

Supplementary Online Content

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eMethods. Modified Version of the Monetary Incentive Delay Task

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Modified Version of the Monetary Incentive Delay Task

To elicit striatal activation during reward anticipation a modified variant of the monetary incentive delay task was presented during the fMRI acquisition (eFigure 1).

Patients were initially presented with a cue indicating one of six trial conditions (2.5 s).

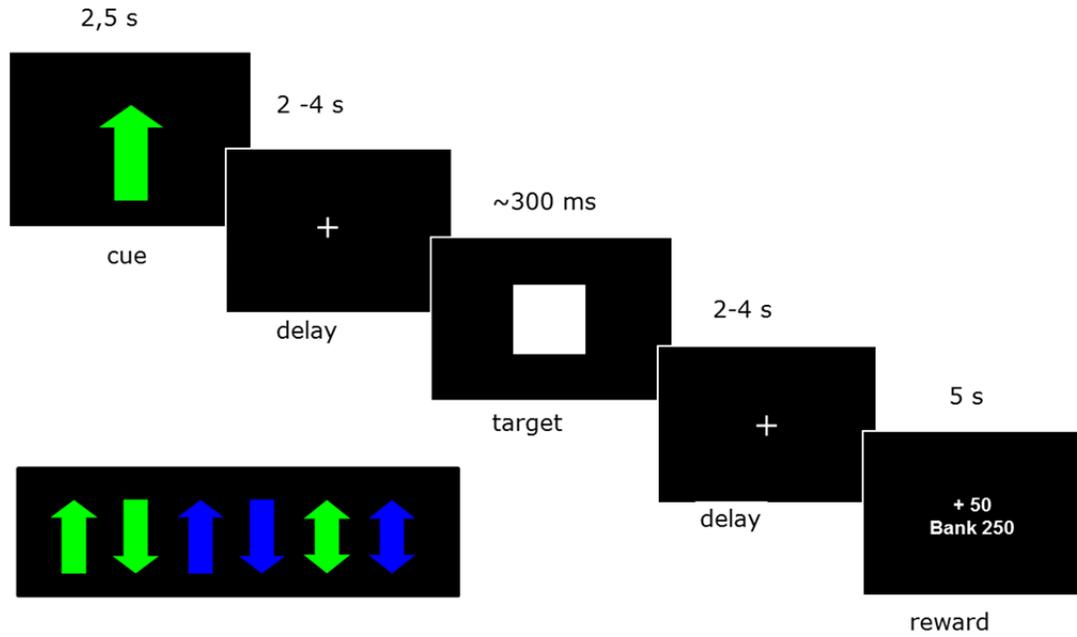
After a delay (2-4 s), a visual target appeared on the screen (200-300 ms), and patients were instructed to press a button while the target was on screen. After another delay (2-4 s), feedback on the outcome of the current trial and on the amount of money they had gained in total was displayed (5 s). Target duration was individually adjusted to a hit-rate of approximately 66%. Each trial lasted 15 seconds, and one run consisted of 72 trials.

After the scan, participants received the amount of money they had gained.

The trial consisted of 6 different trial conditions representing 2 levels of uncertainty (uncertain and certain), combined with 3 levels of value expectation (gain, neutral, and loss). Uncertain gain trials (green upwards arrow) indicated that the outcome required that the participant pressed the button in time. A timely hit would then pay 50 DKK (approximately €7). A miss resulted in no gain or loss. Similarly, uncertain loss trials (green downwards arrow) indicated that a timely hit would 'pay' 0 DKK, but a miss would result in a loss of 50 DKK. During the two certain conditions (blue arrows), gain or loss of 50 DKK was solely determined by the direction of the arrows and independent of participant performance. Finally, arrows pointing both up- and downwards (regardless of color) were neutral trials, always resulting in 0 DKK. Participants were instructed to respond rapidly on all trials, regardless of trial condition. Before fMRI scans, participants

were trained in the meaning of the cues, and they practiced the game for 10 minutes outside of the scanner.

eFigure 1. Modified Version of the Monetary Incentive Delay Task



FMRI analyses

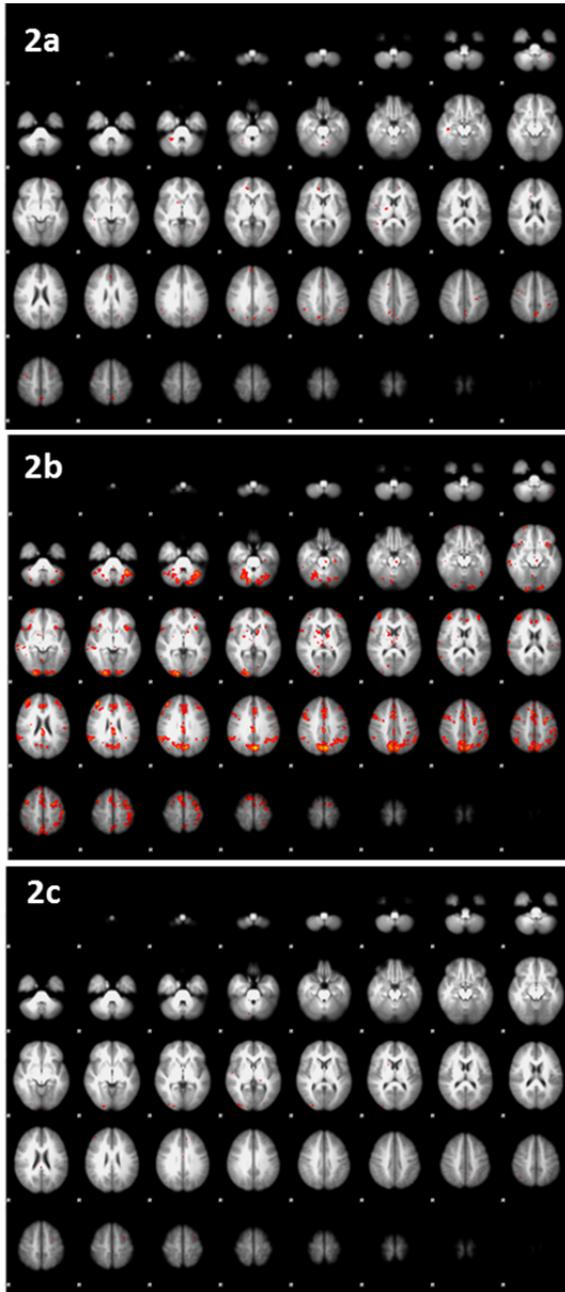
A general linear model was constructed for statistical analysis. For the anticipation phase, each of the six different cues was modeled as separate predictors: uncertain gain; certain gain; uncertain loss; certain loss; uncertain neutral; and certain neutral. Target onset and the delay to outcome was modeled with two different predictors, one for uncertain events, and one for certain and neutral events. The outcome phase was modeled with seven predictors, one for each of the possible outcomes. All explanatory variables were convolved with the hemodynamic response function.

Main effect of the task

In previous studies^{1,2}, the largest effect of the task and the most aberrant response in schizophrenia patients was found using the contrast between uncertain gain and loss cues versus neutral cues. Therefore, the main effect of this anticipation contrast and the effect of time were examined in the patients of the current study. At baseline, where the patients were antipsychotic-naïve, there was no significant effect of the contrast in striatal regions (eFigure 2a). This is in line with previous findings in unmedicated patients.^{1,3-5} At follow-up, there was a significant contrast activity in several areas of the brain, including striatum (areas in both putamen and ventral striatum, eFigure 2b), which is also in line with previous longitudinal findings². There was no significant effect of time in striatal regions, but a significant effect of time showing an increased signal at follow up in left occipital cortex (eFigure 2c).

eFigure 2. Main Effect of Anticipation Contrast

a, b and c. The main effect of the anticipation contrast (uncertain vs. neutral cues) in the patients at baseline (2a) and follow up (2b) and the effect of time (2c). There were only areas with increased activation at follow-up compared to baseline, and no areas with a significant decrease in activity was found. Images were thresholded $P < 0.001$, uncorrected.



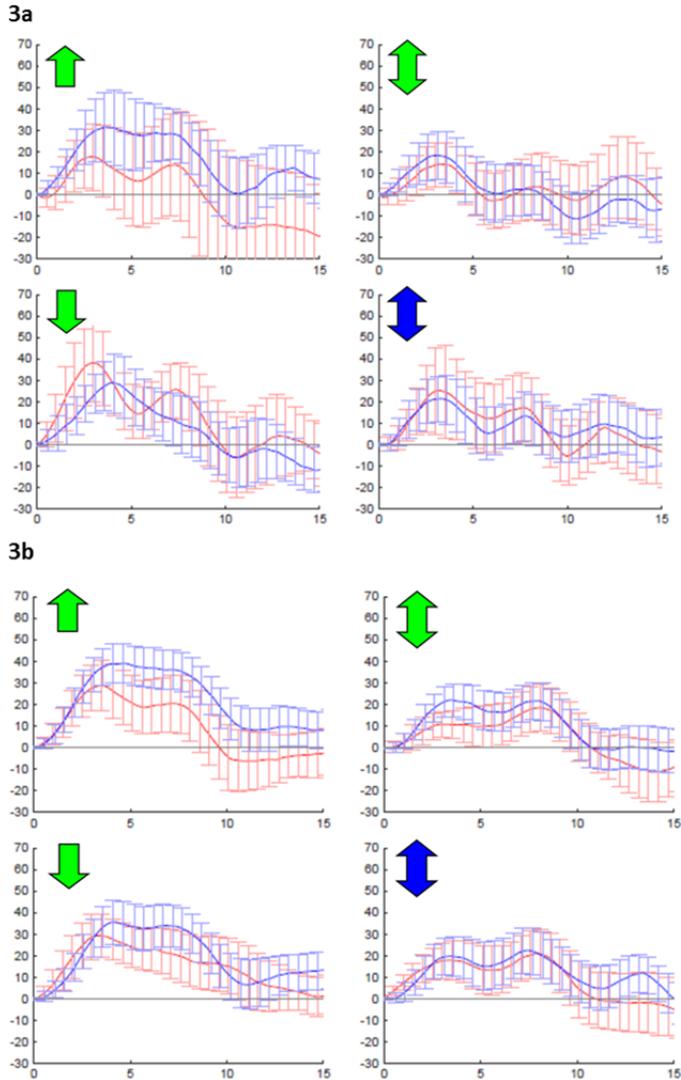
Event related time courses of the task

To explore the specific effects of each of the cues in the contrast, event related time courses were extracted and values from ROIS at the right side are presented in eFigure 3a and eFigure 3b.

The event related time courses at baseline (red curves) indicate comparable BOLD responses evoked by the uncertain and neutral cues, which is in line with previous results in unmedicated patients^{1;3-5}. At follow-up (blue curves), the BOLD response evoked by the uncertain cues increased slightly. This increase is similar to the observation previously published on a smaller group of patients.²

eFigure 3. Event-Related Time Causes for Each of the Cues in the Anticipation Contrast

a and b. The event-related time causes for each of the cues in the anticipation contrast were extracted from the predefined ROIs of right ventral striatum (S3a) and right putamen (S3b). Baseline curves are shown in red, and follow-up curves are blue.



eReferences

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- (4) Schlagenhauf F, Sterzer P, Schmack K et al. Reward feedback alterations in unmedicated schizophrenia patients: relevance for delusions. *Biol Psychiatry* 2009;65:1032-1039.
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