EDITORIAL

The Salience of Reward

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An important and so far minimally addressed aspect of psychosis research is the manifestation of genetic psychosis susceptibility, as measured with polygenic risk profile scores (RPSs), on human brain function. The study of more than 1500 adolescents by Lancaster et al[1] in this issue of *JAMA Psychiatry* reveals that the genetic vulnerability to developing psychosis is associated with increased brain activity in the ventral striatum during reward processing. This finding suggests that the genetic risk of psychosis may shape the adolescent response to rewarding stimuli.

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Aberrant processing of salience is a fundamental factor underlying psychotic disorders.[2] Aberrant salience in this respect refers to the inappropriate attribution of incentive salience to environmental cues, which is the process by which a stimulus grabs attention and motivates goal-directed behavior because of associations with reward or punishment. This phenomenon is thought to underlie the formation of psychotic symptoms and is most likely driven by elevated striatal dopamine function,[3] which is 1 of the most robust pathophysiologic features of psychosis. Since the early 2000s, numerous functional magnetic resonance imaging (MRI) studies[4-6] have investigated the effect of incentive cues on human brain activity patterns with a monetary incentive delay task that involves reward anticipation and receipt. In this task, individuals are required to press a button as fast as possible when seeing a target stimulus. The cue that precedes the target stimulus indicates whether a timely button press is rewarding or nonrewarding. The time between cue and target is considered the anticipation time, and reward receipt is assessed when feedback on performance is given at the end of every trial. Results of studies with healthy individuals have unequivocally indicated the ventral striatum as the brain area critically involved in reward processing[4] and have also revealed the heritability of brain activity patterns underlying reward processing.[7] Neuroimaging in patients with a psychotic disorder has consistently revealed significantly attenuated activity in the ventral striatum during reward anticipation, as confirmed by a recent meta-analysis[5] that included 23 functional MRI studies. This pattern of reduced striatal activity during reward anticipation has also been found in unaffected siblings[8] and offspring[9] of patients with a psychotic disorder, which suggests that genetic risk of psychosis contributes to the response to rewarding cues.

Recently, the ability to stratify individuals on the basis of polygenic RPSs for psychiatric disorders, such as schizophrenia and bipolar disorder, has offered new opportunities for clinical and epidemiologic research. Risk profile scores are derived from large genome-wide association studies[10,11] that examined individual genetic variants associated with a particular disorder and indicate an individual's genetic susceptibility of developing this disorder. Thereby, RPSs provide the possibility to examine phenotypic manifestations of large groups of healthy individuals according to genetic risk. For example, in the general population, genetic schizophrenia susceptibility as assessed by RPSs has been associated with measures of creativity,[12] the deleterious effect of cannabis use on cortical brain development,[13] and the presence of negative psychotic symptoms and anxiety disorder.[14] However, research on the manifestation of the genetic risk of psychotic disorders in human brain function has been limited.

Lancaster and colleagues[1] investigated how genetic vulnerability to developing psychosis relates to ventral striatal activity during reward processing using functional MRI and the monetary incentive delay task in a large cohort of healthy adolescents. The psychosis RPSs were acquired by combining the RPSs for schizophrenia and bipolar disorder because both psychiatric disorders include, although not necessarily, psychotic symptoms, share genetic liability,[15] and involve altered reward processing.[16] They found that higher psychosis RPSs were significantly associated with increased activity in the ventral striatum during reward anticipation and, to a lesser extent, during reward receipt. These effects were controlled for IQ and were not related to depressive symptoms and smoking behavior, which are potential confounding factors. Increased striatal activity was driven by the RPSs for schizophrenia and bipolar disorder. These findings suggest that genetic psychosis susceptibility is associated with enhanced incentive salience during adolescence. The reported findings support results from a previous study[17] that found associations between single genetic risk variants for psychosis and reward processing. In addition, the findings are consistent with results of neuroimaging studies[8,18] that found altered reward processing in first-degree relatives of patients with psychosis. Findings of this study are of significant importance because they indicate that an altered neurophysiologic response to rewarding cues, which has consistently been found in patients diagnosed as having psychosis, is present before the onset of the disorder in those at a higher genetic risk for psychosis.

As pointed out by Lancaster and colleagues,[1] the demonstrated association between a higher psychosis RPS and increased ventral striatal activity during reward processing is not consistent with results of a recent meta-analysis[5] of 23 studies on reward anticipation, which found significantly attenuated ventral striatal activity in patients with a psychotic disorder. Previous neuroimaging studies[8,18] with first-degree relatives of patients with psychosis also found reduced ventral striatal activity during reward anticipation. One possible factor that may

explain these discrepant findings is the age of the study participants. Whereas Lancaster et al[1] examined reward processing in a large sample of adolescents, other studies[5,8,18] included adult study participants. Importantly, a recent study by Vink and colleagues[9] revealed a significantly different pattern of reward-related striatal activity across age between healthy controls and offspring of patients with psychosis. Where younger offspring had an increased response to rewarding stimuli compared with controls, the older participants at genetic risk for psychosis had relatively lower striatal activity during reward anticipation. This finding suggests that manifestation of genetic psychosis susceptibility in reward brain function may vary across the lifespan. The genetic vulnerability to psychosis is possibly associated with enhanced incentive salience during adolescence, which is attenuated during later stages of brain development.

Another possible explanation for the apparently discrepant findings on ventral striatal activity during reward processing between adolescents at high genetic risk for psychosis and patients may be that the results are driven by altered reactivity to nonrewarding rather than rewarding stimuli. Most functional MRI studies using the monetary incentive delay task compared brain activity during rewarding task conditions with activity during nonrewarding conditions. With this approach, reduced ventral striatal activity as reported during reward processing in patients with a psychotic disorder could be the result of reduced reactivity to rewarding or a stronger response to nonrewarding cues. However, Lancaster and colleagues[1] reported brain activity patterns across rewarding and nonrewarding conditions, rather than contrasting both task conditions. This finding implies that the increased ventral striatal activity in those adolescents at higher risk for psychosis could be explained by higher reactivity to incentive and neutral stimuli. Thus, the reported increase in ventral striatal activity during reward processing in those with a higher psychosis RPS and the demonstrated reduced response to rewarding cues in patients and siblings could be attributable to a stronger response to nonrewarding cues. This finding would be consistent with contemporary models that propose that psychotic symptoms arise from the inappropriate attribution of salience to otherwise insignificant stimuli.[2]

Notwithstanding the significance of the findings presented by Lancaster et al,[1] one alternative interpretation of their results has not been addressed. A significant association between an increased psychosis RPS and task performance was reported, with those individuals at a higher genetic risk for psychosis having a lower performance accuracy. Because task performance could be reflected in brain activity patterns, this significant effect on performance accuracy may be involved in the association between the genetic vulnerability to develop psychosis and striatal activity during reward processing.

In summary, this interesting new study reports that adolescents at higher genetic risk for developing psychosis have increased brain activity in the ventral striatum during reward processing. This finding suggests that genetic psychosis susceptibility is associated with enhanced incentive salience during adolescence. The findings by Lancaster et al[1] support the notion that genetic vulnerability to psychosis is reflected in an altered neurophysiologic response to rewarding cues.

ARTICLE INFORMATION

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