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Commentary

The Role of Dysfunctional Reward Processing in Psychotic Disorders

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Alterations of the reward system in patients with psychotic disorders are well documented (1). However, their role has been interpreted in multiple ways, for example as an expression of genetic vulnerability for psychotic disorders (2), as a consequence of environmental insults such as childhood trauma, or as a state marker associated with the expression of different symptom dimensions. This list is certainly not exhaustive, and while different concepts may not be mutually exclusive, the various aspects of (mal)adaptive reward processing across the psychosis continuum remains to be uncovered. Thus, studies aiming to differentiate the different roles of reward system alterations in vulnerable populations are of high interest.

In the current issue of *Biological Psychiatry: Global Open Science*, Nielsen *et al.* (3) present an important study on dysfunctional processing of reward anticipation and outcomes as an indicator of genetic vulnerability. They recruited patients with schizophrenia, their unaffected twins, and healthy control twins. To investigate processing of reward anticipation and outcome, Nielsen *et al.* (3) used the established monetary incentive delay task and functional magnetic resonance imaging. This study provides several important findings that are of great interest and the results raise several interesting questions for further research.

I would like to turn first to an important negative finding. Nielsen *et al.* (3) did not observe reduced ventral striatal activation during reward anticipation in unaffected co-twins. This was contrary to the hypotheses, because reduced striatal activation has consistently been shown not only in patients with schizophrenia, but also in their relatives and in patients in earlier stages of psychotic disorders (1,4). Nielsen *et al.* (3) propose several potential explanations of this negative finding that are related to the temporal dynamics of reduced striatal activation over a lifetime. It is of note that the mean age of 40 years was higher in their study than in many other studies. In short, the absence of a striatal effect at the moment of testing does not mean that the unaffected twins have never shown reduced striatal activation during their lifetimes. This underlines the need for future longitudinal studies despite the associated challenges.

Another point concerning reward anticipation is worth mentioning. It must be kept in mind that different tasks do not necessarily measure the same construct. In the present study, the anticipation contrast compared the anticipation of unexpected outcomes with the anticipation of neutral outcomes. Since unexpected outcomes can be either wins or losses, this contrast may measure anticipation of salient outcomes rather than rewards in the strict sense of positive outcomes. Reduced striatal activation during salience processing has been linked to positive symptoms, while reduced activation during anticipation of rewards may rather be associated with negative symptoms (5,6). This complexity may render it difficult to disentangle brain–symptom associations in meta-analyses (1,7). In the present study, unaffected co-twins had low expression of positive symptoms, which may have contributed to the absence of reduced striatal activation during anticipation of salient outcomes. The extent to which dysfunctional salience processing shows more state or trait characteristics is not yet clear, and again, longitudinal studies would be needed to explore this point.

The main positive finding of the study does not concern the anticipation phase but rather the processing of missed targets. Here, unaffected co-twins show increased activation of the dorsolateral prefrontal cortex compared with control twins and their twins affected by schizophrenia. Dorsolateral prefrontal cortex activation was associated with better performance on an intra-extra dimensional set shifting task. This latter finding supports the hypothesis of a compensatory mechanism that could contribute to the protection from psychosis despite genetic vulnerability. However, as the authors point out, it is difficult to reach a definitive conclusion concerning this interpretation, which would have to be confirmed in longitudinal studies.

Interestingly, unaffected co-twins also showed increased activation during missed targets in several other brain regions, notably the cerebellum. The authors point out the potential role of the cerebellum for performance monitoring and associative learning. In the past, the cerebellum has received attention as an important node in Andreasen's theory of cognitive dysmetria (8). The cerebellum has not been the main focus of functional magnetic resonance imaging studies in schizophrenia for a long time, either because the imaging protocols were not optimized to include the cerebellum or because the respective results were not reported. More recent functional magnetic resonance imaging work has emphasized the role of the cerebellum in goal-directed behavior and the relevance of its dysfunction for patients with schizophrenia (9).

Where do we go from here? The authors' strategy to focus on twins of patients with schizophrenia as genetically predisposed individuals and examining dimensional mechanisms of aberrant reward processing is certainly promising and should be developed further. Genetic risk could also be determined by other means, for example by recruiting children of patients with a psychotic disorder (4). The use of polygenic risk scores to determine genetic risk could also be an interesting avenue (10). While the use of polygenic risk scores has been somewhat limited by the small proportion of variance explained, precision is

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steadily increasing. Of course, risk states that are determined by clinical rather than genetic risk are also of high interest.

However, to fully understand the interaction of risk for psychotic disorders and reward system dysfunction we will not get around conducting longitudinal studies of longer duration. This will be all the more important for understanding the interplay of dysfunctional and compensatory processes in the manifestation of psychosis. Prospective studies of compensatory mechanisms in at-risk individuals may be of particular interest to better understand how the brain adapts to genetic psychosis risk, which could then be used to inform potential biological prevention interventions. The problem, of course, is the considerable cost associated with longitudinal study designs, and not only in terms of money. Researchers involved in longitudinal studies must remain invested over a long period of time and accept considerable risks, because the most interesting results will only be obtained after many years. In this situation, research institutions and funding agencies should provide conditions that encourage longitudinal studies. Reward system dysfunction in psychosis will only be one of the domains benefiting from such an approach.

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Article Information

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