}$ -MRS studies have found that overall, in the medial frontal cortex (mFC) levels of glutamatergic metabolites are decreased and Glx (glutamate + glutamine signal) levels in the basal ganglia are elevated in schizophrenia compared to healthy volunteers. Furthermore, higher levels of glutamatergic metabolites in the mFC and medial temporal lobe are also associated with greater illness severity and may be reduced by antipsychotic medication (Merritt et al., 2021; Nakahara et al., 2021; Merritt et al., 2019). GABA levels appear unaltered in patients compared to controls across most brain regions (Nakahara et al., 2021; Egerton et al., 2017b), with reductions limited to the midcingulate cortex (Nakahara et al., 2021).

Multimodal imaging allows quantification of regional glutamate or GABA concentrations using  $^1\text{H}$ -MRS and of BOLD response and fMRI activation using fMRI during a single imaging session. In healthy volunteers, multimodal  $^1\text{H}$ -MRS - fMRI studies show a negative association between GABA levels and local activation in regions such as the occipital cortex and ACC, and a positive association between glutamate levels and activation in distal regions (Duncan et al., 2014; Kiemes et al., 2021). Locally, the BOLD response is affected by excitatory and inhibitory neural activity (Logothetis, 2008; Muthukumaraswamy et al., 2009 May 19; Buzsáki et al., 2007). Distally, glutamate and possibly GABA may influence neural activity via regulation of excitatory long-range projections resulting in downstream BOLD effects (Kiemes et al., 2021). Whilst these simple linear relationships are attractive, they are likely an over-simplification, given the highly interconnected nature of brain networks and the complex interactions within and between them (Pedersen et al., 2018). Local changes in excitability may have broad (and non-linear) excitatory or inhibitory effects on distal regions in the same network, and similar downstream effects on other networks. Nonetheless, it is unclear whether the observed relationships in healthy volunteers are disrupted in psychosis.

To address this question, we conducted a systematic review of multimodal  $^1\text{H}$ -MRS - fMRI studies investigating the relationship between regional glutamatergic or GABAergic metabolite levels and fMRI activation in psychosis.

## 2. Methods

### 2.1. Study selection

The systematic review protocol was registered with PROSPERO (Reference CRD42021236051) and conducted in accordance with PRISMA guidelines (Moher et al., 2009). Medline and Embase electronic databases were searched by two independent authors (UZ and EH) to identify relevant journal articles, followed by hand-searching of reference lists and cited-by lists of the included articles. Studies were included if they: were published in peer-reviewed journals in English, reported in vivo  $^1\text{H}$ -MRS measurements of glutamate, glutamine, Glx or GABA, and fMRI data in the same participants, and examined participants with a diagnosis of schizophrenia, psychosis, or schizoaffective and related disorders. Conference abstracts were excluded. An additional exclusion criterion was studies that included novel drugs or placebo. Where there were cases of overlapping samples under the same paradigms the study with the largest sample was included. Returned articles were initially screened for inclusion through reading of article titles and abstracts. Full texts were then screened to identify articles meeting the inclusion criteria.

The search terms were (schizo\* OR psychosis) AND (glutamate OR glutamine OR Glx OR GABA OR magnetic resonance spectroscopy) AND (resting state OR functional magnetic resonance imaging OR fMRI OR connectivity).

### 2.2. Data extraction

Three authors independently extracted the data into a structured

template (UZ, ECO, EH). Any discrepancies were discussed between the three authors, and unresolved issues were reconciled with a senior researcher (AE). To describe the study characteristics, the following data were extracted: the metabolite investigated;  $^1\text{H}$ -MRS voxel location; fMRI paradigm; MRI field strength; sample size; age; sex; study design, diagnosis, duration of illness, current antipsychotic medication, duration of antipsychotic treatment, reported differences between the patient and healthy volunteers in metabolite level and fMRI outcomes; the  $^1\text{H}$ -MRS -fMRI relationships in the patient and healthy volunteer samples; and differences in  $^1\text{H}$ -MRS - fMRI relationships between the patient and healthy volunteer samples.

### 2.3. Study quality

The methodological quality of studies was assessed with the Newcastle-Ottawa Scale for case-control studies (NOS; (Wells et al., 2011) by two authors (UZ and EH). In case of disagreement, issues were resolved with a senior researcher (AE). Using a star rating scale, the adapted tool assesses two categories of study quality: selection and comparability. Total possible scores range from zero to six stars. There is no threshold for determining 'good' and 'poor' quality studies but accumulating stars index increasing study quality (see Supplementary Table 1).

## 3. Results

The initial search identified 505 articles, of which 482 articles were excluded during title and abstract screening. A further 6 studies were excluded during full-text screening for the following reasons: one did not include a patient group (Duncan et al., 2014), one did not include glutamate, glutamine, Glx or GABA (Monin et al., 2015), one did not include a comparison healthy volunteer group (McQueen et al., 2021) two did not report the relationships between  $^1\text{H}$ -MRS and fMRI data (Gawne et al., 2020; Xiang et al., 2019) one (Limongi et al., 2021) reported overlapping findings with (Limongi et al., 2020). This resulted in the final inclusion of 17 original articles (Fig. 1).

These seventeen articles examined  $^1\text{H}$ -MRS-fMRI relationships in a total of 594 patients and 538 healthy volunteers. Table 1 presents the sample characteristics. Sample sizes ranged from 17 (Falkenberg et al., 2014) to 76 patients (McCutcheon et al., 2021). Fifteen studies were cross-sectional case-control studies. Two studies additionally examined patients at two time points, before and after 6 weeks of risperidone-treatment (Cadena et al., 2018) and before and after 8 weeks of antipsychotic treatment (Li et al., 2022b). Six studies examined patients treated with antipsychotic medication (Falkenberg et al., 2014; White et al., 2015; Hutcheson et al., 2012; Reid et al., 2010; Horne et al., 2021; Overbeek et al., 2019; Overbeek et al., 2021). Four studies examined patients who were not currently on antipsychotic medication (Cen et al., 2020; Maximo et al., 2021; Kraguljac et al., 2014; Nelson et al., 2020). Three studies included both medicated and unmedicated patients (Limongi et al., 2020; McCutcheon et al., 2021; Shukla et al., 2019). One study compared medicated and unmedicated patients (Kaminski et al., 2020) (Table 1).

Supplementary Table 2 presents the methodological characteristics. Fourteen studies were performed at a field strength of 3 Tesla (3 T) (Falkenberg et al., 2014; McCutcheon et al., 2021; Cadena et al., 2018; Li et al., 2022b; White et al., 2015; Hutcheson et al., 2012; Reid et al., 2010; Horne et al., 2021; Cen et al., 2020; Maximo et al., 2021; Kraguljac et al., 2014; Nelson et al., 2020; Shukla et al., 2019; Kaminski et al., 2020) and three were performed at 7 Tesla (7 T) (Limongi et al., 2020; Overbeek et al., 2019; Overbeek et al., 2021).  $^1\text{H}$ -MRS voxel locations included the ACC / medial frontal cortex (mFC) and prefrontal cortex (mPFC) (11 studies) (Limongi et al., 2020; Falkenberg et al., 2014; McCutcheon et al., 2021; Cadena et al., 2018; Li et al., 2022b; Reid et al., 2010; Horne et al., 2021; Overbeek et al., 2019; Overbeek et al., 2021; Maximo et al., 2021; Shukla et al., 2019), hippocampus (3 studies)

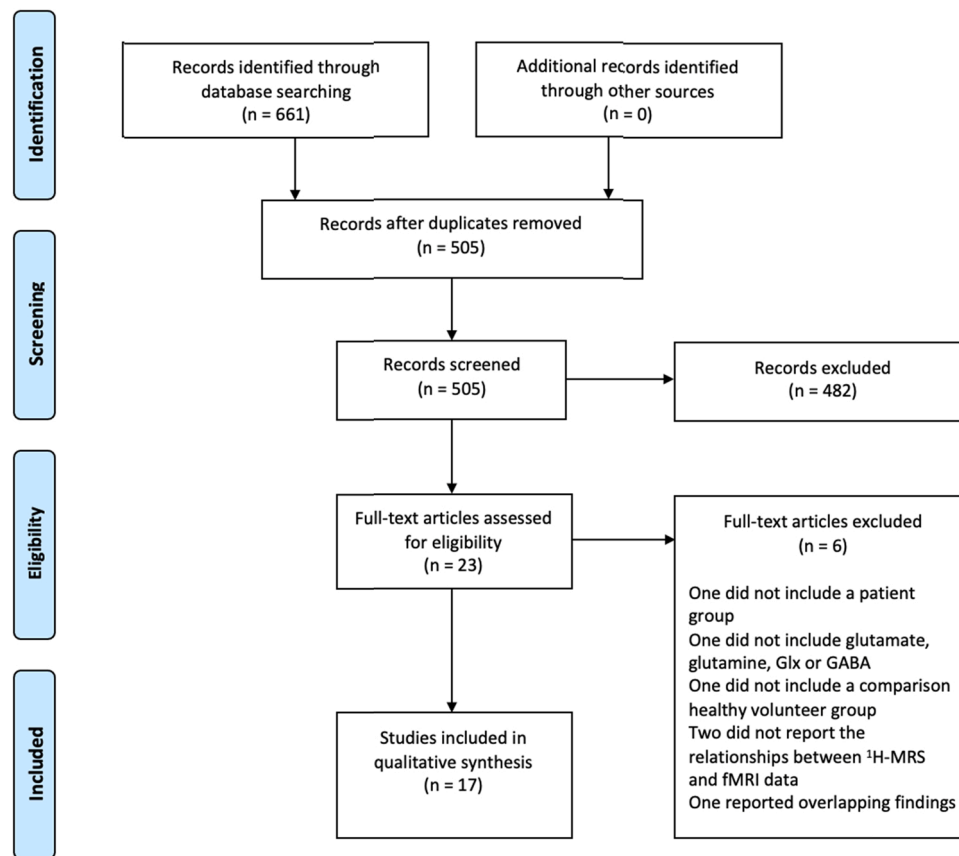


Fig. 1. PRISMA flow diagram showing identification, screening and inclusion for studies examining <sup>1</sup>H-MRS-fMRI relationships in psychosis compared to healthy volunteers.

(Hutcherson et al., 2012; Kraguljac et al., 2014; Nelson et al., 2020), dorsolateral prefrontal cortex (DLPFC) (one study) (Kaminski et al., 2020), ventromedial prefrontal cortex (vmPFC) (1 study) (Cen et al., 2020) and substantia nigra (1 study) (White et al., 2015). Sixteen studies evaluated glutamatergic metabolites (glutamate, glutamine or Glx) (Limongi et al., 2020; Falkenberg et al., 2014; McCutcheon et al., 2021; Cadena et al., 2018; Li et al., 2022b; White et al., 2015; Hutcherson et al., 2012; Reid et al., 2010; Horne et al., 2021; Overbeek et al., 2019; Cen et al., 2020; Maximo et al., 2021; Kraguljac et al., 2014; Nelson et al., 2020; Shukla et al., 2019; Kaminski et al., 2020). Five studies evaluated GABA (Li et al., 2022b; Overbeek et al., 2019; Overbeek et al., 2021; Cen et al., 2020; Shukla et al., 2019).

Resting state functional connectivity (rsFC) was examined in 9 studies (Limongi et al., 2020; McCutcheon et al., 2021; Li et al., 2022b; Overbeek et al., 2021; Cen et al., 2020; Maximo et al., 2021; Kraguljac et al., 2014; Nelson et al., 2020; Shukla et al., 2019). Task-related fMRI was examined in 8 studies. Tasks included the Stroop task (Cadena et al., 2018; Reid et al., 2010; Overbeek et al., 2019), auditory cognitive control (Falkenberg et al., 2014) episodic memory (Hutcherson et al., 2012) n-back working memory (Kaminski et al., 2020) probabilistic monetary reward decision (White et al., 2015) and reward learning (Horne et al., 2021) tasks.

Table 2 summarises the relationships between glutamate levels and BOLD response in schizophrenia relative to healthy volunteers. Group comparisons of glutamate levels and BOLD response are provided in Supplementary Table 2.

### 3.1. Anterior Cingulate Cortex (ACC) Glutamatergic Metabolites and neurofunctional responses

#### 3.1.1. ACC glutamate metabolites and rsFC

Six studies examined glutamatergic metabolites in the ACC in relation to resting state functional connectivity (rsFC) (Limongi et al., 2020; McCutcheon et al., 2021; Li et al., 2022b; Overbeek et al., 2021; Maximo et al., 2021; Shukla et al., 2019). An overall finding of these studies is that relationships between ACC glutamate and rsFC observed in healthy volunteers appear to be weaker in schizophrenia (McCutcheon et al., 2021; Maximo et al., 2021). Shukla et al. (2019) found significant positive relationships between ACC glutamate and ACC rsFC to the inferior frontal gyrus or superior temporal gyrus in healthy volunteers that did not reach significance in patients, although the group interaction was non-significant (Shukla et al., 2019). McCutcheon et al. (2021) found that ACC glutamate was negatively associated with the rsFC within the salience network across both the schizophrenia and healthy volunteer samples and that this relationship was significantly weaker in individuals with schizophrenia (McCutcheon et al., 2021). Maximo et al. (2021) found that in healthy volunteers, higher ACC Glx levels predicted greater rsFC in the dACC and insula, and diminished rsFC of the lateral parietal cortex but that these relationships were weaker or absent in FEP. Limongi et al. (2020), examined the relationship between dACC glutamate and connectivity in core nodes of the salience network (dorsal ACC and anterior insula) at 7 T in medicated FEP (Limongi et al., 2020). Across both the FEP and healthy volunteer groups, ACC glutamate levels were positively associated with inhibitory activity within the dACC, and negatively associated with inhibitory activity within the anterior insula. However, in the FEP group compared to healthy volunteers dACC glutamate was negatively associated with inhibition of excitatory activity within the ACC, such that as dACC glutamate increased, inhibition

**Table 1**  
Sample characteristics of studies examining.

Author	Study design	Sample size		Mean (SD) age in years		Sex, m/f		Patient diagnosis	Mean (SD) duration of illness (months)	Current antipsychotic medication	
		Patients	Healthy volunteers	Patients	Healthy volunteers	Patients	Healthy volunteers			Medicated	Unmedicated
Li et al., 2022b	Longitudinal	B: 32 FU: 24	30	B: 26.8 (6.1) FU: 27.0 (5.8)	27.1 (4.3)	B: 16/16 FU: 12/12	15/15	FEP	NR	At follow-up: 24	At baseline: 32
Overbeek et al. (2021)	Cross-sectional	19	21	22.9 (4.4)	23.4 (4.4)	15/4	16/5	FEP	NR	19	0
Maximo et al. (2021)	Cross-sectional	70	52	24.0 (6.1)	24.62 (6.3)	44/26	34/18	Schizophrenia; SAD; BDP; SFD; Psychosis NOS; Brief psychotic disorder; MDDP	21.4 (40.2)	0	52
Horne et al. (2021)	Cross-sectional	41	24	41.4 (10.5)	38.4 (10.0)	35/6	6/18	Schizophrenia	NR	41	0
McCutcheon et al. (2021)	Cross-sectional	76	82	38.0 (12.2)	35.4 (13.9)	68/8	55/27	Schizophrenia	NR	68	8
Shukla et al. (2019)	Cross-sectional	58	61	36.9 (12.9)	37.7 (13.3)	44/14	35/26	SSD	15.4 (14.0)	56	2
Limongi et al. (2020)	Cross-sectional	19	20	21.7 (12.3)	21.2 (13.9)	12/7	11/9	FEP; SSD	13.0	8	11
Cadena et al. (2018)	Longitudinal	22	20	33.0 (9.8)	33.1 (9.3)	17/5	14/6	Schizophrenia; SAD	NR	At follow-up: 22	At baseline: 22
Reid et al. (2010)	Cross-sectional	26	23	40.4 (13.1)	37.2 (12.4)	18/8	15/8	Schizophrenia; SAD	NR	26	0
Overbeek et al. (2019)	Cross-sectional	21	21	23.2 (4.4)	23.5 (4.5)	16/5	16/5	FEP	NR	21	0
Falkenberg et al. (2014)	Cross-sectional	17	17	30.0 (10.0)	28.0 (4)	10/7	10/7	Schizophrenia	108.0 (60.0)	17	0
Kraguljac et al. (2014)	Cross-sectional	22	22	33.8 (9.3)	35.1 (11.3)	15/7	15/7	Schizophrenia; SAD	111.8 (102.8)	0	22
Nelson et al. (2020)	Cross-sectional	43	37	24.2 (6.3)	24.7 (6.3)	36/19	27/14	FEP; SSD	NR	0	43
Hutcheson et al. (2012)	Cross-sectional	28	28	36.7 (12.2)	35.6 (11.1)	20/08	17/11	Schizophrenia	190.0 (142.8)	28	0
Kaminski et al. (2020)	Cross-sectional	55	35	Medicated Schizophrenia 35.7 (7.8) Unmedicated Schizophrenia 33.0 (9.9)	34.4 (8.5)	37/18	29/12	Schizophrenia	NR	36	19
Cen et al. (2020)	Cross-sectional	23	26	27.0 (6.5)	25.9 (4.6)	9/14	11//15	FES; schizophreniform disorder	NR	0	23
White et al. (2015)	Cross-sectional	22	19	39.4 (6.7)	36.5 (12.1)	17/5	11/8	Schizophrenia; SAD	212.2 (138.4)	22	0

<sup>1</sup>H-MRS-fMRI relationships in psychotic disorders compared to in healthy volunteers. First episode psychosis = FEP; Schizophrenia spectrum disorders = SSD; Major Depressive Disorder with psychosis = MDDP; first episode schizophrenia = FES; Schizoaffective disorders = SAD; Bipolar disorder with Psychosis = BDP; Schizophreniform disorder = SFD; not reported = NR; Baseline = B; follow up = FU.

**Table 2**

Individual and group associations between metabolite levels and BOLD response in cases (schizophrenia, FEP...) and healthy volunteers (HV). The table summarises the statistical findings for each study, as reported in the original publication.

Author	Functional association with neurometabolite level: patients	Functional association with neurometabolite level: healthy volunteers	Group differences in associations between neurometabolites and functional response	Statistical analysis for group differences
Glutamatergic <sup>1</sup> H-MRS x fMRI				
Li et al., 2022b	At baseline (medication naïve) mPFC Glx was not associated with the mPFC, PCC and DLPFC DMN rsFC strength After 8 weeks of antipsychotic medication: NR	At baseline mPFC Glx was not associated with the mPFC, PCC and DLPFC DMN rsFC strength	NR	NR
Overbeek et al. (2021)	dACC Glu positively associated with the superior precuneus, the bilateral supramarginal gyrus and the bilateral insula dACC Glu negatively associated with the mPFC, the L orbitofrontal cortex, the retrosplenial cortex, the L temporal lobe and the R angular gyrus	dACC Glu positively associated with the bilateral supramarginal gyrus dACC Glu negatively associated with the L angular gyrus and the L inferior temporal lobe	In the bilateral supramarginal gyrus, superior precuneus and left angular gyrus, the relationship was significantly more positive in patients In the supplemental motor area, medial prefrontal cortex, R orbitofrontal cortex, retrosplenial cortex and temporal cortex, the relationship was more positive in HV	$P_{FDR} < 0.05$ $P_{FDR} < 0.05$
Maximo et al. (2021)	dACC Glx positively associated with rsFC in the ACC, L superior frontal gyrus, and L inferior parietal lobule dACC Glx negatively associated with rsFC in the L middle temporal gyrus, L and R hippocampus and R fusiform gyrus	dACC Glx positively associated with rsFC in the dACC, L superior medial gyrus, L and R insula, and L putamen dACC Glx negatively associated with rsFC in the R angular gyrus, R and L fusiform gyrus and R parahippocampal gyrus	Group x Glx interaction in the dACC, bilateral insula and putamen, with positive associations in HV and negative associations in patients. Group x Glx interactions were found in the inferior and superior parietal areas, with negative rsFC-Glx associations in HV and positive associations in patients	$P < 0.01$ using TCCE $P < 0.01$ using TCCE
McCutcheon et al. (2021)	Medial frontal cortex Glx negatively associated with rsFC in network intersecting salience network	Medial frontal cortex Glx negatively associated with rsFC in network intersective salience network	Mean connectivity with the glutamate associated network was weaker in individuals with schizophrenia	$P = 0.027$
Shukla et al. (2019)	ACC Glu not associated with ACC rsFC	ACC Glu positively associated with ACC-R IFG rsFC and ACC-bilateral STG rsFC	There were no group x Glu interactions on functional connectivity abnormalities	$P > 0.005$
Limongi et al. (2020)	ACC Glu positively associated with BOLD response (intrinsic inhibition) in the dACC and negatively associated with BOLD response in the AI	ACC Glu positively associated with BOLD response (intrinsic inhibition) in the dACC and negatively associated with BOLD response in the AI	dACC Glu was associated with weaker dACC inhibitory connections in patients compared to HV	$PP = 0.98$
Cadena et al. (2018)	At baseline (off-medication) ACC Glx associated with bilateral ACC and R insula (SN) and bilateral hippocampus, precuneus, IPL and PCC (DMN) BOLD response	At baseline ACC Glx associated with R ACC and bilateral insula (SN) and bilateral hippocampus, precuneus, IPL and PCC (DMN) BOLD response	At baseline, in the SN the BOLD x group x Glx interaction was significant in the bilateral ACC and insula, with positive correlations between ACC Glx and ACC BOLD in HV but not in patients. Group differences in ACC Glx – BOLD correlation were significant in the L ACC and bilateral insula. In the DMN the BOLD x group x Glx interaction was significant in the precuneus and IPL, with positive correlations between ACC Glx and precuneus BOLD in HV but not in patients. Group differences in ACC Glx – BOLD correlation were significant in the bilateral IPL, precuneus, R hippocampus and R PCC At 6 weeks in the SN the BOLD x group x Glx interaction was significant in the ACC and insula, with positive correlations between ACC Glx and ACC BOLD in patients but not in HV. Group differences in ACC Glx – BOLD correlation were significant in the bilateral insula and ACC. In the DMN the BOLD x group x Glx interaction was significant in the precuneus, PCC, and IPL, with positive correlations between ACC Glx and precuneus BOLD in patients but not HV. Group differences in Glx – BOLD correlation were significant in the bilateral precuneus, IPL, R hippocampus, and R PCC	$P_{SVC} < 0.05$ $P_{SVC} < 0.05$
	After 6 weeks of medication, ACC Glx associated with bilateral ACC and insula BOLD response (SN) and bilateral hippocampus, IPL, and R precuneus (DMN)	At 6 weeks, ACC Glx associated with bilateral insula BOLD response (SN) and in the L IPC (DMN)	At 6 weeks in the SN the BOLD x group x Glx interaction was significant in the ACC and insula, with positive correlations between ACC Glx and ACC BOLD in patients but not in HV. Group differences in ACC Glx – BOLD correlation were significant in the bilateral insula and ACC. In the DMN the BOLD x group x Glx interaction was significant in the precuneus, PCC, and IPL, with positive correlations between ACC Glx and precuneus BOLD in patients but not HV. Group differences in Glx – BOLD correlation were significant in the bilateral precuneus, IPL, R hippocampus, and R PCC	$P_{SVC} < 0.05$ $P_{SVC} < 0.05$
Reid et al. (2010)	dACC Glx positively associated with percentage BOLD response in the ACC	dACC Glx not significantly associated with percentage BOLD response in the ACC	No significant group differences in strength of association between dACC Glx and ACC BOLD response	$P = 0.223$
Overbeek et al. (2019)	dACC Glu positively associated with the BOLD response in the PCC, precuneus and R DLPFC extending to the OC and bilateral thalamus	dACC Glu negatively associated with the BOLD response in the PCC and precuneus extending to the OC and cerebellum	The BOLD x group x Glu interaction between dACC Glu and R DLPFC, PCC, precuneus, and bilateral IPL BOLD was more positive in patients compared to HV. There were no regions where ACC Glu-correlations were more negative in patients than HV.	$P_{FWE} < 0.05$
	dACC Gln negatively associated with BOLD response in R insula, DLPFC, thalamus, and putamen	dACC Gln negatively associated with BOLD response in bilateral SMA, preCG, postCG, ACC, MCC, insula, and R DLPFC	The BOLD x group x Gln interaction between dACC Gln and dACC, SMA, and SFL BOLD was more positive in patients than HV	$P_{FWE} < 0.05$

Pp values > 0.95

(continued on next page)



Table 2 (continued)

Author	Functional association with neurometabolite level: patients	Functional association with neurometabolite level: healthy volunteers	Group differences in associations between neurometabolites and functional response	Statistical analysis for group differences
Horne et al. (2021)	ACC Glu positively associated with ACC-fusiform and ACC-amygdala effective connectivity in treatment-responsive patients ACC Glu not significantly associated with ACC-ACC, -fusiform, -caudate or -amygdala effective connectivity in treatment-resistant patients	ACC Glu positively associated with ACC-fusiform effective connectivity	Significant negative group $\times$ glutamate interaction on ACC-fusiform connectivity for resistant > HC and resistant > responsive No group $\times$ Glu interaction on ACC-fusiform connectivity for responsive > HC Significant group $\times$ glutamate interaction on ACC-amygdala and -caudate connectivity in the resistant > responsive No significant group $\times$ glutamate interaction on ACC-amygdala and caudate connectivity in the resistant > HC comparison. Significant negative group $\times$ glutamate interaction on ACC-caudate connectivity in responsive > HC comparison. The BOLD $\times$ group $\times$ Glu interaction was significant in the bilateral IPL, with a positive association between R ACC Glu and bilateral IPL BOLD in patients and a negative association in HV. L ACC Glu did not show any significant group interaction with BOLD response	Pp values $\leq 0.95$ Pp values > 0.95 Pp values $\leq 0.95$ Pp values > 0.95
Falkenberg et al. (2014)	R ACC Glu positively associated with BOLD response in the bilateral IPL under high demands for cognitive control	R ACC Glu negatively associated with BOLD response in the bilateral IPL under high demands for cognitive control		NR
Kraguljac et al. (2014)	Hippocampus Glx not significantly associated with rsFC of the hippocampus and precuneus or any of the precuneus subregions. Hippocampus Glx not significantly associated with rsFC between hippocampus and the precuneus	NR		NR
Nelson et al. (2020)	L hippocampus Glx positively associated with rsFC between hippocampus and anterior and posterior DMN (PCC/precuneus and vmPFC)	L hippocampal Glx positively associated with rsFC between hippocampus and anterior and posterior DMN (PCC/precuneus and vmPFC)	The hippocampal connectivity $\times$ group $\times$ Glx interaction was significant. Significant regions included the entorhinal and orbitofrontal cortices, where higher hippocampal Glx levels were associated with greater hippocampal rsFC in HV, and lesser hippocampal rsFC in patients	$P_{FDR} \leq 0.05$
Hutcheson et al. (2012)	L hippocampus Glx not significantly associated with L hippocampus or L IFG BOLD response	L hippocampus Glx not significantly associated with L hippocampus BOLD response but positively associated with L IFG BOLD response	No significant group difference in L hippocampus Glx-IFG BOLD association. Effect of group on L hippocampus Glx-L hippocampus BOLD association not reported.	P = 0.162 NR
Kaminski et al. (2020)	L hippocampus Glx not significantly associated with IFG-hippocampus FC In unmedicated patients, L DLPFC Glu positively associated with DLPFC BOLD response In medicated patients, L DLPFC Glu not significantly associated with DLPFC BOLD response	L hippocampus Glx positively associated with IFG-hippocampus FC L DLPFC Glu not significantly associated with DLPFC BOLD response	Effect of group on L hippocampus Glx and IFG-hippocampus FC not reported. The BOLD $\times$ group $\times$ L DLPFC Glu interaction was significant, with a positive association in unmedicated patients but not medicated patients or HV.	NR $P_{FWE} = 0.017$
White et al. (2015)	SbN Glx not significantly associated with SbN BOLD response	SbN Glx positively associated with SbN BOLD response	NR	NR
Author	Functional association with neurometabolite levels: patients	Functional association with neurometabolite level: healthy volunteers	Group differences in associations between neurometabolites and functional response	Statistical analysis for group differences
GABA <sup>1</sup> H-MRS $\times$ fMRI				
Li et al. (2021)	At baseline (off-medication) mPFC GABA was not associated with MPFC, PCC and DMN rsFC strength At baseline (off-medication) there was no association between mPFC GABA and mPFC-DLPFC rsFC After 8 weeks of medication mPFC GABA was negatively associated with the mPFC DMN rsFC strength	At baseline mPFC GABA was not associated with mPFC, PCC and DMN rsFC strength At baseline mPFC GABA was negatively associated with the mPFC-DLPFC rsFC	NR	NR
Overbeek et al. (2021)	dACC GABA was positively associated with retrosplenial cortex, R orbital frontal cortex extending into the inferior frontal lobe dACC GABA was negatively associated with the caudate, insula, rolandic operculum, supramarginal gyrus and calcarine	dACC GABA was positively associated dACC rsFC in the medial and orbital prefrontal cortex and the caudate dACC GABA was negatively associated with the L temporal cortex and occipital regions	Interaction effects revealed that dACC brain connectivity with the caudate, putamen and R supramarginal gyrus was more negative in patients than HV There were no regions that had a significantly more negative association in HV than in patients	$P_{FDR} < 0.05$
Shukla et al. (2019)	ACC GABA not significantly associated with ACC-L PCC rsFC	ACC GABA negatively associated with ACC-L PCC rsFC	The association between ACC GABA and PCC rsFC differed between groups, with a negative association in HV but not patients. The ACC GABA $\times$ group $\times$ rsFC interaction between ACC and R medial frontal gyrus was	P = 0.006 P = 0.001 P = 0.001 P = 0.001

(continued on next page)

Table 2 (continued)

Author	Functional association with neurometabolite level: patients	Functional association with neurometabolite level: healthy volunteers	Group differences in associations between neurometabolites and functional response	Statistical analysis for group differences
Overbeek et al. (2019)	Bilateral dACC GABA positively associated with BOLD response in the ACC that extended to the caudate and thalamus. Bilateral dACC GABA negatively associated with R SI that extended to the superior temporal lobe and insula	Bilateral dACC GABA negatively associated with BOLD response in the L parietal cortex and L DLPFC	significant, with negative associations in HV The ACC GABA x group x rsFC interaction between ACC and R IPL was significant, with negative associations in HV The ACC GABA x group x rsFC interaction between ACC and R precuneus was significant, with negative associations in HV The BOLD x group x GABA interaction revealed dACC GABA was more positively associated with ACC BOLD and more negatively associated with SMA, insula, DLPFC, superior temporal lobe, preCG, and post central CG BOLD in patients compared to HV	$P_{FDR} < 0.05$
Cen et al. (2020)	vmPFC GABA positively associated with rsFC between vmPFC and L MOFC	vmPFC GABA not significantly associated with rsFC between vmPFC and L MOFC	NR	NR

NS = not significant; NR = not reported; N/A = not applicable; R = right; L = left; d = dorsal; Glu = Glutamate; Gln = Glutamine; Glx = Glutamate + Glutamine; rsFC = resting state functional connectivity; BOLD = blood-oxygen-level-dependent; DMN = default mode network; SN = salience network; AI = anterior insula; vmPFC = ventromedial prefrontal cortex; ACC = anterior cingulate cortex; IPC = inferior parietal cortex; IFG = inferior frontal gyrus; IPL = inferior parietal lobe; PCC = posterior cingulate cortex; STG = superior temporal gyrus; MCC = middle cingulate cortex; OC = occipital cortex; preCG = precentral gyrus; postCG = postcentral gyrus; MOFC = middle orbitofrontal cortex; SC = somatosensory cortex; SbN = substantia nigra; SFL = superior frontal lobe.

(attributed to GABAergic activity) decreased. Overbeek et al. (2021) found that dACC glutamate differentially predicted ACC rsFC in patients with FEP relative to healthy volunteers. In the bilateral supramarginal gyrus, superior precuneus and left angular gyrus, the relationship was significantly more positive in patients, whereas in the supplemental motor area, medial prefrontal cortex, right orbitofrontal cortex, retrosplenial cortex and temporal cortex, the relationship was more positive in healthy volunteers. In a longitudinal study Li et al. (2022b) sought to investigate the relationship between default mode network rsFC change and mPFC Glx levels before and after 8 weeks of antipsychotic treatment and reported no significant relationship at either time point.

### 3.1.2. ACC glutamate metabolites and task-induced BOLD response

The ACC is involved in several cognitive processes, including emotional learning, decision making and cognitive control (Stevens et al., 2011). To examine whether differences in ACC cognitive control networks in schizophrenia are related to differences in ACC glutamate levels, three studies investigated the relationship between ACC glutamatergic metabolites and the Stroop task BOLD response (Cadena et al., 2018; Reid et al., 2010; Overbeek et al., 2019). The cross-sectional study of Reid et al. (2010) found a positive association between ACC Glx levels and local BOLD response in patients, and no significant association in healthy volunteers. The cross-sectional study of Overbeek et al. (2019) hypothesised that patients with FEP would show an aberrant relationship between ACC glutamate and BOLD response in areas distal from the ACC during the Stroop task. They found that both the relationships between glutamate levels and BOLD response in regions of the posterior default mode network and between Gln and BOLD response were more positive in patients and negative in healthy volunteers.

While both the studies of Reid et al. (2010) and Overbeek et al. (2019) examined medicated patients, the longitudinal study of Cadena et al., (2018) specifically investigated the influence of antipsychotic medication on ACC Glx - Stroop BOLD responses, by examining patients in the absence of medication and again following a 6-week course of risperidone. There were significant group x BOLD x Glx interactions for the relationship between ACC Glx and BOLD locally in the ACC and more distally in the insula and posterior default mode network (DMN). In unmedicated schizophrenia there was a negative relationship between ACC Glx and BOLD response in these regions whereas the relationship was positive in healthy controls. After 6 weeks of risperidone treatment the ACC Glx-BOLD response relationship in patients was positive and contrasted to a negative relationship in healthy controls.

Parallel to these studies using the Stroop task, Falkenberg et al. (2014) investigated the bilateral dACC glutamate-BOLD response relationship during an auditory cognitive control task (Falkenberg et al., 2014). Right (but not left) ACC glutamate differentially predicted the distal BOLD response in the inferior parietal lobe in medicated patients compared to healthy volunteers; the relationship was positive in patients and negative in healthy volunteers.

Overall, the findings of Reid et al. (2010), Overbeek et al. (2019), Cadena et al. (2018) and Falkenberg et al. (2014) are similar in indicating that ACC glutamate levels are positively associated with local and distal neural responses measured during cognitive control tasks in medicated patients with schizophrenia. Furthermore, the results of Cadena et al. (2018) suggest that antipsychotic treatment may change the direction of the relationship between ACC glutamate and Stroop BOLD response from a negative to a positive relationship.

ACC glutamate levels may be elevated in patients who show a poorer response to antipsychotic medication including treatment resistance (Egerton et al., 2012, 2018, 2021; Demjaha et al., 2014; Tarumi et al., 2020; Iwata et al., 2019; Mouchlianitis et al., 2016; Nakahara et al., 2021). To better understand mechanisms relating to ACC glutamate in treatment resistant schizophrenia, Horne et al. (2021) compared the relationship between ACC glutamate and cognitive control network connectivity during an emotional reward learning task in treatment responsive patients, treatment resistant patients, and healthy volunteers. They found that healthy volunteers and treatment responsive patients showed positive relationships between ACC glutamate and connectivity of the ACC with the fusiform gyrus, which was absent in treatment resistant patients.

## 3.2. Hippocampal Glutamatergic Metabolites and neurofunctional responses

### 3.2.1. Hippocampal glutamate metabolites and rsFC

Three studies examined glutamate metabolites in the hippocampus. Of these, two studies, both in unmedicated patients investigated the relationship between left hippocampus Glx and rsFC (Kraguljac et al., 2014; Nelson et al., 2020). One cross-sectional study found that left hippocampal Glx levels were not significantly associated with hippocampus-precuneus rsFC in schizophrenia but did not report the relationship in healthy volunteers or whether this differed that seen in schizophrenia (Kraguljac et al., 2014). A more recent cross-sectional study including a larger sample of younger participants found that

hippocampal Glx-connectivity was positively associated with hippocampal rsFC to areas of the posterior and anterior DMN in both healthy volunteers and unmedicated FEP, but that for the entorhinal and orbital frontal cortices the relationship between hippocampal Glx and rsFC was positive in healthy volunteers and negative in FEP (Nelson et al., 2020).

### 3.2.2. Hippocampal glutamate metabolites and task-induced BOLD response

A single study investigated the relationship between left hippocampal Glx and BOLD signal response using an episodic memory task, which was conducted in medicated patients with chronic schizophrenia (Hutcherson et al., 2012). Glx was not significantly associated with the local left hippocampus BOLD response in either patients or healthy volunteers. The positive relationships between Glx and left IFG activity and IFG-hippocampal connectivity in healthy volunteers were not apparent in the patient group.

In summary, the studies examining hippocampal Glx indicate a positive association with BOLD response in distal regions in healthy volunteers which are non-significant in patients.

### 3.3. Glutamatergic metabolites in other regions

Kaminski et al. (2020) investigated the relationship between left DLPFC glutamate levels and BOLD activity during the N-back working memory task (Kaminski et al., 2020). They found that, in unmedicated patients but neither in medicated patients nor in healthy volunteers, glutamate levels in the left DLPFC were positively associated with local DLPFC BOLD response.

White et al. (2015) examined substantia nigra Glx levels in relation to the local BOLD response during a monetary reward decision task, to investigate the contribution of glutamate to prediction error signals. In medicated patients, substantia nigra Glx levels were not significantly associated with local BOLD response, whereas in healthy volunteers this relationship was positive.

### 3.4. GABA and Neural Activity

Five studies have investigated the relationships between GABA and neural activity in schizophrenia (Li et al., 2022b; Overbeek et al., 2019; Overbeek et al., 2021; Cen et al., 2020; Shukla et al., 2019). GABAergic interneurons inhibit local neural activity, and these studies have focussed primarily on the relationships between GABA and local BOLD activity rather than on longer range networks. Four studies examined GABA in the ACC, with three investigating the relationship with rsFC (Li et al., 2022b; Overbeek et al., 2021; Shukla et al., 2019) and the other examining the relationship with BOLD response during the Stroop task (Overbeek et al., 2019). In a large cross-sectional study Shukla et al. (2019) found local negative associations between ACC GABA and left posterior cingulate cortex rsFC in healthy volunteers but not in medicated schizophrenia. Similar patterns in healthy volunteers relative to patients were observed for the associations between ACC GABA and resting activity in the right medial frontal gyrus, right inferior parietal lobe and right precuneus (Shukla et al., 2019). Conversely, in a 7 T study Overbeek et al. (2021) found that dACC GABA differentially predicted dACC rsFC to the distal regions of caudate, putamen and right supra-marginal gyrus, with more negative associations in patients than healthy volunteers. They report no regions which had significantly more negative association in healthy volunteers relative to patients. In a longitudinal study Li et al. (2022b) found mPFC GABA levels were negatively associated with the mPFC-DLPFC rsFC in healthy volunteers and this relationship was absent in unmedicated FEP. However, in FEP after 8-weeks of treatment, the DMN rsFC strength values for the mPFC region were negatively associated with local mPFC GABA levels. Follow-up scans were not acquired in healthy volunteers. The study examining Stroop BOLD response was conducted at 7 T in medicated FEP (Overbeek et al., 2019). In patients compared to healthy volunteers, ACC

GABA was more positively associated with local fMRI activation in the ACC. However, this study also detected more negative associations between ACC GABA and activity in the more distal regions of the left parietal cortex and left DLPFC in patients (Overbeek et al., 2019).

Cen et al. (2020) examined the relationships between vmPFC GABA and local rsFC in antipsychotic naïve first episode schizophrenia. GABA levels in the vmPFC were positively associated with rsFC between the vmPFC and left middle orbitofrontal cortex in schizophrenia, but these relationships were not significant in healthy volunteers (Cen et al., 2020).

## 4. Discussion

This systematic review summarises the <sup>1</sup>H-MRS-fMRI literature examining the relationships between metabolite levels and BOLD response in both healthy controls and patients with psychotic disorders. Studies have examined glutamatergic metabolites or GABA in several <sup>1</sup>H-MRS voxel locations (ACC, DLPFC, vmPFC, hippocampus and substantia nigra) in relation to either resting or task-evoked neural activity. Across locations and conditions, all but one study provided evidence that relationships between glutamate or GABA and neural activity are disrupted in psychosis, although not all studies directly compared <sup>1</sup>H-MRS-fMRI relationships between groups statistically. Overall, the ACC/mFC was the most investigated region. Our main findings were that in psychosis, positive associations between ACC/mFC glutamate levels and network activity are reduced during rest but increased during cognitive control tasks. There was also evidence that the negative relationships between ACC/mFC GABA and local activity seen in healthy volunteers are diminished in psychosis.

Previous reviews of <sup>1</sup>H-MRS-fMRI relationships have focussed on GABA and glutamate in healthy volunteers during task-related MRI (Duncan et al., 2014; Kienes et al., 2021). The main finding from these reviews is that, in the healthy brain, ACC/mFC GABA is negatively related to task-evoked BOLD response (Duncan et al., 2014; Kienes et al., 2021). Our review indicates that in schizophrenia these negative relationships between GABA and local neural activity are diminished or become positive.

For ACC/mFC glutamate, we identified more positive relationships with local BOLD response during cognitive control tasks and weaker relationships with resting state network activity in psychosis compared to healthy volunteers. In the healthy brain, glutamate may be more closely related to resting state than task-related activity (Enzi et al., 2012) and could mediate the transition from resting state deactivation to task-induced activation (Duncan et al., 2014). Indeed, findings from Goulden and colleagues suggest that the salience network, which the ACC is a key part of, is responsible for switching between resting and task-engaged states (default mode network/central executive network) (Goulden et al., 2014). Additionally, ketamine, an NMDA receptor antagonist which may be administered in experimental models recapitulating key symptoms and behaviours associated with schizophrenia (Beck et al., 2020; Moghaddam and Javitt, 2012; Javitt and Zukin, 1991), disrupts the reciprocal relationship between resting state and task-positive networks, and induces a transient state resembling schizophrenia in healthy volunteers (Anticevic et al., 2012). The summarised findings indicate that in psychosis both resting state and task-activated networks may be influenced by glutamatergic mechanisms. These findings may provide key insights into the neurobiology of psychotic disorders by informing how the relationship between neurochemistry and neurophysiology may be altered prior and across disease stages. It would also be of interest for future studies to examine whether local changes in glutamate concentrations in response to tasks influences transitioning between default mode and task-positive networks in schizophrenia and the potential relationships with cognition and symptoms.

In schizophrenia, abnormalities within cortical neuronal circuits, including NMDA receptor hypofunction, deficits in parvalbumin



GABAergic interneurons and disinhibition of pyramidal neurons, may lead to neural discoordination and network disconnection (Egerton et al., 2020; Kaar et al., 2019; Volk et al., 2000; Hashimoto et al., 2003; Lewis et al., 2005; Gao and Snyder, 2013; Krajcovic et al., 2019; Friston et al., 2016a). <sup>1</sup>H-MRS quantifies the total amount of MR-visible glutamate and GABA in the voxel, which will relate to excitatory and inhibitory neurotransmission but is also linked to other cellular processes such as glucose metabolism and glutathione synthesis (Danbolt, 2001). The BOLD signal, which reflects changes in deoxyhemoglobin driven by localised changes in brain blood flow and oxygenation, provides an indirect measure of neural activity, representative of the excitatory-inhibitory balance arising between glutamatergic pyramidal neurons and GABAergic interneurons in cortical microcircuits (Logothetis, 2008; Muthukumaraswamy et al., 2009 May 19; Buzsáki et al., 2007). The mechanisms linking glutamatergic and GABAergic neurotransmission to the BOLD signal during resting and task-activated conditions have not been fully characterised either in the healthy brain or in schizophrenia. However, within local microcircuits, net increases in glutamatergic excitation may increase regional metabolic energy demands and the haemodynamic response, while net increases in GABAergic inhibition may produce more complex, indirect and circuit dependent effects (Logothetis, 2008; Muthukumaraswamy et al., 2009 May 19; Buzsáki et al., 2007). In schizophrenia, our findings in the ACC/mFC of more positive glutamate-BOLD relationships during task activation could indicate disinhibition, and weaker glutamate-BOLD relationships during rest may suggest impaired deactivation (Anticevic et al., 2012; Gu et al., 2019).

Distally, glutamate and possibly GABA may positively and negatively influence neural activity via regulation of excitatory long-range projections resulting in downstream BOLD effects (Kienes et al., 2021). Although glutamate has typically shown positive associations with distal neural activity (Duncan et al., 2014) negative associations are also seen in healthy volunteers (Kienes et al., 2021). The direction of these relationships may also differ temporally within the same individuals (Cadena et al., 2018) which might make interpretation of results challenging.

We found evidence that both the significance and the direction of association between neurometabolites and BOLD response may differ in schizophrenia patients compared to healthy volunteers. Several studies have detected aberrant relationships in schizophrenia in the absence of differences in neurometabolite levels compared to control (Cadena et al., 2018; Hutcheson et al., 2012; Reid et al., 2010; Horne et al., 2021; Overbeek et al., 2019; Cen et al., 2020; Maximo et al., 2021; Nelson et al., 2020; Kaminski et al., 2020). This indicates the added potential of combining fMRI with <sup>1</sup>H-MRS to reveal abnormalities in excitatory or inhibitory signalling in schizophrenia and other psychiatric disorders.

The relationships between glutamate or GABA and neural activity in psychosis are likely influenced by the presence of antipsychotic medication and other clinical factors, such as illness severity or duration (Merritt et al., 2021). Antipsychotic medication may reduce glutamate levels (Merritt et al., 2021; McQueen et al., 2021; Egerton et al., 2017a); and alter resting state activity (Wang et al., 2017) and task related BOLD responses (Fusar-Poli et al., 2007). The relationships between glutamate and neural activity also appear altered by antipsychotic medication. Negative relationships between ACC Glx and task-related neural activity in unmedicated schizophrenia patients became positive after 6 weeks of treatment with risperidone (Cadena et al., 2018). Positive relationships between DLPFC glutamate and local task-related activity in unmedicated patients was not apparent in either medicated patients or in healthy volunteers (Kaminski et al., 2020). Some studies have suggested ACC glutamate levels may vary according to the degree of clinical response to treatment, with higher levels in patients who show a poorer response to antipsychotic medication including treatment resistance (Nakahara et al., 2021; Egerton et al., 2021; Egerton et al., 2018; Egerton et al., 2012; Demjaha et al., 2014; Mouchlianitis et al., 2016; Tarumi et al., 2020; Iwata et al., 2019). Although Horne et al. (2021) did

not detect significant group differences in ACC glutamate levels between treatment resistant and treatment responsive patients in their cohort, they found that treatment resistant patients lacked the positive relationship between ACC glutamate and ACC-fusiform gyrus connectivity seen in treatment responsive schizophrenia.

There are several limitations to this review. The relatively small number of studies and the heterogeneities between them (in terms of e. g., voxel placement; resting state versus task fMRI; patient sub-populations) preclude a meta-analysis and some direct comparisons. Adoption of emerging consensus recommendations for <sup>1</sup>H-MRS (Wilson et al., 2019) and fMRI (Esteban et al., 2019) studies may enable better comparison of future studies. Glutamate, GABA and resting and task-induced neural activity likely vary with illness stage, medication effects or treatment response amongst other factors (Merritt et al., 2021; Nakahara et al., 2021; Chan et al., 2019) which will require a larger evidence base for evaluation. Some of the studies have small sample sizes, this potentially makes them low-power and unreliable. Some of the studies had poor control of sex with disproportionately more males in the patient group. This is important when considering molecular and cellular processes, clinical traits, response to treatments, health, and disease (Arnegard et al., 2020). Most studies placed <sup>1</sup>H-MRS voxels within the ACC/MFC region, and there is less information available on other areas which have generally been less investigated with <sup>1</sup>H-MRS (Merritt et al., 2016). Moreover, two studies in the review placed the voxel in the medial prefrontal cortex (McCutcheon et al., 2021; Li et al., 2022b), and one study placed a portion of the voxel in the medial prefrontal cortex (Shukla et al., 2019). Glutamate concentrations vary in different regions of the ACC (Dou et al., 2013) and differentially relate with whole brain resting state functional connectivity (Li et al., 2022a). Therefore, findings may be confounded from other regions in such instances. While there are some emerging common findings, the patterns of relationships are likely to be complex and influenced by medication and other factors and will require detailed further investigation. Finally, <sup>1</sup>H-MRS studies provide a static measure of the overall concentration of metabolites of interest in the voxel at rest. Furthermore, <sup>1</sup>H-MRS cannot distinguish neuronal glutamate or GABA concentrations from glutamate or GABA concentrations in other cell types and involved in metabolic processes. However, multiple lines of evidence indicate that the pre-synaptic neurotransmitter and metabolic pools of glutamate are tightly associated (Sibson et al., 1998), including a recent *in vivo* finding that glutamate levels estimated by <sup>1</sup>H-MRS and synaptic density estimated using [<sup>11</sup>C]UCB-J PET are significantly positively associated in the healthy human brain (Onwordi et al., 2021). Moreover, glutamate concentrations are high in glutamatergic nerve terminals, and low in glial and extracellular compartments (Danbolt, 2001; Bramham et al., 1990). These findings lend support to the hypothesis that levels of glutamate estimated by <sup>1</sup>H-MRS reflect the concentration of glutamate in the neurotransmitter pool (Gallinat et al., 2006; Horder et al., 2018; Yüksel and Öngür, 2010).

## 5. Conclusions

Emerging findings of these initial <sup>1</sup>H-MRS - fMRI studies examining psychosis indicate disruptions in the normal relationships between glutamate or GABA levels and neurophysiological activity during rest and task performance. In addition to increasing mechanistic understanding of neurotransmitter-BOLD relationships in psychiatric illness, further work in this area may reveal how these interactions may relate to clinical variables, including illness stage, severity or treatment outcomes, as differences in glutamate and network activity have been independently associated with psychosis onset (Egerton et al., 2020; Supekar et al., 2019), symptom severity (Merritt et al., 2021; Sendi et al., 2021) or response to treatment (Nakahara et al., 2021; McQueen et al., 2021; Egerton et al., 2021; Egerton et al., 2018; Egerton et al., 2012; Demjaha et al., 2014; Mouchlianitis et al., 2016; Tarumi et al., 2020; Iwata et al., 2019; Chan et al., 2019; Bojesen et al., 2020). Deeper

characterisation of disrupted relationships between glutamate, GABA and neurophysiological responses in psychosis may also develop their potential as biomarkers, including for predicting clinical outcomes, selecting patient subgroups or monitoring target engagement during development of novel therapeutics. For example, identification of the specific networks affected could guide targets for neuromodulation (Wada et al., 2022).

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## Conflicts of interest

MBW's primary employer is Invicro LLC., a contract research organization which provides services to the pharmaceutical and biotechnology industries. RMM has received honoraria for non-promotional talks for 'Janssen, Sunovion, Otsuka, Lundbeck'. The remaining authors report no conflicts of interest.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neubiorev.2022.105010](https://doi.org/10.1016/j.neubiorev.2022.105010).

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