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**Commentary**

# Is there Evidence for Neurotoxicity in the Prodromal and Early Stages of Schizophrenia?

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Retrospective and prospective studies in schizophrenia have identified a period of time, termed the prodromal period, that precedes the first episode of frank psychosis by a variable length of time (days–years) and is characterized by subthreshold psychotic symptoms. Importantly, both the prodromal phase and the early stages of the schizophrenia illness are associated with significant loss in social and intellectual abilities (Yung *et al*, 2005), as well as gray matter volume (Cahn *et al*, 2006; Pantelis *et al*, 2003). In addition, patients' response to antipsychotic medication decreases from first to subsequent episodes (Agid *et al*, 2011). It has been hypothesized that a neurobiological process might underlie this early progressive deterioration. In order to gain insight into this period, researchers have identified and followed subjects at 'ultra high risk', either because of a strong family history of schizophrenia or because of the presence of subthreshold symptoms. In addition, studies of first-episode subjects have become more common, in part because they lack the confounding effect of antipsychotic medication treatment.

In this issue of *Neuropsychopharmacology*, de la Fuente-Sandoval *et al* (2011) use $^{1}$H magnetic resonance spectroscopy (MRS) to obtain glutamate measurements in the caudate nucleus of antipsychotic-naïve prodromal subjects, antipsychotic-naïve first-episode psychosis subjects, and matched healthy control subjects. These investigators report that the high-risk and first-episode groups showed higher levels of glutamate than controls, without differences between ultra high risk and first episode. These findings are noteworthy for several reasons. Few studies have compared ultra high-risk and first-episode populations cross-sectionally. Because only 15–35% of high-risk subjects transition to psychosis, the interpretation of purely cross-sectional studies is somewhat ambiguous. Yet, in this study, the identification of the same pattern of high glutamate levels in the high-risk and first-episode populations provides stronger support for the relevance of this abnormality. Clearly, prospective studies of ultra high-risk populations are needed to address whether the degree of this early abnormality is predictive of the illness. Nevertheless, this study suggests that high levels of glutamate measured in the precommissural dorsal-caudate nucleus, a region with prominent projections throughout the cortical mantle, could induce cortical neuronal toxicity leading to a progressive functional and intellectual deterioration. Because there is preliminary evidence that stable medicated subjects either do not show a difference or evidence a decrease in glutamate levels compared with normal subjects (de la Fuente-Sandoval *et al*, 2011; Reid *et al*, 2010), it is tempting to hypothesize that a time-limited neurotoxic process may characterize the prodromal period and the early stages of the illness. Although more research is needed in this area, this suggests the possibility of curtailing functional deterioration by intervening therapeutically during the early stages. Importantly, this study provides strong clues as to the nature of these interventions, as well as specific targets, that is, glutamate level, to monitor treatment intervention. This study also points towards potential prediction algorithms to identify those who might, or might not, go on to develop the illness.

These data need to be considered in light of a recent study that reported increased striatal $^{18}$F-dopa uptake, which reflects increased presynaptic dopaminergic function, in another group of ultra –high-risk subjects (Howes *et al*, 2009). These data parallel findings of increased presynaptic dopamine function in psychotic and first-episode subjects. Do glutamatergic and dopaminergic dysfunctions coexist in the prodromal period, and is one the consequence of the other? In the caudate, both glutamatergic and dopaminergic afferents synapse on the same dendritic spines and shafts of medium-sized GABA-ergic projection neurons, providing an ideal anatomical arrangement for interactions between these neurotransmitters (Sesack, 2010). Alternatively, because of the use of different operational definitions of the at-risk population, the studies of Howes *et al* (2009) and de la Fuente-Sandoval *et al* (2011) may have enrolled

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slightly different populations. Nevertheless, these studies emphasize the need for prospective multimodal brain imaging of the prodromal period. The stakes are high. Any breakthrough in the neurobiology of the prodromal period could dramatically impact the life of subjects with schizophrenia.

Finally, the study of de la Fuente-Sandoval *et al* (2011) re-emphasizes the role of MRS technology for the non-invasive investigation of the brain's neurochemistry. It needs to be remembered that there are a number of limitations to this technique, such as factors that can confound measurements, including but not limited to age, nicotine and substances of abuse, and psychotropic medications (Licata and Renshaw, 2010). Thus, more than ever, caution will need to be exercised when matching populations. Nonetheless, with the introduction of more powerful magnets (that is, 7T), MRS will acquire greater precision and become an even more important tool to characterize, *in vivo*, key elements underlying the neuropathology of psychiatric conditions, especially with regard to glutamate, and to assess novel treatment strategies.

## DISCLOSURE

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