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Elevated cortical glutamate in young people at increased familial risk of depression



Matthew J. Taylor¹, Zola N. Mannie¹, Ray Norbury^{1,3}, Jamie Near² and Philip J. Cowen¹

¹ Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK

² The Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, John Radcliffe Hospital, Oxford, UK

³ The Oxford Centre for Magnetic Resonance Research (OCMR), John Radcliffe Hospital, Oxford, UK

Abstract

Using proton magnetic resonance spectroscopy (MRS), we have demonstrated regional abnormalities in cortical γ -aminobutyric acid (GABA) and glutamate in medication-free recovered depressed patients. It is unclear whether these changes represent an underlying trait vulnerability to depression, or an after-effect of episodes of illness or its treatment. We sought to examine this question by examining a group of high-risk, never-depressed, individuals. We used MRS to measure GABA and glutamate in parieto-occipital cortex in young people (ages 16–21 yr) with a family history of parental depression ($n=24$) but no personal history of illness and a control group without a history of depression in any first-degree relative ($n=28$). Participants with a parental history of depression had significantly higher levels of glutamate than controls in parieto-occipital cortex ($F_{1,47}=5.5$, $p=0.02$). These findings suggest that abnormalities in glutamate neurotransmission may reflect a trait marker of vulnerability to depression.

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Key words: Depression, GABA, glutamate, magnetic resonance spectroscopy, vulnerability.

Introduction

The monoamine theory of depression has dominated biochemical research in the field of depression for over 50 yr, but there is growing interest in the role of the amino-acid neurotransmitters, γ -aminobutyric acid (GABA) and glutamate, in the pathophysiology and treatment of mood disorders (Sanacora *et al.* 2008; Taylor *et al.* 2003). Using proton magnetic resonance spectroscopy (¹H-MRS), Sanacora *et al.* (2004) demonstrated decreased levels of GABA and increased glutamate in occipital cortex in patients suffering from acute major depression and we found the same pattern in recovered depressed and bipolar patients withdrawn from medication (Bhagwagar *et al.* 2007). It is unclear whether these changes in GABA and glutamate reflect an underlying trait vulnerability to depression, or are an after-effect ('scar') of episodes of illness or its treatment. Resolving this issue is important because it may have implications for preventative strategies in people at high risk of illness.

Numerous factors that increase the risk of depression have been described but one of the most reliable is family inheritance. For example, it has been estimated that by young adulthood up to 40% of children of parents with a clinical mood disorder will have suffered a personal episode of depression (Beardslee *et al.* 1998). Previous studies have shown that such at-risk individuals demonstrate a number of neurobiological abnormalities relevant to depression, including, for example, hypersecretion of cortisol (Mannie *et al.* 2007) and decreased hippocampal volume (Rao *et al.* 2010). The aim of the present study was to use ¹H-MRS to test the hypothesis that occipital GABA levels would be lower and glutamate levels higher in young people who had a depressed parent but who had not themselves been clinically depressed.

Method

Participants

We recruited 24 young people (14 females, age range 16–21 yr) who had never personally suffered from major depression but who had a biological parent with a history of major depression (FH). Potential

Address for correspondence: Dr M. J. Taylor, University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX, UK.

Tel.: +44 1865 226466 Fax: +44 1865 251076

Email: matthew.taylor@psych.ox.ac.uk

participants were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders Schedule (SCID-I) to exclude a personal current or previous history of major depression. The presence of major depression in a parent was assessed by the family history method using the participant as an informant as described previously (Mannie *et al.* 2010). We also recruited 28 controls (14 female, age range 17–21 yr) who were determined by the same instruments to have no current or past history of major depression and no history of depression in a biological parent or other first-degree relative (HC).

Participants were assessed on the Beck Depression Inventory (BDI) for current mood state and the State and Trait Anxiety Inventory (STAI) for current and trait anxiety. After complete description of the study, all participants gave full informed written consent to participate in the study, which was approved by the local ethics committee. Participants received an honorarium for their participation.

MRS methodology

Scanning was performed on a 3-T Varian INOVA system with a head-optimized gradient coil (Tesla Engineering, UK) and a head-only transmit/receive quadrature birdcage RF coil. Data were acquired from a $30 \times 30 \times 20$ mm voxel positioned manually by reference to an axial T₁-weighted gradient-echo image. The voxel included parts of the posterior cingulate gyrus, parietal lobe and occipital lobe as previously described [Supplementary Fig. S1 (available online); Bhagwagar *et al.* 2007].

Point-resolved spectroscopy (PRESS) data with water suppression (TE 26 ms, TR 3 s, 64 averages), and without (TE 26 ms, TR 3 s) were acquired. PRESS-J data (Hurd *et al.* 2004) were similarly acquired for glutamate quantitation (TE 35–185 ms, 10-ms increments; water-suppressed data, total acquisitions = 128; non-water-suppressed data, total acquisitions = 16; TR = 3 s). A MEGA-PRESS sequence (Mescher *et al.* 1998) was employed for J-difference editing of the 3.0 ppm GABA resonance (TR 3 s, TE 68 ms, 128 averages). For some participants ($n=44$), data were also acquired similarly where a pre-inversion (TI 800 ms) was added to the MEGA-PRESS sequence to null the metabolite signal, to allow for correction of GABA estimates for the contribution of co-edited macromolecules. T₁-weighted structural images of whole brain were acquired with 2 mm³ voxel resolution. PRESS data were analysed with LCModel software (Provencher, 1993), using the non-water-suppressed data for eddy current correction and water

referencing, calculating metabolite concentrations for glutamate+glutamine (Glx), *N*-acetyl aspartate (NAA), myo-inositol, choline, and NAA relative to creatine in conventional fashion using metabolite basis spectra and simulated lipid and macromolecule components, and rejecting metabolite estimates with Cramer Rao Lower Bound (CRLB) > 20%.

Measurements from the edited PRESS-J and MEGA-PRESS spectra were performed using AMARES (advanced method for accurate, robust and efficient spectral fitting) (Vanhamme *et al.* 1997). PRESS-J spectra were zero-order phased, apodised with a 5 Hz Gaussian filter, and summed (Hurd *et al.* 2004) before analysis, and glutamate levels measured relative to creatine. GABA levels were measured relative to NAA in the MEGA-PRESS spectra and expressed relative to creatine using the voxel-specific NAA/creatin ratios from PRESS spectra. FMRIB's automated segmentation tool (FAST) (Zhang *et al.* 2001) was employed to segment the structural brain images into grey matter, white matter, and CSF, to allow estimation of voxel composition.

Statistical analysis

Statistical analyses were performed in SPSS version 15 (SPSS Inc., USA). The available MRS measures (Glx, glutamate, myo-inositol, choline, NAA, GABA) were initially compared between groups by multivariate analysis using Wilks' lambda, with voxel grey-matter content, age, and BDI score included as covariates. Two-tailed univariate analysis for each measure independently was then performed to identify the basis of any overall group effect. To investigate the sensitivity of the results to the use of creatine as reference, levels of creatine referenced to tissue water were compared between groups, and multivariate analyses repeated as above using measures referenced to tissue water. Exploratory comparisons of other measures between groups were performed by *t* test or χ^2 test as appropriate.

Results

In demographic terms the FH group and controls were similar (Table 1). BDI scores in both groups were in the normal range, although statistically significantly higher in the FH group ($p=0.005$). The average age of the FH group was 0.9 yr higher than of the controls ($p=0.02$).

MRS analyses revealed significant effects of group ($F_{6,42}=2.35$, $p=0.048$) and BDI score ($F_{6,42}=2.63$, $p=0.03$), but no effect of age ($p=0.4$). The group effect was driven by differences in levels of glutamate (Fig. 1;

Table 1. Group characteristics

	Parental history of major depression (n=24)	No family history of depression (n=28)
Age, yr, mean (range)	18.9 (16–21)*	19.8 (17–21)
Gender	14 female	14 female
Beck Depression Inventory	4.5 (0.80)*	2.3 (0.44)
Spielberger Trait Anxiety	34.8 (1.7)	31.3 (1.3)
Spielberger State Anxiety	30.0 (1.2)	28.8 (5.0)
Smoking history	7 smokers	3 smokers

Mean values with standard deviation unless otherwise stated.

* $p < 0.05$, t test.

$F_{1,47} = 5.5$, $p = 0.02$). There was no significant effect of group on Glx ($F_{1,47} = 0.003$, $p = 0.95$) or on other measures ($p > 0.15$ in all cases). In a subgroup ($n = 44$) where data was available to allow for macromolecule correction of GABA levels, no effect of group was seen ($p = 0.86$, t test). The effect of BDI identified by multivariate analysis above was found on univariate analysis to be explained an effect of BDI on choline ($F_{1,47} = 4.4$, $p = 0.04$). In particular, no significant effect of BDI on glutamate was observed ($F_{1,47} = 1.3$, $p = 0.26$).

The groups did not differ significantly in gender breakdown or smoking status (Table 1), and neither factor was associated with differences in glutamate ($p > 0.3$ in both cases). Levels of creatine relative to tissue water did not differ between groups ($p = 0.28$), and repeating MRS analyses with levels referenced to tissue water rather than creatine produced a similar pattern of results including a significant multivariate effect of group ($F_{6,42} = 2.50$, $p = 0.037$) and a significant difference in glutamate between groups ($F_{1,47} = 6.6$, $p = 0.013$), but no difference in GABA levels ($F_{1,47} = 0.001$, $p = 0.98$).

Discussion

In FH participants we found an increase in glutamate in occipital cortex but no change in GABA. Our findings are consistent with the notion that abnormalities in glutamate neurotransmission might be present in people at risk of depression as well as in patients with acute depression and those recovered from it (Bhagwagar *et al.* 2007; Sanacora *et al.* 2004). Usually in MRS studies at conventional field strengths, glutamate is measured as a composite with glutamine (Glx) and it is noteworthy that using the PRESS-J technique we were able to identify an increase in glutamate

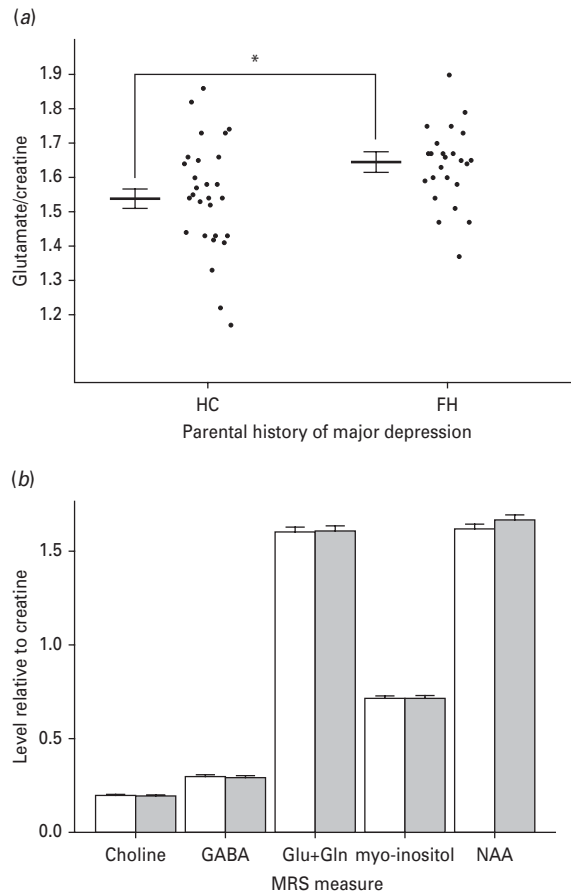


Fig. 1. MRS measures relative to creatine in parieto-occipital cortex of healthy participants with (FH, $n = 24$) or without (HC, $n = 28$) a history of major depression in at least one parent. (a) Glutamate: individual data and summary statistics by group (left HC; right FH; * $F_{1,47} = 5.5$, $p = 0.02$). (b) Choline, GABA, total glutamate + glutamine (Glu + Gln), myo-inositol, and *N*-acetyl aspartate (NAA) by group (\square , HC; \blacksquare , FH). Estimated marginal means (\pm S.E.M.) for Beck Depression Inventory score 3.1, voxel grey-matter content 49%, age 19.75 yr.

specifically. This is consistent with the finding of Sanacora *et al.* (2004) who found increased occipital glutamate but normal levels of glutamine in patients with acute depression. However, the increase in glutamate found by these authors was about 12%, substantially greater than that seen in the present study. This raises the possibility that acute depression might be associated with a further increase in glutamate over that seen in people who are at risk but currently euthymic. Alternatively, the magnitude of effect seen here might be diluted by the (inevitable) inclusion of some participants who will not go on to develop depression themselves. Longitudinal studies are required to clarify this issue.

It is important to note that the increase we found in glutamate in FH subjects might well be region specific. MRS studies in depression have been performed in many brain regions (Yildiz-Yesiloglu & Ankerst, 2006). Of particular note, in contrast to the findings in occipital cortex, MRS measures of Glx in anterior brain regions in acutely depressed patients tend to report decreased levels (Auer *et al.* 2000; Hasler *et al.* 2007), and using the PRESS-J technique, we found normal glutamate concentrations in anterior cingulate cortex in recovered depressed patients (Taylor *et al.* 2009). GABA levels are also lowered in occipital cortex in acutely depressed and recovered depressed patients (Bhagwagar *et al.* 2007; Sanacora *et al.* 2004); however, we found no change in GABA in our FH participants suggesting that diminished cortical GABA might be a feature of established depression rather than being associated with vulnerability to its onset.

Interpreting the functional effect of a change in a static measure of MRS glutamate is difficult because of the dynamic nature of glutamate-glutamine cycling (Danbolt, 2001). Astrocytes play a key role in this process and our findings are of interest in view of the neuropathological evidence for glial cell deficits in patients with mood disorders (Rajkowska & Miguel-Hidalgo, 2007). However, when such abnormalities occur in relation to the course of illness is not known. This process might be investigated further using ¹³C-MRS which permits the measurement not only of overall glutamate levels, but also rates of glutamate-glutamine cycling through glia (Shen *et al.* 1999). Emerging evidence suggests that such MRS findings may reveal the biochemical underpinnings of altered resting state activity in depression (Alcaro *et al.* 2010).

Our study has a number of limitations including modest sample size. Our findings will therefore need to be confirmed in a larger cohort of at-risk individuals preferably using MRS at higher field strength to permit more sensitive and accurate determination of glutamate in both occipital cortex and anterior brain regions. Our FH participants identified themselves by self-report on the family history method and there would have been more confidence in this assessment if we had also interviewed the relevant parent. FH participants also had small but significant increased scores on the BDI. However, we controlled for this by including mood score as covariates in our MRS analysis. While we aimed to exclude individuals with a past history of major depression, it is possible that some FH participants might have experienced previous depressive symptomatology which was not detected by our screening method and which could have led to the changes we found in occipital glutamate levels

(Bhagwagar *et al.* 2007). Finally, while our FH participants are at increased risk of depression many of them will not develop clinical illness and we do not know whether elevated glutamate levels are, in fact, linked to future major depression. Prospective studies are required to elucidate this important question.

Note

Supplementary material accompanies this paper on the Journal's website (<http://journals.cambridge.org/pnp>).

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Statement of Interest

Professor Cowen has been a paid member of advisory boards of Eli Lilly, Servier, Wyeth and Xytis and has been a paid lecturer for Eli Lilly, Servier and GlaxoSmithKline. He has received remuneration for scientific advice given to legal representatives of GlaxoSmithKline. Dr Taylor's spouse is an employee of GlaxoSmithKline.

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