# Standard Behavioral Tests

## Implicit Learning Serial Reaction Time Task (SRTT)

To exclude the possibility of global learning deficits in MDD, an implicit learning serial reaction time task (Nissen & Bullemer, 1987) will be administered before fMRI scanning. The SRTT will be used to probe procedural learning, a form of implicit memory used to acquire, for example, simple stimulus-response associations. The task involves five blocks of 100 stimuli (an asterisk appearing in one of four boxes aligned horizontally). Each box,designated 1–4, corresponds to a button on a keyboard. When a cue appears, at the start of each trial, a participantselects the appropriate response button, which ends the trial. At the end of eachtrial, there is a short fixed delay before another cue is presented. In blocks 1-4, the visual cues play outa repeating sequence of positions (i.e., each location can be predicted by the preceding sequence of two locations), and subjects show systematic RT reduction in spite of no declarative knowledge of the sequence rule. In block 5, the sequence is fully random, and the visual cue no longer plays out a repeating pattern of positions. Performance on the SRTT is interpreted by measuring the gradual reduction in response time that takes place across the sequential trials. This provides a measure of participants’ growing expertise in performing the sequence and learning the visuomotor association, or mapping, between the position of the visual cute and the required response.

## Probabilistic Reward Task (PRT)

The probabilistic reward task (PRT) has been successfully used by the PI to assess reward responsiveness (e.g., Pizzagalli et al 2005, 2007, 2009b), and will be administered before and after the drug administration. In each trial, subjects choose which of two difficult-to-differentiate stimuli was presented. Stimuli consist of simple cartoon faces (diameter: 25 mm; eyes: 7 mm) presented in the center of the monitor. At the beginning of the trial, the face has no mouth. After a given delay, either a straight mouth of 11.5 mm (“short mouth”) or 13 mm (“long mouth”) is presented for 100 ms. Subjects are instructed to press an appropriate button to decide whether a long or small mouth had been presented. Unbeknownst to subjects, correct identification of one stimulus (“rich stimulus”) is rewarded three times more frequently (*“Correct! You won 20 cents”*) than the other (“lean”) stimulus. In healthy controls, this reinforcement schedule leads to a response bias (i.e., a preference for the more frequently rewarded stimulus). The degree of response bias toward the more frequently reinforced alternative will be used for operationalizing sensitivity to reward.

To avoid carry-over effects, participants complete the PRT twice in which only the stimuli type will vary. In the second version, instead of determining the length of the mouth, participants will need to decide whether a long or short ‘nose’ had been presented on the cartoon face by pressing the appropriate button. All other task parameters remain identical.

One version of the PRT is completed prior to the drug administration and the other is completed after the drug administration. The order of the two versions (mouth vs. nose) will be counterbalanced across subjects.

## Social Reinforcement Learning Task (SRLT)

During the fMRI data collection, participants will complete the SRLT. The task will last 15 minutes, and is designed to investigate whether learning deficits in MDDare specific to tasks involving monetary incentives or are, rather, more global and affected even when learning from social rewards and punishments. In the SRLT two fractal stimuli (conditioned stimuli) will be presented at any one time on the computer screen. Depending on the condition, participants have to choose one of the two stimuli to obtain reward or avoid punishment. During the reward block (R), one of the pictures will be associated with a reward (cheer sound + visual image) more often than the other picture and these associations change throughout the block. During the punishment block (P), one picture will be associated with a punishment (booing sound + visual image) more often than the other picture and these associations change throughout the block. During the mixed reward-punishment block (RP), one picture will be associated with a reward (cheer sound + visual image) and other picture will be associated with a punishment (booing sound + visual image) and these associations change to complete reversals throughout the block. During complete reversal, the picture that was previously associated with reward will be followed by a punishment and picture that was previously associated with punishment will be followed by a reward. The probabilities of associations change from 80% to 20% throughout the game. Each block will have 60 trials, with each trial lasting approximately 5s. One sec after the start of a trial, stimuli will be presented on screen for 1.5 sec; participants have to make a choice by pressing an appropriate key within this duration. Few seconds (jittered between 500ms – 5000ms) after the end of cue stimuli, reward or punishment will be presented for 1.5 seconds. The reward and punishment presentation will be based on a pre-defined sequence, so that the maximum rewards and punishments that a participant can obtain are the same for all participants.

The following instructions will be given to all participants,

“You will be presented with two pictures on the screen and you have to choose one of them by pressing the corresponding keys. There will be 3 different blocks that you will make responses to. During the Reward block (R), one of the pictures will be followed by a reward (cheer sound + visual image) more often than the other one and this will change as the game goes on. You have to pick the picture that you think is giving you reward at that time and your objective is to get as many cheers (rewards) as you can. During the Punishment block (P), one of the pictures will be followed by punishment (booing sound + visual image) more often than the other one and this will change as the game goes on. You have to pick the picture that you think will not give you punishment at that time and your objective is to get as less boos as you can. During mixed reward-punishment block (RP), one of the previously presented pictures will be followed by a reward and the other picture will be followed by punishment. These associations will keep changing throughout the game. Again, your objective is to get as many cheers and as few boos as you can. I will give you a practice now with example pictures”

A practice task with example pictures will be given to all participants, so that they are aware of how the task works and exposed to the feedback stimuli

## Probabilistic Stimulus Selection Task (PSST)

The PSST task (Frank, Seeberger, & O'Reilly R, 2004) will allow us to examine whether participants exhibit a bias for choosing frequently reinforced stimuli or avoiding frequently punished stimuli, and thus to assess positive and negative reinforcement learning. Of note, this task has been found to be sensitive to DA modulations, suggesting that hypodopaminergic states affect phasic DA signals required for learning from positive outcomes. Thus, MDD subjects and individuals at increased risk for depression are expected to be better at learning from punishment than reward in the PSST. The task has two phases: a learning and testing phase. In the learning phase, subjects are randomly presented with three different stimuli pairs (AB, CD, EF), and are instructed to choose one of the two stimuli by pressing a key. After the response, feedback is given to indicate whether the choice was correct or incorrect. Importantly, the feedback is probabilistic: for AB trials, a choice of stimulus A leads to positive feedback in 80% of the trials, while a choice of stimulus B leads to negative feedback in 80% of the trials. The stimulus pair CD is less reliable, with stimulus C being correct in 70% of the trials, and the stimulus pair EF is the least reliable, with stimulus E being correct in 60% of the trials. Subjects learn to choose stimuli A, C, and E more frequently than B, D, or F, during the learning phase. Of note, learning to choose A over B can be achieved either by learning that A usually leads to positive feedback or that B usually leads to negative feedback, or both. The learning phase ends after participants reach performance criteria (65% accuracy for A, 60% for C, and 50% for E) or after 6 blocks. The performance criteria are set so that all subjects are at the same level before starting the testing phase. In the testing phase, the same three pairs as well as all novel combinations of stimuli pairs are presented, and no feedback is provided. To examine whether subjects learned more about positive or negative outcomes of their decisions, the stimuli pairs of interest are those involving an A or B stimulus paired with a novel stimulus (e.g., AC, AD, BC, BD), referred to as transfer pairs. These transfer pairs will allow us to assess whether subjects learn from prior positive feedback to choose the most reinforced stimulus (“Choose A”) or learn from prior negative feedback to avoid the most punished stimulus (“Avoid B”).

## Doors Task

In each trial of this task adapted from the work of Greg Proudfit (2015), subjects are presented with two doors and are asked to choose one. Monetary gain feedback is presented in exactly 50% of trials, while monetary loss feedback is presented in the other 50% of trials, in random order. To account for the greater relative salience of losses compared to gains (Tversky & Kahneman, 1992), and to establish a net monetary gain for a participant, gains are in the amount of $0.50 and losses are in the amount of $0.25.

# Other Standard Procedures

**Abnormal Involuntary Movement Scale (AIMS)**

The AIMS is a 12-item scale designed to record the occurrence of dyskinetic, involuntary movements (Guy, 1976). Participants will complete the AIMS task during the screening visit, prior to dismissal from the study and, in the case of a dystonic reaction during the scanning visit, during a final exit interview one to two weeks after the scanning visit. The AIMS task will be administered and scored by one of the study staff physicians (e.g., David Olson, M.D., Ph.D.). During the AIMS task, participants are observed in stationary positions as well as during activated movements and any involuntary movements are recorded. This scale provides a quantitative measure of symptoms of dyskinesia and will help identify possible adverse reactions to the study drug, which are deemed unlikely due to the low and single dose administration.