COMMENTARY

Some Rewarding Insights into the Cognitive and Neurobiological Basis of Negative Symptoms in Schizophrenia

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Throughout each and every day we constantly make complex choices related to our present and future actions. Our estimation of the utility of these choices and the rewards and punishments that might be associated with them exerts a major influence over each and every choice and action. Many people with schizophrenia seem to find decision making difficult, stressful, and perplexing, and many also show a decrease in the pursuit of potentially rewarding activities in everyday life (1). Attempts to understand this aspect of the illness and to relate it clinically to specific negative symptoms have become increasingly important as our treatment goals for this schizophrenia evolve from one of psychotic symptom management and relapse prevention to a more rehabilitative, quality-of-life–enhancing approach.

In recent years the investigation of reward processing and decision making has become a major focus of basic cognitive neuroscience. Early observations of the role of dopamine (DA) in reward processing and error prediction (2), a growing understanding of the role of the basal ganglia (BG) and prefrontal cortex (PFC) in these functions (3–5), and a growing awareness of the complexity and context dependence of reward processing and decision making (6,7) provide an important theoretical framework for the investigation of these aspects of schizophrenia. Indeed, recent functional magnetic resonance imaging studies have begun to apply this approach, implicating alterations in frontal and/or striatal functions in decision making and reward processing in schizophrenia (8).

In the study by James Waltz, Benjamin Robinson, and James Gold of the University of Maryland and Michael Frank of the University of Arizona (9; in this issue), an interdisciplinary group of cognitive neuroscientists and clinical investigators seek to obtain insights into the nature of deficits in reward-based learning and its relationship to choice behavior in people with schizophrenia. They begin by addressing a curious discrepancy in the literature on feedback-based learning in schizophrenia, namely that patients are very reliably impaired on the Wisconsin Card Sort Task, which depends upon using feedback to guide, acquire, and update rules and guide performance card, although they have often been shown to perform reasonably well on tasks involving procedural learning. Both kinds of learning are feedback-based, yet the former is consistently impaired, whereas the latter seems generally spared in studies of schizophrenia. What could account for this curious separation across different tasks? Could it be that there are different mechanisms underlying their performance and, if so, could relative preservation of procedural learning in the presence of impairment on other forms of feedback-based learning provide insights not only at the behavioral level but also into the neurobiology of the illness?

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To address the aforementioned discrepancy in the literature and to obtain a deeper understanding of the underlying mechanisms, the authors apply new insights into the neurobiology of reward-based learning obtained with a computational model of reward-based learning developed by Frank and Claus (10). This is a highly developed model that is deeply informed by our current knowledge of the neurobiology of the reward and decision making circuitry in the primate brain. Modules in the model represent distinct frontal striatal circuits, and their functions are modulated by DA through distinct receptor specific (D1 and D2). Lesioning structural elements of the model or manipulating neuromodulatory functions captures many elements of disordered behavior (e.g., in Parkinson's disease or frontal lobe damage), providing a detailed account of the possible underlying neurobiological perturbations in these clinical syndromes.

Important aspects of the architecture of the model that might shed light on these inconsistencies in reward-based learning in schizophrenia include the specification of distinct roles for reward-based learning in the BG the PFC. In the model BG-based learning supports the slow acquisition of reward-based choice behavior though changes in connection strengths that are driven by phasic DA activity (as in many procedural learning tasks), whereas the orbitofrontal cortex (OFC) supports the rapid acquisition of these associations by maintaining choice-feedback history in working memory (as in the Card Sorting Task). The model also specifies distinct roles for DA activity in the BG, with reward-related increases supporting "Go" responses (that are mediated by direct pathway via D1 receptors) and punishment-related decreases supporting avoidant "No Go" choices (that are mediated through the indirect pathway via D2 receptors). In the context of feedback-related learning in schizophrenia, the model provides substantial leverage in interpreting the results of previous studies and allows the authors to make specific predictions on the basis of hypothesized prefrontal and dopaminergic deficits in schizophrenia that they then test experimentally.

In step with the modeling work the investigators use a task developed by Frank, the performance of which is readily simulated by the computational model, which in turn can be manipulated to express the behavioral sequelae of a range of neurobiological perturbations hypothesized to be present in schizophrenia. The task has an acquisition phase, where choice behavior is shaped by rewarding and punishing feedback, and a transfer phase, during which subjects respond without feedback to choices that reflect differing reward associations acquired during the acquisition phase. Converging results were obtained with both verbalizable and non-verbalizable materials, although the data using non-verbalizable stimuli were difficult to interpret, owing to very poor patient performance with this more difficult version of the task. The authors hypothesized that if the ability of the PFC to rapidly update response-reward contingencies is impaired but BG mechanisms underlying reward signaling are basically intact then schizophrenia patients will learn these contingencies more slowly but to the same degree as healthy

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control subjects. They also hypothesized—perhaps non-intuitively but on the basis of the model, previous results from Parkinson's disease patients and data suggesting reduced D1 but enhanced D2 function in schizophrenia—that there would be an impairment in the effects of reward on choice behavior during transfer testing but a preservation of punishment effects on choice behavior during this phase of the task.

Interestingly, patients' performance quite clearly reflected the distinct forms of feedback learning captured by Frank's computational model. Overall measures of choice learning driven by rewarding and punishing feedback were reduced in the schizophrenia group, but patients did learn the easier associations. This is consistent with the prediction of a disturbed OFC-based system for rapid learning of choice outcome associations. Furthermore, during the transfer phase of the task that is thought to reflect DA effects in the direct (D1-dependant) and indirect (D2 dependent) pathways, an interesting dissociation was seen between impaired performance in selecting rewarded stimuli and preserved (perhaps even enhanced) performance avoiding previously punished stimuli. Performance during the acquisition phase of the task, hypothesized to reflect a PFC deficit, was selectively correlated with measures of negative symptoms. The results also suggest that preservation of BG-based procedural learning in schizophrenia is relative rather than absolute, with impaired reward-based learning but intact punishment-related learning. The authors conclude that there are impairments of both prefrontal- and BG-dependant aspects of feedback-dependant learning, with the latter specific to reductions in the direct pathway-based "Go" signal. They also suggest that D1-based deficits (reduced phasic DA) might account for both PFC- and BG-based "Go" learning deficits and that upregulation of D2 receptors by antipsychotic medications might be related to the preservation of the indirect pathway–mediated "No Go" signal.

The clarification of mechanisms of impaired feedback-dependant learning in schizophrenia and their potential relationship to negative symptoms represents a potentially important advance for the field. The observation that negative feedback-related learning is preserved in patients might have implications for the development of future rehabilitative approaches. Questions about the effects of antipsychotic medications raised by the authors (subjects were mid-life, chronic, medicated patients) could be addressed by studying unmedicated subjects, first episode subjects undergoing systematic treatment, or even the unaffected first degree relatives of patients. Systematic studies in healthy volunteers using DA agonists and antagonists could also be very highly informative for the proposed model of impaired reward-based learning and its relationship to negative symptoms. Functional imaging studies using tasks such as the one in the present study could provide a strong test of some of the functional neuroanatomical predictions of the Frank model as it applies to schizophrenia.

The Waltz *et al.* study is an important example of how translational behavioral research can provide new insights into the neural basis of clinically important behavioral deficits in schizophrenia as well as important avenues for the development of targeted therapies for these treatment refractory aspects of the illness. Tools and constructs from cognitive neuroscience, in this case a powerful neurobiologically informed computational model and a related behavioral paradigm, were successfully applied to increase our understanding of the clinical problem of negative symptoms in schizophrenia. This success testifies to the value of building interdisciplinary teams translating basic cognitive neuroscience approaches into clinical neuroscience investigations. The results of the study support a role for DA-mediated frontal and striatal disturbances in mediating impaired feedback-related learning and set the groundwork for more targeted imaging and pharmacological studies in the future. They complement previous work implicating abnormalities in the PFC in negative symptoms of schizophrenia and suggest a stronger emphasis on the role of the OFC in future studies. Finally, it is important to note the value of performing this very demanding behavioral study ahead of any future neuroimaging studies, so that the design of those studies can be refined and targeted to directly test the novel hypothesis suggested by the computational modeling work and confirmed in the behavioral data of the present one.

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