COLORADO SPRINGS, Colorado — Two neuroimaging studies shed important new light on the neural underpinnings of schizophrenia, showing differences between patients who do and do not develop psychosis, as well as identify patients who do and do not respond to treatment.

In the first study, significant distinctions in hippocampal glutamate levels were shown among high-risk individuals who transitioned to full psychosis, compared with those who did not transition.

"We found hippocampal glutamate levels to be selectively elevated in ultra-high-risk subjects who made a transition to psychosis," said lead author Matthijs G. Bossong, PhD, from the Department of Psychosis Studies, Institute of Psychiatry, King's College London, United Kingdom.

"Neuroimaging measures of hippocampal glutamate function could be used to help predict outcomes of ultra-high-risk individuals," he said.

The research was presented here at the 15th International Congress on Schizophrenia Research (ICOSR).

Glutamate Function

Previous animal studies have shown strong evidence of elevated glutamatergic function underlying the pathophysiology of psychosis, and a subsequent study published in 2013 in *JAMA Psychiatry* showed similar patterns on increased hippocampal glutamate function in unmedicated patients with schizophrenia.

In seeking to answer the important question of whether those increases in glutamate function are altered before the onset of psychosis, Dr Bossong and colleagues assessed levels in the left hippocampus in MRI of 68 patients considered to be ultra-high-risk, defined according to Comprehensive Assessment of At-Risk Mental States (CAARMS) criteria, and 30 healthy controls.

The ultra-high-risk patients were scanned at their first clinical presentation and then for a mean duration of 19 months, which was the mean time from baseline to transition to psychosis. Nine of the patients developed psychosis.

At the study's baseline, hippocampal glutamate levels did not significantly differ between the ultra-high-risk patients and the controls as a group.

However, in re-assessing the baseline MRIs of the 9 ultra-high-risk patients who developed psychosis in a post hoc analysis, the researchers found those patients, as a group, stood out as having significantly higher glutamate levels compared with the high-risk patients who did not develop psychosis ($P = .04$) and compared with the healthy controls ($P = .01$).

There were no significant differences between the controls and the ultra-high-risk patients who did not develop psychosis.

When the researchers looked at other metabolites, including N-acetylaspartate, total choline, myo-inositol, and creatine, there were no significant differences with the exception of myo-inositol. This a marker of glia activity in the brain was also significantly higher in ultra-high-risk patients who did transition to psychosis than in healthy controls ($P = .01$).

"Higher hippocampal myo-inositol levels were associated with higher CAARMS-positive symptoms scores," Dr Bossong said.

Global Efforts

Dr Bossong emphasized that the findings represent differences at the group level, and not all patients with high glutamate concentrations necessarily developed psychosis.
"In fact, the two subjects with the highest levels did not make a transition (yet?)," he told Medscape Medical News. "But, as a group the converters showed significantly higher levels than non-converters."

"However, in order to make this clinically relevant for patients, we need to be able to reliably predict transition to psychosis at an individual level."

The findings are important in the context of broader efforts taking place at multiple research centers around the world focusing on large cohorts of at-risk patients, trying to get at the crux of what occurs when patients transition into psychosis.

"[The consortia] are trying to predict transition on the basis of the combined predictive value of measures of psychopathology, including symptoms, psychosocial function, brain structure and function (neuroimaging), cognition and biological markers in blood," Dr Bossong explained.

"The assessment of hippocampal glutamate is one promising aspect that could be taken into account."

The study represents only the second time that glutamate levels in the hippocampus have been assessed in people at high risk for psychosis in vivo, coauthor Philip McGuire, MD, also from the Institute of Psychiatry at King's College London, told Medscape Medical News.

"Neuroimaging measures like this could help clinicians to predict which people at high risk will subsequently develop psychosis," he explained.

Dr McGuire also stressed the nature of the findings as group differences, however.

"A clinical test needs to be used to make predictions on data from a single individual."

Optimized Management

Adrienne C. Lahti, MD, who was the senior author of the 2013 JAMA Psychiatry study but was not involved in the new study, said the findings support what was previously shown in terms of elevated glutamate levels in unmedicated patients with schizophrenia.

"It indicates that glutamate levels are elevated before the illness expresses itself, thus glutamate elevation does not appear to be a consequence of treatment or illness progression," said Dr Lahti, who is the director of the Division of Behavioral Neurobiology in the Department of Psychiatry and Behavioral Neurobiology at the University of Alabama at Birmingham.

In the clinical setting, the findings could feasibly help guide management, with the understanding of an even higher risk for psychosis, she told Medscape Medical News.

"Those individuals [shown to be at higher risk] might need to be followed very closely so that they receive treatment as soon as they transition to psychosis, as longer duration of untreated psychosis is associated with poorer outcome," Dr Lahti said.

A separate study that Dr Lahti and her colleagues presented at the meeting further underscored the potential clinical benefits of neuroimaging for schizophrenia management — showing distinctive differences in the neurobiology of patients who do and do not respond to treatment.

This study involved 21 unmedicated patients with schizophrenia who were entered into a 6-week trial and were treated with the front-line antipsychotic risperidone.

MRI scans during and at the end of the study showed that pretreatment connectivity of the ventral tegmental area, thought to be critical for antipsychotic activity, to the dorsal anterior cingulated cortex was positively correlated with good response to the treatment, while connectivity to the default mode network was negatively correlated with treatment success.

With as many as 30% of schizophrenic patients not improving with antipsychotic treatment, such findings are particularly important," Dr Lahti said.
"It typically takes several months before psychiatrists can figure out whether a patient is responding to treatment [and since] the patient stays poorly treated during that period of time, it increases the risk of hospitalization, et cetera."

"Again, it is going to take some time to figure out which is the best combination of brain measures that most accurately predicts treatment response at this individual level," she said.

"I believe that use of multimodal brain imaging might hold the promise of being able to predict early in the treatment the likelihood that a patient might respond or not to antipsychotic medication."

Dr Bossong's study received funding from the Wellcome Trust. Dr McGuire and Bossong have disclosed no relevant financial relationships. Dr Lahti reports that her research has been funded by the National Institutes of Health. Janssen Pharmaceuticals provided the study medication.


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