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Single-dose effects of Citalopram on neural responses to affective stimuli in borderline personality disorder: A randomized clinical trial

Short title: Single-dose effect of Citalopram on neural responses

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Abstract

Background: Psychiatric medication that has a soothing effect on the limbic responses to affective stimuli could improve affective instability symptoms as observed in Borderline Personality Disorder (BPD). The objective of this study was to investigate whether Citalopram vs. Placebo reduces the response of the affective neural circuitry during emotional challenge.

Methods: N=30 female individuals with BPD diagnosis participated in a Placebo-controlled, double-blind crossover trial design. Three hours after oral drug intake, individuals with BPD viewed affective pictures while undergoing functional Magnetic Resonance Imaging. Blood Oxygenation Level Dependent responses to images of negative affective scenes and faces showing negative emotional expressions were assessed in regions-of-interest (amygdala, anterior cingulate cortex, anterior insula, dorsolateral prefrontal cortex). Blood perfusion at rest was assessed with arterial spin labeling.

Results: The neural response to pictures showing negative affective scenes was not significantly affected by Citalopram (N=23). Citalopram significantly reduced the amygdala response to pictures of faces with negative affective expressions (N=25, treatment difference left hemisphere: -0.06 ±0.16, P<0.05, right hemisphere: -0.06±0.17, P<0.05). We observed no significant effects of Citalopram on the other regions. The drug did not significantly alter blood perfusion at rest.

Conclusions: Citalopram can alter the amygdala response to affective stimuli in BPD, which is characterized by overly responsive affective neural circuitry.

The study was registered to EudraCT (www.clinicaltrialsregister.eu) ID 2018-001212-30.
Keywords: Borderline Personality Disorder, Citalopram, Neuroimaging, MRI,

Affective Instability, Emotional Reactivity
1 Introduction

Pharmaceutical compounds that engage affective brain circuits are promising candidates for treating affective instability in Borderline Personality Disorder (BPD)(1). Hyperreactivity of the amygdala and hyporeactivity of dorsolateral prefrontal cortex (DLPFC) characterize neural emotion processing in BPD(2). Individuals with BPD often use damaging self-regulation strategies such as non-suicidal self-injury and dissociation to soothe highly aversive emotional states – an effect that may be mediated by downregulation of the amygdala(3–6). A previous literature review identified brain regions such as the amygdala, insula, dorsal anterior cingulate cortex as well as prefrontal areas as promising neural targets for treatment of emotion dysregulation in BPD(7). Treatment of choice for this disorder is psychotherapy(8), and clinical trials found decreased responding of the amygdala after effective psychotherapy(9,10). These and other studies(4,5,11,12) suggest a link between affective instability symptoms and dysregulation of prefrontal-limbic brain circuits. Assuming a causal pathway from the brain to behavior, the question is pressing whether medication can alter the neural circuits of affective processing in BPD. Thereby, it could be possible to ameliorate symptoms of affective instability. Evidence is currently lacking to show effective neural modulation in BPD with existing pharmaceuticals.

Different symptoms of BPD were linked to dysfunctions of the serotonergic system. In detail, impulsivity and aggression were related to lower levels of 5-hydroxyindoleaceticacid in CSF(13,14) and to blunted response to fenfluramine challenge(15–17). Likewise, 5-HTTLPR polymorphism was associated with affective instability, impulsivity, and self-aggression(18,19). Consequently, the Selective Serotonin Reuptake Inhibitor (SSRI) Citalopram is one of the most commonly used...
antidepressants in the treatment of patients with BPD, although randomized controlled trials are lacking to support this choice(20,21). Meta-analyses found little evidence for effectiveness of antidepressants on BPD symptoms and no significant effect could be detected for SSRIs(22). However, only little evidence exists and trials with Citalopram are currently missing.

Neuroimaging studies in healthy participants show that Citalopram can reduce the amygdala response to affective material(23–26). If it would do the same in individuals with mental disorder, Citalopram could act upon limbic hyperreactivity and consequently on affective instability symptoms in BPD. It is the hope that first evidence of neural target engagement can inform future clinical trials to assess psychopharmaceutical compounds in the treatment of BPD.

We conducted a pharmacological (ph) functional magnetic resonance imaging (fMRI) study to investigate neural responses to pictures with negative affective content in female patients with BPD within a double-blind, randomized crossover placebo-controlled design. The main purpose of this study was to assess the immediate effect of a single dose of Citalopram (20 mg) as compared to Placebo on Blood Oxygen Level Dependent (BOLD) responses. We hypothesized that a single dose of Citalopram results in changes in brain activity during fMRI tasks, which are designed to elicit affective responses. The main endpoints of efficacy were the BOLD responses induced by affective stimuli in the amygdala, the DLPFC, the anterior insula, and the anterior cingulate cortex (ACC). We defined responses to pictures showing negative scenes as primary endpoints, whereas responses to faces with emotional expressions were defined as secondary endpoints.
2 Materials and methods

2.1 Sample

N=30 female right-handed individuals were enrolled in this study, who were recruited via our department’s database and in our clinical department. Inclusion criteria were a diagnosis of BPD according to DSM-IV(27), age between 18-45 years, and physical health as determined by the investigator, based on a medical evaluation. Exclusion criteria comprised history of alcohol or substance dependence within 12 months prior to study, positive alcohol or drug test, consumption of large amounts of caffeinated drinks, and any contraindications to participate in an MRI study (see Supplement section 2 for full list). Individuals who passed inclusion assessments were invited for the first MRI scan one week later. They received financial reimbursement (€ 200) for participation.

From N=30 participants randomized to the trial, MRI data from N=23 could be analyzed to test our hypotheses in the scene-task, and N=25 could be analyzed for the face-task. Arterial Spin Labeling (ASL) data from N=21 individuals could be used in the final analysis. For details on participant flow according to CONSORT guidelines(28), see Figure 1. The CONSORT checklist is provided in the Supplement.

Asked about previous exposure to SSRIs, N=8 confirmed experience with Citalopram and two of them reported mild adverse events such as restlessness, sleep problems and nausea. N=3 had taken Escitalopram and two of them reported mild adverse events such as sleep problems, nausea and gastrointestinal complaints. N=17 reported no exposure to SSRIs at all. Data was missing for two participants.
1 2.2  **General procedure**

The clinical diagnosis of BPD was confirmed via clinical interview by a trained
psychologist or physician carrying out the German Versions of the Structured Clinical
Interview for DSM-IV(27), and the International Personality Disorder Examination
(IPDE)(29). Two clinical interviews were conducted to assess depression severity
(MADRS)(30) and severity of borderline personality disorder (ZAN-BPD)(31).

At this visit (Day 1), participants also filled in questionnaires on
psychopathology. Depression severity was assessed with the German version of the
Beck Depression Inventory (BDI-II)(32); anxiety was assessed with Beck Anxiety
Inventory (BAI)(33), and borderline symptoms were assessed with the borderline
symptom list (BSL-23)(34).

Due to the within-subjects design, there were two treatment visits: Visit 2 (Day
7) and Visit 3 (Day 14). On one visit, placebo was administered. On the other visit
participants received verum (20 mg Citalopram, single-dose) within a double-blind,
randomised, crossover design. The subject was administered the study medication orally
(20 mg of Citalopram or placebo). After a waiting period of 3h, participants were asked
to report current mood with the Positive and Negative Affect Schedule (PANAS)(35).
Afterwards, they participated in the fMRI experiment.

Adverse events were reported rarely, headaches were reported most (n=11) and
with similar frequency in both treatment arms (Supplement Table S1).
2.3 **FMRI experiment**

The two tasks were administered in fixed order, as introduced below, and were presented with Presentation software (Neurobehavioral Systems, Inc, Berkeley, USA) via a 40” monitor located in the back of the scanner, which was visible for subjects through a mirror placed on top of the head coil. The patient operated a button box with the right hand to record behavioral responses.

2.3.1 **Faces task**

Participants viewed faces with emotional expression (disgust, sadness, and fear were chosen based on meta-analyses(36)) from the Warsaw Set of Emotional Facial Expression Pictures (WSEFEP, http://www.emotional-face.org/). A block design of 12 blocks with 6 faces each (aversive condition, AC; negative emotional expressions were randomly mixed within blocks) and 12 blocks with scrambled faces (neutral condition, NC) was used. Scrambled faces were chosen as control because of two reasons: First, we wanted to match the faces task with the scenes task in terms of the analyzed contrast. Second, previous work suggested altered responding in BPD not only to emotional expressions but also to faces with neutral expression (37), which would compromise the sensitivity of our design to detect drug-induced changes. In sum, 72 negative faces of 24 actors (12 female, 12 male) were shown for 3 seconds each. The inter-trial interval was jittered to nine, 10, or 11 seconds and contained a white fixation cross on a black background. To ensure attention, participants were asked to press a button to indicate for every picture whether the person was male or female (AC), or whether color of the bounding box around scrambled faces was blue or green (NC).
2.3.2 Scenes task

The task was adapted from Paret et al.(38). We presented 42 pictures from the OASIS picture set (39) to induce negative affect. We used pictures with negative affective valence and high arousal (AC) in a block-design. During each of 14 blocks, lasting 18 seconds, three picture stimuli were presented for 6 seconds each, resulting in a set of 42 negative pictures in total. Due to the within-subject design, we used two picture sets with similar characteristics concerning affective valence and arousal to avoid habituation to picture content. These two sets were randomized between treatment visits to avoid undesired effects of systematic presentation order. Scrambled pictures were used in a non-affective control condition (NC) with the same number of trials and presentation time. During the intertrial interval (jittered to nine, 10, or 11 seconds), participants viewed a white fixation cross on a black background. To ensure attention, participants were asked to press a button to indicate for every picture whether it showed a person or not (AC), or whether the color of the bounding box around scrambled pictures was blue or green (NC).

2.3.3 Neuroimaging parameters

Brain images were acquired using a 3 Tesla MRI scanner (TRIO, Siemens Medical Systems, Erlangen, Germany) with a 64-channel head coil and a T2*-weighted gradient echo-planar imaging sequence (repetition time=2000ms, echo time=30ms, flip angle=80°, voxel size =3x3x3mm, matrix 64x 64, number of slices=36, FOV [Field of view]=192x192x143mm). The FOV used for scanning included the whole brain for all participants. This was achieved by rotating the bounding box relative to AC-PC as recommended in Mennes et al. (40). TE was minimized using a parallel acquisition technique (generalized autocalibrating partially parallel acquisitions [GRAPPA]) with
an acceleration factor of 2 and 24 reference lines. Slices were tilted -16° from AC-PC orientation. Perfusion imaging was done afterwards. Anatomy was imaged with a 3D T1-weighted scan (Magnetization Prepared Rapid Acquisition Gradient Echo [MPRAGE] sequence, TE=3.03 ms, TR=2.3 s, 192 slices and FOV=256x256x192 mm, voxel size = 1x1x1 mm). ASL imaging parameters are reported in the Supplement, Section 3.

2.4 Data analysis

2.4.1 BOLD imaging

All imaging preprocessing and first-level analyses were carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl)(41). The following preprocessing steps were performed: volume realignment to correct for participant head motion, B0 unwarping using field map data to correct for EPI distortions, grand-mean scaling, and spatial smoothing with a 5mm FWHM kernel. Next, FSL’s melodic was applied to extract independent data components and ICA-AROMA(42) was applied to identify and remove secondary effects of head motion. Finally, a temporal high-pass filter with 0.01 Hz cut-off was applied to remove scanner drifts. We obtained the transformation of the fMRI data to the participant’s high resolution T1 anatomical space using FSL’s Boundary-Based Registration tool. A transformation from the participant’s T1 space to MNI152 standard space was obtained using linear alignment via FSL FLIRT with 12 degrees of freedom, and subsequently refined using non-linear steps as implemented in FSL FNIRT. Data were screened for quality and excluded from further analysis in case of superthreshold movement during a scan (>4mm, N=2 patients) and heavy
BOLD-signal dropout in one scan (N=1). More information on the composition of the sample to be analyzed can be obtained from Figure 1.

After preprocessing, we conducted first-level statistical analyses for both the Faces and the Scenes task separately. For each task, we included two regressors respectively modelling the onset times of the faces/scenes (AC) and scrambled stimuli (NC), convolved with a double-gamma HRF. The onset regressors consisted of 18-second blocks. The contrast of interest compared BOLD activity between the scenes/faces and the scrambled control stimuli.

To show target engagement by the tasks, we prepared whole-brain maps from a mass-univariate whole-brain analysis implemented in Statistical Parametric Mapping (SPM12) software (Wellcome Department of Cognitive Neurology, London, UK).

Regions-of-interest (ROIs) were localized by intersecting the AC>NC (faces-task and scenes-task) activation maps derived from a 15-participant prestudy (unpublished data) with substructures of the Harvard-Oxford atlas (HOA) implemented in FSL (41). The statistical maps were thresholded at $z > 2.3$, while the atlas regions were thresholded at 50% probability. We used these substructures (to define ROIs): amygdala, paracyngulate gyrus (ACC), inferior frontal gyrus (anterior insula), and middle frontal gyrus (DLPFC). We report complementary analysis with ROIs defined from the automated anatomical labelling (AAL) atlas (43) in the Supplement, which was layed down in the original study protocol. The analysis brought overall consistent results (Supplementary Material 2).

For the hypothesis-test, we used the mean percent signal change of all voxels within each ROI. We did not correct for multiple comparisons where we had a-priori hypotheses about treatment effects. First-level GLM results were converted into %BOLD signal change values and initially characterised at the group level as the 90th
percentile value per participant within pre-specified ROIs (Supplement, Figure S1). To
test for the effect of Citalopram versus Placebo we derived p-values based on
permutation analyses. Specifically, we compared the average within-participant
difference between compounds (Citalopram - Placebo) with a distribution of
randomized within-participant differences. The effect of compound was deemed
significant if the true compound difference was smaller than 5% of the randomly
calculated differences. Random differences were obtained by within-participant
compound randomization, randomly re-assigning the compound to the two sessions and
calculating the difference score. This was repeated 10,000 times per participant,
yielding a distribution of 10,000 average differences across participants which was used
to assess the significance of the true difference (alpha=p<0.05). Complementary voxel-
wise analysis within ROIs was conducted using FWE-correction with Small Volume
Correction in accordance with the original study protocol (Supplementary Material 2).

To follow up the results, we explored whether the neural response to Citalopram
would correlate with baseline symptom severity (i.e., BSL-23 score).

Analysis of ASL data is reported in the Supplement section 3.

3 Results

3.1 Psychometrics and Behavior

Mood was assessed before patients entered the scanner and showed no difference
between treatment conditions (Supplement, Table S2). During the task, participants
identified picture content with high accuracy, confirming that they paid attention to the
stimuli (Supplement, Table S3). We did not observe any significant differences in response accuracy between treatments in the scenes task (difference per condition [M±SD]: AC, 0.60±6.92, P=0.64; NC, 1.59±4.25, P=0.99) and in the faces task (AC, -0.29±3.75, P=0.36; NC 1.45±5.19, P=0.90, Supplement Figure S2). Response times did not significantly differ between treatments in the scenes-task (AC, -1.66±209.05, P=0.48; NC, -49.59±179.99, P=0.10). While response times in the faces-task did not differ significantly between treatments in the face-picture condition (AC, -24.06±103.70, P=0.14), we observed an unexpected difference in the scrambled-picture condition (NC, -53.16±130.24, P<0.05, Supplement Figure S3).

3.2 Functional neuroimaging

Whole-brain analyses of activated voxels showed robust activation in all four ROIs in the scenes-task (Supplement, Figure S4 for illustration). In the faces-task, we observed activation of the amygdala and the DLPFC, too, while no activation was observed in the insula and the ACC (Supplement, Figure S5).

Testing our hypothesis that a single dose of 20 mg Citalopram as compared to Placebo results in changes in brain activity during both fMRI tasks, we observed no Citalopram-related effects on brain responses in the first task presenting affective scenes (Figure 2, Table 2A). However, the amygdala response in the second task using face-stimuli (AC), as compared to scrambled images (NC), was reduced in the Citalopram condition, evidenced by a significant difference between treatments (Figure 3, Table 2B). No significant differences between Citalopram versus Placebo treatment were detected for the other ROIs. Explorative whole-brain analyses of Citalopram versus Placebo treatment did not show any significant voxels or voxel clusters with family-wise error correction. Additionally, correlations between BPD symptom severity at...
baseline and neural response were consistently negative, although modest and not significant (Supplement, Table S4). Finally, we did not find differences between Citalopram and Placebo treatment in blood perfusion as assessed with ASL (Supplement, Figure S6, Table S5).

4 Discussion

A single dose of Citalopram vs. Placebo reduced the amygdala response to emotional faces as compared to scrambled images in individuals diagnosed with BPD. Neural modulation by the compound was restricted to the amygdala, whereas Citalopram did not significantly affect other ROIs involved in emotion and emotion regulation. Differently than expected, we did not find reduced neural response to affective scenes (primary endpoint), and we did not observe altered amygdala blood perfusion at rest. These findings partially corroborate immediate alteration of limbic responding by Citalopram as reported previously (23–26). For the first time, we could demonstrate that this effect extends to BPD. The significant effects are limited to analyses of secondary endpoints, though, and require corroboration by future studies to proof robustness. Citalopram did not influence behavioral decisions about picture content and results indicate that patients followed the task instructions and paid attention to the stimuli. Citalopram reduced the amygdala response to affective images, thus targeting a neural phenotype of the disorder (9,10,12,44). The drug did not significantly affect current mood, although it is possible that downregulation of the amygdala reflected more subtle attenuation of affective response, which was not accessible via
introspection. The study was not designed to detect potential effects of Citalopram on BPD symptoms.

We found reduced amygdala response to faces with negative affective expression, but not in response to pictures with scenes of negative affective content. Most previous Citalopram phfMRI studies used face stimuli to probe modulation of affective response (see references below). We selected neural responses to scene images as primary endpoint, because this type of stimuli, like face stimuli, was also widely applied in BPD-fMRI work(2). It is interesting that we did not observe similar Citalopram effects with two frequently used affective stimulation paradigms from psychiatric neuroscience.

An unplanned follow-up analysis was done to elucidate potential influences from BPD symptom severity on the treatment response. Although not significant, across all a-priori ROIs, patients with higher symptom severity differentiated less between Citalopram and Placebo. Future investigations with larger sample sizes are necessary to study how parameters of interest such as symptom severity moderate the Citalopram response.

In comparison to the face stimuli, the scenes were more diverse and complex. Furthermore, six faces were presented during a trial, three seconds each, which was twice the number and duration of scene-images. That is, the frequency with which salient picture information changed was higher in the faces-task compared to the scenes-task. Descriptively, we found overall smaller effects for amygdala responses in the main effect for stimulus material (AC versus NC) when directly comparing the scenes-task vs. faces-task. Consequently, smaller effects within the scenes-task might have reduced the likelihood to detect differences between the Citalopram condition and the Placebo condition in the scenes-task.
On the other side, the finding that attenuation of the amygdala response was limited to emotional expressions may reflect a mediocre reliability of the Citalopram effect on neural responses (45). Indeed, a review of the literature raises doubts about the robustness of such effect. While the majority of studies in healthy samples reported attenuation of amygdala activation (23–26), one study found amygdala potentiation (46), and others found no significant Citalopram effect on the amygdala. However, comparison of methods used in previous phfMRI studies reveals considerable differences. For example, three studies investigated only men (23, 25, 46), one studied only women (45), and three other studies mixed sexes (24, 26, 47). Most tasks report a time difference from drug to task administration between one and three hours, while one study administered the task only 35 min after beginning of medication infusion (25).

Most studies used a crossover design like ours (23, 25, 45–47), but washout time ranged between a few days and four weeks, with high intersubject variability within a number of studies. Furthermore, some studies administered the task repeatedly before and after drug-administration and quantified response post-administration relative to pre-administration baseline (45, 46), while other designs look more like ours and administered the task only post-administration, without a pre-administration baseline.

Not all studies used placebo control (24) and only one other study reported double-blinding (46). Critically, methods for significance testing greatly differ between trials, and some studies assess response to different stimulus categories separately such as angry and fearful emotional expression, and in several ROIs, while they do not report control for type one error (23, 24, 26). In light of this, critical interpretation of our findings is demanded, because our study suffers from similar shortcomings, given the number of statistical tests conducted for two tasks and several ROIs. The literature can gain from future trials who also preregister their hypothesis and analysis plan.
We used ASL to compare absolute blood perfusion after Citalopram vs. Placebo treatment and did not find significant differences. This finding is in accordance with a previous study in healthy participants (48). The ASL sequence was acquired to quantify overall perfusion in absence of an ongoing task. Of note, the goal of this was to investigate the effect of Citalopram on perfusion in the amygdala and not to investigate the effect of Citalopram on perfusion during task performance.

Due to our sample composition, conclusions are limited to female participants only. Furthermore, the small sample size precluded detection of small/moderate effects of Citalopram.

In conclusion, Citalopram can immediately act on amygdala processing of emotion in BPD, but corroboration by future studies is needed.
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Disclosures

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Figure legends

Figure 1. Flowchart

Figure 2. The statistical comparison between Citalopram and Placebo of brain responses to affective scenes was not significant. N=23. Boxplots cover the lower to the upper quartile. The notches indicate 95% intervals and the median is displayed as the waist. The Whiskers mark minimum and maximum values. The mean value of the right and left lateral region of interest is shown. ACC=anterior cingulate cortex, DLPFC=dorsolateral prefrontal cortex, IFG=inferior frontal gyrus.

Figure 3. Compound effect on BOLD response to affective faces. Citalopram reduced the amygdala response to face pictures. N=25. Boxplots cover the lower to the upper quartile. The notches indicate 95% intervals and the median is displayed as the waist. The Whiskers mark minimum and maximum values. The mean value of the right and left lateral region of interest is shown. ACC=anterior cingulate cortex, DLPFC=dorsolateral prefrontal cortex, IFG=inferior frontal gyrus.
# Tables

| Characteristic (at baseline)               | Citalopram to Placebo (n=15) | Placebo to Citalopram (n=15) | Total (n=30)     |
|-------------------------------------------|-----------------------------|------------------------------|-----------------|
| Age (years)                               | 28.53 ± 7.74                | 33.40 ± 7.28                 | 30.97 ± 7.78    |
| Number of BPD-DSM-5 criteria              | 5.53 ± 0.83                 | 5.87 ± 0.92                  | 5.70 ± 0.88     |
| MADRS                                     | 15.47 ± 7.99                | 14.53 ± 6.70                 | 15.00 ± 7.26    |
| ZAN-BPD                                   | 10.40 ± 4.52                | 12.47 ± 3.50                 | 11.43 ± 4.11    |
| BDI                                       | 21.20 ± 8.65                | 24.33 ± 11.65                | 22.77 ± 10.21   |
| BAI                                       | 20.53 ± 8.88                | 15.47 ± 8.84                 | 18.00 ± 9.08    |
| BSL-23                                    | 33.53 ± 15.45               | 34.33 ± 18.96                | 33.93 ± 17.00   |

*Psychiatric comorbidity – lifetime/ongoing*

|                      | Citalopram to Placebo (n=15) | Placebo to Citalopram (n=15) | Total (n=30)     |
|----------------------|------------------------------|------------------------------|-----------------|
| Major Depression     | 9/9                          | 12/12                        | 21/21           |
| Dysthymia            | 1/1                          | 1/1                          | 2/2             |
| Double Depression    | 0/0                          | 1/1                          | 1/1             |
| Panic Disorder       | 2/0                          | 0/0                          | 2/0             |
| Social Phobia        | 2/2                          | 3/2                          | 5/4             |
| Specific Phobia      | 2/1                          | 0/0                          | 2/1             |
| PTBS                 | 4/2                          | 7/6                          | 11/8            |
| Anorexia Nervosa     | 2/0                          | 5/1                          | 7/1             |
| Bulimia Nervosa      | 3/3                          | 5/2                          | 8/5             |
| Binge Eating Disorder| 0/0                          | 0/0                          | 0/0             |
| other                | 12/4                         | 8/6                          | 20/10           |

Table 1. Baseline demographic and clinical characteristics by sequence and by total (M±SD).
### Table 2. Comparison of brain response to A) scene pictures vs. scrambled pictures (primary endpoint) and B) face pictures vs. scrambled pictures (secondary endpoint).

|                  | Citalopram | Placebo | Treatment difference | P  |
|------------------|------------|---------|----------------------|----|
| **Scenes task**  |            |         |                      |    |
| N=23             |            |         |                      |    |
| Amygdala         | left       | 0.17 ± 0.10 | 0.16 ± 0.14 | 0.02 ± 0.16 | 0.71 |
|                  | right      | 0.17 ± 0.10 | 0.18 ± 0.14 | 0.01 ± 0.16 | 0.59 |
|                  | left       | 0.06 ± 0.11 | 0.03 ± 0.11 | 0.03 ± 0.16 | 0.80 |
|                  | right      | 0.05 ± 0.14 | 0.04 ± 0.12 | 0.02 ± 0.18 | 0.68 |
| ACC              | left       | 0.21 ± 0.13 | 0.20 ± 0.18 | 0.03 ± 0.16 | 0.82 |
|                  | right      | 0.17 ± 0.17 | 0.16 ± 0.17 | 0.03 ± 0.22 | 0.70 |
| A insula         | left       | 0.19 ± 0.11 | 0.155 ± 0.154 | 0.04 ± 0.18 | 0.82 |
|                  | right      | 0.22 ± 0.19 | 0.20 ± 0.20 | 0.04 ± 0.24 | 0.77 |
| DLPFC            | left       | 0.19 ± 0.11 | 0.23 ± 0.15 | -0.06 ± 0.16 | 0.03 |
|                  | right      | 0.19 ± 0.12 | 0.26 ± 0.14 | -0.06 ± 0.17 | 0.04 |
|                  | left       | -0.01 ± 0.08 | -0.03 ± 0.07 | 0.02 ± 0.11 | 0.74 |
|                  | right      | 0.00 ± 0.09 | -0.02 ± 0.10 | 0.00 ± 0.14 | 0.53 |
|                  | left       | 0.08 ± 0.14 | 0.10 ± 0.13 | -0.01 ± 0.20 | 0.38 |
|                  | right      | 0.11 ± 0.10 | 0.12 ± 0.13 | -0.02 ± 0.18 | 0.26 |
|                  | left       | 0.04 ± 0.11 | 0.04 ± 0.13 | 0.00 ± 0.17 | 0.51 |
|                  | right      | 0.12 ± 0.16 | 0.11 ± 0.20 | -0.01 ± 0.23 | 0.44 |

Percent signal change is reported per region of interest (M±SD). Statistically significant results (P<0.05) are marked with an ansterisk. ACC=anterior cingulate cortex, A insula=anterior insula, DLPFC=dorsolateral prefrontal cortex.
Within-participant between-session difference in mean % BOLD Signal Change in Task ROIs for Faces > Scrambled

ACC

Amygdala

Anterior Insula

DLPFC
Enrollment
Assessed for eligibility (n=209)

Randomized (n=30)

Allocation
Allocated to sequence Citalopram to Placebo (n=15)
15 Received Citalopram

Dropped out (n=1): 1 Lack of compliance

14 Received Placebo

Period 1

Allocated to sequence Placebo to Citalopram (n=15)
15 Received Placebo

Dropped out (n=1): 1 Lack of compliance

14 Received Citalopram

Period 2

Analysis
Analyzed (scenes task n=10, faces-task n=12):
2 Excluded from both tasks:
1 Heavy BOLD-signal drop-out
1 Data loss
2 Excluded from scenes-task: Superthreshold motion

Analyzed (scenes-task n=13, faces-task n=13):
1 Excluded from both tasks:
Heavy BOLD-signal drop-out
1 Excluded from scenes-task: Protocol violation

Excluded (n=179)
111 Not meeting inclusion criteria
37 Change in medication not possible
17 No time
17 Age > 45 years
8 Left-handedness
6 BMI range outside 18-35
6 Pregnant or breast-feeding
6 Patient canceled first visit
3 Claustrophobia
3 Remitted
3 Physical illness
3 Other MRI exclusion criteria met
1 Substance use within past year
1 Ability for informed consent questionable
32 Not interested to participate
29 Expressed interest at first call, but were not anymore reached
7 Other reason
Within-participant between-session difference in mean % BOLD Signal Change in Task ROIs for Scenes > Scrambled