Biological Psychiatry: Celebrating 50 Years

Glutamatergic System and Neuroimaging Studies of Treatment-Resistant Schizophrenia

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In this issue of *Biological Psychiatry*, Iwata *et al.* (1) tackle an important and challenging topic by aiming to better understand the neurobiological correlates of treatment-resistant schizophrenia (TRS). TRS remains a significant clinical and public health problem, with a poor response to antipsychotic treatment in up to one third of patients with schizophrenia (2). The higher disease burden in TRS is associated with worse prognosis, a greater number of hospitalizations, decreased quality of life, and loss of functioning. There is an urgent need to understand the underpinnings of TRS, which may be important in elucidating the pathophysiology of schizophrenia and developing more effective treatments. In addition, identifying biological markers of TRS early in the illness could guide clinical decision making. The heterogeneity of TRS and teasing apart the effects of chronic antipsychotic medication use and illness progression on the brain are major challenges. Furthermore, to date, most studies of neurobiological markers of TRS have used varying definitions of treatment response and adequate antipsychotic treatment.

Several lines of evidence indicate abnormalities in glutamatergic neurotransmission and *N*-methyl-D-aspartate receptor function in schizophrenia (3). Glutamatergic metabolites can be measured in vivo in the brain using proton magnetic resonance spectroscopy (^{1}H-MRS). Studies of brain ^{1}H-MRS in schizophrenia have found abnormalities of glutamate, glutamine, and a combination of glutamate and glutamine (Glx) levels in several brain regions. According to a recent meta-analysis of ^{1}H-MRS studies by Merritt *et al.* (4), elevations in levels of glutamatergic metabolites are present in the basal ganglia, thalamus, and medial temporal lobe across early and later stages of the illness, possibly pointing to excessive glutamatergic neurotransmission. Some prospective studies have examined the effects of antipsychotic treatment on glutamatergic neurotransmission (5), most showing a drug-induced reduction in glutamate metabolites. There is also evidence to suggest that glutamate alterations play a role in TRS (6,7). Iwata *et al.* (1) make an important contribution to this literature by studying glutamatergic metabolites with ^{1}H-MRS in patients with and without TRS.

Iwata *et al.* (1) examined glutamate and Glx in patients with ultra-TRS (URS), patients with TRS, and patients without TRS compared with healthy control participants. They carried out their study using ^{1}H-MRS at 3T in the dorsal anterior cingulate cortex, the dorsolateral prefrontal cortex, and the caudate. Iwata *et al.* (1) defined URS and TRS using modified criteria from the Treatment Response and Resistance in Psychosis Working Group (8) and clearly delineated their classification. The Clinical Global Impression Severity and all Positive and Negative Syndrome Scale–positive subscales were used to define treatment response and failure. Specifically, treatment response was defined as a Clinical Global Impression Severity score of $\leq$3, Positive and Negative Syndrome Scale–positive symptom items with scores of $\leq$3, and an absence of relapse in the last 3 months before study entry. An adequate antipsychotic medication trial was determined by a duration of $\geq$6 consecutive weeks and a daily antipsychotic dose of $\geq$400 mg chlorpromazine equivalents. Patients with URS (n = 26) were taking clozapine without a treatment response (a minimum of 300 mg/day for $>$6 weeks) and had a history of previous treatment failure with two non-clozapine antipsychotics. Patients with TRS (n = 27) were on clozapine with treatment response and had a history of previous treatment failure with two non-clozapine antipsychotics. Patients without TRS (n = 21) were taking a single nonclozapine antipsychotic (first- or second-generation) with adequate treatment response. Patients with URS had higher Positive and Negative Syndrome Scale total scores (82.8) compared with patients with TRS (56.1) and patients without TRS (57.2), as well as higher Clinical Global Impression Severity scores. Iwata *et al.* (1) reduced the heterogeneity of current antipsychotic use in the patient groups with the inclusion of patients on clozapine antipsychotic monotherapy in the URS and TRS groups and non-clozapine antipsychotic monotherapy for the non-TRS group.

Iwata *et al.* (1) found that levels of Glx were higher in the dorsal anterior cingulate cortex in patients with URS compared with healthy control participants, without differences in glutamate metabolites across groups in the caudate and dorsolateral prefrontal cortex. Their results did not show differences in glutamate or Glx between patient groups. In addition, they did not find that glutamatergic metabolites were associated with symptom severity, nor did they find differences in glutamate or Glx between more symptomatic (URS) and less symptomatic (TRS and non-TRS) patient groups. Thus, a significant alteration of glutamate metabolites in the URS group uniquely distinguished it from the healthy control group in this study. These findings highlight the potential value in subgrouping TRS to elucidate the role of glutamatergic signaling, with groups distinguished here by response to clozapine and current symptomatic status. Interestingly, the authors reported sex differences in the URS group with regard to glutamate and Glx levels, with men showing higher levels of glutamate and Glx in the dorsal anterior cingulate cortex compared with women. The percentage of women was low in this group (19.2%), but not statistically different from other groups. Overall, these results indicate that elevations in levels

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of glutamatergic metabolites may be a feature of URS. In line with these findings, there is evidence to suggest that schizophrenia that is responsive to antipsychotic treatment and TRS may have distinct underlying neurobiological mechanisms. Specifically, it has been suggested that TRS may be associated with comparatively normal striatal dopamine synthesis, but with abnormalities in glutamatergic metabolites (6). The findings by Iwata *et al.* (1) are consistent with predictions based on this approach. It is thus possible that treatments targeting glutamatergic dynamics may be salutary in TRS and particularly URS. Iwata *et al.* (1) rightly point out the need for prospective longitudinal neuroimaging studies of glutamatergic metabolites to follow up on these findings and to consider the effects of antipsychotic use, symptomatology, and illness progression in TRS.

Additional neuroimaging studies with multimodal approaches are necessary to understand the neurobiological basis of TRS (9). An important question may be how we best define TRS in neurobiological studies. Interpretation across neuroimaging studies of TRS is complicated by the use of different definitions of TRS and non-TRS comparison groups. Response to antipsychotic treatment in schizophrenia has generally been categorized in the following way: 1) treatment-responsive schizophrenia, 2) TRS, and 3) URS. To distinguish these groups, various definitions have been used for treatment response, including symptom severity, duration of symptoms, methods of assessment, and symptom domains. The absence of response to clozapine and two other antipsychotic trials has been considered ultra–treatment resistance. One of the complexities in defining treatment response is that schizophrenia involves heterogeneous symptoms, including positive, negative, and cognitive symptoms, which are not equally targeted by current antipsychotic treatment. The Treatment Response and Resistance in Psychosis (TRRIP) working group recently proposed consensus criteria of TRS for research (8), defining criteria for response and adequate antipsychotic treatment, while requiring specification of the symptom domain assessed (positive, negative, or cognitive) and presence of measured functional impairment. The TRRIP criterion for functional impairment in TRS considers that many patients have good social and occupational functioning despite ongoing psychotic symptoms. The TRRIP criteria for treatment resistance include symptom severity, as measured by a standardized rating scale, which is at least moderate with less than 20% symptom reduction. Current TRS criteria are necessarily clinically based, but using criteria consistently may help to elucidate the neurobiology of TRS in longitudinal prospective neuroimaging studies. It may also be fruitful to further consider symptom dimensions—for example, treatment-resistant auditory verbal hallucinations. Considering specific symptoms could reduce heterogeneity and perhaps further disentangle the common or distinct underlying mechanisms of responsive and resistant symptoms.

Schizophrenia involves complex interacting perturbations with anomalies in glutamatergic and dopaminergic systems, brain structural components, and basic biochemical functions, such as energy metabolism, myelination, and immune activity, among others (10). As we learn how to best multimodally examine these complex systems in the brain, studying TRS presents a clinically expedient opportunity that provides deeper insight into the neurobiology of schizophrenia, its treatment, and the different stages of illness.

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