The effect of acute citalopram on self-referential emotional processing and social cognition in healthy volunteers

NCT Number: Not yet available

Date: 23/09/19

1. Study Information

1.1 Purpose and Academic Rationale

Antidepressants are thought to operate by changing the way patients process emotional information[1]. After a single dose of citalopram or fluoxetine healthy volunteers have been found to display an increased recognition of happy facial expressions and a reduced recognition of sad faces, in the absence of changes in mood [2]. Studies using depressed participants have produced similar results[3].

However, there has been comparatively little research on changes in emotional processing biases about the self following antidepressant administration. Sense of self has been proposed as fundamental for mental health, with self-schemas acting as a focus through which valence and reward influenced perception, memory and decision-making [4]. Antidepressants may increase learning of positive information about the self, potentially remediating negative self-schema and subsequently reducing depression symptoms.

In this study, we aim to examine whether acute administration of citalopram is associated with an increase in positive emotional learning biases about the self. Using a parallel-group double-blind design, participants will be randomised to receive either an acute dose of citalopram or placebo. Participants will then complete a number of widely used computer-based cognitive tasks measuring emotional processing biases.

Identifying early changes in cognition and behaviour following antidepressant treatment will increase our knowledge of how antidepressants operate, and provide putative targets to identify early response to antidepressants.

1.2 Hypotheses

H1 Social Evaluation Learning
Participants administered citalopram will display a positive bias towards the self compared to participants administered a placebo, as indicated by fewer errors made before learning the like rule compared to the dislike rule. This effect will be strongest when learning about the self, compared to when learning about the friend or stranger.

H2 Self Associative Learning
Participants administered citalopram will show a greater prioritisation of learning self-related stimuli compared to those administered a placebo, as measured by faster reaction times and greater accuracy when matching neutral shapes to self-related stimuli, than stimuli related to a friend or a stranger.

H3 Reward Associative Learning
Participants administered citalopram will show a greater prioritisation of higher levels of reward compared to those administered a placebo, as measured by faster reaction times and greater accuracy when matching neutral shapes to high-reward stimuli, than stimuli related to medium and low levels of reward.

H4 Valence Associative Learning
Participants administered citalopram will show a greater prioritisation of positive stimuli compared to those administered a placebo, as measured by faster reaction times and greater accuracy when matching neutral shapes to positive (happy) stimuli, than stimuli related to neutral or negative (sad) stimuli.

H5 Social Cooperation
Participants administered citalopram will show greater levels of social cooperation compared to those administered a placebo, as measured by a greater proportion of cooperative behaviours in the prisoner's dilemma task.

H6 Self-Esteem Go/No-Go Task
Participants administered citalopram will show a greater implicit positive self-esteem compared to those administered a placebo, as measured by a greater sensitivity towards categorising positive words about the self and reduced sensitivity towards categorising negative words about the self.

This effect will be strongest when categorising words about the self; there will be smaller differences between participants administered citalopram versus placebo in sensitivity towards categorising positive and negative words with others.

H7 Emotional Categorisation and Recall
Participants administered citalopram will categorise a greater number of positive words and a fewer number of negative words as describing themselves compared to those administered a placebo. This effect will be strongest when categorising words about the self; there will be smaller differences between groups in the number of positive and negative words categorised about others.

Participants administered citalopram will recall a greater number of positive words and a fewer number of negative words about the self. This effect will be strongest when recalling words about the self; there will be smaller differences between groups in the number of positive and negative words recalled about others.

2. Sampling Plan

2.1 Data Collection Procedures
2.1.1 Recruitment
Participants will be recruited by word of mouth, emails to departmental mailing lists, and posters located in University of Oxford Departments. Adverts will be displayed in Junior and Middle Common Rooms, Colleges and University Departments and local community buildings. Adverts will also be placed on local information websites (e.g. Daily Info, Oxford University Gazette), newspapers, local magazines, and on the lab webpage, Facebook page, and Twitter account. The adverts will contain brief information about the inclusion criteria for the study, as well as contact details for the named researchers.

Participants will also be recruited via advertisement through Oxford Brookes, following approval from Oxford Brookes University Research Ethics Committee. The following

additional statement will be inserted into any recruitment documents for Oxford Brookes students and/or staff: "Oxford Brookes University has knowledge of this study and has permitted recruitment at the University. In the event of any questions about the study, please contact the researchers in the first instance. Should you need to contact anyone at Oxford Brookes about this further, please email: ethics@brookes.ac.uk".

2.1.2 Inclusion/Exclusion Criteria

Inclusion

- Male or Female
- Aged 18 -45
- Fluent in written and spoken English at a sufficient level to understand and complete the tasks
- Body Mass Index (BMI) 18-30
- Participant is willing and able to give informed consent for participation in the study
- Not currently taking any regular medications (expect the contraceptive pill)

Exclusion

- Any past or current Axis 1 DSM-V psychiatric disorder
- Current use of psychoactive medication (except the contraceptive pill, the Depo-Provera injection or the progesterone implant)
- Current or past history of drug or alcohol dependency
- History of current significant neurological condition (e.g. epilepsy)
- Known hypersensitivity to the study drug
- Currently pregnant or breast feeding
- Previous participation in a study that uses the same or similar computer tasks as those used in the present study
- Previous participation in a study that involves the use of a medication within the last three months
- Significant medical condition
- Smokers consuming > 5 cigarettes per day
- Individuals consuming > 6 caffeinated drinks per day
- Lactose Intolerance (as the placebo contains lactose)

2.1.3 Study Timeline

Prior to taking part in the study participants will be asked to complete a screening session, lasting a maximum of two hours. In this screening session participants will be asked to provide demographic information (name, gender, age, occupation, ethnicity, highest education level obtained, contact details). Participants will also be asked whether they are fluent in English, their first language, whether they smoke (and how much if yes), their

approximate alcohol consumption per week, their maximum alcohol consumption on a single occasion, and their average number of caffeinated drinks per day. To ensure eligibility participants will be asked whether they have taken part in any studies at the Departments of Psychiatry or Psychology before, and whether they have taken part in a study involving a drug or medicine before. The participants' height and weight will be measured, to calculate their Body Mass Index (BMI). Participants will be asked whether they have experienced any significant medical problems. To ensure participants are not taking any concomitant medication participants will be asked whether they are currently taking any medication or street drugs. Female participants will be asked whether they are currently pregnant, trying to become pregnant or breastfeeding, and about their menstrual cycle. To ensure participants are not currently experiencing any psychiatric disorder the structured clinical interview for DSM-V axis 1 disorders will be administered. Participants will also be asked about their personal and family history of psychiatric disorders. (Appendix E: screening form to be completed by the researcher).

Research visits will take place no later than four weeks following the screening. In the event that this timeframe is exceeded the screening procedure will be repeated.

Following the screening, eligible participants will be randomised to receive either a single 20mg oral dose of citalopram or a matched placebo tablet using an online randomisation tool.

On the day of the research visit participants will be asked to eat only a light meal prior to their appointment. Upon their arrival participants will be asked to complete a number of self-administered questionnaires to measure baseline mood:

- Patient Health Questionnaire (PHQ-9)
- Beck Depression Inventory (BDI-II)
- Generalised Anxiety Disorder Questionnaire (GAD-7)
- Brief Fear of Negative Evaluation Scale (BFNE)
- Positive and Negative Affect Schedule (PANAS)
- Eysenck Personality Questionnaire Abbreviated (EPQR-A)
- State and Trait Anxiety Inventory (STAI)
- Visual Analogue Scales measuring subjective state (happy, sad, disgusted, angry, frightened, anxious and alert)
- Side-Effects Questionnaire (to determine baseline bodily symptoms / 'side-effects')

Female participants will also be asked to provide another urine sample for a pregnancy test to ensure eligibility is continued following the screening visit. They will then be administered the medication and asked to rest for three hours. Following the rest period participants will again be asked to complete the state self-administered questionnaires outlined previously (the PANAS scale, the State subscale of the State Trait Anxiety Inventory (STAI-S), visual analogue scales measuring subjective state and the side effects questionnaire) before completing the cognitive tasks outlined below.

- Social Evaluation Learning[5]: Participants will be asked to learn how much the computer likes them, their friend, and a stranger. In each referential condition

participants are presented with positive-negative word pairs and are asked to select the word which they feel most represents the computer personas' attitude. Participants are given feedback concerning their selection's accuracy (correct or incorrect) and based on this feedback learn whether the computer likes the person. Feedback is manipulated to create two rules, 'like' (60-80% of positive words correct) or 'dislike' (20-40% of positive words correct).

- Associative Learning Task[6-8]: Participants will be asked to match neutral shapes with stimuli relating to the self (self, friend, stranger), reward (£1, £3, £9) and valence (happy facial expression, neutral facial expression, sad facial expression) in three separate tasks. Participants are instructed at the beginning of the task that particular words/pictures belong to particular shapes. Randomised word/picture-shape pairs are then presented briefly on the screen, and participants are asked to indicate whether these presentations match with the pairings presented at the beginning of the task.
- Prisoner's Dilemma Task[9, 10]: Participants are asked to invest points in each round in a cooperative or non-cooperative manner with a computer simulated 'other player', and earn points dependent upon their choice. The proportion of cooperative behaviours will be examined.
- Self-Esteem Go/No-Go Association Task[11] : In this task participants will be asked to categorise characteristics (positive and negative) and referential words (self and other) into predetermined categories, by pressing the spacebar if the presented word belongs to the category being tested.
- Emotional Categorisation and Recall: Participants will be asked to indicate whether characteristics describe themselves and an 'other'. In each referential condition participants will be presented with 20 positive and 20 negative characteristics, each displayed for 500 ms. Participants will be asked to indicate whether these words describe themselves/the other (yes or no) using the keyboard. They will then be asked to recall as many characteristics they can in 2 minutes.

Following completion of these tasks participants will again be asked to complete the PANAS scale, the State subscale of the State Trait Anxiety Inventory (STAI-S), visual analogue scales measuring subjective state and the side effects questionnaire. Finally, participants will be asked to guess which treatment they received to measure the success of blinding.
This visit will last a maximum of 5 hours in total (including the three hour rest period).

2.2 Sample Size and Rationale

Previously, the effect of citalopram on emotional processing has been investigated in healthy volunteers using a facial expression recognition task. On the facial expression recognition task, one of the main outcome variables is accuracy at recognising fearful facial expressions. A sample size of 22 per group would provide 90% power to detect changes of the magnitude of those we have seen in a previous antidepressant healthy volunteer study [drug mean 10.64 (SD 9.77) vs. placebo mean 3.36 (SD 5.96)[12]]. 44 participants will therefore be recruited (22 per group).

3. Variables

3.1 Manipulated Variables
Participants will be randomly assigned to be administered a single acute dose of citalopram or placebo.

3.1.1. Citalopram
Participants randomised to the citalopram group will be administered a single acute oral 20 mg dose of citalopram, using tablets encapsulated in opaque capsules. Citalopram is a licensed drug that is widely used to treat depressive illness.

3.1.2 Placebo
Participants will be administered one lactose placebo tablet encapsulated in opaque capsules.

3.2 Measured Variables

3.2.1 Social Evaluation Learning-
This task has been previously used by the research group[13, 14].

Participants learning of evaluations (i.e. others' perceptions) in social interactions will be measured using a cognitive test on E-Prime. This is a reinforcement learning task within a social context, adapted from previous versions to incorporate an additional referential condition [5, 15]. Participants are presented with word pairs and are asked to select the word which they feel most represents the computer personas' attitudes. No time limit is imposed on word selection. Participants are given feedback concerning their selection's accuracy (presented for 2000 ms), and based on this, must learn the computer's attitude.

Referential condition will be manipulated to reflect learning of social evaluations towards the self, a friend and a stranger. Feedback contingencies (the proportion of positive words that are 'correct') will also be manipulated throughout with trials corresponding to 20%, 40%, 60%, and 80%. Participants will therefore learn varying levels of positive 'like' rules (60, 80%) and negative 'dislike' rules (20, 40%). There will 12 blocks, corresponding to each possible rule-condition combination (three referential conditions, four rules), with 24 trials in each. Referential condition will be randomised.

Accuracy of responses (proportion correct in each rule-set) and reaction times (in ms) will be measured. Ability to acquire the stimulus feedback association (i.e., to learn the rules) will be assessed by the number of errors made before reaching the criterion of eight consecutive rule-congruent responses. These outcomes will be collapsed across the differing levels of like (60%, 80%) and dislike (20%, 40%) to create overall positive 'like' and negative 'dislike' rules.

At the end of each block participants will be asked to provide a global rating of how much the computer liked them, their friend and the stranger, using a visual analogue scale ranging from 'Complete Dislike' (0) to 'Complete Like' (100). At the end of each of the condition blocks participants will be asked to make an overall global rating.

We also aim to examine how participants incorporate learned evaluations into their perception of themselves, their friend and the stranger. At the beginning of each block of referential condition participant's will be asked 'How do you feel about [yourself / friend / stranger]?'. After the global rating measure in each block participants will be asked 'How does this make you feel about [yourself / friend / stranger]?'. Finally, at the end of each referential block participants will be asked 'How do you now feel about [yourself / friend / stranger?'. A visual analogue scale ranging from Very bad (0) to Very good (100) will be used for each of these questions.

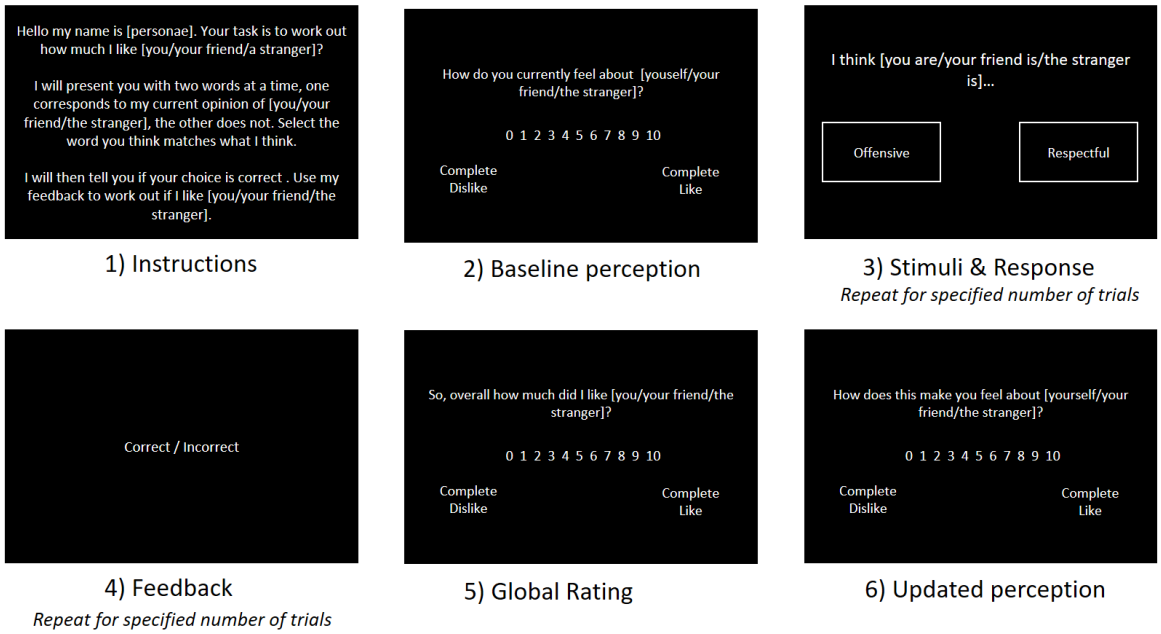

Figure 1

Social Evaluation Learning Task Procedure

3.2.2 Associative Learning

This task has been previously used by the research group[13, 14].

Three tasks will be used to examine different aspects of associative learning (self, reward and valence). These tasks have been adapted from Sui, Ohrling and Humphreys (2016)[8]. They were created using E-Prime v.2. Participants will undergo 9 practice trials, and two blocks of 60 testing trials, for each task.

Accuracy of responses (proportion correct in each condition) and reaction times (in ms) will be measured for each task.

3.2.2.1 Self

Referential condition will be manipulated to measure salience of self-related information, compared to information about a chosen friend and a stranger.

In this task participants are told that they will learn to associate words relating to 'self', 'friend' and 'stranger' with three different shapes: a triangle, a square, and a circle. The words will be personalised to each participant (i.e. the word 'self' will be replaced with the participants' first name). Word-shape pairs are randomised. Participants are then presented with various combinations of these word-shape pairings and asked to press the 'n' or 'm' key to indicate whether these match with what they have previously learnt. In each trial a fixation point is displayed for 2000 ms, followed by a word-shape pairing for 100 ms. Participants must provide a response within 1100 ms. Feedback, displayed for 500 ms, is provided for each trial. At the end of each block participants are informed of their accuracy (% correct responses) for that block.

3.2.2.2 Reward

The same procedure as outline the self associative learning task will be used for the reward condition, but varying levels of monetary values (e.g. High £9, Medium £3, Low £1) will instead be used instead of words relating to the self, friends and strangers. Again, these monetary values will be paired with three different shapes (pentagon, oval, diamond) and participants will be asked to indicate whether these match with what they have initially learnt. Participants will receive a monetary reward dependent on their task performance for each shape. To calculate this the number of words correct for the shape will be divided by the number of trials completed for the shape, and multiplied by the corresponding value of the label paired with the shape (e.g. £1, £3 or £9). This will be calculated for each shape and added together to ascertain the reward the participant will receive.

3.2.2.3 Valence

In the valence task varying intensities of cartoon facial expressions (e.g. sad, neutral, happy) will be paired with shapes (hexagon, rectangle, star). Again various combinations of these pairings will be presented and participants will be asked to indicate whether this matches with what they have previously learnt.

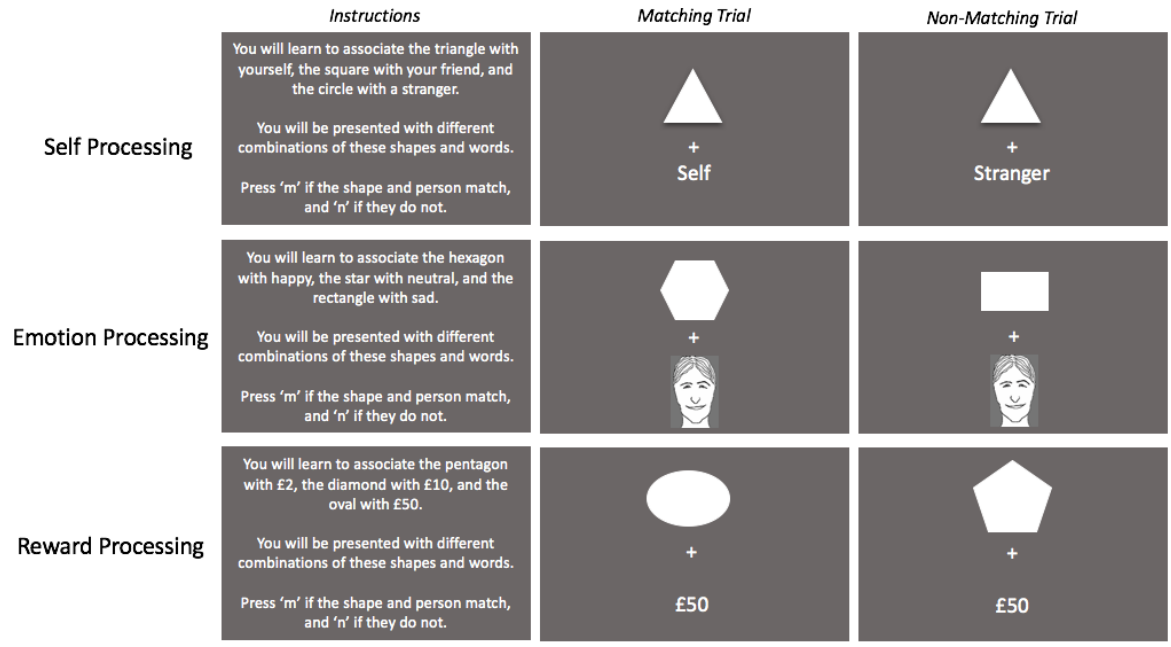

Figure 2
Examples of instructions, matching (the shape-label combination matches the instructions) trials, and non-matching (the shape-label combination does not match the instructions) trials in the three variations of the associative learning task

3.2.4 Prisoner's Dilemma Task

An iterated prisoner's dilemma task will be used to measure cooperative behaviour using the procedure outlined by Rilling et al[9] and Wood et al[10]. In this task participants are asked to invest points in each round in a cooperative or non-cooperative manner with a computer simulated 'other player'. Participants earn points depending upon their and the other player's choice. Each round has four possible outcomes: (1) both players cooperate, (2) the participant cooperates but the other player does not cooperate, (3) the participant does not cooperate but the other player does cooperate, (4) both players do not cooperate. Payoffs are structured so that maximum reward is obtained if the participant chooses not to cooperate while the other player chooses to cooperate. However, maximum loss occurs if the participant chooses to cooperate and the other player does not. In each round participants are shown a 2 x 2 matrix demonstrating these outcomes, and are asked to choose whether to cooperate or not cooperate.

The task will be completed in two blocks; in one block the other player will initially choose to cooperate, while in another block the other player will initially choose to not cooperate. Order of blocks will be counterbalanced. Each player will independently choose to either cooperate or not cooperate (i.e. the participant will not be informed of the other player's choice until they have made their selection), before being shown the other's choice and the resulting payoff. After the initial response the other player will follow a 'tit for tat' strategy, mirroring the choice of the participant (i.e. if the participant chooses to cooperate in the previous round the other player will cooperate in the next round and vice versa). 24 trials will be completed per block. Participants will also complete a training trial at the beginning of the task to ensure their understanding.

3.2.5 Self-Esteem Go/No-Go Task

This task has been previously used by the research group[13].

To measure implicit self-schema a go/no-go task will be completed using Inquisit Lab. This will follow the procedure outlined by Gregg and Sedikides[11], but will be adapted to use the 64 positive-negative characteristic word-pairs used in the social evaluation learning task, rather than overall positive or negative words.

Participants will be asked to categorise characteristics (positive and negative) and referential words (self and other) into predetermined categories, by pressing the spacebar if the presented word belongs to the category being tested. Response feedback is given. In the training phase participants are asked to categorise words belonging to single categories (e.g. positive, negative, self, other). There will be 20 trials for each category. In the test phase participants are asked to categorise words belonging to paired categories (e.g. positive OR

self, positive OR other, negative OR self, negative OR other). There will be 16 practice trials and 48 test trials for each paired combination of categories. A response timeout of 600 ms will be applied. Block order will be randomised.

Responses in the go/no go association task will be categorised into 'hits' (correctly categorising the word as belonging to the target category), 'misses' (incorrectly categorising the word as not belonging to the target category), correct rejections (correctly categorising the word as not belonging to the target category) and false alarms (incorrectly categorising the word as belonging to the target category). Reaction times will also be recorded.

3.2.6. Emotional Categorisation and Recall

This task has been previously used by the research group[14].

Participants will be asked to indicate whether characteristics describe themselves and an 'other'. In each referential condition participants will be presented with 20 positive and 20 negative characteristics, each displayed for 500 ms. Participants will be asked to indicate whether these words describe themselves/the other (yes or no) using the 'k' or 'j' keys. The allocation of key commands to responses (e.g. whether 'k' or 'j' indicates yes or no) will be counter-balanced across participants, but will remain consistent within participants across time-points. Participants will then be asked to recall as many characteristics they can in 2 minutes. Order of referential condition will be randomised. The characteristics used will be randomly assigned to each referential condition. Different words will be used to those in the social evaluation learning task. Number of accurate responses (hits) and incorrect recollections (intrusions) will be recorded.

3.2.7 State Mood

The Positive and Negative Affect Scale (PANAS)[16] will be used to measure mood. Participants will be asked to indicate to what extent they currently experience ten positive and ten negative emotions, ranging from (1) 'very slightly or not at all' to (5) 'extremely'. The PANAS will be completed before administration of the study drug, three hours after administration of the study drug, and following completion of the cognitive tests.

3.2.8 Depressive Symptoms

The Beck Depression Inventory (BDI-II) [17] and Patient Health Questionnaire (PHQ-9) [18] will be used as self-administered measures of depression severity. The PHQ-9 is a briefer measure than the BDI-II (9 items versus 21 items), and is more widely used in primary care. Conversely, the BDI-II is based on the cognitive theory of depression, and thus better relates to the concept of negative self-schemata.

3.2.9 Anxiety

The Generalised Anxiety Disorder-7 (GAD-7)[19] will be used to measure generalised anxiety. The GAD-7 is widely used in clinical settings to screen for anxiety disorders.

3.2.10 Social Anxiety

The Brief Fear of Negative Evaluation (BFNE) Scale will be used at each time-point, as a measure of social anxiety [20]. This is a 12-item self-report measure of fear of negative evaluation by others.

3.2.11 Neuroticism
The Eysenck Personality Questionnaire Abbreviated (EPQR-A) will be used to measure neuroticism at baseline[21].

3.2.12 State and Trait Anxiety Inventory
The Trait subscale of the State and Trait Anxiety Inventory (STAI) will be completed at baseline only. The State subscale of the STAI will be completed before administration of the study drug, three hours after administration of the study drug, and following completion of the cognitive tests[22].

3.2.13 Visual Analogue Scales
Visual Analogue Scales (VAS) will be used to measure the subjective states of happiness, sadness, disgust, anger, fear, anxiety and alertness. Participants will be asked to place a mark on a line to indicate the extent to which they feel each emotion. These will be completed before administration of the study drug, three hours after administration of the study drug, and following completion of the cognitive tests.

3.2.14 Side Effects Questionnaire
A short questionnaire will be used to measure side effects of the study drug before administration of the study drug, three hours after administration of the study drug, and following completion of the cognitive tests. This will determine baseline bodily symptoms and changes following administration of the study drug. Participants will be asked to what extent they experience the following side effects: nausea, dizziness, dry mouth, headache, alert, agitation.

3.3 Indices

3.3.1 Social Evaluation Learning
An overall index of positive or negative bias will be calculated for each referential condition (self, friend, stranger) using errors to criterion. Bias is calculated by subtracting errors to criterion made when learning the dislike rule from errors to criterion made when learning the like rule. A positive value indicates a negative bias, as fewer errors are made learning the dislike rule compared to the like rule. Conversely, a negative value indicates a positive bias, as fewer errors are made learning the like rule compared to the dislike rule.

Mean global ratings will be calculated separately for each referential-rule combination block (i.e. self-like, self-dislike, friend-like, friend-dislike, stranger-like, stranger-dislike). Overall mean ratings for each referential condition will also be generated. As the feedback contingencies (% of positive words correct) average to 50% across blocks in each referential condition, global ratings above 50% will be considered as a positive bias and those below as a negative bias.

Mean perception ratings will be calculated for each referential-rule block, and overall for each condition.

3.3.2 Associative Learning

Mean accuracy and reaction times will be calculated for each referential condition (self, friend, stranger), reward condition (high, medium, low) and valence condition (positive, neutral, negative) for each respective task.

3.3.3 Social Cooperation

The main outcome for this task is the proportion of rounds on which participants choose to cooperate. Reaction times for cooperation versus non-cooperation choices will also be calculated. The conditional probability of cooperating will be calculated according to the proportion of rounds on which participants cooperated following each of the four possible outcomes.

3.3.4 Self-Esteem Go/No-Go Task

Discriminative accuracy (*d'*) will be calculated through applying Z-score transformations, and subtracting hit z-scores from false alarm z-scores. Z-scores are adjusted by adding or subtracting .005 if hit or false-alarm rates are 0 or 1. d' –values can then be compared for each possible categorical combination to examine implicit self-biases.

3.3.5 Emotional Categorisation and Recall

The mean number of positive and negative words categorised as describing or not describing the participant/the other will be recorded. Mean hits and false intrusions will be collected for each referential condition and valence.

3.3.6 Questionnaires

Scores will be calculated by totalling scales and subscales, following standard procedures for each questionnaire.

4. Design Plan

4.1 Study Type
Randomised double-blind placebo-controlled parallel-group

4.2 Blinding
Double-blind

4.3 Study Design
A parallel group design will be used with study group (citalopram versus placebo) as a between-subject factor.

4.4 Randomisation
Participants will be randomly assigned to receive placebo or citalopram on the day of the study visit.

5. Analysis Plan

5.1 Statistical Models

5.1.1 Primary Analyses

H1 Social Evaluation Learning
Participants administered citalopram will display a positive bias towards the self compared to participants administered a placebo, as indicated by fewer errors made before learning the like rule compared to the dislike rule.

A mixed-effects linear regression model will be conducted with bias scores as the outcome, and referential condition, group, and the interaction between referential condition and group as predictors. Subject will be entered as a random effect to account for the within-subject effect of referential condition.

To further examine whether associations between bias and group are driven by learning within a particular rule (e.g. better learning of 'dislike' or worse learning of 'like'), a mixed-effects linear regression model will be conducted with errors to criterion as the outcome and referential condition, rule, group, and the interaction between these variables as predictors. Subject will be entered as a random effect to account for the within-subject effect of referential condition and rule.

H2 Self Associative Learning
Participants administered citalopram will show a greater bias towards the self compared to those administered a placebo, as measured by faster reaction times and greater accuracy when matching neutral shapes to self-related stimuli, than stimuli related to a friend or a stranger.

A mixed-effects linear regression model will be conducted with reaction time as the outcome, and group, referential condition (self, friend, stranger), and the interaction

between group and referential condition as predictors. Subject will be entered as a random effect to account for the within-subject effect of condition. This model will be repeated with accuracy as the outcome.

5.1.2 Secondary Analyses

H3 Reward Associative Learning
Participants administered citalopram will show a greater bias towards higher levels of reward compared to those administered a placebo, as measured by faster reaction times and greater accuracy when matching neutral shapes to high-reward stimuli, than stimuli related to medium and low levels of reward.

The model outlined for hypothesis 2 will be repeated with data from the reward associative task. Reward condition (high, medium, low), rather than referential condition, will be used as a predictor.

H4 Valence Associative Learning
Participants administered citalopram will show a greater bias towards positive stimuli compared to those administered a placebo, as measured by faster reaction times and greater accuracy when matching neutral shapes to positive (happy) stimuli, than stimuli related to neutral or negative (sad) stimuli.

The model outlined for hypothesis 2 will be repeated with data from the valence associative task. Valence condition (happy, neutral, sad), rather than referential condition, will be used as a predictor.

H5 Social Cooperation
Participants administered citalopram will show greater levels of social cooperation compared to those administered a placebo, as measured by a greater proportion of cooperative behaviours in the prisoner's dilemma task.

A mixed-effects linear regression model will be conducted with the proportion of rounds participants chose to cooperate as the outcome, and group, block (cooperative versus non-cooperative), and the interaction between these variables as predictors. Subject will be entered as a random effect to account for the within-subject effect of block.

H6 Self-Esteem Go/No-Go Task
Participants administered citalopram will show a greater implicit positive self-esteem compared to those administered a placebo, as measured by a greater sensitivity towards categorising positive words about the self.

A mixed-effects linear regression model will be conducted with d' as the outcome, and group, referential condition (self vs. other), valence (positive vs. negative), and the interaction between these variables as predictors. Subject will be entered as a random effect to account for the within-subject effect of condition and valence. This model will be repeated separately with hits and false alarms as the outcome.

H7 Emotional Categorisation and Recall
Participants administered citalopram will categorise a greater number of positive words as describing themselves and recall a greater number of positive words about the self compared to those administered a placebo

A mixed-effects linear regression model will be conducted with number of words recalled as the outcome, and group, referential condition (self vs. other), valence (positive vs. negative), and the interaction between these variables as predictors. Subject will be entered as a random effect to account for the within-subject effect of condition and valence. This model will be repeated separately with number of positive words and number of negative words categorised as the outcome.

Baseline differences between groups
Differences between groups for demographic and baseline measures will be analysed using independent t-tests.

Influence of drug administration on mood
A mixed-effects linear regression model will be conducted for each measure of mood as the outcome in separate models. In each model group, timepoint and the interaction between these will be entered as predictors. Subject will be entered as a random effect to account for the within-subject effect of timepoint.

5.2 Transformations
Data that deviates from normality will be transformed to a normal

5.3 Follow-up Analyses
None planned

5.4 Inference Criteria
Frequentist analyses with an alpha value of 0.05 will be used.

5.5 Data Exclusion

5.5.1 Associative Learning Task
Responses less than 200 ms will be excluded[6].

5.5.2 Self-Esteem Go/No-Go Task
In accordance with Gregg and Sedikides'[11] procedure, participants will be considered non-compliant and excluded if overall bias scores (average hits + false alarms) are below 12 or above 36, and/or discrimination scores (average hits – false alarms) are below 5. Participants data will also be removed at the block level if identical responses are made throughout the block (e.g. all responses are ‘go’ or all responses are ‘no-go’).

5.6 Missing Data
If less than 5% of data is missing overall, listwise deletion methods will be used. If greater than 5% of data is missing single imputation methods will be used, where the data is replaced with the group mean to which the participant belongs (i.e. citalopram versus

placebo). Participants with data missing from a specific test will be excluded from analyses for that particular test, but will be included in other analyses if data are available.

6. Funding Source

This study is being funded by the National Productivity Innovation Funded awarded to Catherine Hobbs at the University of Bath through the GW4 MRC BioMed Doctoral Training Programme.
Recruitment and data collection for this study will take place within the University of Oxford Psychopharmacology and Emotion Research Lab.

References

1. Pringle A, Browning M, Cowen P, Harmer C. A cognitive neuropsychological model of antidepressant drug action. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2011;35(7):1586-92.
2. Harmer C, Shelley N, McTavish S, Cowen P, Goodwin G, editors. Repeated administration of citalopram or reboxetine reduces the perception of negative emotions from facial expression2002.
3. Harmer CJ, O'Sullivan U, Favaron E, Rachel Massey-Chase B, Ayres R, Reinecke A, et al. Effect of acute antidepressant administration on negative affective bias in depressed patients. American Journal of Psychiatry. 2009.
4. Button K, Sui J. Reinforcing the self in anxiety and depression: implications for treatment. Manuscript in preparation.
5. Button KS, Kounali D, Stapinski L, Rapee RM, Lewis G, Munafò MR. Fear of negative evaluation biases social evaluation inference: Evidence from a probabilistic learning task. PloS one. 2015;10(4):e0119456.
6. Sui J, He X, Humphreys GW. Perceptual effects of social salience: evidence from self-prioritization effects on perceptual matching. Journal of Experimental Psychology: Human Perception and Performance. 2012;38(5):1105.
7. Sui J, Humphreys GW. The interaction between self-bias and reward: Evidence for common and distinct processes. The Quarterly Journal of Experimental Psychology. 2015;68(10):1952-64.
8. Sui J, Ohrling E, Humphreys GW. Negative mood disrupts self-and reward-biases in perceptual matching. The Quarterly Journal of Experimental Psychology. 2016;69(7):1438-48.
9. Rilling JK, Gutman DA, Zeh TR, Pagnoni G, Berns GS, Kilts CD. A neural basis for social cooperation. Neuron. 2002;35(2):395-405.
10. Wood RM, Rilling JK, Sanfey AG, Bhagwagar Z, Rogers RD. Effects of tryptophan depletion on the performance of an iterated Prisoner's Dilemma game in healthy adults. Neuropsychopharmacology. 2006;31(5):1075-84.
11. Gregg AP, Sedikides C. Narcissistic fragility: Rethinking its links to explicit and implicit self-esteem. Self and Identity. 2010;9(2):142-61.
12. Harmer CJ, Shelley NC, Cowen PJ, Goodwin GM. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. American Journal of Psychiatry. 2004;161(7):1256-63.
13. Hobbs C, Kessler D, Munafo MR, Sui J, Button KS. Biased Self-Referential Processing in Depression. . Pre-Registration on Open Science Framework. 2018.
14. Hobbs C, Sui J, Penton-Voak I, Munafo MR, Kessler D, Button KS. A neurocognitive investigation of the role of self-referential processing in antidepressant action: study protocol. Open Science Framework. 2019.
15. Button KS, Browning M, Munafò MR, Lewis G. Social inference and social anxiety: evidence of a fear-congruent self-referential learning bias. Journal of behavior therapy and experimental psychiatry. 2012;43(4):1082-7.
16. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of personality and social psychology. 1988;54(6):1063.
17. Beck AT, Steer RA, Brown GK. Beck depression inventory-II. San Antonio. 1996;78(2):490-8.

18. Kroenke K, Spitzer RL, Williams JB. The phq-9. Journal of general internal medicine. 2001;16(9):606-13.
19. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Archives of internal medicine. 2006;166(10):1092-7.
20. Leary MR. A brief version of the Fear of Negative Evaluation Scale. Personality and Social Psychology Bulletin. 1983;9(3):371-5.
21. Francis LJ, Brown LB, Philipchalk R. The development of an abbreviated form of the Revised Eysenck Personality Questionnaire (EPQR-A): Its use among students in England, Canada, the USA and Australia. Personality and individual differences. 1992;13(4):443-9.
22. Spielberger CD. State-trait anxiety inventory: a comprehensive bibliography: Consulting Psychologists Press; 1989.