



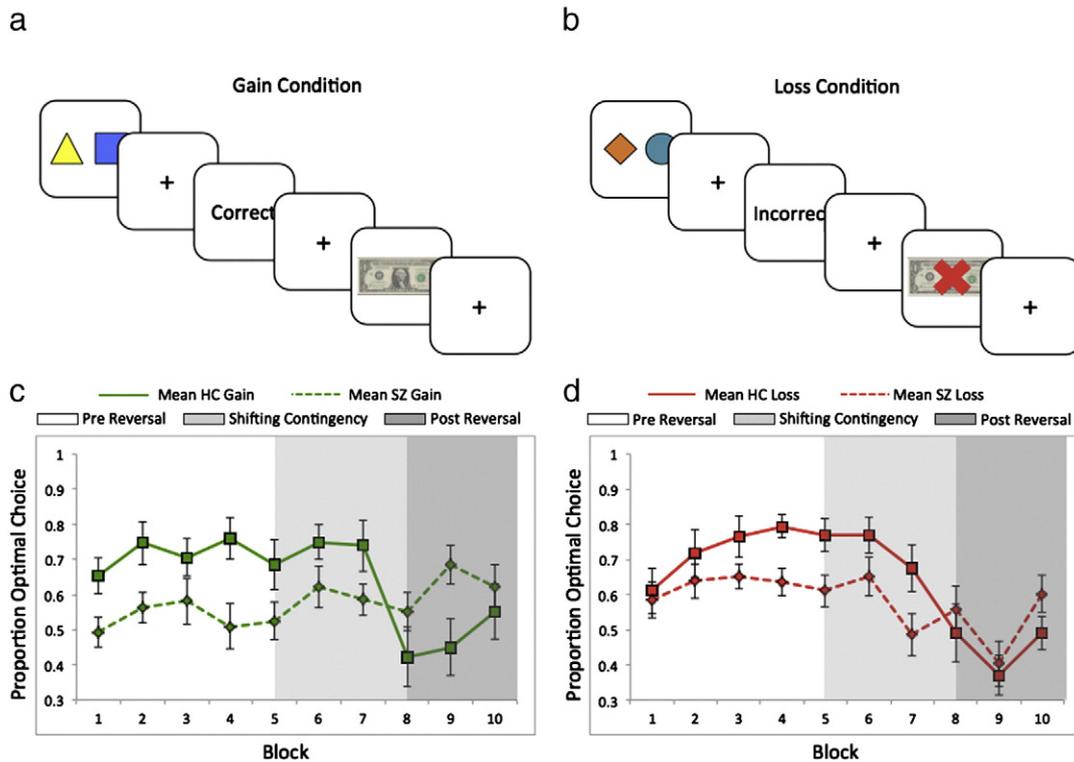
## Letter to the Editor

### Patients with schizophrenia are impaired when learning in the context of pursuing rewards



Recent findings suggest that patients with schizophrenia have a probabilistic learning impairment that is selective to learning from positive, relative to negative, feedback (Gold et al., 2012), and is more compromised in those with worse negative symptoms (Waltz et al., 2010). This is consistent with evidence linking motivational and affective symptoms of schizophrenia with dysfunctional signaling across neural systems in the dopamine-mediated reward network (Gold et al., 2008; Waltz et al., 2009; Maia and Frank, 2011). While prior studies have examined this selective learning impairment using tasks comprised of intermixed positive and negative trial types that collapse feedback and reward outcome together, an extension of this work would aim to isolate and examine the impact of motivational context. As such, we designed a task, presented in two *separate* Gain and Loss conditions, in which feedback was held constant, and the outcome was varied with respect to accumulating gains or avoiding losses. It was hypothesized that there would be an effect of motivational context, such that patients would perform better in the Loss condition despite identical types of feedback.

In an exploratory study, 17 stable outpatients (age:  $40.9 \pm 11.4$  years; 10 male, 7 female; education:  $13.6 \pm 2.8$  years; meeting DSM-IV criteria for schizophrenia or schizoaffective disorder; taking one or two second-generation antipsychotic medication(s) for  $\geq 2$  months), and 17 controls (age:  $29.6 \pm 8.5$  years; 6 male, 10 female [1 not reported]; education:  $15.7 \pm 1.8$  years) participated. On each trial, subjects made a choice between two stimuli, received feedback (“correct” or “incorrect”), and received an outcome (monetary gain or loss). Feedback was probabilistically linked to choice such that each subject was instructed to “find the lucky shape” associated with *correct* feedback 70% of the time, while the other shape was associated with *incorrect* feedback 70% of the time. These probabilities gradually switched after the first half of the experiment to ensure that subjects were dynamically updating feedback as opposed to adopting an explicit strategy (Daw et al., 2006; Gershman et al., 2009). Reward outcome was random; in the Gain condition subjects received a good (\$1) or medium (\$0.50) reward following correct feedback and a medium or bad (\$0) reward following incorrect feedback; in the Loss condition these earnings were deducted from an endowment given at the beginning of the experiment (Fig. 1a,b). Each subject completed both conditions, which were counterbalanced (randomly) and comprised of at least 100 trials. Subjects were unaware of the contingencies, but were aware that they would keep all earnings.



**Fig. 1.** Task structure for the Gain condition (a) and for the Loss condition (b). Optimal choice performance over time in the Gain condition (c) and in the Loss condition (d) for healthy control (HC) subjects and patients with schizophrenia (SZ).

Comparisons were performed using the proportion of times subjects chose the optimal choice as the dependent measure. Pre-reversal, patients performed worse than controls in the Gain condition ( $t = 3.67$ ,  $p < 0.001$ ) but not in the Loss condition ( $t = -1.23$ ,  $p = 0.23$ ). Further, performance across conditions differed significantly for patients ( $t = -2.12$ ,  $p = 0.05$ ) but not for controls ( $t = 0.27$ ,  $p = 0.79$ ). Post-reversal, performance was expected to initially decrease once the contingencies were switched, and then to improve. The expected decrease was observed in controls (G:  $t = 3.13$ ,  $p < 0.01$ ; L:  $t = 4.08$ ,  $p < 0.01$ ), but only for patients in the Loss ( $t = 2.63$ ,  $p = 0.02$ ), but not the Gain ( $t = -1.26$ ,  $p = 0.23$ ) condition, Fig. 1c,d.

Simple response to feedback was examined in each condition. Using logistic regression (Rutledge et al., 2009), it was assumed that subjects' choices and feedback received were combined linearly in a four-trial sliding window (N-4 to N-1) to predict subject choice on subsequent trial N. Overall, the model fit better for controls than patients, with a larger deviance-of-fit between groups in the Gain ( $t = 2.66$ ,  $p < 0.01$ ) compared to Loss ( $t = 1.54$ ,  $p = 0.13$ ) conditions, suggesting response to feedback alone may be influenced by motivational context. These findings were confirmed when examining the proportion of times subjects stayed with a choice following correct feedback (win-stay) and switched their choice following incorrect feedback (lose-shift). While lose-shift analyses did not reveal any significant effects, patients were less likely than controls to win-stay in the Gain condition ( $t = -3.66$ ,  $p < 0.01$ ). Finally, given prior findings, the relationship with optimal choice performance and negative symptoms was examined. A trend emerged toward a negative correlation between pre-reversal mean optimal choice performance in the Gain condition and SANS global score ( $r = -0.47$ ,  $p = 0.06$ ).

In summary, compared to controls, patient performance was impaired while learning, especially in the Gain condition where it also appeared to be inversely correlated with negative symptom severity. This suggests that the motivational context of reward-seeking behavior may impact people with schizophrenia during learning. Defining the mechanisms involved in this deficit may provide a basis for motivational and affective symptoms in schizophrenia. Limitations include a small sample size, a group imbalance on age and education and the potentially confounding effects of antipsychotic medications. However, no correlations emerged between the dependent measures and antipsychotic dose or demographics. Future studies should examine the neural correlates underlying contextual differences in patients, and how affective meaning of value (Roy et al., 2012) differs between people with schizophrenia and healthy controls.

#### Contributors

EES, LFJ and JR designed the study and wrote the protocol. JR and EES wrote the first draft of the manuscript. JR, RK and EES performed statistical analyses. All authors contributed to data interpretation, meaningful manuscript revision, and all authors have approved the final manuscript.

#### Conflict of interest

During the past 3 years, Dr. Jarskog has received research grant support from GlaxoSmithKline, Novartis, Roche, Sunovion, and Amgen and has served on a DSMB for Janssen. The remaining authors declare no conflicts of interest.

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