Ketamine Modulates the Neural Correlates of Reward Processing in Unmedicated Patients in Remission from Depression

Supplemental Information

Description of the MID task

The version of the task that was used for this study has been described in Knutson et al., 2001. Prior to performing the task in the scanner participants learned to associate different shapes- task cues- with different monetary rewards which they could win by making a fast button press upon the presentation of a white square -target. The task cues consisted of: a circle with one line (Low win trials-0.20£), a circle with two lines (High win trials-2.00£) and a triangle (Neutral trials) which is not associated with a specific monetary reward. Training for the MID took place during the screening visit and on each study day to ensure that participants have learned the associations between the different task cues and the monetary rewards.

In the scanner, the task consisted of 96 trials. During each trial, participants saw one of the three task cues (task cue, 500ms) and then fixated on a crosshair as they waited for a variable interval (anticipation phase, 4050-4500ms). When the target appeared on the screen, participants were asked to respond with a left button press (target, 150-350ms). The outcome of the trial and the total amount won at that point during the task were then presented on the screen (feedback phase, 1450ms). The target duration was adjusted so that participant would succeed on approximately 66% of the trials that were associated with a reward. The task also included the presentation of the letter "X" on the screen and for this trial participants were told not to respond (passive trial, 4250ms). The total duration of the task was approximately 15min.

The MID task was performed on each study session and the order of the trials was randomised between sessions to avoid any learning carry-over effects.

Modelling of the MID task

The anticipation and feedback phases of the MID were modelled separately. For the anticipation phase of the task, three regressors were created corresponding to the task cues and were named “High win anticipation”, “Low win anticipation” and “Neutral anticipation”. The feedback phase of the win and no-win trials of the task were modelled separately. For the win trials, where the monetary reward signalled by the cue is actually obtained, two regressors were created: “High win feedback” and “Low win feedback”. For the no win trials, where the signalled monetary reward was not successfully obtained two regressors were created: “High no win feedback” and “Low no win feedback”. A regressor named “Neutral feedback” was created for the feedback phase of the neutral trials. The passive trials of the MID were also modelled as single events.

In order to explore the anticipation phase of the task, the “High win anticipation” and “Low win anticipation” regressors were contrasted to “Neutral anticipation”. Reward magnitude during the anticipation phase of the task was explored by contrasting the “High win anticipation” with the “Low win anticipation” regressor. The feedback phase of win trials was examined by contrasting the “High win feedback” and “Low win feedback” regressors with the “Neutrals feedback” regressors. The “High win feedback” and “Low win feedback” feedback regressors were also contrasted to each other to examine the role of reward magnitude on the feedback phase of the MID task. The same contrasts were created for the no win MID trials.

Brain activations for the different MID contrasts on placebo

The brain activations during the anticipation and feedback phases of the MID task were first examined for the placebo session, to confirm they aligned from expectations based on the previous studies.

Anticipation phase

For the whole brain analysis, the anticipation phase of all trials associated with reward-predicting cues were compared to neutral trials. Several brain areas including the left supplementary motor area (SMA), the bilateral precentral gyrus, the left middle occipital gyrus, the right thalamus ($p<0.05$, FDR corrected) presented with increased activation.

Decreased activations for this contrast were in the left middle temporal gyrus, the bilateral angular gyrus, the left precuneus and the bilateral superior frontal gyrus. For all *a priori* defined ROIs there was an increase in activation for anticipation during reward trials compared to neutral trials. All ROIs, except the amygdala, survived Bonferroni correction ($p_{corr}=0.0008$) for multiple comparisons (Figure S1.A). When high and low reward trials were compared to neutral trials, the brain areas presented with increased and decreased activations overlapped with those identified for all win trials compared to neutral trials.

Feedback phase – win trials

At the whole brain level, feedback for the win vs neutral trials revealed significant decreases in activation in the bilateral SMA, the right precentral gyrus, the right superior frontal gyrus, the left inferior parietal gyrus and the bilateral postcentral gyrus. Of the *a priori* defined

ROIs, the NAc, the caudate and putamen had decreased activation for the same contrast whereas the caudate and putamen activations survived testing for multiple comparisons (p_{corr}= 0.0008) (Figure S1.B).

Feedback phase – no-win trials

When the feedback phase of no-win was contrasted to neutral feedback significant decreases were identified in the bilateral putamen, the right superior temporal gyrus and the left angular gyrus. Of the ROIs the activation of the caudate significantly decreased whereas the VTA presented with increased activation for the same contrast and survived Bonferroni correction (p_{corr}= 0.0008) (Figure S1.C).

Feedback phase- win trials vs no-win trials

For the whole brain analysis increases in activation for win compared to no-win (i.e outcomes for trials where rewards were actually obtained compared to unsuccessful trials) were identified for several brain areas including the bilateral occipital gyrus, the left inferior parietal gyrus, the right middle and inferior temporal gyrus. The left postcentral gyrus had decreased activations. Amongst the pre-defined ROIs, the VTA had decreased activation and the NAc, the caudate, the putamen, the amygdala and the insula presented with increased activations (Figure S2.D). All the activations, except the amygdala, survived Bonferroni correction (p_{corr}= 0.0008).

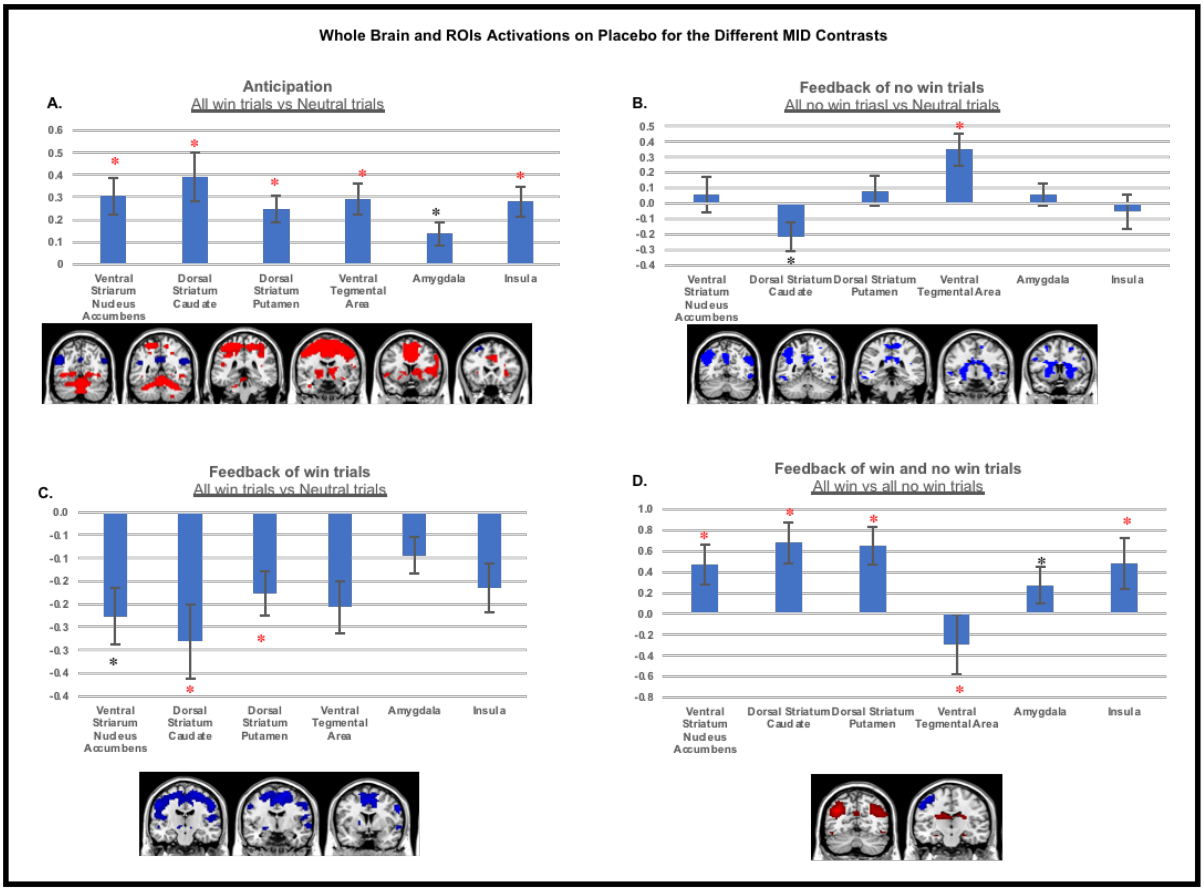
Exploratory Analysis of the sgACC

A bilateral ROI was used and beta values were extracted for all the anticipation and feedback contrasts of high and low, win and no win trials, for the ketamine and placebo condition. Ketamine, 2h post administration, did not produce any significant changes in the activation of that region in our cohort of remitted depressed volunteers. Figure S2 shows some representative the task contrasts for the activation of that region between ketamine and placebo.

Additional Contrasts of Interest

In order to add some clarity to our results and help with the interpretation of our findings we have plotted the betas for the ketamine and placebo condition for the following contrasts: 1. Anticipation- Low win trials vs Neutral trials 2. Anticipation- All win trials vs Neutral trials 3. Feedback phase – High win trials vs Neutral trials and 4. Feedback phase – All win trials vs Neutral trials. Ketamine, 2h post, administration did not produce any significant changes in the activation of our ROIs. The plots for each contrast can be found in Figure S3.

Figure S1



A. When the anticipation phase of all trials associated with reward-predicting cues were compared to neutral trials several brain areas presented with increased activation ($p<.05$, FDR corrected) and are shown in red. Decreased activations for this contrast are shown in blue (A). For the same contrast, all *a priori* defined ROIs presented with a significant increase (One Sample t-test, $p<.05$) in activation and all the ROIs except the amygdala, survived Bonferroni correction ($p_{corr}=.0008$) for multiple comparisons (red asterisk).

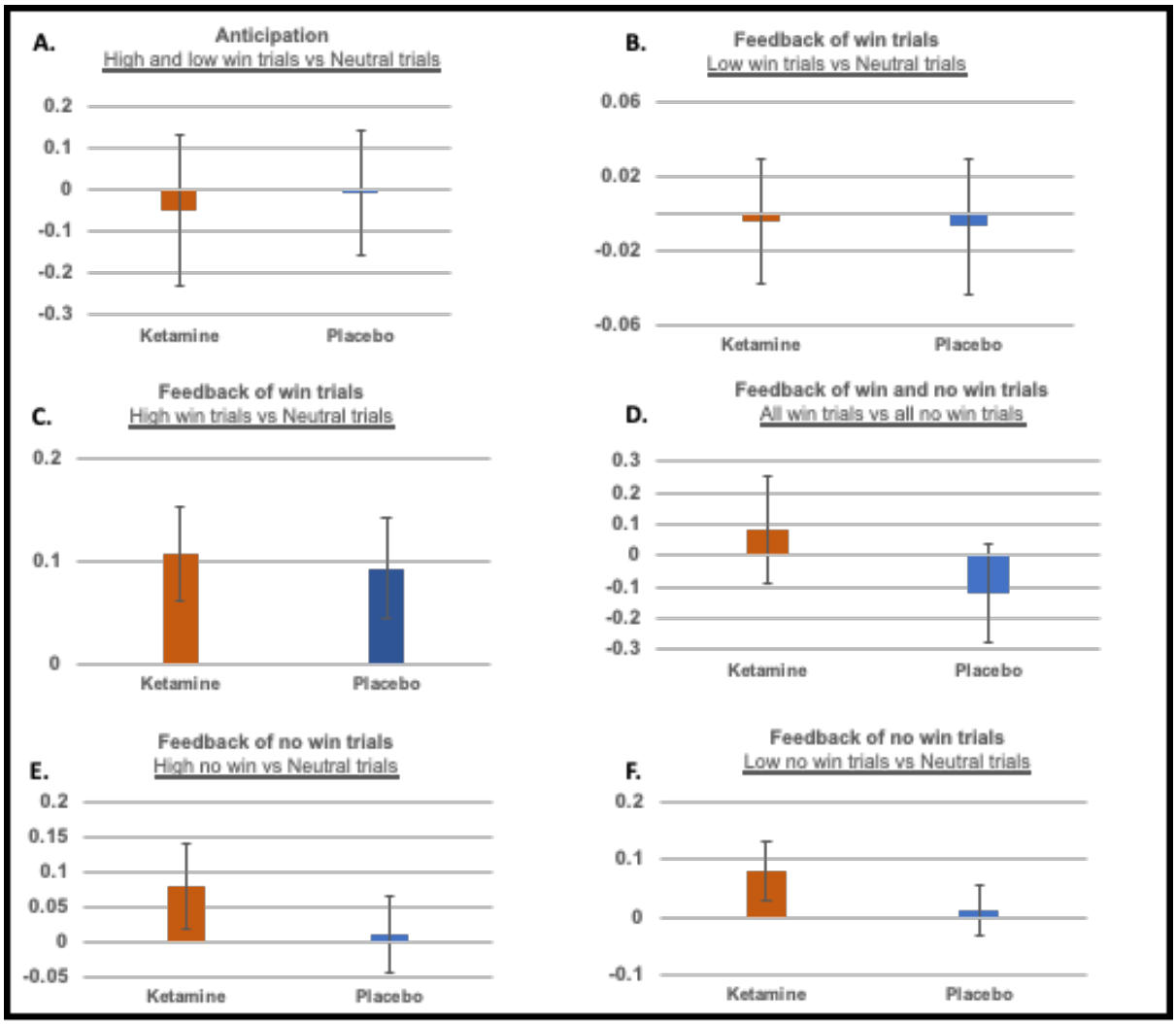
B. Feedback for the win vs neutral trials revealed significant decreases ($p<.05$, FDR corrected, clusters shown in blue) in several brain areas at the whole brain level. The a priori defined ROIs that presented with significantly decreased activation for that contrast are marked with a

black asterisk. The caudate and putamen activations survived Bonferroni correction (p_{corr}=.0008) for multiple comparisons (red asterisk).

C. When the feedback phase of no-win trials was contrasted to neutral feedback, significant decreases (p<.05, FDR corrected, clusters shown in blue) were identified in the bilateral putamen, the right superior temporal gyrus and the left angular gyrus. Of the ROIs the activation of the caudate significantly decreased (One Sample t-test, p<.05) whereas the VTA presented with increased activation (black asterisk) for the same contrast and this increase survived Bonferroni correction (p_{corr}=.0008) for multiple comparisons (red asterisk).

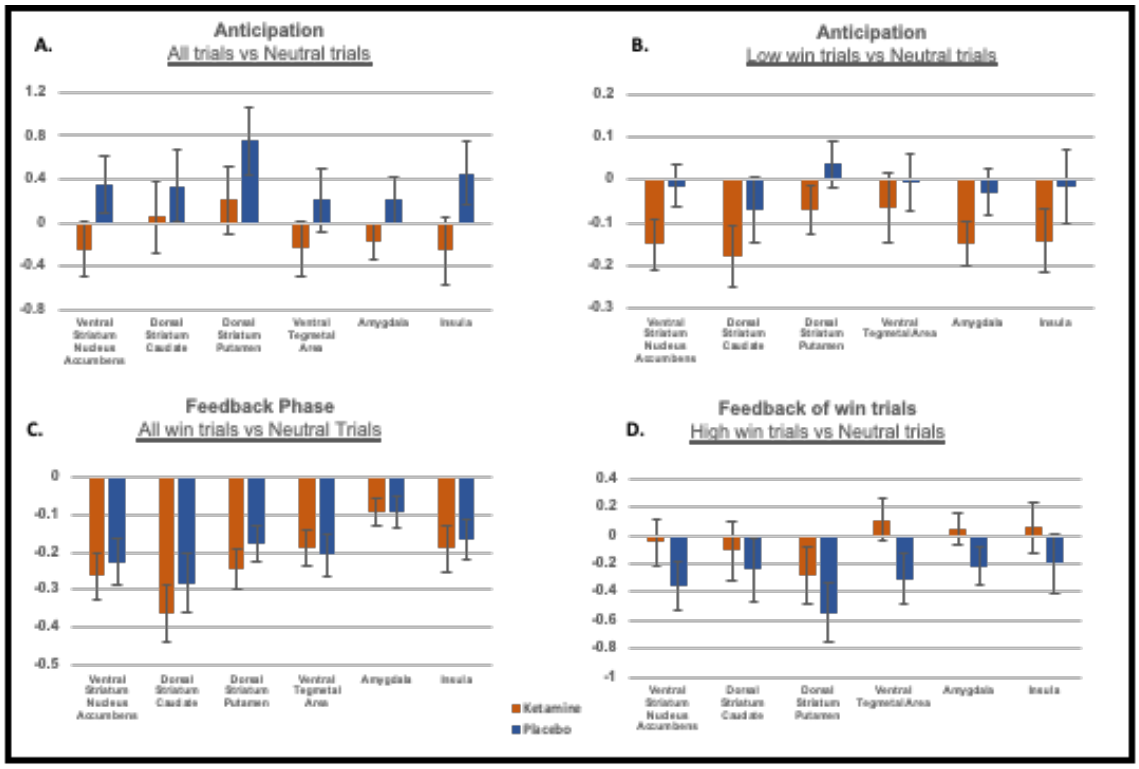
D. For the whole brain analysis significant increases in activation (p<.05, FDR corrected, clusters shown in red) and decreases were identified for several brain areas (p<.05, FDR corrected, clusters shown in blue). Amongst the pre-defined ROIs, the VTA had decreased activation and the NAc, the caudate, the putamen, the amygdala and the insula presented with increased activations and all the ROIs except the amygdala (black asterisk) survived Bonferroni correction (p_{corr}=.0008) for multiple comparisons (red asterisk).

Figure S2



Ketamine did not produce any significant changes ($p>.05$) in the activation of the sgACC. For this exploratory analysis all the task contrasts were examined and here we show the activation of the sgACC, for the ketamine and placebo conditions, in our group of remitted depressed volunteers. In this panel we show sgACC activations for the anticipation phase of high and low win trials compared to neutral trials (A). Activations of the feedback phase of low (B) and high (C) win trials as well as high no win (E) and low no win (F) win trials did not differ significantly for the ketamine and placebo conditions. Finally, sgACC activation did not differ for the feedback phase of win compared to the feedback phase of no win trials (D) between the ketamine and placebo conditions.

Figure S3



The beta values for the ketamine and placebo condition are plotted here for the anticipation phase of all trials compared to neutral trials (A) and the anticipation phase of low win trials compared to neutral trials (B). Ketamine did not produce any significant changes ($p>.05$) in the beta values of our ROIs, for these contrasts. For the feedback phase of the task, ketamine did not produce any significant changes ($p>.05$) in the activation of our ROIs when the feedback phase of all win trials was compared to that of neutral trials (C) and the feedback phase of high win trials was compared to that of neutral trials (D).