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Probabilistic reversal learning impairments in schizophrenia: Further evidence of orbitofrontal dysfunction

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Abstract

Impairments in feedback processing and reinforcement learning appear to be prominent aspects of schizophrenia (SZ), which may relate to symptoms of the disorder. Evidence from cognitive neuroscience investigations indicates that disparate brain systems may underlie different kinds of feedback-driven learning. The ability to rapidly shift response tendencies in the face of negative feedback, when reinforcement contingencies are reversed, is an important type of learning thought to depend on ventral prefrontal cortex (PFC). Schizophrenia has long been associated with dysfunction in dorsolateral areas of PFC, but evidence for ventral PFC impairment in more mixed. In order to assess whether SZ patients experience particular difficulty in carrying out a cognitive function commonly linked to ventral PFC function, we administered to 34 patients and 26 controls a modified version of an established probabilistic reversal learning task from the experimental literature [Cools, R., Clark, L., Owen, A.M., Robbins, T.W., 2002. Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. J. Neurosci. 22, 4563–4567]. Although SZ patients and controls performed similarly on the initial acquisition of probabilistic contingencies, patients showed substantial learning impairments when reinforcement contingencies were reversed, achieving significantly fewer reversals [$\chi^2(6)=15.717$, $p=0.008$]. Even when analyses were limited to subjects who acquired all probabilistic contingencies initially (22 patients and 20 controls), patients achieved significantly fewer reversals [$\chi^2(3)=9.408$, $p=0.024$]. These results support the idea that ventral PFC dysfunction is a prevalent aspect of schizophrenic pathophysiology, which may contribute to deficits in reinforcement learning exhibited by patients. Further studies are required to investigate the roles of dopaminergic systems in these impairments.

Keywords: Schizophrenia; Dopamine; Reinforcement; Basal ganglia; Prefrontal; Orbitofrontal

One of the most common neuropsychological findings in the schizophrenia (SZ) literature is that of impaired attentional set-shifting, as evidenced by studies using tasks like the Wisconsin Card Sort Test (WCST) and the intradimensional/extradimensional (ID/ED) attentional set-shifting task. This deficit has often been linked to dysfunction of dorsolateral prefrontal cortex (DLPFC), one of the most frequently-observed neural correlates of schizophrenia (Weinberger et al., 1986; Berman et al., 1988). One possible source of set-shifting deficits in patients may be set-*learning* impairments related to limitations in DLPFC-dependent attentional and working memory resources. Another possible source of set-shifting difficulties, however, may be a specific

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impairment in reversing learned associations. The reversal of learned associations is known to depend on ventral and medial areas of prefrontal cortex (PFC) from a variety of studies involving both human and nonhuman animal subjects, including both lesion studies (Dias et al., 1996; Fellows and Farah, 2003; Hornak et al., 2004) and those using physiological data acquisition (Rolls et al., 1996; Cools et al., 2002; Evers et al., 2005). It is thought that ventral PFC contributes to the rapid reversal of learned associations through the integration and online representation of the reinforcement value of stimuli and actions (Rolls, 1996; Roesch and Olson, 2005; Schoenbaum and Roesch, 2005), while areas of medial prefrontal cortex, such as anterior cingulate cortex (ACC), figure critically in the monitoring of performance and detection of errors, processes which lead to behavioral modifications (Carter et al., 1998; Paulus et al., 2002; Holroyd et al., 2004).

The idea that dysfunction in ventral and medial areas of PFC might be a prominent feature of SZ is supported by an increasing amount of evidence pointing to both structural (Goldstein et al., 1999; Crespo-Facorro et al., 2000; Pantelis et al., 2003; Davatzikos et al., 2005) and functional (Bertollo et al., 1996; Carter et al., 2001; Quintana et al., 2003) abnormalities in these brain regions in schizophrenia. Behaviorally, schizophrenia patients have shown impairment on a number of tasks thought to be dependent on intact ventral PFC, including delayed alternation/object alternation (Seidman et al., 1995) and the Iowa Gambling Task (IGT; Ritter et al., 2004; Shurman et al., 2005), although these results have not been unequivocal (see, e.g., Wilder et al., 1998). Up to this point, the possibility that schizophrenia involves a specific impairment in reversal learning has been most directly addressed by studies using the ID/ED attentional set-shifting task (Elliott et al., 1995; Pantelis et al., 1999). Studies involving schizophrenia patients using this task have found that, even when compared with patients with PFC lesions, significantly more patients with SZ fail to reach criterion on reversals of relatively simple rules not requiring the consideration of multiple stimulus dimensions (Elliott et al., 1995; Pantelis et al., 1999).

While the above results suggest that patients with schizophrenia have particular difficulty using feedback to guide future choices, none of the paradigms mentioned above was designed to test the ability of subjects to adjust to sudden shifts in reinforcement contingencies in a sensitive way. In the ID/ED task, for example, the stimulus–response (S–R) rules are easily acquired by most subjects, and the difficulty in the task comes from the need to associate responses with increasingly complex stimuli. In probabilistic reversal learning tasks, the choice of a particular stimulus is reinforced most, but not all of the time, and correct responses are occasionally followed by negative feedback. Thus, the difficulty in performing these tasks comes from the need to integrate feedback over a number of trials (Cools et al., 2002). Because not all instances of negative feedback signal a shift in reinforcement contingencies, subjects need to consider each single instance of feedback in the context of the recent history of reinforcement. Thus, participants typically make more errors, and require more trials to reach the learning criterion than when performing reversal learning when guided by probabilistic, as opposed to fully-reliable, feedback.

Neuroimaging studies (Cools et al., 2001, 2002, 2007) have demonstrated the dependence of probabilistic reversal learning on ventral PFC (especially the lateral aspect), as well as dopaminergic systems in the brain. In addition, several studies (Huettel et al., 2002; Paulus et al., 2004) support a role for this same region in monitoring reinforcement trends during learning tasks. By contrast, there is evidence that the gradual acquisition of probabilistic contingencies depends more heavily on subcortical structures in the basal ganglia, and less on cortical structures (Knowlton et al., 1996; Seger and Cincotta, 2005). The results of multiple studies (Keri et al., 2000; Weickert et al., 2002; Beninger et al., 2003; Keri et al., 2005) suggest that the *acquisition* of probabilistic contingencies in schizophrenia patients may be relatively unimpaired, perhaps indicative of a relatively intact basal ganglia function in schizophrenia. Thus, patients with SZ could show intact initial discrimination learning, but impaired reversal learning.

Adopting a modified version of the paradigm used by Cools et al. (2002), we performed a direct test of probabilistic reversal learning performance in patients and controls. In order to assess whether patients showed particular impairment in the reversal of learned discriminations, we compared the proportions of discriminations achieved and reversed, and the proportions of errors made in discrimination and reversal stages by subjects. We predicted that patients would perform as well as controls on the acquisition of initial discriminations, but show substantial impairment, relative to controls, in the reversal of learned discriminations. Such a dissociation, we argue, would reflect a particular dysfunction in schizophrenia of ventral PFC circuits involved in the detection of sudden shifts of reward contingencies.

1. Method

1.1. Patients

Thirty-four outpatients with a diagnosis of schizophrenia, based on the Structured Clinical Interview for