

Single-Dose Effects of Citalopram on Neural Responses to Affective Stimuli in Borderline Personality Disorder: A Randomized Clinical Trial

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ABSTRACT

BACKGROUND: Psychiatric medication that has a soothing effect on 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 versus placebo reduces the response of the affective neural circuitry during an emotional challenge.

METHODS: A total of 30 female individuals with a 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 oxygen 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 , $p < .05$; right hemisphere: -0.06 ± 0.17 , $p < .05$). 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.

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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 the dorsolateral prefrontal cortex (DLPFC) characterize neural emotion processing in BPD (2). Individuals with BPD often use damaging self-regulation strategies such as nonsuicidal 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, and dorsal anterior cingulate cortex (ACC), as well as prefrontal areas as promising neural targets for the treatment of emotion dysregulation in BPD (7). Treatment of choice for this disorder is psychotherapy (8), and clinical trials have found decreased response 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. At present, there is a lack of evidence 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-hydroxyindoleacetic acid in cerebrospinal fluid (13,14) and to blunted response to fenfluramine challenge (15–17). Likewise, the 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 to support this choice are lacking (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 a small amount of evidence exists, and trials with citalopram are currently missing from the literature.

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 disorders, citalopram could act on 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 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) compared with 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 end points of efficacy were the BOLD responses induced by affective stimuli in the amygdala, DLPFC, anterior insula, and ACC. We defined responses to pictures showing negative scenes as primary end points, whereas responses to faces with emotional expressions were defined as secondary end points.

METHODS AND MATERIALS

Sample

A total of 30 female right-handed individuals were enrolled in this study, recruited via our department's database and in our clinical department (Table 1). Inclusion criteria were a diagnosis of BPD according to DSM-IV (27), age between 18 and 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 before study, positive alcohol or drug test, consumption of large amounts of caffeinated drinks, and any contraindications to participate in an MRI study (see section 1 in Supplement 1 for full list of eligibility criteria). Individuals who passed inclusion assessments were invited for the first MRI scan 1 week later. They received financial reimbursement (€200) for participation.

From the 30 participants randomized to the trial, MRI data from 23 could be analyzed to test our hypotheses in the scenes task, and 25 could be analyzed for the faces task. Arterial spin labeling (ASL) data from 21 individuals could be used in the final analysis. For details on participant flow according to CONSORT (Consolidated Standards of Reporting Trials) guidelines (28), see Figure 1. The CONSORT checklist is provided in Supplement 1. When asked about previous exposure to SSRIs, 8 participants confirmed experience with citalopram and 2 of them reported mild adverse events such as restlessness, sleep problems, and nausea. Of the 3 participants who had taken escitalopram, 2 reported mild adverse events such as sleep problems, nausea, and gastrointestinal complaints. Seventeen participants reported no exposure to SSRIs at all. Data were missing for 2 participants.

General Procedure

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 (29). Two clinical interviews were conducted to assess depression severity (Montgomery-Åsberg Depression Rating Scale) (30)

Table 1. Baseline Demographic and Clinical Characteristics by Sequence and by Total

Characteristic (at Baseline)	Treatment Sequence		Total, N = 30
	Citalopram to Placebo, n = 15	Placebo to Citalopram, n = 15	
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			
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
Posttraumatic stress disorder	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

Values are presented as mean ± SD or n/n.

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BPD, borderline personality disorder; BSL-23, Borderline Symptom List-23; MADRS, Montgomery-Åsberg Depression Rating Scale; ZAN, Zanarini Rating Scale.

Single-Dose Effect of Citalopram on Neural Responses

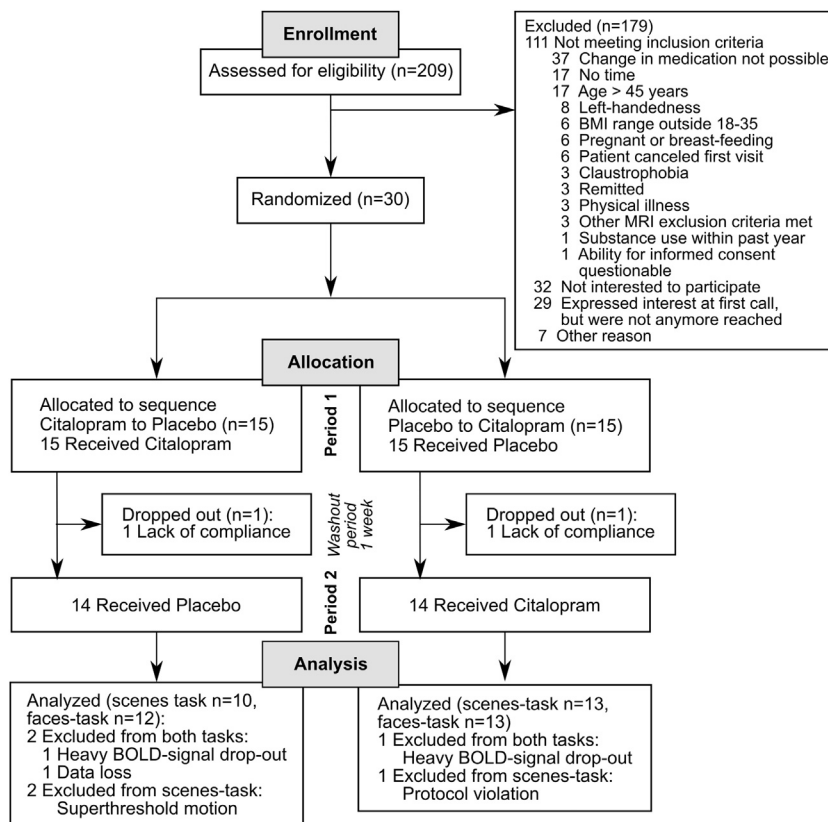


Figure 1. Flowchart. BMI, body mass index; BOLD, blood oxygen level-dependent; MRI, magnetic resonance imaging.

and severity of borderline personality disorder (Zanarini Rating Scale for 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-II (32), anxiety was assessed with the Beck Anxiety Inventory (33), and borderline symptoms were assessed with the Borderline Symptom List-23 (34).

Because of the within-subjects design, there were two treatment visits: visit 2 (day 7) and visit 3 (day 14). At one visit, placebo was administered. At the other visit, participants received verum (20 mg citalopram, single dose) within a double-blind, randomized, crossover design. The subjects were administered the study medication orally (20 mg of citalopram or placebo). After a waiting period of 3 hours, participants were asked to report current mood with the Positive and Negative Affect Schedule (35). Afterward, they participated in the fMRI experiment.

Adverse events were reported rarely; headaches were reported most often ($n = 11$) and with similar frequency in both treatment arms (Table S1 in Supplement 1).

fMRI Experiment

The two tasks were administered in a fixed order, as introduced below, and were presented with Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA) via a 40-inch

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.

Faces Task. Participants viewed faces with emotional expressions [disgust, sadness, and fear were chosen based on meta-analyses (36)] from the Warsaw Set of Emotional Facial Expression Pictures (<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 for 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 response in BPD to not only emotional expressions but also 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 intertrial interval was jittered to 9, 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 the color of the bounding box around scrambled faces was blue or green (NC).

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 the 14 blocks, lasting 18 seconds, three picture stimuli were presented for 6 seconds each, resulting in a set of 42 negative pictures in total. Because of 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 9, 10, or 11 s), 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).

Neuroimaging Parameters. Brain images were acquired using a 3T 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 = 2000 ms, echo time = 30 ms, flip angle = 80°, voxel size = $3 \times 3 \times 3$ mm, matrix = 64×64 , number of slices = 36, field of view = $192 \times 92 \times 143$ mm). The field of view used for scanning included the whole brain for all participants. This was achieved by rotating the bounding box relative to anterior commissure–posterior commissure as recommended in Mennes *et al.* (40). Echo time was minimized using a parallel acquisition technique (generalized autocalibrating partially parallel acquisitions) with an acceleration factor of 2 and 24 reference lines. Slices were tilted -16° from anterior commissure–posterior commissure orientation. Perfusion imaging was done afterward. Anatomy was imaged with a 3D T1-weighted scan (magnetization prepared rapid acquisition gradient-echo sequence, echo time = 3.03 ms, repetition time = 2.3 s, 192 slices, field of view = $256 \times 256 \times 192$ mm, voxel size = $1 \times 1 \times 1$ mm). ASL imaging parameters are reported in section 3 in Supplement 1.

Data Analysis

BOLD Imaging. All imaging preprocessing and first-level analyses were carried out using FEAT Version 6.00, part of FSL (www.fmrib.ox.ac.uk/fsl) (41). The following preprocessing steps were performed: volume realignment to correct for participant head motion, B0 unwarping using fieldmap data to correct for echo-planar imaging distortions, grand-mean scaling, and spatial smoothing with a 5-mm full width at half maximum 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 cutoff 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 nonlinear steps as implemented in FSL FNIRT. Data were screened for quality and excluded from further analysis in case of superthreshold movement during a scan (>4 mm, $n = 2$ 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 tasks separately. For each task, we included two regressors, respectively, modeling the onset times of the faces/scenes (AC) and scrambled stimuli (NC), convolved with a double-gamma hemodynamic response function. 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 SPM12 software (Wellcome Department of Cognitive Neurology, London, United Kingdom).

Regions of interest (ROIs) were localized by intersecting the AC > NC (faces task and scenes task) activation maps derived from a 15-participant prestudy (S. Grimm, Ph.D., *et al.* unpublished data, March 2019) with substructures of the Harvard-Oxford atlas 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, paracingulate gyrus (ACC), inferior frontal gyrus (anterior insula), and middle frontal gyrus (DLPFC). We report complementary analysis with ROIs defined from the automated anatomical labeling atlas (43) in Supplement 1, which was laid down in the original study protocol (Supplement 2). The analysis brought overall consistent results.

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 general linear model results were converted into percent BOLD signal change values and initially characterized at the group level as the 90th percentile value per participant within prespecified ROIs (Figure S1 in Supplement 1). 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 a 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 reassigning 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 ($\alpha = p < .05$). Complementary voxelwise analysis within ROIs was conducted using familywise error correction with small volume correction in accordance with the original study protocol (Supplement 2).

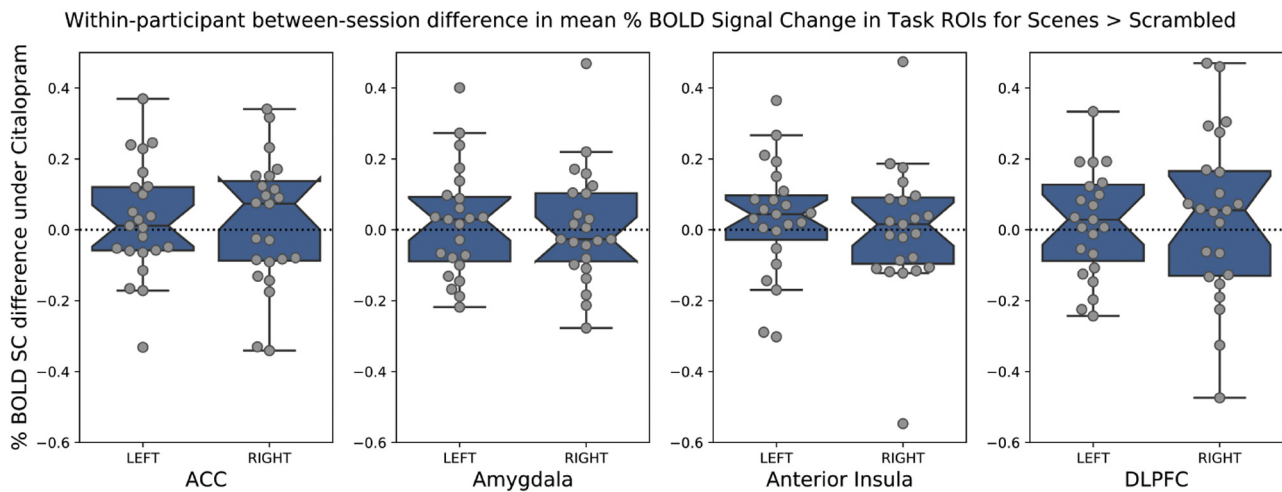


Figure 2. The statistical comparison between citalopram and placebo of brain responses to affective scenes was not significant. $n = 23$. Boxplots cover the lower to the upper quartile. The notches indicate 95% intervals, and the median is displayed as the waist. The whiskers mark minimum and maximum values. The mean value of the right and left lateral region of interest (ROI) is shown. ACC, anterior cingulate cortex; BOLD, blood oxygen level-dependent; DLPFC, dorsolateral prefrontal cortex; SC, signal change.

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

Analysis of ASL data is reported in section 3 in [Supplement 1](#).

RESULTS

Psychometrics and Behavior

Mood was assessed before patients entered the scanner and showed no difference between treatment conditions ([Table S2](#) in [Supplement 1](#)). During the task, participants identified picture content with high accuracy, confirming that they paid attention to the stimuli ([Table S3](#) in [Supplement 1](#)). We did not observe any significant differences in response accuracy between treatments in the scenes task (difference per condition [mean \pm SD]: AC, 0.60 ± 6.92 , $p = .64$; NC, 1.59 ± 4.25 , $p = .99$) and in the faces task (AC, -0.29 ± 3.75 , $p = .36$; NC, 1.45 ± 5.19 , $p = .90$) ([Figure S2](#) in [Supplement 1](#)). Response times did not significantly differ between treatments in the scenes task (AC, -1.66 ± 209.05 , $p = .48$; NC, -49.59 ± 179.99 , $p = .10$). While response times in the faces task did not differ significantly between treatments in the face picture condition (AC, -24.06 ± 103.70 , $p = .14$), we observed an unexpected difference in the scrambled picture condition (NC, -53.16 ± 130.24 , $p < .05$) ([Figure S3](#) in [Supplement 1](#)).

Functional Neuroimaging

Whole-brain analyses of activated voxels showed robust activation in all four ROIs in the scenes task (see [Figure S4](#) in [Supplement 1](#)). In the faces task, we observed activation of the amygdala and the DLPFC, whereas no activation was observed in the insula and the ACC ([Figure S5](#) in [Supplement 1](#)).

Testing our hypothesis that a single dose of 20 mg citalopram as compared with placebo results in changes in brain activity during both fMRI tasks, we observed no

citalopram-related effects on brain responses in the scenes task ([Figure 2](#) and [Table 2](#)). However, the amygdala response to faces (AC), as compared to scrambled faces (NC), was reduced in the citalopram condition, evidenced by a significant difference between treatments ([Figure 3](#) and [Table 2](#)). No significant differences between citalopram and 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 familywise error correction. In addition, correlations between BPD symptom severity at baseline and neural response were consistently negative, although modest and not significant ([Table S4](#) in [Supplement 1](#)). Finally, we did not find differences between citalopram and placebo treatment in blood perfusion as assessed with ASL ([Figure S6](#) and [Table S5](#) in [Supplement 1](#)).

DISCUSSION

A single dose of citalopram versus placebo reduced the amygdala response to emotional faces as compared with 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. Different than expected, we did not find reduced neural response to affective scenes (primary end point), 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 end points, however, and require corroboration by future studies to prove 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.

Table 2. Comparison of Brain Response to Scene Pictures vs. Scrambled Pictures (Primary End Point) and Face Pictures vs. Scrambled Pictures (Secondary End Point)

Brain Region		Citalopram	Placebo	Treatment Difference	p Value
Scenes Task, <i>n</i> = 23					
Amygdala	Left	0.17 ± 0.10	0.16 ± 0.14	0.02 ± 0.16	.71
	Right	0.17 ± 0.10	0.18 ± 0.14	0.01 ± 0.16	.59
ACC	Left	0.06 ± 0.11	0.03 ± 0.11	0.03 ± 0.16	.80
	Right	0.05 ± 0.14	0.04 ± 0.12	0.02 ± 0.18	.68
Anterior Insula	Left	0.21 ± 0.13	0.20 ± 0.18	0.03 ± 0.16	.82
	Right	0.17 ± 0.17	0.16 ± 0.17	0.03 ± 0.22	.70
DLPFC	Left	0.19 ± 0.11	0.16 ± 0.15	0.04 ± 0.18	.82
	Right	0.22 ± 0.19	0.20 ± 0.20	0.04 ± 0.24	.77
Faces Task, <i>n</i> = 25					
Amygdala	Left	0.16 ± 0.11	0.23 ± 0.15	−0.06 ± 0.16	.03 ^a
	Right	0.19 ± 0.12	0.26 ± 0.14	−0.06 ± 0.17	.04 ^a
ACC	Left	−0.01 ± 0.08	−0.03 ± 0.07	0.02 ± 0.11	.74
	Right	0.00 ± 0.09	−0.02 ± 0.10	0.00 ± 0.14	.53
Anterior Insula	Left	0.08 ± 0.14	0.10 ± 0.13	−0.01 ± 0.20	.38
	Right	0.11 ± 0.10	0.12 ± 0.13	−0.02 ± 0.18	.26
DLPFC	Left	0.04 ± 0.11	0.04 ± 0.13	0.00 ± 0.17	.51
	Right	0.12 ± 0.16	0.11 ± 0.20	−0.01 ± 0.23	.44

Percent signal change is reported per region of interest (mean ± SD).
ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

^aStatistically significant results (*p* < .05).

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 pharmacological fMRI studies used face stimuli to probe modulation of affective response [see (23–26,45,46)]. We selected neural responses to scene images as the primary end point because this type of stimuli, similar to face stimuli, was also widely applied in BPD fMRI work (2). It is interesting

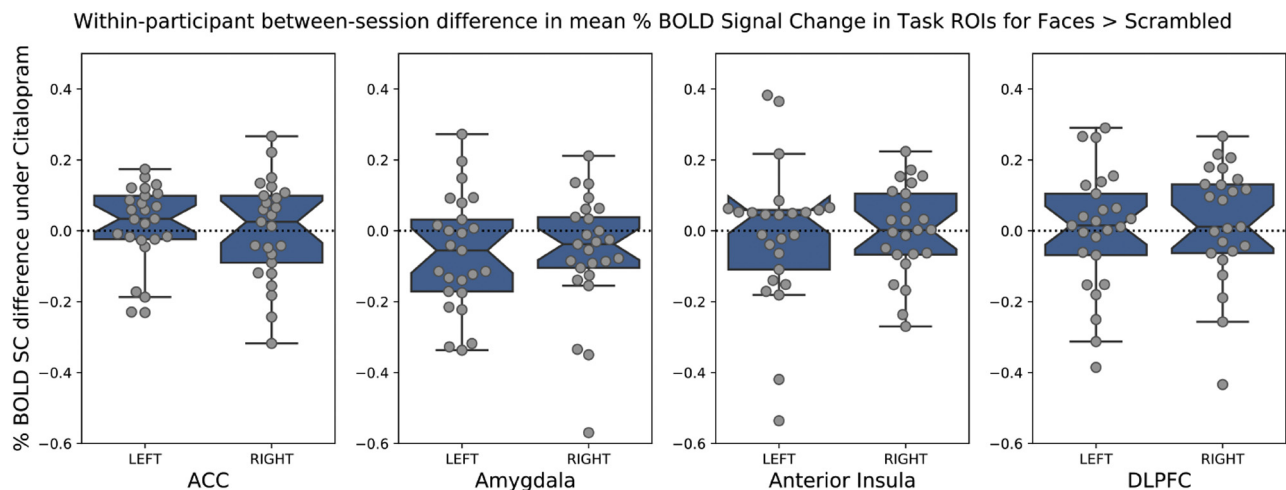


Figure 3. Citalopram reduced the amygdala response to face pictures. *n* = 25. Boxplots cover the lower to the upper quartile. The notches indicate 95% intervals, and the median is displayed as the waist. The whiskers mark minimum and maximum values. The mean value of the right and left lateral regions of interest (ROIs) is shown. ACC, anterior cingulate cortex; BOLD, blood oxygen–level dependent; DLPFC, dorsolateral prefrontal cortex; SC, signal change.

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, 3 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 than in the scenes task. Descriptively, we found overall smaller effects for amygdala responses in the main effect for stimulus material (AC vs. NC) when directly comparing the scenes task versus 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.

In contrast, 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 pharmacological fMRI 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 1 and 3 hours, while one study administered the task only 35 minutes after the beginning of medication infusion (25). Most studies used a crossover design similar to ours (23,25,45–47), but washout time ranged between a few days and 4 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 postadministration relative to preadministration baseline (45,46), while other designs look more like ours and administered the task only postadministration, without a preadministration 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 I 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 that also preregister their hypothesis and analysis plan.

We used ASL to compare absolute blood perfusion after citalopram versus 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 the absence of an ongoing task. Of note, the goal of this study 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.

Because of 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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EU Clinical Trials Register: A Trial to Study Effects of a Single Dose Citalopram on Emotion Processing in Female Patients With Borderline Personality Disorder and the Associated Modulation of fMRI BOLD Signals; <https://www.clinicaltrialsregister.eu/ctr-search/trial/2018-001212-30/DE>; 2018-001212-30.

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