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The Wisconsin Card Sorting impairment in schizophrenia is evident in the first four trials

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Abstract

Background: Schizophrenia (SZ) patients' low scores on the Wisconsin Card Sorting Test (WCST) are often attributed to frequent perseverative errors, a pattern typically interpreted as a failure to shift from previously rewarded behavior in response to negative feedback. In this study we tested the hypothesis that SZ patients, due to dysregulated error-processing mechanisms, are more fundamentally impaired in their on-line, trial-to-trial use of feedback to guide behavior.
Methods: Analysis of archival WCST data from 145 adults with schizophrenia and 80 healthy comparison subjects.
Results: Schizophrenia patients' impaired use of negative feedback was evident on the first four WCST cards, where they were significantly less accurate than comparison subjects. Performance on these early cards significantly predicted overall task success as indexed by categories completed and proportion of perseverative errors.
Conclusions: Patients' poor performance on pre-shift WCST trials likely reflects a fundamental impairment in the ability to use feedback to guide behavior. Recent data from both humans and primates suggest that reward-based learning processes like those employed in the WCST are driven by phasic changes in midbrain dopamine activity. It might, therefore, be possible to interpret higher order executive dysfunction in schizophrenia as a manifestation of altered DA signaling.

Keywords: Schizophrenia; Reinforcement learning; Reward; Dopamine; Wisconsin Card Sorting Test

1. Introduction

Schizophrenia is associated with a variety of cognitive deficits including executive functions, which support problem solving and the capacity to plan and control behavior. A common index of executive function is the Wisconsin Card Sorting Test (WCST (Milner, 1963; Nelson, 1976)), in which subjects must discover, follow and switch rules for sorting cards into categories. Schizophrenia patients typically perform poorly on the WCST, failing to achieve as many categories as healthy subjects and showing an abnormally high rate of perseverative errors, which has been thought to reflect an inability to abandon a previously-correct response after receiving negative feedback. WCST performance has been linked to activity in the prefrontal cortex (Haut et al., 1996; Konishi et al., 1999; Lie et al., 2006; Lombardi et al.,

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1999; Mansouri et al., 2006; Monchi et al., 2001; Nagahama et al., 1996), but the source of SZ patients' deficit remains obscure given the complexity of the task. Various accounts focus on the role of abstracting and rule-learning (Keri et al., 2001; Perrine, 1993), working memory demands (Glahn et al., 2000; Gold et al., 1997; Hartman et al., 2003), attentional deficits and unmodulated perseverative behavior (Amos, 2000; Koren et al., 1998; Li, 2004). We took a different approach, examining behavior over the first four trials of the test in order to determine if a very elementary deficit in the ability to use feedback on a rapid, trial-to-trial basis can provide a biologically motivated account of SZ patients' impairment.

The earliest trials of the WCST can be conceptualized within the framework of temporal difference error (TDE) reinforcement learning models (Montague et al., 2004; Schultz, 2002), in which learning is driven by the outcomes of actions. Outcomes that are better than expected result in positive TDE signals, which increase the probability of repeating the action. Outcomes that are worse than expected result in negative TDE signals, which decrease the likelihood of repeating the action. On early WCST trials, the ability to learn from positive outcomes would be evident in repetition of a reinforced response, and the ability to learn from negative outcomes would be evident in the abandonment of previously unsuccessful responses in favor of new ones.

On a biological level, there is compelling evidence from electrophysiological studies in behaving primates that transient increases and decreases in dopamine (DA) cell activity appear to be coding positive and negative TDEs and serving as teaching signals to DA cell target areas (Schultz, 2002, 2006, 2007). Human fMRI studies also show that, during learning tasks, the receipt of positive and negative reinforcers is associated with variations in activity in DA target areas (Aron et al., 2004; Liu et al., 2007; Monchi et al., 2004, 2001; Ullsperger and von Cramon, 2003; Yacubian et al., 2006).

The co-occurrence of learning deficits and abnormal DA function in schizophrenia (Abi-Dargham and Laruelle, 2005; Hirvonen et al., 2005; Kapur et al., 2005; Meyer-Lindenberg et al., 2002; Rybakowski et al., 2005; Tauscher et al., 2004; Yang et al., 2004; Yasuno et al., 2005) motivated the present investigation into whether deficits in SZ patients' WCST performance could be understood within the TDE framework. We hypothesized that SZ patients' poor WCST performance stems from compromised negative error signaling which may be critical to the ability to shift away from non-rewarded behaviors (i.e., negative feedback) in favor of those more likely to be rewarded. This impairment should be evident on the initial WCST learning trials where errors cannot be due to a failure to abandon a previously-rewarded response because subjects have not yet received positive feedback. So, while the traditional view of perseveration hinges on over-valuing positive feedback, we investigated whether the same behavior could reflect under-valuing of negative feedback.

2. Experimental materials and methods

2.1. Participants

We examined archival WCST data from 145 patients with SZ and 80 healthy comparison subjects (HCs, see Table 1 for participant characteristics). Patients' data were originally collected for a clinical treatment trial (Group 1, N=45), and two psychopathology studies (Group 2, N=100). All patients met criteria for DSM-IV diagnosis of SZ or schizoaffective disorder and were screened for medical/neurological conditions that could influence cognitive performance. All patients were receiving treatment with antipsychotic drugs (APDs). Specific descriptive data are limited by procedural differences between the source protocols. In general, Group 1 was a highly disabled sample, as recruitment for the source protocol targeted patients with moderate or severe treatment-resistant negative symptoms. Group 2 was more heterogeneous, perhaps over-representing high-functioning patients, in which approximately 1/3 of patients were competitively employed and 2/3 were unemployed. HCs' data were originally collected for a study of normative performance on a cognitive test battery (N=16) and as a comparison sample in the two psychopathology studies (N=64). HCs were screened for Axis I and (in the latter two samples) Axis II diagnoses, as well as mental retardation and other brain disorders or medical conditions with potential effects on cognition.

Table 1

	Schizophrenia Subjects	Comparison Subjects	Test statistic
N	145	80	
Age (SD)	43.1 (8.9)	37.2 (10.3)	$t(144)=4.4, p<.001$
Edu (SD)	12.6 (2.2)	14.1 (1.9)	$t(222)=-5.1, p<.001$
% Female	26.2	41.3	x^2 $p=.02$
APD (N)			
Conventional	25		
Atypical	96		
Combination	6		

Education data available for 144 patients. APD data available for 127 patients.

2.2. Analyses

Our analyses of WCST data primarily focused on two areas. First, we measured accuracy on the first four cards in the deck. Second, we investigated the relationship between accuracy on these very early trials and two of the full task's main outcome variables. For these analyses we chose categories completed because it is a clear global index of task success, and percent perseverative errors because it is the central measure of the behavior we set out to investigate. We coded the sorting responses on Cards 1–4 with a score of 1 or 0 reflecting whether the response was correct or incorrect. Since the deck-size differences for Groups 1 (64 cards, Heaton, 2000) and 2 (128 cards) would not influence performance on the early cards alone, those analyses were performed on the entire sample of 145 SZ patients and 80 comparison subjects. For these whole-sample analyses we used *t*-tests to compare the two groups' accuracy on Cards 1–4, and Fisher's *Z* and Chi-square analyses to compare the groups' use of positive and negative feedback on those cards.

However, since deck-size would have a direct effect on the number of categories a subject was able to complete, this variable was analyzed for the two versions independently. For these version-specific analyses we calculated Pearson correlations between accuracy on the early cards and the number of categories completed in the task as well as the proportion of perseverative errors. To account for the different discontinuation rules used in Group 2 (sorting all 128 cards vs. discontinuing the task after completing 6 categories), we calculated an adjusted categories completed score where possible values are 1 through 5 and also "6 or more."

3. Results

Consistent with prior research, subjects with SZ completed fewer categories than HCs in both the 64-card and 128 card version of the WCST (1.6 vs. 3.2, $t(59)=-3.1$, $p<.01$; adjusted categories score: 3.4 vs. 5.5, $t(152.3)=-7.6$, $p<.001$, respectively). Similarly, patients' proportion of perseverative errors was greater than HCs' in both WCST versions (30.7 vs. 13.5, $t(56.4)=4.7$, $p<.001$; 23.8 vs. 11.4, $t(132.2)=6.3$, $p<.001$). A comparison of patients treated with conventional APDs and those treated with atypical APDs showed no effect of medication type on either WCST outcome measure ($F<.40$, $p>.50$ in all comparisons).

Patients' impairment was evident from the very first trials of the test (Fig. 1). Patients were significantly less likely than HCs to sort correctly on Card 2 ($t(223)=4.0$, $p<.001$), Card 3 ($t(212)=6.0$, $p<.001$) and Card 4 ($t(219)=4.9$, $p<.001$).

Efficient use of negative feedback should fully eliminate two of the three possible sorting rules by Card 4. As there are three possible sorting rules (color, form and number) it would make sense that subjects making maximal use of negative feedback could use Cards 1 and 2 to eliminate two of the three possible rules, arriving at the only possible correct response on Card 3, not Card 4. An idiosyncrasy of the WCST's design, however, makes this process of elimination less clear-cut. The first card in the deck matches one of the four key cards on two dimensions, not one. The stimulus card features a single red triangle and when a subject chooses, as nearly all did, to match it to the key card with a single green triangle, the two cards match on both form (triangle) and number (one). Because the correct answer is color, subjects receive negative feedback for that response. While some subjects might deduce from that negative feedback that both form and number have been eliminated as possible rules, thereby leaving only color, others might choose to explore the possibility that either form or number alone might be the correct response. In the latter case the subject would use Cards 2 and 3 to eliminate those two dimensions one at a time, thereby arriving at the remaining option on Card 4. Therefore, regardless of a subject's elimination strategy, Card 4 marks the trial by which the correct answer would be achieved with the appropriate use of negative feedback.

In Fig. 2A, the bars' overall heights show that both groups were increasingly likely to receive positive feedback as they progressed through the first four cards (reflecting increased accuracy, as shown in Fig. 1), though this trend was less pronounced in the patient group. Also in Fig. 2A, the ratio within each bar of

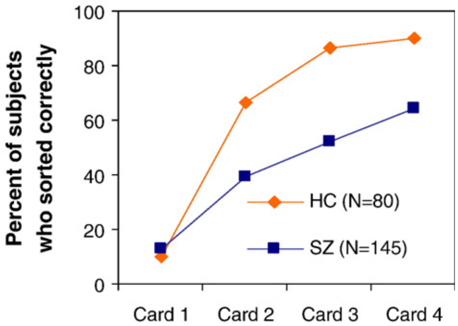

Fig. 1. Accuracy on Cards 1–4 by subject group. Performance on Card 1 reflects guessing and is therefore omitted from statistical comparisons.

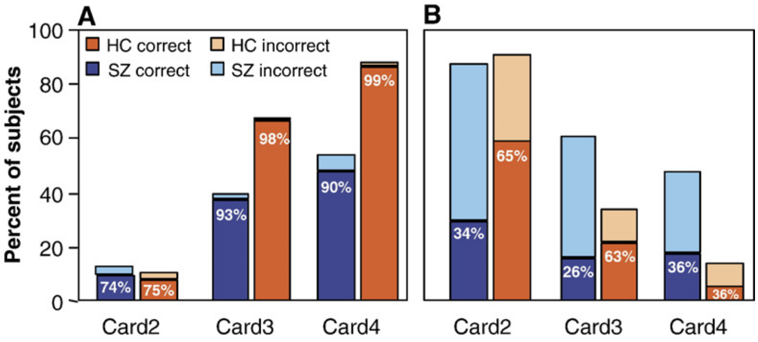

Fig. 2. (A) Accuracy when responding to positive feedback. Bars represent response accuracy on Card N having just received positive feedback for the response to Card $N-1$. In both groups, the percent of subjects who receive positive feedback *increases* with each card (overall height of the bars). In both groups, responses to positive feedback are mostly correct (darker portions of the bars). For example, Middle two bars: Of the SZ patients who received positive feedback for their responses to Card 2, 93% went on to respond correctly to Card 3 (versus 98% in the HC group). (B) Accuracy when responding to negative feedback. Bars represent response accuracy on Card N having just received negative feedback for the response to Card $N-1$. In both groups, the percent of subjects who receive negative feedback *decreases* with each card (overall height of the bars). Proportion of correct responses to negative feedback (darker portions of the bars) is mostly *lower in the SZ group* than in the HC group. For example, Middle two bars: Of the SZ patients who received negative feedback for their responses to Card 2, 26% went on to respond correctly to Card 3 (versus 63% in the HC group).

accurate to inaccurate indicates that, among the patients who did receive positive feedback, most were able to respond appropriately on the subsequent trial, sorting to the correct dimension. Fisher's exact tests (2-tailed) show that, although patients and HCs were not statistically different in their ability to heed positive feedback to arrive at the correct responses to Cards 2 ($p=1.0$) and 3 ($p=.37$), the patients did perform worse than HCs on Card 4 ($p=.04$).

Conversely, in Fig. 2B, the bars' overall heights indicate that both groups showed a decreased likelihood of receiving negative feedback as they progressed through the first four cards (reflecting increased accuracy shown in Fig. 1), and this trend was again less pronounced in the patient group. Here, the ratio within each bar of accurate to inaccurate indicates that patients receiving negative feedback were less likely than HCs to use that feedback appropriately. That is, patients were less likely than HCs to use negative feedback to guide successful response selection on the following trial. Chi-square tests show significant differences between the groups' use of negative feedback on Cards 2 ($p<.001$) and 3 ($p<.001$). The groups did not differ significantly on Card 4 ($p=1.0$), perhaps because the small number of comparison subjects who were still receiving negative feedback at that point in the task are the poorest performers in the comparison group whose capacity to use feedback is closer to that in the patient group. Thus, a clear majority of patients were able to use positive feedback to guide a win-stay response to the next card, whereas a substantial proportion of patients failed to make a lose-shift response when confronted by an instance of negative feedback.

Accuracy on these early cards was highly predictive of subsequent performance on the test (here we report results for Version 2, the larger sample, but the correlations were of similar magnitude in Version 1). The total number of correct responses to Cards 2, 3 and 4 was significantly correlated with patients' rate of perseverative errors ($r=-.51$, $p<.01$) and with the number of categories they completed ($r=.60$, $p<.01$). Indeed, patients' performance on Card 2 alone correlated significantly with both of those performance measures ($r=-.35$, $p<.01$ and $r=.48$, $p<.01$, respectively). Fig 3 illustrates the relationship between patients' accuracy on Cards 2–4 and categories

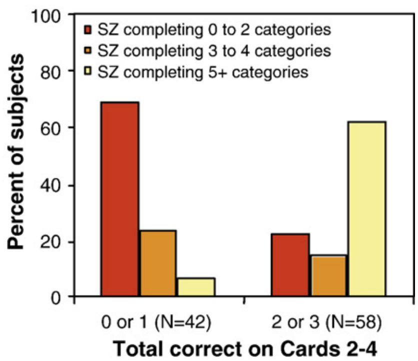

Fig. 3. Early accuracy predicts overall WCST performance. Of the patients with the poorest accuracy on Cards 2, 3 and 4 ($N=42$), 69% were unable to complete more than 2 categories. Of the patients with good accuracy on Cards 2, 3 and 4 ($N=58$), 62% completed 5 or more categories.

completed. A similar trend was found in HCs, where accuracy on Cards 2 through 4 correlated significantly with categories completed ($r=.30$, $p<.05$) and perseverative error rate ($r=-.45$, $p<.001$), and accuracy on Card 2 alone correlated significantly with perseverative error rate ($r=-.30$, $p<.05$). Further evidence of the strong relationship between performance on the early cards and overall task performance is found in point-biserial correlations indicating that both perseverative error rate and categories completed are more effectively predicted by accuracy on Cards 2–4 ($r=-.55$ and $-.60$, $p<.001$) than by diagnosis (patient versus comparison) ($r=.39$ and .46, $p<.001$).

4. Discussion

It is evident from these data that, as early as Card 2, SZ patients are significantly less able than HCs to use negative feedback to rapidly direct their behavior toward a rewarded response. Whereas controls, on Card 2, after just one instance of negative feedback, are already 66% likely to sort correctly, only 40% of patients are able to do so. That these errors are occurring prior to the receipt of any positive feedback suggests that patients' difficulty stems not from a failure to abandon previously rewarded behavior, but rather a failure to use negative feedback appropriately. This disruption in error-processing can account for the poor initial concept-formation in the WCST, as we have shown here, as well as the later mid-task perseverative responses typical of patients with SZ.

Our findings are consistent with much of the literature on errorless learning and cognitive rehabilitation in SZ. Several studies have shown that errorless learning, a paradigm in which errors are minimized during skill acquisition, is more effective for SZ patients than traditional trial-and-error techniques (Kern et al., 2003; O'Carroll et al., 1999; Pope and Kern, 2006). Related methods have been successful in improving SZ patients' performance on the WCST. In those studies training usually involves explicit, trial-by-trial instruction, strategy verbalization and other methods of reducing the likelihood of future errors (Goldman et al., 1992; Kern et al., 1996; Perry et al., 2001; Rossell and David, 1997). Two general themes shared by studies of errorless learning and of WCST training in SZ are the value of establishing a correct learning strategy early in a task, and the difficulty of overcoming a maladaptive strategy once it is implemented. These themes are consistent with our proposed understanding of feedback-processing in SZ, as they highlight positive reinforcement's benefit over negative reinforcement as a learning tool for SZ patients.

Our reanalysis of WCST data cannot, by itself, prove that an interpretation based in error-processing mechanisms is correct. The task was not designed to provide an unambiguous test of the error-processing model. Our aim was to assess whether it is feasible to link a well-documented behavioral deficit with a well-developed basic neuroscience literature which has rarely been addressed in schizophrenia research despite its clear relevance (Waltz et al., 2007). While admittedly speculative, we believe that the dopaminergic error signaling account invoked here may be a valuable heuristic device in integrating the extensive literature demonstrating broad learning and feedback processing deficits in patients with schizophrenia.

The idea that a specific deficit in the processing of negative feedback is responsible for the WCST impairment in SZ is open to challenge. One alternative explanation is patients simply failed to attend to the task, and this type of failure on early trials would have a negative effect on subsequent task performance. We would argue, however, that this scenario cannot fully account for our patients' poor performance because they were not equally impaired in their use of negative and positive feedback. Since patients responded well to positive feedback by continuing to use the correct sorting rule but were less successful in response to negative feedback, a general attentional deficit does not seem like an adequate account for all the data.

Consistent with views that have emphasized the role of working memory in SZ patients' WCST deficits, the reinforcement learning account stresses the need to be able to keep the results of previous trials in mind to guide subsequent response selection. Our interpretation differs by emphasizing the specific importance of negative feedback, something that is not captured by a more general working memory account that would be equally relevant for both positive and negative feedback trials. Consistent with views that have emphasized the role of perseveration in SZ patients' poor WCST performance, we recognize SZ patients' apparent failure to shift when instructed by feedback to do so. But, while perseveration typically is associated with failure to shift from a previously rewarded response, a more fundamental error-processing deficit can also explain failures to shift in the absence of previous reward. Our interpretation is also compatible with a conception of perseveration as difficulty switching from a prepotent response (even if not rewarded in the testing context). In a two-choice guessing task SZ patients' response sequences depended less on external cues than on their own response history (Paulus et al., 1999). An apparently weak influence of external cues and a commitment to familiar responses are amenable to the error-based approach described here.

Is it possible that DA blocking antipsychotic medications are implicated in these results? There are multiple reports of impaired WCST performance and prefrontal neurophysiological abnormalities in medication naïve and medication free patient cohorts (Daban et al., 2005; Verdoux et al., 1995; Williamson et al., 1989) as well as clinical trial evidence suggesting that antipsychotic drugs have either minimal or beneficial effects on WCST performance (Borkowska et al., 2002; Daban et al., 2005; Sumiyoshi et al., 2003; Verdoux et al., 1995). Indeed, our own data indicate that, despite their different mechanisms, conventional and atypical APDs did not affect patients' WCST performance differently. Thus, we doubt that the patients' deficits can be fully attributed to the negative effects of antipsychotics. Detailed card-by-card analysis of data from drug free patients would clearly resolve this issue. Though further research can help determine whether the deficits we observed are iatrogenic or ideopathic, the presence of marked deficits in medicated patients is important in its own right. Patients receiving available treatments can be expected to demonstrate marked impairments in the ability to use negative feedback to mediate learning, a critical impairment that complicates rehabilitation efforts. These results provide a strong rationale for developing novel approaches for making better use of learning systems that are not impacted by the disease or the drugs currently used to treat it, and for developing novel treatments that are less likely to influence these reinforcement learning mechanisms.

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Contributors

The analyses reported in this manuscript were of archival data. R. Buchanan carried out the studies for which the data were originally collected. K. Prentice and J. Gold planned and undertook the analyses of the archival data and K. Prentice wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None of the authors declare any conflict of interest.

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