ORIGINAL ARTICLE

ONLINE FIRST

# Thalamic Glutamate Levels as a Predictor of Cortical Response During Executive Functioning in Subjects at High Risk for Psychosis

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**Context:** Alterations in glutamatergic neurotransmission and cerebral cortical dysfunction are thought to be central to the pathophysiology of psychosis, but the relationship between these 2 factors is unclear.

**Objective:** To investigate the relationship between brain glutamate levels and cortical response during executive functioning in people at high risk for psychosis (ie, with an at-risk mental state [ARMS]).

**Design:** Subjects were studied using functional magnetic resonance imaging while they performed a verbal fluency task, and proton magnetic resonance spectroscopy was used to measure their brain regional glutamate levels.

**Setting:** Maudsley Hospital, London, England.

**Patients and Other Participants:** A total of 41 subjects: 24 subjects with an ARMS and 17 healthy volunteers (controls).

**Main Outcome Measures:** Regional brain activation (blood oxygen level–dependent response); levels of glutamate in the anterior cingulate, left thalamus, and left hippocampus; and psychopathology ratings at the time of scanning.

**Results:** During the verbal fluency task, subjects with an ARMS showed greater activation than did controls in the middle frontal gyrus bilaterally. Thalamic glutamate levels were lower in the ARMS group than in control group. Within the ARMS group, thalamic glutamate levels were negatively associated with activation in the right dorsolateral prefrontal and left orbitofrontal cortex, but positively associated with activation in the right hippocampus and in the temporal cortex bilaterally. There was also a significant group difference in the relationship between cortical activation and thalamic glutamate levels, with the control group showing correlations in the opposite direction to those in the ARMS group in the prefrontal cortex and in the right hippocampus and superior temporal gyrus.

**Conclusions:** Altered prefrontal, hippocampal, and temporal function in people with an ARMS is related to a reduction in thalamic glutamate levels, and this relationship is different from that in healthy controls.

*Arch Gen Psychiatry. 2011;68(9):881-890.*
*Published online May 2, 2011.*
*doi:10.1001/archgenpsychiatry.2011.46*

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COGNITIVE DEFICITS ARE A robust feature of schizophrenia and a major contributor to the substantial functional disability associated with the disorder. Compared with controls, patients with schizophrenia show impaired behavioral performance on tasks that engage executive functions[1] (such as verbal fluency paradigms), and neuroimaging studies have confirmed abnormal engagement of the prefrontal areas that normally mediate these processes during such tasks in patients with schizophrenia.[2-5] Recent studies have reported that qualitatively similar impairments in behavioral performance and alterations in prefrontal activation are also evident in subjects who have prodromal symptoms of psychosis but are not frankly psychotic.[6-8] The prodromal symptoms of psychosis can be identified using standardized, structured assessments, based on a combination of clinical criteria: the presence of attenuated psychotic symptoms, a family history of psychosis in connection with deterioration in social functioning, or a self-limiting psychotic episode that lasted less than 1 week.[9] Individuals meeting these criteria have an at-risk mental state (ARMS) that is associated with a high risk of developing a psychotic disorder within 2 years.[10]

Functional magnetic resonance imaging (fMRI) studies of verbal fluency in the individuals with an ARMS indicate that the level of activation in the prefrontal cortex is intermediate between that in psy-



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chotic patients and that in controls,[11] independent of differences in task performance or potential effects of antipsychotic medication. The relationship between prefrontal cortical dysfunction in this context and the neurochemical changes associated with psychosis is unclear. Over the past 2 decades, there has been growing interest in the effect of glutamate, the main excitatory neurotransmitter in the brain, on the pathophysiology of psychosis. Experimental administration of ketamine, an uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, in healthy volunteers can produce impairments on tasks of executive function[12,13] and alterations in cortical activation during verbal fluency that are comparable to those seen in schizophrenia.[14] Animal models of psychosis suggest that blockade of NMDA receptors can lead to increased cortical glutamate release[15,16] and the loss of cortical neurons.[17] These effects appear to be driven by NMDA receptor blockade in the thalamus rather than a direct effect on NMDA receptors in the cortex.[16,18] Proton magnetic resonance spectroscopy (1H-MRS) permits direct measurement of glutamate and glutamine (a marker of glutamate release) in living human subjects. Recent 1H-MRS studies have shown an increase in anterior cingulate levels of glutamine, following the acute administration of ketamine,[19] closely resembling the previously reported findings in animals.[15,16] Abnormal anterior cingulate glutamine levels have also been reported in patients undergoing the first episode of schizophrenia.[20] In subjects with an ARMS, we found increased anterior cingulate glutamine levels, but the most striking finding in this group was a reduction in thalamic glutamate levels, which was associated with reductions in prefrontal, temporal, and hippocampal gray matter volume in the same individuals.[21]

The aim of our study was to examine the relationship between the cortical response during a task of executive functioning and central glutamate levels in subjects with an ARMS. We selected this group because it is thought that glutamate dysfunction may be particularly important in the early stages of psychosis,[20,22,23] and because individuals with an ARMS are usually treatment naive, and antipsychotic medication may alter both cortical activation[24] and glutamate activity.[25] We studied the same individuals using 2 different neuroimaging techniques: fMRI was used to assess cortical responses during a verbal fluency task, and 1H-MRS was used to measure regional glutamate levels. These techniques were applied to a sample of subjects with an ARMS and a demographically matching group of healthy volunteers. We tested the hypothesis that, within the ARMS group, the severity of the alteration in cortical function would be related to thalamic glutamate levels.

## METHODS

### SUBJECTS

Individuals meeting criteria for the an ARMS (n=24) were recruited from Outreach and Support in South London.[26] The diagnosis was based on assessment by 2 experienced clinicians, using the Comprehensive Assessment for At-Risk Mental States,[9] as well as a consensus meeting with the clinical team. All subjects were antipsychotic naive at the time of the scanning. Two subjects were receiving antidepressant medication. The subjects were representative of the local population of people presenting with an ARMS in terms of age, sex, ethnicity, and duration and intensity of symptoms.[26] Subjects were excluded if there was a history of neurological disorder or if they met *DSM-IV* criteria for a substance dependence or abuse disorder. Controls (n=17) were recruited from the same geographical area via advertisements in the local media. Control subjects had no history of psychiatric symptoms, substance dependence or abuse, medical illness, or use of psychotropic medications and no family history of psychiatric illness. All subjects but one (a subject with an ARMS) were right-handed, as evaluated using the Lateral Preferences Inventory,[27] and all were native speakers of English.

### CLINICAL MEASURES

Prior to scanning, all subjects were interviewed about their family and personal psychiatric history and their current and past medication use. No formal structured instrument was employed to assess psychiatric history of participants. The severity of psychotic symptoms in the 2 groups was assessed at the time of scanning using the Comprehensive Assessment for At-Risk Mental States[9] and the Positive and Negative Symptom Scale.[28] Consumption of illicit substances, alcohol, tobacco, and coffee and/or tea was evaluated using a modified version of the Cannabis Experience Questionnaire.[29] Affective symptoms were assessed with the Hamilton Depression and Anxiety Scales.[30] Premorbid intelligence was assessed using the National Adult Reading Test.[31] Although individual differences in the personality dimensions of introversion/extroversion may affect brain function during cognitive activity[32] and glutamate levels,[33] we did not measure these personality domains. The effect of the group on demographic and clinical measures was tested using analyses of variance for parametric variables, and Mann-Whitney *U* tests were used to compare individuals with an ARMS with controls for nonparametric variables after checking for equality of variance with the Levene test.

### fMRI SCANNING

#### Image Acquisition

For each participant, T2*-weighted gradient-echo single-shot echo-planar images were acquired on a 1.5-T Signa system (General Electric, Milwaukee, Wisconsin) at the Maudsley Hospital, London, England. Images consisted of 14 noncontiguous axial planes (7-mm thickness; slice skip, 1 mm) parallel to the anterior commissure–posterior commissure line and were acquired with an echo time (TE) of 40 milliseconds, a flip angle of 70°, a matrix size of 64×64 pixels, and a field of view of 200 mm. Because the experimental paradigm required subjects to articulate a verbal response, we used a "clustered" acquisition sequence.[34,35] A clustered acquisition sequence capitalizes on the delay of the hemodynamic response, which reaches its peak about 3000 to 5000 milliseconds after stimulus onset.[36] A letter cue was presented for 750 milliseconds, and an overt verbal response could be made during a silent period of 2900 milliseconds. An image was then acquired during 1100 milliseconds, resulting in a total repetition time (TR) of 4000 milliseconds.

#### Verbal Fluency Task

Subjects were required to overtly articulate a word beginning with a visually presented letter. The stimuli, each subtending an angle of 5°, were presented in white on a black screen, viewed



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through a mirror. Cognitive load was modulated with 2 levels of task difficulty: "easy" and "hard" conditions using letters that differed with respect to the ease with which volunteers can usually generate words in response to them. The easy condition involved the letters L, T, C, P, and S; the hard condition involved the letters O, N, E, F, and G.[3] Incorrect responses were defined as words that were proper names, repetitions or grammatical variations of the previous word, and "pass" responses. Letters were presented in 28-second blocks of 7 stimuli at 4-second intervals. The control condition of word repetition comprised 28-second blocks of 7 presentations of the word "rest" at 4-second intervals, which subjects were required to read aloud. Five blocks of each condition (hard, easy, and repetition) were presented in random order. Verbal responses were recorded via an MRI-compatible microphone using Cool Edit 2000 software (Syntrillium Software Corp, Scottsdale, Arizona). To ensure that subjects heard their responses clearly, their speech was transmitted by an MRI-compatible microphone, amplified by a computer sound card, and relayed back through an acoustic MRI sound system (Wardray Premise Ltd, Hampton Court, London, England) and noise-insulated, stereo headphones at a mean (SD) volume of 91 (2) dB. The effect of group on response accuracy during scanning was tested using an analysis of variance.

### Analysis of fMRI Data

Functional MRI data were analyzed using Statistical Parametric Mapping (SPM5, Wellcome Department of Cognitive Neurology, London, England) running in MATLAB7.1 (The MathWorks, Natick, Massachusetts). All volumes were realigned to the first volume, corrected for motion, mean-adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and smoothed using a 6-mm full-width at half-maximum Gaussian kernel. The time series were high-pass–filtered to eliminate low-frequency components (filter width 128 seconds). In the first level analysis, the onset times (in seconds) for each trial were convolved with a canonical hemodynamic response function. Because no significant effect of cognitive load on regional activation was observed,[37] each task condition (easy and hard) was then contrasted against the baseline condition (rest) in each subject. Because group differences in task performance could contribute to group differences in activation, the analysis was restricted to images associated with correct responses. To test the hypothesis that there were between-group differences, we performed a second-level analysis comparing the activation during verbal fluency, independent of task demand (easy and hard word generation combined vs word repetition) between the 2 groups (controls and subjects with an ARMS), using an analysis of variance between-subjects test. As we were testing an a priori hypothesis regarding group effects in the frontal lobe,[11,38] we used a frontal lobe mask generated by Wake Forest University PickAtlas (http://www.fmri.wfubmc.edu/)[39] for second-level group contrasts. The mask included frontal regions corresponding to Brodmann areas 4, 6, 8, 9, 46, 10, 11, 47, 45, 44, 32, and 24. The whole-brain voxel-wise threshold was set at $P < .05$ (corrected for familywise error).[37]

## 1H-MRS SCANNING

### Volumetric MRI Acquisition

The fMRI and MRS scans in each subject were performed as close together as was practically possible. In many subjects, both scans were performed in the same week, but restrictions on the availability of scanning slots meant that this was not always possible (mean [SD] interval between scans, 4.5 [2.9] months). All MRS scanning took place on a 3-T MR system (General Electric, Milwaukee, Wisconsin) at the Centre for Neuroimaging Sciences, London, England. After positioning the subjects in the scanner with earplugs and a foam rest under their knees, they were scanned with an initial 3-plane localizer scan. This was used to measure the interhemispheric angle and the anterior commissure–posterior commissure line (the line passing through the upper part of the anterior commissure and the lower part of the posterior commissure). This was followed by an axial 2-dimensional T2-weighted fast spin echo scan and an axial fast fluid-attenuated inversion recovery scan, both prescribed parallel to the anterior commissure–posterior commissure line, which together were used for visual assessment to exclude any gross structural abnormality. These were followed by a whole-brain 3-dimensional coronal inversion recovery prepared spoiled gradient echo scan, prescribed from the midline sagittal localizer images, giving an isotropic 1.1-mm voxel size (TE = 2.82 milliseconds; TR = 6.96 milliseconds; T1 = 450 milliseconds; and excitation flip angle = 20°) in a scan time of approximately 6 minutes. The inversion recovery prepared spoiled gradient echo scans were used for localization of the spectroscopic regions of interest and were subsequently segmented into gray matter, white matter, and cerebrospinal fluid using SPM2 to allow correction of the spectroscopy results for partial-volume cerebrospinal fluid contamination. There was no control voxel for the 1H-MRS acquisition because scanner time was limited and the length of the scan protocol was at the limits of tolerability for some subjects.

### 1H-MRS Protocol

The MRS spectra (point-resolved spectroscopy: TE = 30 milliseconds; TR = 3000 milliseconds; and 96 averages) were acquired in the anterior cingulate, left hippocampus, and left thalamus. An automated shimming and water suppression method was used,[40] and the auto-prescan was performed twice prior to each scan. The center of the 20 × 20 × 20-mm anterior cingulate region of interest was placed 13 mm above the anterior section of the genu of corpus callosum at 90° to the anterior commissure–posterior commissure line (**Figure 1**). A 20 × 20 × 15-mm (right-left, anterior-posterior, superior-inferior) left hippocampal voxel was prescribed from the coronal inversion recovery prepared spoiled gradient echo (Figure 1). A 15 × 20 × 20-mm (right-left, anterior-posterior, superior-inferior) left thalamic voxel was defined at the point in the coronal slices where the thalamus was widest, using sagittal and coronal views to ensure that the voxel was clear of cerebrospinal fluid contamination (Figure 1). For each metabolite spectrum, 16 unsuppressed water reference lines were also acquired as part of the standard PROBE acquisition (GE Medical Systems, Milwaukee, Wisconsin). We aimed for a maximum line width (full-width at half-maximum) of the water peak at prescan of 7Hz for the anterior cingulate voxel, 10 Hz for the thalamus, and 11 Hz for the hippocampus. After the subject left the scanner, each scanning session concluded with the acquisition of a spectrum (from point-resolved spectroscopy) from a phantom containing standard concentrations of brain metabolites to provide calibration data for the LCModel program (http://s-provencher.com/pages/lcmodel.shtml).

### 1H-MRS Quantification

All spectra were analyzed using LCModel version 6.1-4F.[41] The raw spectral data were read into LCMgui, the graphical user interface for LCModel, which automatically combined the data from the 8-channel coil with a weighted coherent average over the 8 receive channels using the intensity of the first point of the free induction decay of the unsuppressed water reference



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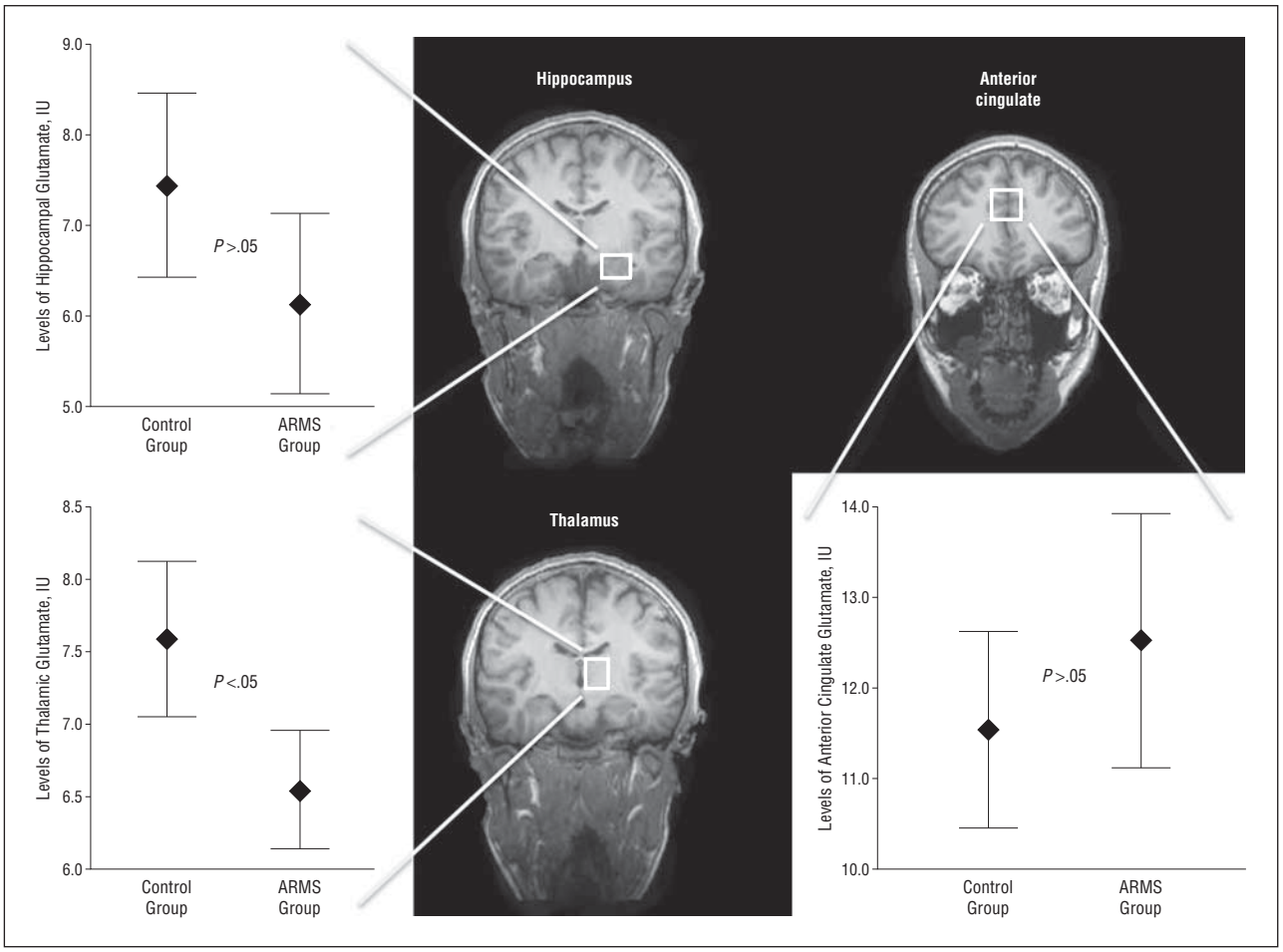


**Figure 1.** Location of voxel placement for proton magnetic resonance spectroscopy acquisition and glutamate levels in the region of interests: left hippocampus (upper left), anterior cingulate (upper right), right thalamus (lower left). Error bars show the 95% confidence intervals of the means. ARMS indicates at-risk mental state.

from each coil. A standard basis set of 16 metabolites (L-alanine, aspartate, creatine, phosphocreatine, γ-aminobutyric acid [GABA], glucose, glutamine, glutamate, glycerophosphocholine, glycine, myo-inositol, L-lactate, *N*-acetylaspartate, *N*-acetylaspartylglutamate, phosphocholine, and taurine), included as part of LCModel and acquired with the same field strength (3 T), localization sequence (point-resolved spectroscopy), and echo time (30 milliseconds) as our study, was used. The model metabolites and concentrations used in the basis set are fully detailed in the LCModel manual (http://s-provencher.com/pages/lcm-manual.shtml). The brain tissue content in the region corresponding to each region of interest was determined by matching its location from the 1H-MRS file headers with the same region in the segmented inversion recovery prepared spoiled gradient echo images. Water-scaled glutamate values were divided by the brain-tissue (gray plus white matter) content of the voxel in each subject (corrected for cerebrospinal fluid). Poorly fitted metabolite peaks (Cramer-Rao minimum variance bounds of >20% reported by LCModel) were excluded from further analysis.

### INTEGRATION OF 1H-MRS AND fMRI DATA

The relationship between the blood oxygen level–dependent (BOLD) response during the verbal fluency task and glutamate levels was investigated by entering the glutamate measures as covariates in the independent-sample *t* test analysis of fMRI data. Glutamate × BOLD response interactions were assessed using whole-brain regressions, conducted separately for subjects with an ARMS and controls. In a second step, we explored the group by BOLD × glutamate interaction by modeling these factors in a different SPM design matrix. For all these contrasts, the whole-brain voxelwise threshold was set at $P<.05$ (corrected for familywise error). Post hoc analyses were performed to evaluate the strength of these associations by extracting the β values and testing them in a regression model in SPSS (SPSS Inc, Chicago, Illinois). Cook's distance test was used to assess the effect of potential outliers on these correlations.

## RESULTS

### CLINICAL CHARACTERISTICS OF THE SAMPLE

Controls and subjects with an ARMS did not differ in age (mean [SD] age of 26.6 [5] years for subjects with an ARMS and 25.5 [3.6] years for controls [$t=1.490$, $P=.146$]), estimated premorbid IQ (mean premorbid IQ of 102.6 [9.2] for controls and 101.7 [12.3] for subjects with an ARMS [$t=1.774$, $P=.09$]), or sex (1 female subject with an ARMS and 7 female controls [$\chi^2=1.502$, $P=.22$]), but controls had a significantly higher level of education than did subjects with an



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ARMS ($\chi^2$=0.049). There were no significant group differences in substance or alcohol use ($P>.05$). Subjects with an ARMS had higher levels of prodromal, psychotic, anxiety, and depressive symptoms than did controls, as measured using the Comprehensive Assessment for At-Risk Mental States (thought disorders severity [$t$=7.789, $P<.001$]; perceptual disorders severity [$t$=3.377, $P$=.002]; speech disorders severity [$t$=2.194, $P$=.04]), the Positive and Negative Symptom Scale (ARMS mean [SD] positive scale score of 12.67 [3.67] for the ARMS group and 7.35 [1.01] for the control group [$t$=4.667, $P<.001$]; mean [SD] negative scale score of 8.95 [2.71] for the ARMS group and 7.07 [0.26] for the control group [$t$=2.583, $P$=.02]; and mean [SD] general scale score of 21.5 [4.2] for the ARMS group and 16.5 [0.77] for the control group [$t$=4.399, $P<.001$]), the Hamilton Depression Anxiety Scale (mean [SD] scale score of 11.29 [3.44] for the ARMS group and 1.70 [0.75] for the control group [$t$=3.308, $P$=.002]), and the Hamilton Depression Scale (mean [SD] scale score of 8.83 [3.14] for the ARMS group and 0.71 [0.32] for the control group [$t$=3.686, $P$=.001]), respectively. No significant correlations between glutamate levels or regional activation and psychotic, anxious, or depressive symptoms were elicited. We did not try to subdivide the ARMS sample according to whether they developed psychosis subsequent to scanning because this sample of individuals is still undergoing clinical follow-up. At least 2 years of follow-up is needed to determine which individuals will become psychotic.[42]

## MRS RESULTS

As previously reported,[21] the quality of the spectra obtained from 1H-MRS was good in the left thalamus and in the anterior cingulate, with a mean (SD) signal-to-noise ratio reported by LCModel of 19 (4) and 20 (6), respectively, and the quality of the spectra was reasonable in the left hippocampus with a mean (SD) signal-to-noise ratio of 12 (3). Line widths recorded by LCModel followed a similar pattern with a mean (SD) line width of 5.1 (1.1) Hz in the anterior cingulate, 6.7 (1.3) Hz in the left thalamus, and 9.2 (3.3) Hz in the left hippocampus. There were no significant differences in spectral quality between the control group and the ARMS group. Subjects with an ARMS had lower glutamate levels ($t$=2.7359, $P$=.023) in the left thalamus than did controls. There was also a trend toward lower glutamate levels in the ARMS group than in the control group in the left hippocampus ($t$=1.877, $P$=.068). There were no significant group differences in glutamate levels in the anterior cingulate gyrus ($P>.05$).

## VERBAL FLUENCY TASK

### Performance

There was no significant difference in the accuracy of responses during the verbal fluency task between the ARMS and control groups ($P$=.109).

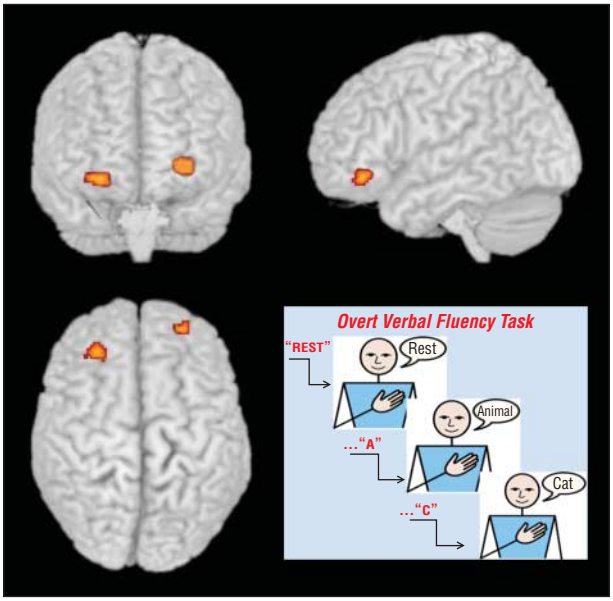


**Figure 2.** Between-group differences in activation during the verbal fluency task. The at-risk mental state group showed greater activation than did the control group (red clusters) in the right superior frontal gyrus and in the left middle frontal gyrus. The left side of the brain is shown on the left side of the figure.

### Regional Activation

**Main Effect of Task.** Across all subjects, word generation relative to word repetition was associated with activation in several regions of the cerebral cortex, with a significant lateralization effect on the left. Brain areas activated by the task included the inferior frontal gyrus bilaterally, the left insula, the superior frontal gyrus, and the anterior cingulate gyrus ($P<.05$). There was also subcortical activation in the left putamen and globus pallidus ($P<.05$) (eTable and eFigure, http://www.archgenpsychiatry.com).

**Main Effect of Group.** The ARMS group showed greater activation than did the control group in the middle frontal gyrus bilaterally ($P<.05$) (eTable and **Figure 2**). Conversely, no brain areas showed greater activation in the control group than in the ARMS group.

## CORRELATION BETWEEN 1H-MRS AND fMRI

### Thalamus

**Within-Group Correlations.** No significant correlations between cortical activation during verbal fluency and thalamic glutamate levels were observed in healthy controls. However, in the ARMS group, thalamic glutamate levels were negatively associated with activation in the right dorsolateral prefrontal cortex (right middle frontal gyrus: $R$=0.784, $R^2$=0.614, $P<.001$) and the left orbitofrontal cortex (left middle frontal gyrus: $R$=0.602, $R^2$=0.362, $P$=.03), but positively associated with activation in the temporal cortex bilaterally (right superior temporal gyrus: $R$=0.801, $R^2$=0.642, $P<.001$; left middle temporal gyrus: $R$=0.465, $R^2$=0.216, $P$=.034) and in the right



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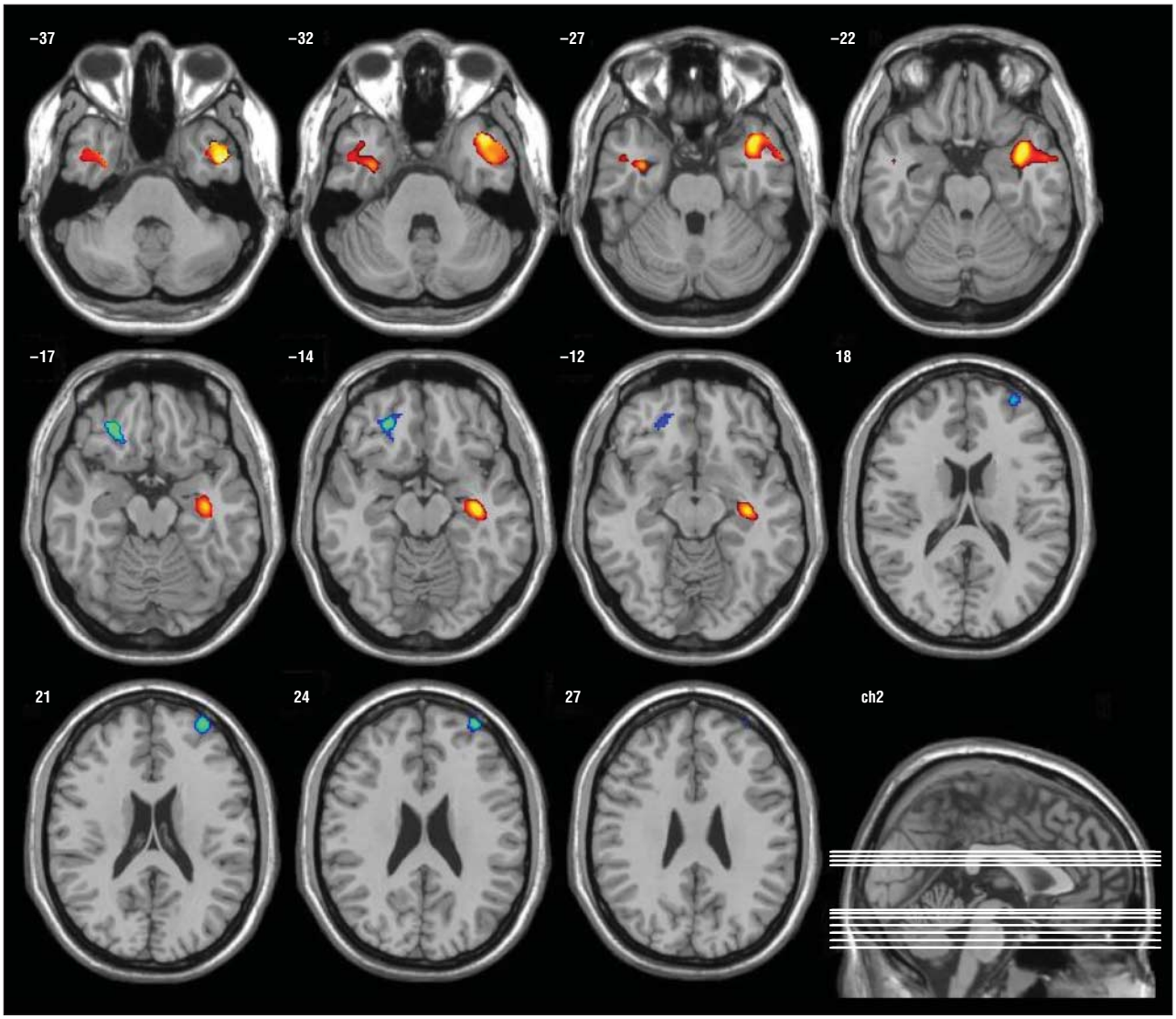


**Figure 3.** Correlations between thalamic glutamate levels and brain activation in subjects with an at-risk mental state during verbal fluency (positive correlations are shown in red, and negative correlations in blue). Positive correlations were evident in the right superior temporal gyrus, the hippocampus, and the left middle temporal gyrus. Negative correlations were evident in the middle frontal gyrus bilaterally.

hippocampus ($R$=0.605, $R^2$=0.366, $P$=.04) (**Figure 3** and **Table**).

**Differences Between Groups.** There were significant interactions between these findings and group ($P<.05$). In the prefrontal cortex bilaterally (left middle frontal and right superior frontal gyri), thalamic glutamate levels were negatively associated with activation in the ARMS group but positively associated with activation in the control group (**Figure 4** and Table). Conversely, thalamic glutamate levels in the right hippocampus and the superior temporal gyrus were positively correlated with brain activation in the ARMS group but negatively correlated with brain activation in the control group.

### Hippocampus and Anterior Cingulate

No significant correlations between cortical response during verbal fluency and glutamate levels in either the hippocampus or the anterior cingulate cortex were observed in the ARMS group or the control group, and there were no significant group × glutamate × cortical activation interactions.

## COMMENT

To our knowledge, ours is the first study to explore the relationship between glutamate levels and cortical activation in relation to psychosis in human subjects. As previously reported,[21] thalamic glutamate levels were lower in the ARMS group than in the control group, and subjects with an ARMS showed increased frontal activation during the verbal fluency task.[37] Within the ARMS group, the glutamate level in the thalamus was positively associated with activation in the temporal cortex and hippocampus, but negatively associated with activation in the prefrontal cortex. Moreover, significant interactions between these findings and the group were detected in the prefrontal and temporal cortex and in the hippocam-



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**Table. Correlation Between Thalamic Glutamate Levels and Cortical Response During the Verbal Fluency Task[a]**

| Brain Region | Side | BA | MNI Coordinates x | y | z | Voxels, No. | *z* Score | FWE-Corrected *P* Value |
|---|---|---|---|---|---|---|---|---|
| ARMS | | | | | | | | |
| Negative correlation | | | | | | | | |
| Middle frontal gyrus | L | 11 | −26 | 40 | −18 | 581 | 5.46 | <.001 |
| Middle frontal gyrus | R | 10 | 32 | 58 | 22 | 286 | 5.38 | <.001 |
| Positive correlation | | | | | | | | |
| Superior temporal gyrus | R | 38 | 38 | 14 | −4 | 518 | 4.43 | <.001 |
| Superior temporal gyrus | R | 38 | 36 | 6 | −24 | | 4.32 | <.001 |
| Inferior temporal gyrus | R | 20 | 44 | 0 | −38 | | 4.31 | <.001 |
| Hippocampus | R | | 34 | −16 | −16 | 89 | 4.15 | <.001 |
| Middle temporal gyrus | L | 21 | −36 | −4 | −30 | 80 | 3.84 | <.001 |
| Inferior temporal gyrus | L | 20 | −32 | −4 | −38 | | 3.49 | <.001 |
| Middle temporal gyrus | L | 38 | −38 | 4 | −38 | | 3.46 | <.001 |
| Interaction | | | | | | | | |
| Control positive × ARMS negative | | | | | | | | |
| Middle frontal gyrus | L | 11 | −26 | 40 | −16 | 48 | 4.30 | <.001 |
| Superior frontal gyrus | R | 10 | 32 | 58 | 24 | 62 | 4.19 | <.001 |
| Control negative × ARMS positive | | | | | | | | |
| Hippocampus | R | | 34 | −16 | −14 | 26 | 3.55 | <.001 |
| Superior temporal gyrus | R | 38 | 38 | 6 | −24 | 25 | 3.45 | <.001 |

Abbreviations: ARMS, at-risk mental state; BA, Brodmann area; FWE, familywise error; L, left; MNI, Montreal Neurological Institute; R, right.
[a]No significant correlations were found in the control group.

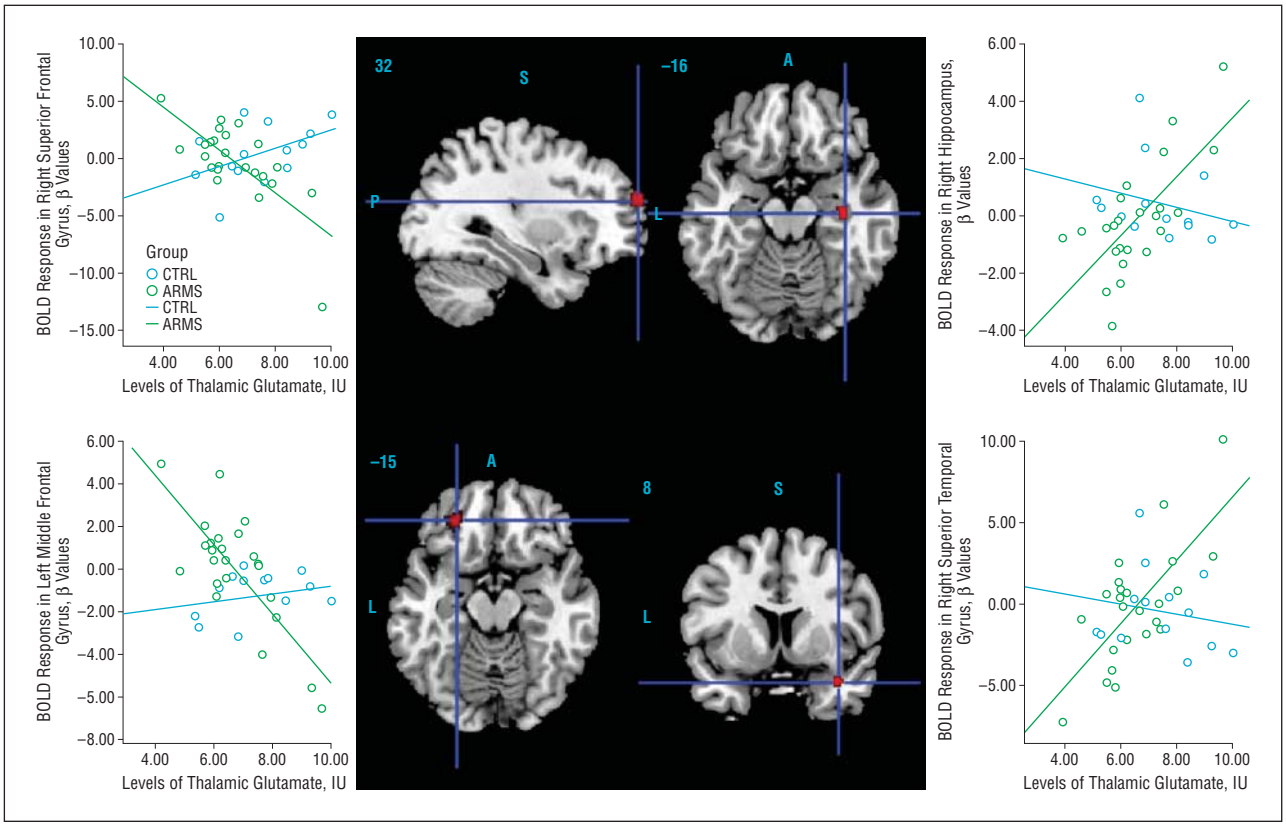


**Figure 4.** Between-group interactions between thalamic glutamate level and cortical responses during the verbal fluency task. In the prefrontal cortex bilaterally (plots on the left of the brain scans), thalamic glutamate levels were negatively associated with activation in the at-risk mental state (ARMS) group, but there was no significant correlation in the control (CTRL) group. In the right hippocampus (bottom right plot) and right superior temporal gyrus (top right plot), the correlation in the ARMS group was negative, whereas the correlation in the CTRL group was again not significant. BOLD indicates blood oxygen level–dependent.

pus, indicating that the relationship between activation and glutamate levels was different in subjects with an ARMS and controls.

In keeping with previous studies of healthy controls[38] and of patients with schizophrenia,[43] our verbal fluency task preferentially activated the left prefrontal cor-



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tex, and this region was differentially activated in subjects with an ARMS and controls, with a greater BOLD response bilaterally in the former group. These differences in activation were evident in medication-naive subjects,[24] in the context of similar levels of task performance. Moreover, the analysis was restricted to images associated with correct responses. The findings may thus reflect a true difference at the neurophysiological level, as opposed to a nonspecific effect of differential task performance. Greater engagement of the prefrontal cortex in clinical subjects has been interpreted as a manifestation of inefficient prefrontal processing[44] and may underlie the behavioral impairment on executive functions that has consistently been observed in neuropsychological studies of subjects with an ARMS.[45,46] Our fMRI findings are consistent with evidence that gray matter volume in prefrontal regions is also abnormal in subjects with an ARMS,[47-49] as well as in subjects with first-episode psychosis[50] or chronic schizophrenia.[51]

In a larger sample, we previously reported reduced glutamate levels in the thalami of subjects with an ARMS.[21] It is not attributable to an effect of antipsychotic medication, because most of the subjects were medication naive, or to an effect of chronic illness, because none of these subjects had ever been frankly psychotic. Our main finding was that the relationship between thalamic glutamate levels and neuronal activation differed between the ARMS and control groups, particularly in the prefrontal and lateral temporal cortices and in the hippocampus. In the lateral temporal and hippocampal regions, the different relationship between thalamic glutamate levels and neuronal activation could be detected in the absence of different brain activation suggesting that, in these regions, alterations in glutamate levels may occur independently of cortical dysfunction.

These findings, taken together, suggest a glutamatergic basis for verbal fluency abnormalities in individuals with an ARMS and imply that the thalamus may be the primary area of abnormal glutamatergic transmission at this stage of illness. They are also consistent with evidence that administration of ketamine, an uncompetitive NMDA receptor antagonist that causes downstream effects through binding in the thalamus,[18] modulates activation during verbal fluency and resting-state activity in these regions in healthy volunteers.[14,52,53] The thalamus plays a key role in cognitive functioning, and prefrontal × thalamic interactions mediate the state of consciousness, the sleep-wake cycle, and executive functions,[54] including those engaged during verbal fluency tasks.[55] A recent study using simultaneous electroencephalographic recordings from deep brain structures and the scalp showed that the human thalamus systematically reacts to language analysis in coordination with cortical regions.[56] We have recently demonstrated that glutamate and *N*-acetylaspartate levels in the thalamus in individuals with an ARMS correspond with abnormalities of P300 and mismatch negativity, suggesting a thalamic basis for these deficits.[57] Neuropathological and in vivo imaging studies in schizophrenia have identified several structural and functional abnormalities in the thalamus,[58] and these changes have been related to cognitive impairments[59] and symptomatology in psychosis.[60] It is thus plausible that abnormalities in thalamic neurotransmission could contribute to the development of psychosis.

The relationship between thalamic glutamate levels and cortical activation during verbal fluency in the ARMS group was significantly different to that in the control group. In the ARMS group, thalamic glutamate levels were negatively associated with the prefrontal cortical response. In the control group, thalamic glutamate levels were positively associated with the prefrontal cortical response, although it was not statistically significant. The negative correlation between frontal activation and thalamic glutamate levels within the ARMS group suggests that the greater the neurophysiological abnormality in the frontal cortex, the greater the neurochemical abnormality in the thalamus. Similarly, the positive correlations with activation in the right hippocampus and superior temporal gyrus in the ARMS group were absent in the control group, which showed a tendency for correlations in a negative direction. The correlation coefficients in the ARMS group were strong (ranging from 0.5 to 0.8), suggesting that there is a close relationship between the alterations in glutamate levels and in cortical function in people with an enhanced risk of psychosis. The opposite direction of the associations between glutamate levels and activation in the prefrontal and temporal cortices may reflect the opposite direction of the BOLD responses in the respective regions during verbal fluency tasks, with activation in prefrontal areas but deactivation in temporal areas.[61] Nevertheless, regardless of the directions of the correlations, there were significant differences in the relationship between glutamate levels and cortical response in subjects with an ARMS compared with controls.

The healthy brain may compensate for the potential effects of intersubject variations in thalamic glutamate levels on cortical function, or vice versa. However, in the ARMS group, the regulation of thalamic and/or cortical function may be compromised, such that variations in glutamate levels can directly affect cortical function. However, because it is not possible to determine the direction of causality from our data, it might equally reflect prefrontal dysfunction resulting in altered top-down influences on thalamic glutamate levels. Although we observed a significant correlation between glutamate levels and cortical activation, there was no evidence of a correlation between glutamate levels and performance on the verbal fluency task ($P > .05$). Task performance can be seen as an indirect measure of the underlying cortical physiology and may be influenced by a range of additional factors. It is thus not surprising that we were able to detect a relationship between glutamate levels and cortical activation, but not with task performance. The latter might have been evident if there had been significant group differences in task performance and if our study had been powered to detect differences at the behavioral, as opposed to the physiological, level.

The limitations of our study are well acknowledged and include the use of different scanners and the time differences between acquisitions. Furthermore, about a third of the subjects with an ARMS will subsequently develop psychosis, some will continue to experience prodromal symptoms but not become psychotic, while oth-



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ers will recover to the extent that they no longer meet criteria for an ARMS.[62] Thus, given the cross-sectional nature of our study, it remains to be determined whether the observed glutamatergic and prefrontal alterations represent "state" risk factors or true "trait" vulnerability markers specifically linked to the later onset of psychosis.[63] This issue will be addressed by the follow-up of the present sample of subjects to determine their long-term clinical outcome. This entails clinical monitoring for at least 24 months after scanning (as most transitions to psychosis occur during this period[42]), and, at present, most of the sample of subjects are still undergoing follow-up. Finally, although we focused on glutamatergic abnormalities in the thalamus, pathways linking the thalamus and the cerebral cortex also involve GABAergic and dopaminergic neurotransmission,[60] and GABA and dopamine may also play a crucial role in the pathophysiology of psychosis.[37,64,65]

In subjects with prodromal signs of psychosis, altered prefrontal, temporal, and hippocampal responses during a verbal fluency task were related to reduced thalamic glutamate levels. This relationship was not evident in controls and may underlie the increased vulnerability to psychosis that is evident in the former group.

**Submitted for Publication:** May 17, 2010; final revision received February 20, 2011; accepted February 22, 2011.
**Published Online:** May 2, 2011. doi:10.1001/archgenpsychiatry.2011.46
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**Financial Disclosure:** Dr Barker has received payments from General Electric for teaching scanner programming courses.
**Funding/Support:** This study was funded by a Medical Research Council Clinical Training Fellowship (grant G050047 awarded to Dr Stone). Infrastructure support was provided by the National Institute for Health Research Biomedical Research Centre for Mental Health at the South London and Maudsley National Health Service Foundation Trust and the Institute of Psychiatry, King's College London.
**Online-Only Material:** The eTable and eFigure are available at http://www.archgenpsychiatry.com.

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