Reinforcement and Reversal Learning in First-Episode Psychosis

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Advance Access publication on July 15, 2008

doi:10.1093/schbul/sbn078

Schizophrenia Bulletin vol. 34 no. 5 pp. 848–855, 2008

Key words: neuropsychology/cognitive function/schizophrenia/orbitofrontal cortex/ventral striatum/set shifting

Introduction

It has long been proposed that there are associative and reinforcement learning deficits in schizophrenia and other psychoses.1–7 Such theories have been strengthened by documentation of dopamine deficits in the pathophysiology and treatment of schizophrenia,8,9 given evidence from animal10,11 and human12 studies implicating a critical role for dopamine transmission in reinforcement learning. Until recently, reinforcement learning in psychosis has received little laboratory study. However, initial evidence has recently emerged demonstrating abnormal reinforcement learning, coupled with disrupted activity of dopamine innervated brain regions in schizophrenia and other psychoses.13–15

Reinforcement learning, in its general sense, involves a subject learning by trial-and-error feedback to select actions that maximize reward over time. One variant of reinforcement learning, termed reversal learning, examines the ability to flexibly adapt the response to a change in learning contingencies. Reversal learning is of particular interest in psychotic illness as a marker of functioning in orbitofrontal cortex–ventral striatal circuitry. Other orbitofrontal cortex–related paradigms, such as the Iowa Gambling Test, have yielded equivocal results in schizophrenia.16,17 Three previous studies have specifically examined reversal learning in psychosis, each finding deficits, but these few existing studies have sampled only patients with chronic schizophrenia.18–20 It remains unclear whether reinforcement and reversal learning are dysfunctional in the early phase of schizophrenia and whether these processes are differentially impaired in schizophreniform psychoses and affective psychoses. We therefore examined simple reinforcement and reversal learning in a large sample of first-episode psychosis patients who undertook the Intra-Extra Dimensional (ID/ED) Set Shift task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) cognitive test battery.21 The ID/ED test involves various stages of rule learning and rule reversal, as well as the formation of attentional set. Because of the highly

Background: Abnormalities in reinforcement learning and reversal learning have been reported in psychosis, possibly secondary to subcortical dopamine abnormalities. Methods: We studied simple discrimination (SD) learning and reversal learning in a sample of 119 first-episode psychosis patients from the Cambridge early psychosis service (CAMEO) and 107 control participants. We used data on reinforcement learning and reversal learning extracted from the Cambridge Neuropsychological Test Automated Battery Intradimensional-Extradimensional shift task, which measures cognitive flexibility but also involves simple reinforcement learning (SD learning) and reversal learning stages. We also gathered diagnostic information to examine whether there were any differences between patients ultimately diagnosed with schizophrenia-spectrum disorders and those diagnosed with affective psychosis. Results: Psychosis patients demonstrated deficits in simple reinforcement learning (SD learning) and in reversal learning, with no differences between affective psychosis and schizophrenia-spectrum psychosis. There was a significant modest correlation between reversal errors and negative symptoms (Spearman ρ = 0.3, P = .02). Conclusions: There are reinforcement learning abnormalities in first-episode psychosis, which correlate with negative symptoms, suggesting a possible role for orbitofrontal cortex and ventral striatal pathology in the pathogenesis of motivational deficits in psychosis.

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structured progression of the task, it is possible to examine specific cognitive-behavioral components involved at different stages of the experiment. We specifically focused on performance of those parts of the test involving reversal learning and compared performance in psychosis patients with matched controls. Furthermore, we followed up patients presenting with first-episode psychosis, and stratified their performance according to formal diagnostic status after 12 months. In this report, we do not focus on ED set shifting performance, as performance there has previously been well studied in early psychosis, including in a partially overlapping sample.

Methods

Participants

One hundred nineteen individuals (mean age 23.4 years; 88 men) with first-episode psychosis were recruited from the Cambridge first-episode psychosis service, Cambridge early psychosis service (CAMEO; www.cameo.nhs.uk), for the study. Inclusion criteria for CAMEO is age between 17 and 35 years, suffering from a first episode of psychosis as defined by the Melbourne criteria of the presence of psychotic symptoms for at least a week, and duration of antipsychotic treatment of under 6 months at time of initial assessment. One hundred seven healthy volunteers (mean age 24.5 years, 72 men) were recruited from the general population by advertisement to act as a control group. The majority of the patients were taking second-generation antipsychotic medication. Most patients in this study were assessed within 6 weeks of their referral to CAMEO and had mild symptoms at the time of the experiment. Twelve months after the experiment, a psychiatrist (G.K.M.) utilized all available clinical information including case history, ongoing clinical assessments, structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and operational criteria diagnostic system to classify the cases as affective psychosis or nonaffective psychosis. The research was approved by the Local Research Ethics Committee; all participants provided written informed consent. The National Adult Reading Test was used to estimate IQ of patients and controls.

ID/ED Shift Test

The ID/ED Shift test was derived from the Wisconsin Card Sort Test. It involves visual discrimination and attentional set formation and tests the maintenance, shifting, and flexibility of attention (see figure 1). Two dimensions are used in the test: color-filled shapes and white lines. Simple stimuli are made up of just one of these dimensions, whereas compound stimuli are made up of both, namely white lines overlying color-filled shapes. At the first stage, simple discrimination (SD), the subject starts by seeing 2 simple color-filled shapes, and must learn which one is correct by touching it. Feedback teaches the subject which stimulus is correct, and after 6 correct responses, the contingencies change and the previously correct element becomes incorrect (simple reversal stage). At this point distracting stimuli (lines) are added in order to provide compound discrimination stages (CD1 and CD2), followed by compound discrimination reversal. After this stage has been learnt, there is an intradimensional shift (IDS), where new exemplars of the 2 dimensions “line” and “shape” are introduced, but the relevant dimension is unchanged, eg, color-filled shapes remain the only relevant dimension. After an intradimensional reversal (IDR), there follows an extra-dimensional shift (EDS, eg, white lines become the relevant dimension) and a final reversal stage (EDR). Subjects progress through the test by satisfying a set criterion of learning at each stage (6 consecutive correct responses). We extracted information on all stages but focus our analysis on the basic acquisition and reversal trials. In cognitive assessments, the ID/ED test is sometimes preceded by a preliminary test called Big/Little Circle, which is a screening test in the CANTAB test battery; we did not use the Big/Little Circle test in our study.

Data Analysis

Demographic characteristics of the 2 groups, and number of subjects failing test stages, were compared using independent samples t tests and chi-squared tests. Error scores were skewed and could not be normalized by mathematical transformation, and were therefore analysed with Mann-Whitney U Tests. Because error scores are count data, the relationship between error scores and symptoms scores were implemented using Poisson regression in intercooled Stata 8.2. Separate analyses with error score as the dependent variable were employed for each predictor variable, and the results confirmed with correlational analyses using Spearman ρ.

Results

Group demographics and diagnostic information:

The psychosis group and the control group were matched on age, gender, and NART estimated verbal IQ (Table 1). When all available information was utilized to apply diagnostic categories after 12 months, 81 patients were classified as schizophrenia-spectrum psychosis and 31 as affective psychosis, with missing information on 6 cases. PANSS scores from initial assessment were available on 78 patients.

Learning analysis: stages passed and failed

In the control group, 1 participant failed at the IDS stage, 2 failed at the IDR stage, 5 failed at the EDS stage, and 1 failed at the final reversal stage (see figure 2). In patients, 2 failed at the compound discrimination stage, 1 at the compound reversal stage, 27 failed at the EDS stage,
and 11 failed at the final reversal stage. Thus, in terms of stage failures, significantly more patients failed the EDS stage \((\chi = 16.5, P < .001)\), and the final reversal stage \((\chi = 9.6, P < .01)\), than controls.

**Learning analysis: error analysis**

For a more sensitive analysis, we examined error scores at each stage. We compared all patients \((n = 119)\) vs all controls \((n = 107)\) on initial discrimination learning (figure 3). By examining the number of errors using the Mann-Whitney U test, we confirmed that psychosis patients made more errors than controls during initial discrimination learning \((z = 2.5, P = .01)\); in contrast, there were no differences between patients and controls on initial reversal learning, compound discrimination learning, ID set shifting, compound reversal, or IDR. However, there were deficits in ED set shifting \((z = -5.1, P < .001)\) and final reversal stages \((z = -3.7, P < .001)\). Next, we examined the total number of reversal errors over the course of the experiment in participants who attempted all stages of the IDED test: ie, those who completed at least the EDS stage and so could attempt the final reversal stage (99 controls and 89 patients, see table 2 and figure 4). Although some psychosis patients showed good performance, as a group patients made more total reversal errors than controls \((z = -2.4, P = .02)\).

We next examined whether, within the patient group, total reversal errors could be explained, at least in part, by SD errors. Utilizing Poisson regression, we found that SD errors did not predict total reversal errors \((z = 0.7, P = .5)\). In contrast, SD errors were a significant predictor of EDS errors \((z = 5.4, P < .001)\).

Having established the differences between first-episode psychosis patients and controls, we proceeded to examine whether patients with schizophrenia-spectrum psychoses differed from patients with affective psychosis. Patients with affective psychosis made fewer ID shifting

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**Table 1.** Demographic Information on Psychosis Cases and Controls and on Psychosis Patients Stratified by Diagnosis of Nonaffective or Affective Psychosis (Diagnostic Information Was Missing on 6 Patients)

|                      | Control, Mean (SD) | All Psychosis, Mean (SD) | Nonaffective Psychosis, Mean (SD) | Affective Psychosis, Mean (SD) | T or \(\chi^2\) | df | P |
|----------------------|--------------------|--------------------------|-----------------------------------|--------------------------------|-----------------|----|---|
| Age (y)              | 24.5 (4.7)         | 23.3 (5.4)               | 23.6 (5.6)                        | 24.2 (1.1)                     | 1.6             | 224 | .1 |
| NART                 | 112 (13)           | 109 (8)                  | 108 (8.2)                         | 111 (7.8)                      | 1.9             | 175 | .1 |
| Gender               | 72 Men, 35 women   | 88 Men, 31 women         | 63 Men, 19 women                  | 20 Men, 11 women               | 1.2             | 1   | .3 |
| PANSS positive       | N/A                | 16.9 (6.2)               | 18.4 (6.2)                        | 13.6 (5.2)                     |                 |     |    |
| PANSS negative       | N/A                | 14.5 (6.6)               | 15.4 (6.7)                        | 12.2 (6.0)                     |                 |     |    |

*Note:* Also shown are statistical comparisons of psychosis patients vs controls in age, National Adult Reading Test Score, and gender.
errors than patients with schizophrenia-spectrum psychosis ($z = -2.3$, $P = .026$), but there were no differences in any other stages of the ID/ED or in total reversal errors ($z = -0.539$, $P = .6$; table 3).

Finally, we examined whether symptom scores correlated with performance on simple and reversal trials in the 56 first-episode psychosis patients who completed at least the ED stage of the ID/ED test and for whom PANSS scores were available. Poisson regression revealed that total reversal errors were predicted by negative symptoms ($z = 3.72$, $P < .001$), but not positive symptoms ($z = -0.6$, $P = .6$), which is consistent with results from a correlational analysis: total reversal errors correlated significantly with negative symptoms (Spearman $\rho = 0.3$, $P = .02$) but not with positive symptoms (Spearman $\rho = 0.2$, $P = .20$). There was no association between SD errors and psychopathology either on correlational analysis (positive symptoms Spearman $\rho = 0.06$, $P = .6$; negative symptoms Spearman $\rho = 0.02$, $P = .98$) or on Poisson regression (positive symptoms $z = 0.52$, $P = .6$, negative symptoms $z = 0.35$, $P = .7$).

Table 2. Comparison of Psychosis Cases and Control Error Scores (Mann-Whitney $U$ Test) in Those Participants Who Attempted All Stages of the ID/ED Test: ie, Those Who Completed At Least the Intradimensional Shift Stage and Who Therefore Were Able to At Least Attempt the Final Reversal Stage

|                     | Psychosis N = 89 | Control N = 98 | z    | P     |
|---------------------|------------------|----------------|------|-------|
| Simple discrimination | 0.84 (0.62)      | 0.68 (0.75)    | -2.33| 0.02  |
| Simple reversal      | 1.27 (0.72)      | 1.27 (0.75)    | -0.04| 1     |
| Compound discrimination 1 | 1.06 (1.41)      | 1.04 (1.61)    | -0.03| 1     |
| Compound discrimination 2 | 0.22 (0.56)      | 0.15 (0.48)    | -0.92| 0.4   |
| Compound reversal    | 1.64 (1.71)      | 1.48 (1.51)    | -0.62| 0.5   |
| Intradimensional shift | 0.67 (1.19)      | 0.67 (1.37)    | -0.22| 0.8   |
| Intradimensional reversal | 1.30 (0.86)      | 1.32 (0.97)    | -0.14| 0.9   |
| Extradimensional shift | 6.55 (5.66)      | 4.36 (4.45)    | -3.44| <0.001|
| Extradimensional reversal | 5.31 (8.39)      | 1.40 (1.20)    | -3.71| <0.001|
| Total reversal errors | 9.60 (9.11)      | 5.72 (3.62)    | -2.41| 0.02  |
Table 3. Comparison of Nonaffective Psychosis and Affective Psychosis Error Scores (Mann-Whitney U Test) in Those Cases Who Attempted All Stages of the IDED Test: i.e., Those Who Completed At Least the Extradimensional Shift Stage and Who Therefore Were Able to At Least Attempt the Final Reversal Stage

|                  | Nonaffective Psychosis, N = 62, Mean (SD) | Affective Psychosis, N = 24, Mean (SD) | z   | P     |
|------------------|------------------------------------------|----------------------------------------|-----|-------|
| Simple discrimination | 0.85 (0.62)                | 0.88 (0.61)                | −0.30 | .77   |
| Simple reversal   | 1.32 (0.81)                | 1.17 (0.48)                | −0.77 | .44   |
| Compound discrimination 1 | 1.13 (1.48)            | 0.88 (1.30)            | −0.89 | .38   |
| Compound discrimination 2 | 0.23 (0.58)            | 0.25 (0.53)            | −0.47 | .64   |
| Compound reversal | 1.65 (1.64)                | 1.58 (1.93)                | −0.91 | .36   |
| Intrdimensional shift | 0.82 (1.29)            | 0.33 (0.92)            | −2.58 | .01   |
| Intrdimensional reversal | 1.32 (0.84)         | 1.29 (0.95)             | −0.57 | .57   |
| Extradimensional shift | 6.26 (4.91)              | 8.16 (6.54)               | −0.97 | .33   |
| Extradimensional reversal | 5.06 (7.83)         | 6.46 (10.15)            | −0.16 | .88   |
| Total reversal errors | 9.35 (8.47)            | 20.82 (11.15)            | −0.54 | .59   |

Discussion

As expected, we found that psychosis patients had deficits in ED set shifting. This deficit has been previously documented in chronic schizophrenia, and in first-episode psychosis, although some studies in first-episode psychosis suggest that there may either be no deficit in this domain or that the deficit may be slight. Given that a number of previous studies have investigated ED set shifting in schizophrenia and early psychosis, here we focus our interpretation on the results concerning simple reinforcement learning and reversal learning.

Elliott et al previously demonstrated reversal learning deficits in chronic schizophrenia. Both these groups extracted reversal learning performance from a version of the ID/ED test: the same approach that we employ in this study. Waltz and Gold showed profound reversal deficits in 34 patients with chronic schizophrenia using a different method; they employed a probabilistic reversal task adapted from Robbins and colleagues. Our results demonstrate that reversal learning deficits are also present in many patients near the time of initial presentation to psychiatric services. We note that these deficits were not universal however, and many patients performed at comparable levels to controls (see figure 4).

In contrast to Waltz and Gold, who argued that patients performed adequately on rule acquisition, we were able to detect subtle abnormalities in simple reinforcement learning (SD learning), possibly because of our large sample size. Our study thus provides further support to long-held contentions that there are reinforcement learning abnormalities in psychosis. Discrimination learning has been shown to be impaired by caudate tail lesions; previous data supports caudate dysfunction in psychosis. Specifically, the tail of the caudate is itself connected to the medial temporal lobe, an area that is strongly implicated in the pathogenesis of psychotic illness as well as playing a role in discrimination learning. Research in rhesus monkeys has shown that lesions to the medial temporal lobe rhinal cortex, and to the inferior temporal cortex, result in mild and severe deficits, respectively, in discrimination learning, possibly through an inferior temporal-frontal-thalamic network. Thus, the SD deficit we note is also consistent with previous evidence for disrupted frontotemporal connectivity in psychosis.

Patients with affective and nonaffective psychosis did not differ significantly in reversal learning errors (or indeed in EDS errors). Previous research has identified deficits in reversal learning to be present in bipolar mania, consistent with other recent research implicating orbitofrontal cortex dysfunction in mania (including manic psychosis), such as the presence of impairment on the Iowa Gambling Test. Interestingly, reversal learning is intact in euthymic bipolar disorder without a history of psychosis, suggesting a state-dependent deficit in nonpsychotic bipolar disorder.

Lesion studies in rodents and nonhuman primates have demonstrated a key role for the orbitofrontal cortex and ventral striatum in reversal learning. Moreover, this evidence is corroborated from human functional imaging studies and from studies of human patients with orbitofrontal lesions. These regions are critical for motivational and goal-directed processing; thus, the present study suggests that there is dysfunction of orbitofrontal/ventral striatal circuitry in psychosis. This contention is consistent with the findings of our correlational analysis in patients, which demonstrates that the greater the reversal impairment, the more severe the negative symptoms (i.e., the greater the impairment in motivational and goal-directed behavior). We note that the specificity of this correlation should be viewed with caution because the magnitude of the significant correlation coefficient between negative symptoms and reversal errors (\(\rho = 0.3\)) differed only slightly from the nonsignificant correlation between positive symptoms and reversal errors (\(\rho = 0.2\)).

Interestingly, we found that the patient group made few errors at the compound discrimination stage, which is in contrast with recent results reported by Jazbec et al. They studied 34 patients with chronic schizophrenia and found pronounced deficits in compound
discrimination. It is possible that this process may deteriorate with disease progression, though longitudinal research will be required to examine this conjecture.

Our study does have a number of limitations. Although we found deficits in SD learning, the ID/ED test is not solely or primarily a test of this cognitive domain. Given that the test starts with SD learning, it is conceivable that some psychosis patients might have had trouble adjusting to the task environment in general, leading to an apparent specific deficit in this domain. In addition, there was only a small range in scores in SD learning, which limits the power of correlation and regression analyses to detect associations with clinical variables. For this reason, the failure to detect association between SD errors and clinical variables should not be overinterpreted. SD learning, and its association with clinical variables, merits further investigation in early psychosis in other cognitive paradigms that focus on SD learning in more detail.

Another limitation of the current study is that the majority of patients were taking second-generation antipsychotic medications. Such medications act on dopaminergic and serotonergic systems, and ascending serotonin and dopamine neurotransmitter systems are known to play a modulatory role in reinforcement learning processes. There are, however, a number of reasons why our current results are unlikely to be secondary to medication effects. First, we note that in a recent functional magnetic resonance imaging study in healthy volunteers, a low dose of the dopamine D2/D3 receptor antagonist, sulpiride, did not modulate brain activations during reversal learning or impair behavioral reversal performance. Secondly, we observed a correlation between the level of negative symptoms and reversal errors, consistent with the theory that both these measures are secondary to one underlying pathological process. Finally, we have, in recent studies, demonstrated behavioral and physiological abnormalities during tests of reinforcement learning and motivational modulations in unmedicated first-episode psychosis patients. Future studies should examine reversal learning in unmedicated patients with psychosis, its relation to symptoms, and the extent to which reinforcement and reversal learning deficits can be modulated by pharmacological interventions. The relationship between reinforcement learning and reversal deficits and functional impairments also merits investigation.

**Funding**

UK Department of Health National Institute of Health Research RCD Award (to GKM); NARSAD Young Investigator Award (to GKM); Bernard Wolfe Health Neuroscience Fund (to PCF); Wellcome Trust Senior Research Fellowship in Clinical Science (to PCF); CAMEO received pump priming funding from the Stanley Medical Research Institute and GlaxoSmithKline, and is now funded by the National Health Service; study completed within the University of Cambridge Behavioural and Clinical Neuroscience Institute, supported by a joint award from the Medical Research Council and the Wellcome Trust.

**Acknowledgments**

We are grateful to staff from CAMEO for help with recruitment and data collection and to the participants. Blackwell is an employee of Cambridge Cognition, which supplies the CANTAB cognitive test battery; Clark and Robbins have acted as consultants for Cambridge Cognition. In addition to his university appointment, Bullmore is seconded part-time to GlaxoSmithKline. Murray, Cheng, Barnett, Fletcher, and Jones declare there are no other competing interests.

**References**

1. Bleuler E. *Dementia Praecox or the Group of Schizophrenias*. New York, NY: International University Press; 1911.
2. Beninger RJ. The slow therapeutic action of antipsychotic drugs. A possible mechanism involving the role of dopamine in incentive learning. In: Simon P, Soubrie P, Widlocher D, eds. *Selected Models of Anxiety, Depression and Psychosis*. Basel, Switzerland: Karger; 1988:36–51.
3. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160:13–23.
4. Miller R. Schizophrenic psychology, associative learning and the role of forebrain dopamine. *Med Hypotheses*. 1976;2:203–211.
5. McKenna PJ. Pathology, phenomenology and the dopamine hypothesis of schizophrenia. *Br J Psychiatry*. 1987;151:288–301.
6. Crow T. Catecholamine reward pathways and schizophrenia: the mechanism of the antipsychotic effect and the site of the primary disturbance. *Fed Proc*. 1979;38:2462–2467.
7. Robbins TW. Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs. *Nature*. 1976;264:57–59.
8. Laruelle M, Abi-Dargham A, van Dyck CH, et al. Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A*. 1996;93:9235–9240.
9. Kapur S, Remington G. Dopamine D(2) receptors and their role in atypical antipsychotic action: still necessary and may even be sufficient. *Biol Psychiatry*. 2001;50:873–883.
10. Robbins TW, Everitt BJ. Neurobehavioural mechanisms of reward and motivation. *Curr Opin Neurobiol*. 1996;6:228–236.
11. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275:1593–1599.
12. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*. 2006;442:1042–1045.
13. Murray GK, Corlett PR, Clark L, et al. Substancia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol Psychiatry*. 2008;13:239–267–276.
14. Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biol Psychiatry*. 2007;62:756–764.

15. Murray GK, Clark L, Corlett PR, et al. Incentive motivation in first-episode psychosis: a behavioural study. *BMC Psychiatry*. 2008;8:34.

16. Beninger RJ, Wasserman J, Zanibbi K, Charbonneau D, Mangels J, Beninger BV. Typical and atypical antipsychotic medications differentially affect two nondeclarative memory tasks in schizophrenic patients: a double dissociation. *Schizophr Res*. 2003;61:281–292.

17. Cavallaro R, Cavedini P, Mistretta P, et al. Basal-corticofrontal circuits in schizophrenia and obsessive-compulsive disorder: a controlled, double dissociation study. *Biol Psychiatry*. 2003;54:437–443.

18. Elliott R, McKenna PJ, Robbins TW, Sahakian BJ. Neuropsychological evidence for frontostriatal dysfunction in schizophrenia. *Psychol Med.* 1995;25:619–630.

19. Pantelis C, Barber FZ, Barnes TR, Nelson HE, Owen AM, Robbins TW. Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage. *Schizophr Res*. 1999;37:251–270.

20. Waltz JA, Gold JM. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. *Schizophr Res*. 2007;93:296–303.

21. Roberts AC, Robbins TW, Everitt BJ. The effects of intradimensional and extradimensional shifts on visual discrimination learning in humans and non-human primates. *Q J Exp Psychol B*. 1988;40:321–341.

22. Joyce E, Hutton S, Mutsatsa S, et al. Executive dysfunction in first-episode schizophrenia and relationship to duration of untreated psychosis: the West London Study. *Br J Psychiatry Suppl.* 2002;43:s38–s44.

23. Barnett JH, Sahakian BJ, Werners U, et al. Visuospatial learning and executive function are independently impaired in first-episode psychosis. *Psychol Med.* Jul 2005;35(7):1031–1041.

24. McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. EPPIC: an evolving system of early detection and optimal management. *Schizophr Bull*. 1996;22:305–326.

25. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV Axis I Disorders*. Washington, DC: American Psychiatric Press; 1997.

26. Craddock M, Asherson P, Owen MJ, Williams J, McGuffin P, Farmer AE. Concurrent validity of the OPCRIT diagnostic system. Comparison of OPCRIT diagnoses with consensus best-estimate lifetime diagnoses. *Br J Psychiatry*. 1996;169:58–63.

27. Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson’s disease: evidence for a specific attentional dysfunction. *Neuropsychologia*. 1989;27:1329–1343.

28. Pantelis C, Barnes TR, Nelson HE, et al. Frontal-striatal cognitive deficits in patients with chronic schizophrenia. *Brain*. 1997;120(Pt 10):1823–1843.

29. Jazbec S, Pantelis C, Robbins T, Weickert T, Weinberger DR, Goldberg TE. Intra-dimensional/extra-dimensional set-shifting performance in schizophrenia: impact of distractors. *Schizophr Res*. 2007;89:339–349.

30. Tyson PJ, Laws KR, Roberts KH, Mortimer AM. Stability of set-shifting and planning abilities in patients with schizophrenia. *Psychiatry Res*. 2004;129:229–239.

31. Braw Y, Bloch Y, Mendelovich S, et al. Cognition in young schizophrenia outpatients: comparison of first-episode with multiphase patients. *Schizophr Bull*. 2008;34:544–554.

32. Hutton SB, Puri BK, Duncan LJ, Robbins TW, Barnes TR, Joyce EM. Executive function in first-episode schizophrenia. *Psychol Med.* 1998;28:463–473.

33. Cools R, Clark L, Owen AM, Robbins TW. Defining the neural mechanisms of probabilistic reversal learning using event-related functional magnetic resonance imaging. *J Neurosci*. 2002;22:4563–4567.

34. Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson’s disease as a function of dopaminergic medication and task demands. *Cereb Cortex*. 2001;11:1136–1143.

35. Divac I, Rosvold HE, Szwardbart MK. Behavioral effects of selective ablation of the caudate nucleus. *J Comp Physiol Psychol.* 1967;63:184–190.

36. Robbins TW. The case of frontostriatal dysfunction in schizophrenia. *Schizophr Bull*. 1990;16:391–402.

37. Corlett PR, Murray GK, Honey GD, et al. Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain*. 2007;130(Pt 9):2387–2400.

38. Arnold SE. The medial temporal lobe in schizophrenia. *J Neuropsychiatry Clin Neurosci*. 1997;9:460–470.

39. Baxter MG, Murray EA. Impairments in visual discrimination learning and recognition memory produced by neurotoxic lesions of rhinal cortex in rhesus monkeys. *Eur J Neurosci*. 2001;13:1228–1238.

40. Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *J Neurosci*. 1989;9:4355–4370.

41. Meunier M, Bachevalier J, Mishkin M, Murray EA. Effects on visual recognition of combined and separate ablations of the entorhinal and perirhinal cortex in rhesus monkeys. *J Neurosci.* 1993;13:5418–5432.

42. Gaffan D, Murray EA, Fabre-Thorpe M. Interaction of the amygdala with the frontal lobe in reward memory. *Eur J Neurosci*. 1993;5:968–975.

43. Murray EA, Gaffan D, Mishkin M. Neural substrates of visual stimulus-stimulus association in rhesus monkeys. *J Neurosci*. 1993;13:4549–4561.

44. Woodruff PW, Wright IC, Shurique N, et al. Structural brain abnormalities in male schizophrenics reflect fronto-temporal disconnection. *Psychol Med.* 1997;27:1257–1266.

45. Fletcher PC, Frith CD, Grasby PM, Friston KJ, Dolan RJ. Local and distributed effects of apomorphine on fronto-temporal function in acute unmedicated schizophrenia. *J Neurosci*. 1996;16:7055–7062.

46. Clark L, Iversen SD, Goodwin GM. A neuropsychological investigation of prefrontal cortex involvement in acute mania. *Am J Psychiatry*. 2001;158:1605–1611.

47. Adida M, Clark L, Pompietto P, et al. Lack of insight may predict impaired decision-making in manic patients. *Bipolar Disorders*. In press.

48. Clark L, Goodwin GM. Attentional and executive functioning in bipolar disorder. In: Goldberg JF, Burdick K, eds. *Cognitive Dysfunction in Bipolar Disorder: A Guide for Clinicians*. Arlington, Va: American Psychiatric Publishing; 2008.

49. Iversen SD, Mishkin M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Exp Brain Res*. 1970;11:376–386.
50. Jones B, Mishkin M. Limbic lesions and the problem of stimulus–reinforcement associations. *Exp Neurol*. 1972;36:362–377.

51. Clarke HF, Dalley JW, Crofts HS, Robbins TW, Roberts AC. Cognitive inflexibility after prefrontal serotonin depletion. *Science*. 2004;304:878–880.

52. Clarke HF, Walker SC, Dalley JW, Robbins TW, Roberts AC. Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. *Cereb Cortex*. 2007;17:18–27.

53. Dias R, Robbins TW, Roberts AC. Dissociation in prefrontal cortex of affective and attentional shifts. *Nature*. 1996;380:69–72.

54. Rogers RD, Andrews TC, Grasby PM, Brooks DJ, Robbins TW. Contrasting cortical and subcortical activations produced by attentional-set shifting and reversal learning in humans. *J Cogn Neurosci*. 2000;12:142–162.

55. O’Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C. Abstract reward and punishment representations in the human orbitofrontal cortex. *Nat Neurosci*. 2001;4:95–102.

56. Fellows LK, Farah MJ. Ventromedial frontal cortex mediates affective shifting in humans: evidence from a reversal learning paradigm. *Brain*. 2003;126(Pt 8):1830–1837.

57. Hornak J, O’Doherty J, Bramham J, et al. Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. *J Cogn Neurosci*. 2004;16:463–478.

58. Clark L, Cools R, Robbins TW. The neuropsychology of ventral prefrontal cortex: decision-making and reversal learning. *Brain Cogn*. 2004;55:41–53.

59. Dodds CM, Muller U, Clark L, van Loon A, Cools R, Robbins TW. Methylphenidate has differential effects on blood oxygenation level-dependent signal related to cognitive subprocesses of reversal learning. *J Neurosci*. 2008;28:5976–5982.