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Relationship between brain glutamate levels and clinical outcome in individuals at ultra high risk of psychosis

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Abstract

Alterations in brain glutamate levels may be associated with psychosis risk, but the relationship to clinical outcome in at risk individuals is unknown. Glutamate concentration was measured in the left thalamus and anterior cingulate cortex (ACC) using 3 Tesla proton magnetic resonance spectroscopy in 75 participants at Ultra High Risk (UHR) of psychosis and 56 healthy controls. The severity of attenuated positive symptoms and overall functioning was assessed. Measures were repeated in 51 UHR and 33 Control subjects after a mean of 18 months. UHR subjects were allocated to either remission (no longer meeting UHR criteria) or non-remission (meeting UHR or psychosis criteria) status on follow-up assessment. Thalamic glutamate levels at presentation predicted UHR remission status (χ^2 (1, N = 51) = 8.63; P = 0.003). In the UHR group, ACC glutamate levels were lower at follow-up compared to baseline (F(80) = 4.28; P = 0.04). These findings suggest that measures of brain glutamate function may be useful as predictors of clinical outcome in individuals at high risk of psychosis.

Keywords

Glutamate; Psychosis; Magnetic Resonance Spectroscopy; Outcome; Thalamus; Anterior cingulate cortex

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Introduction

Abnormalities in glutamatergic neurotransmission are thought to play a key role in the pathophysiology of schizophrenia (Goff and Coyle, 2001; Javitt and Zukin, 1991; Olney and Farber, 1995), and this is supported by evidence from post-mortem, neuroimaging and genetic studies (Harrison and Weinberger, 2005; Konradi and Heckers, 2003; Pilowsky *et al*, 2006). In experimental animals, administration of antagonists at the N-methyl-D-aspartate (NMDA) glutamate receptor complex leads to injury to cortical neurons (Sharp *et al*, 2001) and over-activity of medial temporal glutamatergic projections induces striatal hyperdopaminergia (Lodge and Grace, 2007). Glutamatergic dysfunction could thus contribute to the loss of grey matter and dopamine dysfunction that are robust features of schizophrenia (Carlsson *et al*, 2001; Javitt, 2007; Olney *et al*, 1999).

The thalamus is a central component of the cortical-subcortical circuits through which psychotic symptoms are thought to be generated (Jones, 1997). Post-mortem in schizophrenia, reduced expression of ionotropic glutamate receptor subunits specifically occurs in thalamic relay neurons that send projections to the cortex (Sodhi *et al*, 2011). Thalamic nuclei are especially sensitive to the effects of NMDA antagonist administration, leading to disruptions in cortical activity (Kargieman *et al*, 2008) and cortical damage (Tomitaka *et al*, 2000), probably via increased cortical glutamate release from thalamo-cortical projections (Tomitaka *et al*, 2000).

The first episode of psychosis is often preceded by a clinical syndrome, termed an ‘at risk mental state’, characterized by attenuated psychotic symptoms and a marked decline in functioning, which can be identified using the Ultra High Risk (UHR) criteria (Yung *et al*, 2004). The UHR state is associated with a 20% risk for developing psychosis within one year (Fusar-Poli *et al*, 2012), and risk of transition is greatest in UHR individuals who have low levels of functioning, marked negative symptoms and disorders of thought content (Nelson *et al*, 2013). Recent work has questioned the meaningfulness of no-transition/transition outcomes in UHR research (Yung *et al*, 2010), as the threshold for transition is solely based on the intensity of positive symptoms, and as functional outcomes may be persistently poor in the absence of transition. It is difficult to predict outcome at an individual level on the basis of presenting clinical features (Nelson and Yung, 2010), and neuroimaging measures may be able to help improve prediction (Fusar-Poli *et al*, 2013a).

Proton magnetic resonance spectroscopy (^{1}H-MRS) studies at high field strengths in never- or minimally-medicated early psychosis have reported elevated levels of the glutamate metabolite glutamine in the thalamus and anterior cingulate cortex (ACC) (Theberge *et al*, 2002; Theberge *et al*, 2007), elevated ACC glutamine/glutamate ratio (Bustillo *et al*, 2010), elevated striatal glutamate (de la Fuente-Sandoval *et al*, 2013b; de la Fuente-Sandoval *et al*, 2011), and elevated glutamate plus glutamine in the hippocampus (Kraguljac *et al*, 2013). In an UHR cohort, we reported lower levels of glutamate in the thalamus, but not ACC, compared to healthy individuals (Stone *et al*, 2009a). This reduction in thalamic glutamate is associated with lower grey matter volume (Stone *et al*, 2009a), and abnormal cortical responses during executive functioning (Fusar-Poli *et al*, 2011), and to auditory stimuli (Stone *et al*, 2010). Another study in UHR subjects suggests that glutamate levels may be

elevated in the striatum (de la Fuente-Sandoval *et al*, 2011). These findings are consistent with the proposal that glutamatergic abnormalities predate the onset of psychosis (Stone *et al*, 2009a; Stone and Fusar-Poli, 2009b) leading to the hypothesis that the extent of glutamate dysfunction may contribute to clinical outcome. This issue can best be addressed through longitudinal studies of glutamatergic abnormalities in this group. Preliminary data from a study in a small UHR cohort have recently indicated that greater risk of transition and longer duration of illness were associated with higher glutamate levels in the striatum at baseline (de la Fuente-Sandoval *et al*, 2013a).

The primary aim of this study was to determine whether regional glutamate levels in UHR subjects at first presentation are predictive of subsequent clinical outcome. The secondary aim was to determine relationships between longitudinal changes in glutamate and mental state. In extension of our previous work which identified reduced glutamate in the left thalamus in UHR individuals (Stone *et al*, 2009a), we hypothesised that lower thalamic glutamate levels at presentation would be associated with worse clinical outcome, and that longitudinal decreases in thalamic glutamate may be associated with declining mental state. As studies in early psychosis report elevated glutamine or glutamine/glutamate ratio in the ACC (Theberge *et al*, 2002; Theberge *et al*, 2007), and meta-analysis suggests that decreases in frontal glutamate in schizophrenia may progress over time (Marsman *et al*, 2011), we hypothesised ACC glutamate may decline over the study period and associate with increasing symptom severity.

Participants and Methods

Participants

This study was approved by the Joint South London and Maudsley (SLaM) NHS Trust Research Ethics Committee. All participants gave their written consent to participate. The sample consisted of the 27 healthy control and 27 UHR subjects who had participated in our cross-sectional study (Stone *et al*, 2009a), plus an additional recruitment of 29 Control and 48 UHR subjects, giving total samples of 56 Control and 75 UHR subjects.

UHR subjects were recruited from OASIS (Outreach and Support in South London) (Fusar-Poli *et al*, 2013b), and met at risk mental state criteria (Yung *et al*, 2005) at the time of baseline imaging. The Control group was recruited from the same geographic area, and had no personal history of psychiatric symptoms, psychotropic medication, or medical illness and no family history of psychiatric illness. Exclusion criteria included history of head injury, drug or alcohol dependence, metallic implants or other contraindications for magnetic resonance imaging (MRI).

Symptomatology was assessed using the Comprehensive Assessment of At-Risk Mental State (CAARMS, severity of abnormal thought content, abnormal speech and perceptual abnormalities, which were also summed to provide a total severity score for attenuated psychotic symptoms) (Yung *et al*, 2005) and the Positive and Negative Syndrome Scale for Schizophrenia (PANSS). Social and occupational functioning was assessed using the Global Assessment of Functioning scale (GAF), which provides a single score out of a maximum of

100 for social and occupational functioning as well as symptoms. OASIS uses the CAARMS and GAF to determine UHR inclusion criteria (Fusar-Poli *et al*, 2013b).

^{1}H-MRS

Scans were acquired at 3 Tesla, as described previously (Egerton *et al*, 2012a; Stone *et al*, 2009a) in Control and UHR subjects in parallel. ^{1}H-MRS spectra were acquired using Point RESolved Spectroscopy (PRESS) (TE = 30 msec; TR = 3000 msec; 96 averages), further details of ^{1}H-MRS data acquisition and analysis are provided in Supplementary Material. Spectra were analysed using LCModel version 6.1-4 F (Provencher, 1993), and water-scaled metabolite values were corrected for voxel cerebrospinal fluid (CSF) content. Our approach using PRESS with a TE = 30ms at 3 Tesla is documented to reliably detect glutamate concentrations (Mullins *et al*, 2008), with contamination by glutamine estimated as <10% (Snyder and Wilman, 2010). Regarding spectral quality, the mean ± SD signal to noise ratio and line-width as reported by LCModel were: Left thalamus; 20 ± 3 and 0.05 ± 0.01 Hz respectively and ACC: 21 ± 6 and 0.04 ± 0.06 Hz respectively. There were no significant group differences in spectral quality. Data relating to the voxel tissue content and the Cramer-Rao minimum variance bounds (CRLB) estimates of fit of the metabolite peaks are presented in Supplementary Tables S1 and S2. The primary ^{1}H-MRS glutamate measure was glutamate corrected for voxel CSF content (GLU_{CSF}). For completeness, and to allow comparison with previous literature, where significant results for CSF-corrected glutamate data were detected, CSF-corrected glutamate plus glutamine (GLX_{CSF}) and creatine-scaled glutamate (GLU_{CR}) and glutamate plus glutamine (GLX_{CR}) are also reported.

Statistical analysis

Statistical analysis was performed in SPSS version 15.0 (SPSS, Chicago, Illinois). Group differences in demographic or clinical variables were assessed using 2-tailed independent samples *t*-tests or Pearson Chi square as appropriate. For primary analyses relating to GLU_{CSF}, statistical significance was defined as $P < 0.05$ uncorrected. Exploratory analyses of the other metabolites present in the spectra were corrected for multiple comparisons (threshold *P* for 4 metabolites, 2 voxels; = 0.05÷8 = 0.006).

Group differences in thalamic glutamate levels in the extended cohort of UHR and Control subjects, were initially examined using independent samples t-tests, followed up by ANOVA to control for significant or near-significant group differences in drug use. Potential differences between UHR and Control subjects in glutamate levels at follow-up and in change in glutamate levels over time were determined using linear mixed models with group as the fixed variable and time (baseline and follow-up) as the repeated measure.

In testing the primary hypothesis, that lower thalamic glutamate levels at presentation would be associated with worse clinical outcome, UHR subjects were subdivided into remission (UHR-R) and non-remission (UHR-NR) groups on the basis of the follow-up clinical assessment. The UHR-NR group included UHR patients who still met criteria for attenuated psychosis or who had transitioned to overt psychosis (Phillips *et al*, 2000). The UHR-R group included patients who no longer fulfilled criteria for UHR status and had not converted to psychosis. The number of participants who transitioned to psychosis was too

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small to permit meaningful statistical analysis of data in this group alone, but transition cases are indicated in the figures. The predictive value of thalamic glutamate in determining clinical outcome (UHR-R versus UHR-NR) was assessed using binary logistic regression. Potentially confounding baseline variables, such as drug use, were added to the regression model in secondary analyses. Pearson's correlation was used to determine relationships between glutamate levels at baseline and GAF score or total attenuated psychotic symptoms at follow-up. Where a significant relationship with total attenuated psychotic symptoms was detected, secondary analysis tested the strength of correlation (uncorrected) with the individual attenuated psychotic symptom scales (abnormalities of thought content, speech and perception). Relationships between baseline glutamate concentrations and absolute change in attenuated psychotic symptoms or GAF score over time were calculated using partial correlation coefficients, co-varying for baseline scores to control for regression to the mean. The secondary hypothesis, that longitudinal changes in glutamate may relate to change in mental state, was examined using linear mixed models with group (UHR-R versus UHR-NR) as the fixed variable and time (baseline and follow-up) as the repeated measure.

Results

Demographic and clinical variables

Demographic and clinical variables at baseline are presented in Table 1. Three of the 75 UHR subjects (9%) were taking an antipsychotic medication at the time of baseline imaging (quetiapine, olanzapine and risperidone) and six were taking antidepressant medication (all citalopram). The newly recruited cohort were on average younger than the previous cohort (Mean ± SD age, cohort 1: 25.1 ± 5.3; cohort 2: 22.2 ± 4.2 years; $t(78) = 2.6$; P = 0.012), and had marginally lower GAF scores (mean ± SD cohort 1: 63.0 ± 14.9; cohort 2: 57.0 ± 8.4; $t(78) = 2.0$; P = 0.05) but did not differ in severity of total attenuated positive symptoms (mean ± SD cohort 1: 6.7 ± 3.5; cohort 2: 7.7 ± 3.7; $t(78) = 0.6$; P = 0.57).

Follow-up clinical measures were available in 51 UHR subjects (68% of the original sample) (Table 2). There was no difference in baseline demographic or clinical measures between UHR subjects in whom follow-up assessment was or was not available (data not shown). The mean ± SD time between clinical assessments was 18.1 ± 8.5 months (Min: 2.9; Max: 58.7 months). With the exception of cases where subjects made transition to psychosis, follow-up occurred at least 12 months after baseline imaging. In 18 of the 24 UHR subjects who could not be reassessed in person, follow-up information was available from their clinical records. There was no recorded evidence that any of these subjects had developed psychosis over at least a 12-month period following baseline assessment, but records did not provide sufficient information to assess remission status. At follow-up, 23 UHR participants (45%) still met criteria for attenuated psychosis and 6 met criteria for first episode psychosis (4 from cohort 1 and 2 from cohort 2). The mean ± SD time to transition after baseline assessment was 473 ± 326 days, range 78-898 days. These subjects together formed the UHR-NR group (N=29). In contrast, 22 UHR subjects (43%) no longer met UHR criteria (UHR-R). At follow-up two UHR subjects (both in the UHR-R group) were taking quetiapine. Baseline demographic variables did not differ between the UHR-R and UHR-NR groups (Table 1). The UHR-NR group presented with higher levels of attenuated

positive symptoms (Table 1). Thirty-three subjects in the Control group completed follow-up assessments, with a mean ± SD length of time to follow-up of 16.9 ± 6.7 months (Min: 9.5, Max: 35.1 months).

Glutamate levels in the UHR compared to Control group

At baseline, compared to Control, UHR subjects had lower levels of GLU_{CSF} in the thalamus ($t(127) = 2.15$; $P = 0.03$; d = 0.41, Table 3), but not the ACC ($t(124) = 0.04$; $P = 0.97$, Table 3). This group difference remained significant after co-varying for smoking status (F(1, 128) = 3.75; $P = 0.03$), ketamine use (F(1,128) = 5.51; $P = 0.02$), ecstasy use (F(2,128) = 4.43; P = 0.04) and voxel grey matter proportion (%GM = GM/(GM +WM)*100, where GM = grey matter; WM = white matter) (F(1,128) = 5.83; $P = 0.02$). However thalamic GLX_{CSF}, GLU_{CR} and GLX_{CR} did not differ between UHR and Control ($P = 0.20$-0.43), and differences in glutamate metabolites between UHR and Control groups were not apparent when analysis was restricted to only the newly recruited subjects ($P = 0.56$).

Longitudinal glutamate levels in Control versus UHR groups

Follow-up scans were completed in 33 Control subjects and 47 UHR subjects, including 5 UHR subjects who had developed a psychotic disorder (Table 3). In the linear mixed effect models, there were no significant main effects of group (UHR versus Control), time or group by time interactions on GLU_{CSF}. The P-values associated with the lack of main effect of group, time or time × group interactions for GLU_{CSF} values were thalamus: group $P = 0.49$; time $P = 0.32$; interaction $P = 0.53$ and ACC: group $P = 0.13$; time $P = 0.11$; interaction $P = 0.24$. For the other metabolites present in the spectra there were no significant main effects of group (Table 3), time or group × time interactions (all $P > 0.05$).

Thalamic glutamate levels at intake and prediction of clinical outcome

The predictive value of baseline thalamic GLU_{CSF} on clinical outcome (UHR-R versus UHR-NR) was statistically significant (Chi-square (1, $N = 51$) = 8.63; $P = 0.003$; B = −0.66; SE = 0.25; $df = 1$; Wald = 6.49; OR = 0.52 (0.31-0.85); $P = 0.009$), indicating that baseline thalamic GLU_{CSF} reliably distinguished UHR-R from UHR-NR (Figure 1). This effect remained significant when controlling for baseline severity of attenuated positive symptoms (Chi-square (2, $N = 51$) = 14.61; $P = 0.001$), weekly alcohol units (Chi-square (2, $N = 51$) = 16.19; $P < 0.001$), or %GM (Chi-square (2, $N = 51$) = 8.67; $P = 0.01$), and was also significant for glutamate assessed as $GLX_{CSF,}$ GLU_{CR} and GLX_{CR} ($P = 0.005$ to 0.008). Baseline levels of other metabolites visible in the spectra did not associate with outcome (Table 3).

Thalamic glutamate levels at intake and symptom severity at follow-up

Baseline thalamic GLU_{CSF} was negatively associated with the severity of positive symptoms at follow-up ($r = -0.39$; $df = 51$; $P = 0.004$). This relationship was strongest for the severity of abnormal thought content ($r = -0.42$; $df = 51$; $P = 0.002$), and significant for the severity of perceptual abnormalities ($r = -0.317$; $df = 51$; $P = 0.02$), but not for the severity of speech abnormalities ($r = -0.22$; $df = 51$; $P = 0.12$). The negative relationships

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between baseline thalamic glutamate and follow-up total positive symptoms or abnormal thought content were also significant for $GLX_{CSF,}$ GLU_{CR} and GLX_{CR} (P = 0.037 to 0.004), or co-varying for %GM (P = 0.02). The positive correlation between baseline thalamic GLU_{CSF} and follow-up GAF score was below the threshold for significance (r = 0.27; df = 51; P = 0.06).

Thalamic glutamate levels at intake and longitudinal change in symptom severity

Thalamic GLU_{CSF} was negatively associated with the longitudinal change in attenuated positive symptoms over time, such that an increase in severity of symptoms occurred in those with lower thalamic GLU_{CSF} at presentation (r = −0.40; df = 47; P = 0.005, Figure 2, and where for $GLX_{CSF,}$ GLU_{CR} and GLX_{CR} P = 0.06 to 0.009). This relationship was strongest for the severity of abnormal thought content (r = −0.42; df = 47; P = 0.003; $GLX_{CSF,}$ GLU_{CR} and GLX_{CR} P = 0.005 to 0.04, co-varying for %GM: P = 0.02), significant for the severity of perceptual abnormalities (r = −0.33; df = 47; P = 0.02; $GLX_{CSF,}$ GLU_{CR} and GLX_{CR} P = 0.05 to 0.16) but not speech abnormalities (r = −0.21; df = 47; P = 0.14). Baseline thalamic GLU_{CSF} also correlated with change in GAF score over time, such that lower glutamate levels were associated with declining functioning (r = 0.31; df = 47; P = 0.03), but this relationship did not reach significance for $GLX_{CSF,}$ GLU_{CR} or GLX_{CR} (P = 0.12 to 0.44).

Longitudinal glutamate levels in UHR-R versus UHR-NR groups

Metabolite levels at follow-up are presented in Table 3. The main effect of group (UHR-R versus UHR-NR) on thalamic GLU_{CSF} concentrations over time was slightly above the threshold for statistical significance (F79 = 3.39; P = 0.07), and reached significance for GLX_{CSF} (P = 0.02, Table 3). There was no significant main effect of time (P = 0.10) or group by time interaction (P = 0.58). For ACC GLU_{CSF} concentrations, there was no significant effect of group (P = 0.52) or time × group interaction (P =0.99) but ACC GLU_{CSF} was lower overall in UHR participants at follow-up (main effect of time F(80) = 4.28; P = 0.04). The p-values associated with main effects of time for ACC GLX_{CSF}, GLU_{CR} and GLX_{CR} were P = 0.09, 0.43 and 0.04 respectively. No significant main effects or interactions were apparent for the other metabolites present in the spectra (all P > 0.05 and see Table 3).

Discussion

The main finding of this study was that low levels of thalamic glutamate at presentation are associated with poor clinical outcomes in UHR individuals. Low thalamic glutamate was associated with the persistence or worsening of positive symptoms, and particularly abnormal thought content. This extends previous cross-sectional studies suggesting that brain glutamatergic abnormalities are present in individuals at high risk of developing psychosis (de la Fuente-Sandoval *et al*, 2011; Lutkenhoff *et al*, 2010; Stone *et al*, 2009a; Tibbo *et al*, 2004), in that it suggests that the magnitude of these abnormalities is related to subsequent clinical outcome. In the UHR group, longitudinal data found no evidence that changes in glutamate levels over time were related to change in mental state.

Consistent with our previous report (Stone *et al*, 2009a) in what was a subsample of the UHR group in the present study, we found that the levels of thalamic GLU_{CSF} in the UHR subjects at baseline was significantly lower than that in controls. However this difference does not appear robust, as it did not reach significance when glutamate was analysed in combination with glutamine (Glx) or using scaling to creatine, was less marked following the additional recruitment to the present study (and not significant in only the newly recruited sample), and was not apparent in the smaller sample at the follow-up time point. Consistent with a lack of difference in thalamic glutamate in UHR compared to control subjects, previous studies have reported a lack a difference in thalamic glutamate levels in never- or minimally-medicated early psychosis (Aoyama *et al*, 2011; Theberge *et al*, 2002; Theberge *et al*, 2007), although thalamic glutamine may be elevated (Aoyama *et al*, 2011; Theberge *et al*, 2002; Theberge *et al*, 2007). Our finding that thalamic glutamate levels may be lower specifically in those UHR subjects who show poor outcomes may contribute to the overlap between the overall UHR group and control sample.

In addition to the present finding that low thalamic glutamate levels are associated with poor outcomes in UHR individuals, there is also evidence in a small cohort that striatal glutamate levels may be specifically elevated in UHR individuals who transition to psychosis (de la Fuente-Sandoval *et al*, 2013a). In contrast hippocampal Glx levels do not differ between subsequent transition and non-transition cases (Wood *et al*, 2010), and our present data additionally did not find any association between ACC glutamate and outcome. This may highlight the importance of prospective, rather than simply cross-sectional studies of glutamate in UHR cohorts, and also suggests regionally and perhaps temporarily distinct glutamatergic dysfunctions.

Over the course of this longitudinal study, of the 69 UHR individuals in whom the clinical outcome was known, 6 (8.7%) developed a psychotic disorder. This is lower than the transition rate that has been observed in previous follow-up studies of UHR samples (Fusar-Poli *et al*, 2012), although more transitions may occur as the follow-up period is extended. Nevertheless relatively low transition rates have been reported in some recent studies with long follow-up periods (Yung *et al*, 2007). Further, two individuals made transition within 6 months of baseline assessment, indicating they may have been close to conversion at baseline. As only a small number of subjects in our study developed psychosis, there was inadequate statistical power to test whether regional glutamate levels were significantly related to later transition, and this limits the clinical relevance of our findings. Instead, we classified clinical outcome according to whether or not UHR symptoms had remitted at follow-up, with transition cases forming a subset of the broader ‘non-remission’ group. In our sample, presenting UHR symptoms subsequently remitted in 43% of subjects, which is similar to the rate reported in other cohorts (Simon *et al*, 2013). We found that low thalamic glutamate levels at baseline were related to the non-remission of symptoms, and a progressive worsening of symptoms over time. These findings were also apparent when glutamate was analysed in combination with glutamine, or when using creatine-scaled rather than CSF-corrected data. In the subsample of UHR participants who completed follow-up scans, there was some indication that the lower thalamic glutamate levels in non-remission compared to remission cases were stable over time, as analysis of longitudinal data showed a

near-significant main effect of remission status on glutamate level (P=0.07), which reached significance for Glx. Thus, these results suggest that in UHR subjects, low thalamic glutamate levels are linked to poor clinical outcomes. In line with this, loss of thalamic glutamate plus glutamine has been associated with deteriorations in social functioning in schizophrenia (Aoyama *et al*, 2011).

In the UHR group as a whole, ACC glutamate levels were lower at follow-up than at baseline. However this could not be specifically attributed to declining ACC glutamate levels in the UHR compared to Control group, as the time by group interaction was above the threshold for statistical significance, and there was no evidence in UHR individuals that change in ACC glutamate levels were related to change in mental state. Nonetheless, lower levels of ACC glutamate in UHR subjects would consistent with the lower levels of frontal glutamate in schizophrenia reported by meta-analysis (Marsman *et al*, 2011), and in unaffected twins of patients with schizophrenia (Lutkenhoff *et al*, 2010), and partially consistent with studies in early psychosis that have reported elevated ACC glutamine (Theberge *et al*, 2002; Theberge *et al*, 2007), or elevated glutamine/glutamate ratio (Bustillo *et al*, 2010) as elevated glutamine may correspond to glutamate reduction.

Both the UHR and Control group included participants who currently or previously used recreational drugs. While their inclusion maintains generalizability to the UHR population at our clinical service, drug use may potentially impact on both brain glutamate levels and clinical symptoms or outcomes. Secondary analysis found no evidence for influences of substance abuse, although we did not include analyses of current use of substances (apart from nicotine or alcohol) due to relatively low frequencies. The present study employed a region of interest approach, and thus it was not possible to assess the role of brain areas other than the thalamus and ACC. However, it is likely that glutamatergic transmission in other regions, such as the hippocampus (Kraguljac *et al*, 2013; Lisman *et al*, 2008), and striatum (de la Fuente-Sandoval *et al*, 2013a; de la Fuente-Sandoval *et al*, 2011) is also important. Abnormalities in regional grey matter volume (Mechelli *et al*, 2011) and striatal dopamine synthesis capacity (Howes *et al*, 2011) are also associated with the later transition to psychosis, while functional imaging studies have implicated changes in prefrontal, hippocampal and midbrain regions (Allen *et al*, 2012). At the behavioural level, poor overall functioning, negative symptoms and disorders of thought content at presentation have also been linked to poor subsequent outcomes (Nelson *et al*, 2013). Studies that combine measurements from different imaging modalities along with behavioural measures may be more predictive of outcomes than measures in a single modality, although this has yet to be demonstrated in UHR subjects.

In conclusion, this study found evidence that glutamatergic abnormalities are associated with poor clinical outcomes in subjects at high risk of psychosis. This suggests that altered glutamatergic function may be an early component of a neuropathological process that leads to clinical and functional decline, and may result in a psychotic disorder, and that glutamatergic compounds may have therapeutic potential in the early phases of psychosis, as well as in established schizophrenia (Egerton *et al*, 2012b). Further studies should address the value of brain glutamate measures in predicting transition to psychosis and outcome in psychotic disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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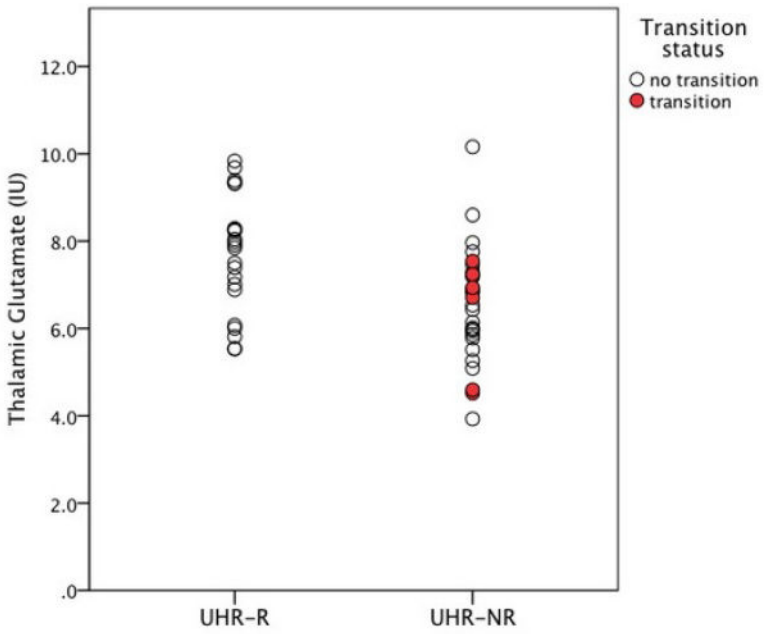

Figure 1.

Left thalamic glutamate at presentation in Ultra High Risk (UHR) subjects grouped by clinical outcome; UHR-R: remission, *N* = 22; UHR-NR: no remission, *N* = 29. Glutamate is presented as data corrected for voxel cerebrospinal fluid content, in institutional units (IU). Glutamate significantly predicted UHR remission status * *P* = 0.003. UHR subjects who made transition to psychosis are indicated in red.

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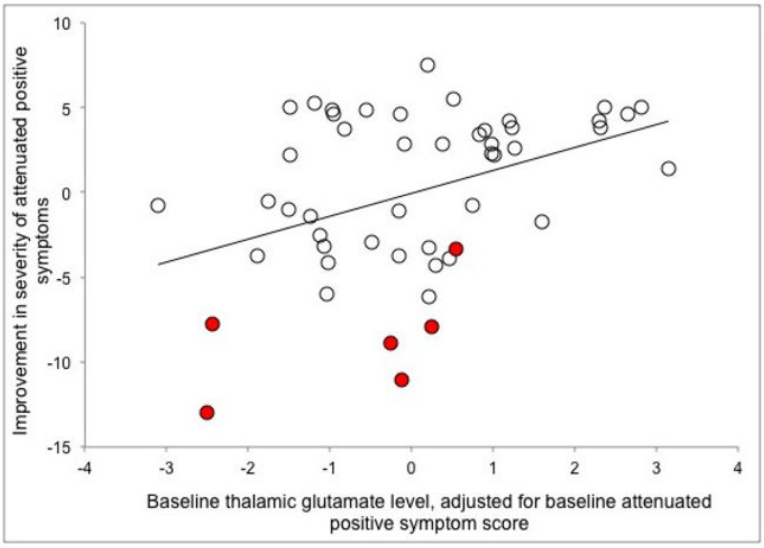

Figure 2.

Partial correlation between the baseline thalamic glutamate level and the change in the severity of attenuated positive symptoms (r = −0.40; *df* = 47; *P* = 0.005). UHR subjects who made transition to psychosis are indicated in red.

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Table 1
Baseline demographic and clinical variables

	Control *N* = 56	UHR *N* = 75	*P*	UHR-R *N* = 22	UHR-NR *N* = 29	*P*
Age, years; mean (SD)	24.6 (4.2)	23.3 (4.8)	0.10	23.8 (5.6)	22.7 (4.7)	0.44
Gender, Male/Female	32/24	41/34	0.79	11/11	16/13	0.78
Handedness, Right/Left	49/7	67/8	0.74	22/0	26/3	0.25
Education, years; mean (SD)	14.9 (2.3)	12.6 (2.0)	<0.001	12.3 (2.0)	13.0 (2.0)	0.24
IQ: NART errors; mean (SD)	17.1 (8.2)	22.6 (10.8)	0.003	20.3 (8.90	23.4 (12.1)	0.32
Baseline antipsychotic medication: No/ Yes	56/0	72/3	-	20/2	29/1	0.57
Baseline antidepressant medication No/Yes	50/0	69/6	-	21/1	24/5	0.22
Current smoker: No/Yes	42/14	29/46	<0.001	11/11	8/21	0.15
Cigarettes/day, mean (SD)	1.7 (3.6)	5.4 (6.4)	<0.001	4.9 (5.9)	6.8 (7.1)	0.30
Current alcohol drinker, No/Yes	9/47	18/57	0.27	6/16	6/23	0.74
Alcohol units/week, mean (SD)	8.4 (8.7)	7.8 (11.5)	0.75	4.0 (5.7)	9.2 (11.7)	0.06
Cannabis, ever used, No/Yes	22/34	24/51	0.39	7/15	11/18	0.77
Amphetamine, ever used, No/Yes	48/8	55/20	0.09	16/6	23/6	0.74
Cocaine, ever used, No/Yes	45/11	50/25	0.08	14/8	19/10	>0.99
Ecstasy/MDMA, ever used, No/Yes	42/14	58/17	0.06	16/6	23/6	0.74
Ketamine, ever used, No/Yes	54/2	65/10	0.06	19/3	25/5	>0.99
Thought Content abnormalities	0.1 (0.4)	3.0 (1.7)	<0.001	2.8 (1.6)	3.2 (1.7)	0.35
Perception abnormalities	0.2 (0.7)	2.7 (2.0)	<0.001	1.7 (1.9)	3.0 (2.0)	0.02
Speech abnormalities	0.1 (0.5)	1.6 (1.6)	<0.001	1.0 (1.2)	1.9 (1.9)	0.05
Total attenuated positive symptoms	0.4 (1.2)	7.3 (3.6)	<0.001	5.5 (3.0)	8.1 (4.1)	0.01
GAF score	85.9 (6.7)	59.2 (11.5)	<0.001	62.4 (12.0)	57.7 (11.3)	0.16
PANSS-P	7.1 (0.6)	12.9 (4.7)	<0.001	10.8 (3.6)	13.4 (4.6)	0.04
PANSS-N	7.1 (0.5)	11.4 (4.3)	<0.001	10.5 (3.7)	11.6 (4.2)	0.33
PANSS-G	16.5 (1.0)	26.2 (6.6)	<0.001	25.3 (7.0)	26.2 (5.9)	0.60
PANSS-T	30.7 (1.5)	50.8(13.1)	<0.001	46.5 (11.8)	51.6 (12.0)	0.14

Abbreviations. UHR: Ultra High Risk; R: remission; NR: no remission; NART: National Adult Reading Test; MDMA: 3,4-methylenedioxy-N-methylamphetamine; GAF: Global Assessment of Functioning scale; PANSS: Positive and Negative Syndrome Scale, P: positive; N: Negative; G: General and T: total.

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Table 2
Follow-up clinical measures in UHR participants

	UHR-R *N* = 22	UHR-NR *N* = 29	*P*
Thought Content abnormalities	0.2 (0.5)	3.6 (1.9)	<0.001
Perception abnormalities	0.2 (0.5)	3.6 (1.9)	<0.001
Speech abnormalities	0.7 (0.9)	2.1 (1.8)	0.001
Total attenuated positive symptoms	1.1 (1.3)	9.3 (3.9)	<0.001
GAF score	72.5 (11.2)	54.6 (15.8)	<0.001
PANSS-P	8.2 (1.7)	14.9 (4.9)	<0.001
PANSS-N	8.3 (2.5)	11.2 (5.0)	0.02
PANSS-G	18.7 (3.7)	25.5 (7.5)	0.001
PANSS-T	35.2 (7.0)	51.6 (15.8)	<0.001

Abbreviations. UHR-R: Ultra High Risk Remission; UHR-NR: No Remission; GAF: Global Assessment of Functioning scale; PANSS: Positive and Negative Syndrome Scale, P: positive; N: Negative; G: General and T: total.

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Table 3

Metabolite levels

Baseline	**Left Thalamus**			**Anterior Cingulate Cortex**			**Left thalamus**			**Anterior Cingulate Cortex**		
	Control *N* = 55	**UHR *N* = 75**	***P****	**Control *N* = 55**	**UHR *N* = 75**	***P****	**UHR-R *N* = 22**	**UHR-NR *N* = 29**	***P****	**UHR-R *N* = 22**	**UHR-NR *N* = 29**	***P****
Glutamate	7.6 ± 1.5	7.0 ± 1.4	0.03	13.2 ± 2.3	13.1 ± 2.8	0.97	7.7 ± 1.3	6.6 ± 1.3	0.003	13.0 ± 2.8	13.4 ± 3.1	0.36
Glx	9.3 ± 2.4	8.8 ± 2.0	0.20	18.0 ± 4.1	18.1 ± 5.6	0.98	9.7+2.1	8.1 ± 1.9	0.01	17.6 ± 5.9	18.8 ± 6.1	0.27
NAA	12.4 ± 0.9	12.1 ± 1.2	0.10	13.0 ± 2.1	12.9 ± 2.0	0.80	12.2 ± 1.8	12.1 ± 0.8	0.65	12.6 ± 2.2	13.2 ± 2.0	0.14
Cr	7.2 ± 0.8	6.9 ± 0.8	0.11	10.1 ± 1.7	10.0 ± 1.7	0.91	7.2 ± 1.1	6.9 ± 0.7	0.33	9.8 ± 2.2	10.2 ± 1.6	0.23
mI	4.9 ± 2.1	4.6 ± 1.5	0.28	8.4 ± 1.4	8.2 ± 1.7	0.45	4.3 ± 1.1	4.4 ± 1.3	0.88	7.9 ± 2.0	8.5 ± 1.7	0.13
TCho	2.1 ± 0.2	1.9 ± 0.3	0.01	2.8 ± 0.7	2.6 ± 0.5	0.24	2.0 ± 0.3	1.9 ± 0.2	0.03	2.6 ± 0.7	2.7 ± 0.5	0.29
Follow-up												
	Control *N* = 33	UHR *N* = 47	*P****	Control *N* = 33	UHR *N* = 47	*P****	UHR-R *N* = 22	UHR-NR *N* = 26	*P****	UHR-R *N* = 21	UHR-NR *N* = 26	*P****
Glutamate	7.1 ± 1.7	6.9 ± 1.4	0.49	13.2 ± 2.4	12.0 ± 2.3	0.13	6.8 ± 1.4	7.1 ± 1.4	0.07	11.8 ± 2.4	12.1 ± 2.4	0.52
Glx	8.7 ± 2.3	8.5 ± 2.1	0.26	17.8 ± 3.7	16.4 ± 3.5	0.56	8.8 ± 2.6	8.2 ± 1.5	0.02	16.5 ± 3.7	16.4 ± 3.4	0.56
NAA	11.6 ± 1.6	11.8 ± 1.1	0.09	13.0 ± 1.5	12.4 ± 1.5	0.14	11.6 ± 1.3	12.0 ± 0.9	0.48	12.2 ± 1.3	12.6 ± 1.6	0.21
Cr	6.9 ± 0.6	6.9 ± 6.2	0.99	9.6 ± 1.4	9.7 ± 1.4	0.38	6.9 ± 0.6	6.9 ± 0.6	0.58	9.3 ± 1.5	10.0 ± 1.3	0.13
mI	4.2 ± 0.9	4.2 ± 0.8	0.07	8.7 ± 2.2	8.0 ± 1.6	0.27	4.1 ± 0.8	4.2 ± 0.9	0.67	7.7 ± 1.6	8.3 ± 1.6	0.10
TCho	1.9 ± 0.2	1.9 ± 0.2	0.17	2.6 ± 0.6	2.5 ± 0.5	0.09	1.9 ± 0.2	1.9 ± 0.2	0.11	2.5 ± 0.5	2.6 ± 0.5	0.63

Abbreviations. UHR: Ultra High Risk, R: Remission, NR: No Remission NAA+NAA: N-acetyl aspartate (NAA plus NAAG); Cr: creatine; mI: myo-inositol; TCho: total choline.

*P** *P*-value determined by independent samples t-test;

*P*** *P*-value determined by binary logistic regression;

*P**** *P* -value relating to main effect of group on follow-up metabolite level determined using linear mixed models.