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A review of altered biochemistry in the anterior cingulate cortex of first-episode psychosis

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Relevant biochemicals of the brain can be quantified *in vivo*, non-invasively, using proton Magnetic Resonance Spectroscopy (¹H MRS). This includes metabolites associated with neural general functioning, energetics, membrane phospholipid metabolism and neurotransmission. Moreover, there is substantial evidence of implication of the frontal and prefrontal areas in the pathogenesis of psychotic disorders such as schizophrenia. In particular, the anterior cingulate cortex (ACC) plays an important role in cognitive control of emotional and non-emotional processes. Thus the study of its extent of biochemistry dysfunction in the early stages of psychosis is of particular interest in gaining a greater understanding of its aetiology. In this review, we selected ¹H MRS studies focused on the ACC of first-episode psychosis (FEP). Four studies reported increased glutamatergic levels in FEP, while other four showed preserved concentrations. Moreover, findings on FEP do not fully mirror those in chronic patients. Due to conflicting findings, larger longitudinal ¹H MRS studies are expected to further explore glutamatergic neurotransmission in ACC of FEP in order to have a better understanding of the glutamatergic mechanisms underlying psychosis, possibly using ultra high field MR scanners.

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The study of first-episode psychosis (FEP) patients is of particular interest because it allows the investigation of neurobiological processes, ruling out the effects of long-term medications and chronicity (Squarcina

et al. 2015). Psychotic disorders are highly debilitating, with symptoms ranging from delusions and hallucinations to cognitive deficits (Altamura *et al.* 2015). In this context, Proton Magnetic Resonance Spectroscopy (¹H MRS) is the only non-invasive imaging technique that can quantify the concentration of relevant biochemicals *in vivo* in localised brain areas such as the anterior cingulate cortex (ACC) (Benes & Berretta, 2001; Stanley, 2002; Brambilla *et al.* 2005). The ¹H metabolites that are commonly reported include N-acetylaspartate (NAA), a marker of functioning neurons (Stanley *et al.* 2007), phosphocreatine plus creatine (PCr + Cr), involved with energetic processes,

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glycerophosphocholine plus phosphocholine (GPC + PC), catabolic and anabolic metabolites of membrane phospholipids, and neurotransmitters, glutamine, glutamate and gamma amino-butyric acid (GABA). ¹H MRS has been largely employed in psychosis with meta-analyses showing, in general, decreased NAA levels in schizophrenia in prefrontal and temporal areas (Kraguljac *et al.* 2012), while glutamate has been found to be altered in schizophrenia and in individuals with a high risk of developing the disease, especially in thalamus and prefrontal regions (Marsman *et al.* 2013; Merritt *et al.* 2013). The investigation of brain metabolites can therefore be of help in shedding light on the aetiology and biological mechanisms of psychosis.

Neuroanatomical models of schizophrenia are in agreement with the hypothesis of a frontal lobe biochemical alteration (Zabala *et al.* 2007). Thus, the study of prefrontal integrity and function in the early stages of the disease is of particular interest. The cingulate cortex, which is part of the cortico-striato-thalamo-cortical networks, is involved in various cognitive control and emotional processes. In particular, the evidence is compelling in implicating the ACC in the pathogenesis of schizophrenia (Baiano *et al.* 2007), particularly concerning negative symptoms (Hardy *et al.* 2011; Bersani *et al.* 2014). The neurobiology underlying psychosis is still unclear: MRS techniques could allow the identification of changes such as neuroplasticity or neuropil loss (Théberge *et al.* 2002). In this review, we consider studies, which focus on brain metabolites in the ACC of FEP patients measured with ¹H MRS. A bibliographic search on PUBMED on MRS studies exploring ACC in FEP was performed. The search terms used to identify the articles of interest were 'MRS', 'spectroscopy', 'anterior cingulate', 'first episode psychosis'. Ten papers, which have been summarised in Table 1, met these inclusion criteria.

Four out of the ten studies reported increased glutamatergic function (considered as glutamate, glutamine or glutamate plus glutamine) in FEP, whereas four studies showed preserved levels. Just one study reported changes in creatine (Tibbo *et al.* 2013). Going into details, Théberge *et al.* (2002) found higher levels of glutamine, and no other metabolites, in the left anterior ACC of FEP, in accordance with the hypothesised abnormal glutamatergic activity in schizophrenia (Marsman *et al.* 2013). These results in FEP were confirmed in a 2007 study (Théberge *et al.* 2007): interestingly, glutamine levels did not decrease after 30 months of follow-up, suggesting that the lower levels found in chronic illness by the same group (Théberge *et al.* 2003), may need more time to appear. An association between glutamine and FEP has been highlighted also by the fact that its levels were found to be

associated with patient performance in neuropsychological tests, such as the Wisconsin Card Sorting Test, the Paced Auditory Serial Addition Task and the Trail Making Test B (Dempster *et al.* 2015). An involvement of the glutamatergic function in the early stage of disease in frontal regions has also been confirmed by several studies, which found altered levels of glutamate. In particular, increased glutamate levels were reported in prefrontal areas of FEP (Smesny *et al.* 2015), including the anterior ACC. Smesny *et al.* (2015) hypothesised that glutamate is linked with cellular energy and membrane lipids metabolism, suggesting a relationship with membrane atypical behavior. This indicates that medication targeting neuroprotection could be of great importance especially at the early stages of disease. Levels of glutamate were found to be higher in non-remitted patients in respect to remitted patients, when compared after antipsychotic treatment, and to be associated with lower functioning and worse negative symptoms (Egerton *et al.* 2012). This indicates that the clinical status of patients could be related with glutamatergic dysfunction, which might then be targeted in patients, especially those not responding to antipsychotics. Results on glutamatergic function in FEP are not always in agreement, as some studies did not find differences between groups (Galinska *et al.* 2009; Tibbo *et al.* 2013). This could be related to the exact positioning of the voxel in the ACC. For example, Tibbo *et al.* (2013) positioned the voxel in the medial prefrontal region, including only part of anterior ACC. All studies considering NAA levels did not find any difference in the ACC of FEP compared with healthy subjects, even when finding differences in chronic schizophrenia patients (Natsubori *et al.* 2014), possibly indicating that neuronal integrity, linked with NAA, is related to the progression of disease.

Finally, Tibbo *et al.* (2013) reported a significant reduction in PCr + Cr of FEP compared with controls. Both PCr and Cr are involved in the processes related with cellular energy: thus, the authors have hypothesised that schizophrenia is associated with dysregulation in maintaining adequate energy pools. Other studies which considered PCr + Cr in their analyses (Théberge *et al.* 2002, 2007; Egerton *et al.* 2012; Tibbo *et al.* 2013; Natsubori *et al.* 2014; Dempster *et al.* 2015) reported pressured PCr + Cr levels in FEP. It has to be noted though that Tibbo *et al.* (2013) utilised an ad-hoc MRS sequence with a long TE (240 ms) and the specific aim of quantifying mainly Cr, which could be accounted for the difference in results in respect to the other studies.

In summary, although there are some findings on increased glutamatergic levels in the ACC of FEP, they are still partially conflicting since some ¹H MRS

Table 1. Selection of studies on first-episode psychosis investigating anterior cingulate cortex metabolism with 1-H magnetic resonance spectroscopy

Study	Sample size (mean age \pm s.d.)	Study design	Field strength	SV or CSI and location (voxel size)	Short or intermediate Echo time (TE time)	Quantification and reported ¹ H metabolites	ACC results only (if possible, include the effect size in brackets for each significant finding)
Th��berge <i>et al.</i> (2002)	21 FEP (26 \pm 7 y.o.), 21 HC (26 \pm 7 y.o.)	Cross-sectional and investigated group differences	4 T	SV Left anterior ACC (1.5 cc) and left medial thalamus (1.5 cc)	Short TE (20 ms)	Absolute relative to water (only NAA Glu Gln GPC + PC PCr + Cr Taurine scyllo-Ins myo-Ins)	Increased Gln in the left ACC
Th��berge <i>et al.</i> (2004)	19 FEP (25 \pm 8 y.o.)	Cross-sectional	4 T	SV Left anterior ACC and left thalamus (1.5 cc)	Short TE (20 ms)	Absolute relative to water NAA GPC + PC	Positive correlation between GPC + PC and duration of untreated psychosis
Blasi <i>et al.</i> (2004)	17 FEP (26.8 \pm 7.6 y.o.), 17 HC (25.5 \pm 6.8 y.o.)	Cross-sectional and investigated group differences	1.5 T	CSI (7.5 \times 7.5 \times 15 mm – 0.84 ml) Four slices Left and right ACC (0.84 cc each) plus other ROIs	Long TE (272 ms)	Metabolite ratios NAA/PCr + Cr NAA/GPC + PC GPC + PC/PCr + Cr	No significant group differences in the right and left ACC
Th��berge <i>et al.</i> (2007)	16 FEP (25 \pm 8 y.o.), 16 HC (29 \pm 12 y.o.)	Longitudinal study design where patients were assessed three times (at baseline, after 10 months of treatment, after 30 months of treatment) and HC assessed twice 35 months apart	4 T	SV left anterior ACC and left medial thalamus (10 \times 10 \times 15 mm ³ each)	Short TE (20 ms)	Absolute relative to water NAA Glu Gln GPC + PC PCr + Cr myo-Ins Taurine scyllo-Ins	At baseline, increased Gln in the left ACC No significant effect for the three-level repeated- measures analysis No correlations with clinical scores

Uhl <i>et al.</i> (2011)	24 FEP (26 ± 6.3 y.o.), 30 UHR (25.6 ± 4.5 y.o.), 31 HC (25.5 ± 5.2 y.o.)	Cross-sectional and investigated group differences	1.5 T	SV Left hippocampus, mid-sagittal ACC, MPFC (8 ml each)	Intermediate TE (140 ms)	Metabolite ratios GPC + PC/Cr NAA/Cr	No significant group differences
Egerton <i>et al.</i> (2012)	32 FEP (30 ± 6 y.o.)	Cross-sectional and investigated group differences	3 T	SV Medial anterior ACC (20 × 20 × 20 mm ³), centre of left thalamus (15 × 20 × 20 mm ³)	Short TE (30 ms)	Metabolite ratios Glu/Cr Glu + Gln/Cr NAA/Cr GPC + PC/Cr myo-Ins/Cr	Increased levels of Glu/Cr in the ACC of non-remitted patients Higher levels of Glu/Cr in the anterior cingulate cortex were associated with a greater severity of negative symptoms and a lower level of global functioning
Tibbo <i>et al.</i> (2013)	33 FEP (21.6 ± 3.4 y.o.), 41 HC (21.9 ± 3.1 y.o.)	Cross-sectional and investigated group differences	3 T	SV Medial prefrontal region including part of anterior ACC (20 × 30 × 30 mm ³)	Short TE (20 ms)	Absolute relative to water NAA PCr + Cr GPC + PC Glu	A negative association was found between age of patients and Cr 16% reduction of Cr levels in patients No association between Cr and clinical variables
Natsubori <i>et al.</i> (2014)	24 UHR (21.7 ± 3.8 y.o.) with 26 matched HC (22.3 ± 3.2 y.o.), 19 FEP (25.4 ± 6.3 y.o.) with 19 matched controls (26.3 ± 1.5 y.o.), 25 scz (32.7 ± 8.6 y.o.) with 28 matched HC (32.8 ± 4.3 y.o.)	Cross-sectional and investigated group differences	3 T	SV MPFC – primarily ACC and left and right paracingulate gyri (20 × 20 × 20 mm ³)	Short TE (15 ms)	Absolute relative to water NAA Glu + Gln PCr + Cr GPC + PC myo-Ins	Reduced levels of NAA and Glu + Gln in the MPFC in scz but not FEP FES or UHR

Continued

Table 1. Continued

Study	Sample size (mean age \pm s.d.)	Study design	Field strength	SV or CSI and location (voxel size)	Short or intermediate Echo time (TE time)	Quantification and reported ¹ H metabolites	ACC results only (if possible, include the effect size in brackets for each significant finding)
Dempster <i>et al.</i> (2015)	16 FEP (17 \pm 7.2 y.o.)	Longitudinal study with patients assessed at baseline and after 10 months	4 T	SV (1.5 cm ³) left ACC, left thalamus	Short TE (20 ms)	Absolute relative to water Glu, Gln	Baseline Gln was positively associated with performance on the PASAT in the left ACC, Glu at the 10-month scanning point was positively associated with TrailsB duration and with WCST perseverative errors Glutamine at 10- month scanning was positively associated with WCST perseverative errors and negatively associated with WCST
Smesny <i>et al.</i> (2015)	31 FEP (25.97 \pm 4.95 y.o.), 31 HC (25.42 \pm 5.18 y.o.)	Cross-sectional and investigated group differences	3 T	CSI region of interest selected in the frontal part of the CSI slab: 8 voxels including (left and right) frontal prefrontal cortex and ACC (15 \times 9 \times 1.5 cm ³) each voxel	Short TE (30 ms)	Absolute concentrations Glu	Increased levels of Glu in FEP Glu positively correlated with frontal/prefrontal PME and right frontal/prefrontal PDE in FEP and not in HC Glu negatively correlated with PCr or ATP values in the frontal/prefrontal cortex bilaterally and in the right ACC in HC and not in patients

MRS, magnetic resonance spectroscopy; FEP, first episode psychosis; SV, single voxel; CSI, chemical shift imaging; HC, healthy controls; SCZ, schizophrenia; WM, white matter; GM, gray matter; CSF, cerebro-spinal fluid; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; NAA, *N*-acetylaspartate; NAAG, *N*-acetylaspartylglutamate; Gln, glutamine; Glu, glutamate; Glc, glucose; PCr + Cr, phosphocreatine + creatine; GPC + PC, glycerophosphocholine + phosphocholine; mI, myo-Inositol; myo-Ins, myo-inositol; scyllo-Ins, scyllo-Inositol; TE, echo time; y.o., years old.

studies found preserved concentrations. Moreover, results in FEP do not fully overlap with those in chronic schizophrenia. This could be due to the fact that metabolite levels are particularly sensitive to the characteristics of the sample, and to the phase of disease. Therefore, although glutamatergic neurotransmission may play a role in the pathophysiology of psychosis onset, the fact that findings are somewhat heterogeneous suggests that a more in-depth investigation is needed to shed light on the glutamatergic processes related to psychosis, by implementing larger longitudinal studies of FEP using ultra high field MR scanners.

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Conflict of Interest

None.

Ethical Standard

The authors declare that no human or animal experimentation was conducted for this work.

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