

Altered Medial Temporal Activation Related to Local Glutamate Levels in Subjects with Prodromal Signs of Psychosis

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Background: Both medial temporal cortical dysfunction and perturbed glutamatergic neurotransmission are regarded as fundamental pathophysiological features of psychosis. However, although animal models of psychosis suggest that these two abnormalities are interrelated, their relationship in humans has yet to be investigated.

Methods: We used a combination of functional magnetic resonance imaging and magnetic resonance spectroscopy to investigate the relationship between medial temporal activation during an episodic memory task and local glutamate levels in 22 individuals with an at-risk mental state for psychosis and 14 healthy volunteers.

Results: We observed a significant between-group difference in the coupling of medial temporal activation with local glutamate levels. In control subjects, medial temporal activation during episodic encoding was positively associated with medial temporal glutamate. However, in the clinical population, medial temporal activation was reduced, and the relationship with glutamate was absent.

Conclusions: In individuals at high risk of psychosis, medial temporal dysfunction seemed related to a loss of the normal relationship with local glutamate levels. This study provides the first evidence that links medial temporal dysfunction with the central glutamate system in humans and is consistent with evidence that drugs that modulate glutamatergic transmission might be useful in the treatment of psychosis.

Key Words: Episodic memory, functional magnetic resonance imaging, glutamate, medial temporal cortex, MRS, psychosis, schizophrenia

Psychotic disorders have frequently been associated with alterations in the structure and function of the medial temporal cortex (1,2), and abnormalities in this region are thought to underlie the memory impairments that are evident in patients with psychosis at the behavioral level (2). An independent body of evidence indicates that perturbed glutamatergic neurotransmission is a key neurochemical feature of psychosis. The *N*-methyl-D-aspartate glutamate (NMDA) receptor antagonists, such as ketamine, induce acute psychotic symptoms and impair memory performance (3), and psychotic disorders are associated with increased glutamine in the anterior cingulate cortex and thalamus (4) and a reduction in activated hippocampal NMDA receptor density (5) and NMDA receptor subunit messenger RNA (6). Animal models of psychosis and circuit analyses suggest that glutamatergic and medial temporal abnormalities are interrelated, with medial temporal cortex considered critical for the memory impairments observed after NMDA antagonists administration and in psychosis (7). The onset of psychotic disorders is preceded by a prodromal phase characterized by attenuated psychotic symptoms and a decline in

global function. Recent studies in this phase of the disorder suggest that both hippocampal dysfunction and perturbed glutamate function are evident before the clinical expression of illness (8,9) and that its onset is associated with progressive volumetric changes in the medial temporal cortex (10).

We examined the relationship between medial temporal function and central glutamate levels in people presenting with prodromal symptoms of psychosis. We first predicted, on the basis of previous studies (8,9), that they would show altered medial temporal activation when performing a memory task and alterations in regional glutamate levels. We then tested our main hypothesis, that the degree of medial temporal dysfunction would be related to the alteration in regional glutamate levels.

Methods and Materials

We used a combination of functional magnetic resonance imaging and proton magnetic resonance spectroscopy (¹H-MRS) in the same individuals. The study was approved by the joint South London and Maudsley and the Institute of Psychiatry National Health Service Research Ethics Committee, and all participants gave written informed consent to participate after a complete description of the study.

Subjects

Twenty-two subjects with an At Risk Mental State (ARMS) for psychosis (11) and a matching group of 16 healthy volunteers took part in the study. However, two of the control subjects were subsequently excluded, due to the poor quality of their MRS data in the hippocampal region. Participants were 18–30 years of age and excluded if their IQ was below 70, if there was a history of a neurological disorder, or if they met DSM-IV criteria for a substance abuse disorder. The clinical population was recruited from Outreach and Support in South London, a clinical service for people at high risk of developing a psychotic disorder, where subjects were assessed by two expert clinicians with the Comprehensive Assessment of At Risk Mental States (11) and diagnosis was confirmed at a consensus

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Received Apr 30, 2010; revised Aug 6, 2010; accepted Aug 20, 2010.

clinical meeting. All subjects were antipsychotic-naïve at the time of scanning; three subjects were receiving antidepressant treatment. The ARMS subjects were matched on the basis of age, gender, and IQ to a sample of healthy control subjects selected from the same sociodemographic area and recruited via advertisement (Table S1 in Supplement 1). All participants were right-handed, as evaluated with the Lateral Preferences Inventory (12), and native English speakers.

Clinical Measures

Current symptoms were assessed in all the participants at the time of scanning with the Comprehensive Assessment of At Risk Mental States and the Positive and Negative Syndrome Scale (13). Premorbid IQ was measured with the Wide Range Achievement Test-Revised.

Imaging

¹H-MRS was used to measure glutamate levels in the medial temporal cortex, anterior cingulate cortex, and thalamus (9). During the functional magnetic resonance imaging session, subjects performed a verbal episodic memory paradigm that normally engages the medial temporal cortex (8) (Tables S3 and S4 in Supplement 1). During an encoding condition they read words aloud and were asked to remember them. In a recognition condition, they were presented with a subset of these words mixed with novel unstudied words and asked whether they remembered them. To examine the correlation between blood oxygen level dependent response during the task and glutamatergic function, β values were extracted from a region showing a between-group difference in activation, and Pearson's correlation was performed in SPSS version 16.0 (SPSS, Chicago, Illinois) to evaluate the association with local glutamate levels. Cook's distance test and leverage plot were used to assess

the effect of potential outliers and influential cases (details of imaging procedures and data analysis in Supplement 1).

Results

During verbal encoding the ARMS group showed, consistent with previous studies (8), reduced activation relative to control subjects in the left parahippocampal gyrus ($p = .047$ family-wise error) (Figure 1), where the degree of activation in the ARMS group was directly correlated with task performance [the number of words correctly recalled during the subsequent recognition condition; $r(20) = .497, p = .019$]. In control subjects, activation in this cluster during encoding was positively correlated with left medial temporal glutamate levels [$r(12) = .592, p = .026$] (Figure 1), whereas there was a negative correlation in the ARMS subjects [$r(20) = -.447, p = .037$]. When Cook's distance test and leverage plot were used, the result in the ARMS group appeared to be driven by one case. When this subject was excluded the correlation in the ARMS group was no longer significant [$r(19) = -.318, p = .16$] (Figure 1). To assess the potential effects of antidepressant treatment on the data, we performed a sensitivity analysis, repeating the correlation after the exclusion of the three medicated ARMS subjects. This did not alter the results: again, there was no significant relationship between activation in the left parahippocampal cluster and medial temporal glutamate [$r(14) = -.414, p = .088$]. Fisher's t to z transformation was used to formally assess the difference in the correlations within each group and showed a significant difference between the respective correlation coefficients ($Z = 2.64; p < .01$).

There were no significant group differences in regional glutamate levels (although there was a trend [$p = .079$] for a reduction in the thalamus in the ARMS group) (details in Table S5 in Supplement 1). There were no group differences in medial temporal activation

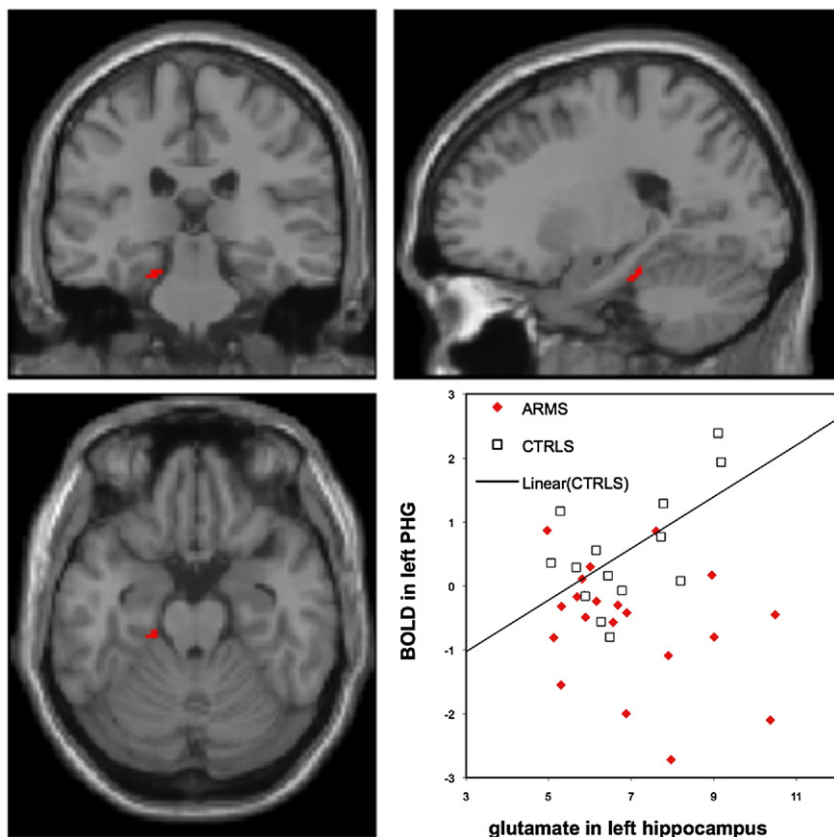


Figure 1. Left parahippocampal (PHG) region ($x = -18, y = -30, z = -20$) where At Risk Mental State (ARMS) subjects showed less activation (in arbitrary units) than control subjects (CTRLS) during encoding ($p = .047$ family-wise error). In this region, activation in CTRLS was positively correlated with left medial temporal glutamate levels, but there was no correlation in the ARMS group. BOLD, blood oxygen level dependent.

during the recognition (as opposed to the encoding) condition. We therefore did not assess the relationship between glutamate levels and medial temporal activation during the recognition phase of the task.

Discussion

These results suggest that medial temporal dysfunction in people with prodromal symptoms of psychosis is related to a loss of the normal relationship between function in this region and local glutamate levels. Although medial temporal dysfunction and altered glutamate levels have each been described separately in relation to psychosis in humans (2,4), this is the first time a link between them has been demonstrated in the same subjects. A direct relationship between them provides support to contemporary animal models of psychosis, which propose that medial temporal dysfunction is associated with a disturbance of glutamate neurotransmission (7).

NMDA receptor antagonists can induce neuronal damage in the limbic cortex of rodents. This effect is prevented by pretreatment with gamma-aminobutyric acid (GABA) receptor agonists, suggesting that it involves blockade of excitatory glutamate receptors on GABAergic inhibitory interneurons (14). An effect on GABAergic interneurons might also underlie the emergence of psychotic symptoms observed after NMDA receptor blockade in humans (15), and a similar mechanism has been hypothesized for the glutamate model of psychosis (15). The specificity of our findings to the encoding, as opposed to the recognition phase of the memory task, is consistent with evidence that infusion of NMDA receptor antagonists in the limbic cortex of rodents impairs memory encoding but not recognition (16). A similar impairment has been observed in humans, where ketamine administration induces robust episodic memory impairments affecting mainly early consolidation processes during the encoding of information (17). This might reflect the role of hippocampal NMDA receptors in the induction of the activity-dependent synaptic plasticity that underlies memory (18).

Although our results suggest that medial temporal dysfunction in people at high risk of psychosis is related to regional glutamate levels, they cannot reveal the direction of causality, nor whether the MRS measure is related to activity in medial temporal pyramidal neurons, in the terminals of afferent projections from other regions or abnormalities at a receptor level. A further caveat is that it is difficult to conclusively discriminate between the signals corresponding to glutamate and glutamine with the MRS method we used. Due to the partial overlap of glutamate and glutamine resonances at 3T, glutamate levels in the present study might thus include a contribution from glutamine. Simulation studies suggest that glutamine might account for 10%–15% of the glutamate concentration at 3T (19). In conclusion, although the group sizes in the present study were modest and unequal, and replication of the findings in a larger sample is indicated, our results are consistent with evidence that drugs that modulate glutamate transmission might be useful in patients with psychosis (20). Moreover, because the changes we observed predated the clinical expression of psychosis, they suggest that glutamatergic drugs might be able to influence the risk of developing the first episode of psychosis.

This research was supported by Medical Research Council Clinical Training Fellowships awarded to IV (Grant No. G0601437), JS (Grant No. G0500477), and SB (Grant No. G0501755) as well as a National

Alliance for Research on Schizophrenia and Depression Young Investigator Award (PA).

We thank Mary McLean and Gareth Barker for very useful discussion and all the participants and the members of the Outreach and Support in South London team.

All authors report no biomedical financial interests or potential conflicts of interest.

Supplementary material cited in this article is available online.

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