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Research paper

Brain activation and connectivity after 2–3 weeks of escitalopram administration in anxiety disorders: A randomised trial

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ABSTRACT

Despite the extensive use of selective serotonin reuptake inhibitors (SSRIs) for anxiety treatment worldwide, their neural mechanism of action remains poorly understood. Based on a systematic line of experimental medicine studies from our laboratory, we posited that SSRI-mediated anxiolysis may be driven by a sustained reduction in positive coupling between the dorsomedial cortex and amygdala in anxious individuals. We conducted a randomised, double-blind, placebo-controlled study investigating amygdala-dorsomedial cortex activation and connectivity during emotion processing after 2–3-week SSRI administration in anxious individuals (ANX) compared to healthy controls (HC). The baseline analysis included 96 HC and 45 ANX participants. The follow-up analysis included 86 HC (placebo $n = 40$, 73 % female, SSRI $n = 46$, 74 % female) and 42 ANX participants (placebo $n = 22$, 86 % female, SSRI $n = 20$, 80 % female). Consistent with predictions, 2–3 weeks of escitalopram administration altered bilateral amygdala connectivity with the dorsomedial cortex during emotional face processing in people with anxiety disorders compared to healthy controls. However, the effect was in the *opposite direction* to predicted – positive coupling *increased* following SSRI in the patient group (right amygdala: ANX-SSRI vs HC-SSRI $t = 2.4$, $p = 0.02$; left amygdala: ANX-SSRI vs HC-SSRI $t = 2.6$, $p = 0.01$). A follow-up sensitivity analysis confirmed this to be a bilateral effect. These findings suggest that our simple hypothesis of SSRIs inducing a reduction in amygdala-dorsomedial cortex connectivity is incorrect, and the associated brain connectivity may instead increase in the initial weeks of drug administration.

The study is registered as a clinical trial at https://www.clinicaltrials.gov. Its clinical trial name is: 'The Effect of SSRIs on Threat of Shock Potentiated Neural Circuitry', number: NCT07074652, URL: https://www.clinicaltrials.gov/study/NCT07074652.

1. Introduction

Anxiety disorders are one of the most prevalent mental health conditions (Kessler et al., 2005), affecting approximately 300 million individuals worldwide (Institute of Health Metrics and Evaluation, n.d.). The first-line pharmacological treatments for anxiety disorders are

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selective serotonin reuptake inhibitors (SSRIs) (National Institute for Health and Care Excellence, 2020). Despite extensive use worldwide, their neural mechanism of action remains poorly understood (Carlisi and Robinson, 2018).

Robust evidence indicates that the amygdala (Brühl et al., 2014a; Chavanne and Robinson, 2021; Etkin and Wager, 2007; Freitas-Ferrari et al., 2010; Gentili et al., 2016; Hattingh et al., 2012; Ipser et al., 2013) and dorsomedial cortices (Carlisi and Robinson, 2018; Goossen et al., 2019; Kalisch and Gerlicher, 2014; McTeague et al., 2020; Mochcovitch et al., 2014) are involved in anxiety disorder pathophysiology. Given heavy projections between the amygdala and dorsomedial cortex, the connectivity between the dorsomedial cortex and the amygdala is thought to play a key role in generating anxiety symptoms (Hiser and Koenigs, 2018; Joyce and Barbas, 2018). Accordingly, we have previously found increased positive coupling between the dorsomedial cortex and amygdala during the processing of fearful but not happy faces, 1) following induced anxiety in healthy controls (Robinson et al., 2012) and 2) at baseline in people with anxiety disorders (Robinson et al., 2014). Moreover, consistent with observations that serotonergic function in the amygdala and dorsomedial cortex is important for anxiety expression (Bocchio et al., 2016) and aversive processing (Duerler et al., 2022; Garcia-Garcia and Soiza-Reilly, 2019), we found that when serotonin was (putatively) *decreased* in healthy controls using acute tryptophan depletion, this positive coupling *increased* relative to placebo (Robinson et al., 2013). Accordingly, acute tryptophan depletion was found to attenuate the bias towards positively valenced stimuli characteristic of healthy controls (Roiser et al., 2007), resembling the bias towards negative stimuli in anxiety disorders (Carlisi and Robinson, 2018). Thus, we hypothesised that increased serotonin in patients following SSRI administration should serve to reverse this effect and *decrease* positive coupling between the dorsomedial cortex and amygdala in patients (Carlisi and Robinson, 2018).

However, evidence from human neuroimaging studies investigating the effect of SSRI administration on the amygdala-dorsomedial frontal circuit in anxiety disorders has been inconsistent and limited. Studies focusing on amygdala activation have shown increases (Giménez et al., 2014), decreases (Faria et al., 2012; Phan et al., 2013), or no change (Liebscher et al., 2016; Schneier et al., 2011) in local activation after prolonged SSRI treatment. To our knowledge, only one study to date has explicitly reported dorsomedial cortex activation in anxiety after SSRI treatment, and found that dorsal anterior cingulate cortex activity predicted adjunctive SSRI treatment response (Frick et al., 2018). As such, more research on changes in activation of the amygdala and dorsomedial cortex in anxiety disorders is warranted. Critically, no studies to date have explored the effect of SSRI treatment on amygdala-dorsomedial coupling as a circuit. We therefore set out to conduct a new neuroimaging study of 2–3-week SSRI administration in the largest sample to date, focusing on the amygdala-dorsomedial cortex circuit recruitment during emotional face processing. Regarding connectivity, we predicted that there would be a significant main effect of group (ANX/HC) on bilateral amygdala and dorsomedial cortex activation across time points, whereby 1) at baseline, the ANX group would show elevated amygdala-dorsomedial cortex positive connectivity relative to healthy controls (alongside increased amygdala and dorsomedial cortex activation) during the viewing of fearful as opposed to happy or neutral faces, and that 2) at follow-up, the ANX group would show a reduction in amygdala-dorsomedial cortex positive connectivity and activity as compared to healthy controls during the viewing of fearful as opposed to happy or neutral faces. Regarding activation, we predicted that there would be a significant main effect of group (ANX/HC) on bilateral amygdala and dorsomedial cortex activation across time points, whereby 1) at baseline, bilateral amygdala and dorsomedial cortex activation will be higher in the ANX group than in the HCs during the viewing of fearful as opposed to happy or neutral faces, and that 2) at follow-up, the ANX group with show a reduction in bilateral amygdala and dorsomedial cortex activation after SSRI administration compared to placebo during the viewing of fearful as opposed to happy or neutral faces.

2. Methods and materials

The study was approved by the UCL Research Ethics Committee (6198/002). After data collection, the analysis plans were pre-registered at https://osf.io/5pdvh). The healthy control sample had been analysed and reported separately elsewhere (Lukow et al., 2024).

2.1. Participants

Forty-seven participants meeting criteria for anxiety disorders (ANX) and 98 healthy controls (HC) were recruited from the general population through public advertisement between December 2017 and June 2022, until drug expiry (note that patient recruitment was negatively affected by the COVID-19 pandemic). Two HC participants were excluded from both baseline and follow-up analyses: one due to excessive movement at baseline, and one due to a technical issue with the recording of task parameters during fMRI acquisition at the baseline visit. Ten HC participants were excluded from the follow-up analyses due to either withdrawal from the study before the follow-up visit (medication side effects ($n = 4$), personal reasons ($n = 2$), misadministration of the medication ($n = 1$)), a technical issue with the recording of task parameters ($n = 1$), or excessive motion ($n = 2$). Two ANX participants were excluded from the baseline analysis due to incomplete data and data not passing motion criteria (see *fMRI acquisition, pre-processing, exclusions and subject-level modelling* below). Three ANX participants were excluded at follow-up additionally to those who did not complete the follow-up session: two due to withdrawal from the study (medication side effects ($n = 1$), scanner discomfort ($n = 1$)) and excessive motion ($n = 1$). All participants were between 18 and 50 years old, fluent in English, registered with a GP and able to provide written informed consent. None reported having consumed alcohol within 12 h prior to the study, used illicit drugs within 3 months prior to study participation, had any contraindications to MRI scanning, were pregnant or breastfeeding, or had impaired or uncorrected vision or hearing. Additional inclusion criteria for the HC group were no personal history of long-term medical conditions or psychiatric illness (including substance dependence; assessed with the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998)), and had no family history of mood disorder, including panic disorder. All ANX participants met criteria for generalised anxiety disorder, panic disorder and/or agoraphobia (also assessed with the MINI); permitted comorbid conditions were: major depressive disorder, obsessive-compulsive disorder and/or post-traumatic stress disorder. All participants provided informed written consent according to the Declaration of Helsinki ("World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects", 2013)] and were advised that they may withdraw from the study at any point without giving a reason.

2.2. Study procedures and medication

This was a randomised, between-subject, double-blind study. After an initial clinical assessment visit (at the Institute of Cognitive Neuroscience, Alexandra House, 17–19 Queen Square, WC1N 3AZ), participants underwent an fMRI scanning visit, before and after taking either 10 mg escitalopram or placebo in the form of a tablet matched in colour and size, manufactured and donated for research by Lundbeck (tablet core: microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, talc, magnesium stearate; tablet coating: hypromellose 6 cP, titanium dioxide (E171), macrogol 6000). The randomisation to drug arms was performed by an independent researcher before participant recruitment by pre-generating a list of group allocations with a random number generator. Participants were instructed to take one tablet per day, around the same time each day,

with or without food. At the scanning visit, participants performed an emotional face processing task during an fMRI acquisition. The task comprised of alternating blocks of happy, fearful and neutral faces, counterbalanced for sex (Fig. 1). Note that this emotional face task was chosen over the task previously used in our experimental medicine studies (e.g., Robinson et al., 2012) because we showed it to have considerably better test-retest reliability (Nord et al., 2019) whilst also measuring brain function during emotion processing, a phenomenon central to anxiety disorder pathophysiology (Mathews and MacLeod, 2005). There were twelve blocks in total, four of each valence. Participants were instructed to label the gender of each face. No participant performed worse than chance (50 % or more wrong answers).

2.3. fMRI acquisition, pre-processing, exclusions and subject-level modelling

fMRI data were acquired on a 1.5 T Siemens Avanto scanner at the Birkbeck-UCL Centre for Neuroimaging, 26 Bedford Way, London WC1H 0AP. The data was then pre-processed using fMRIPrep version 20.2.7 (Esteban et al., 2018). As a part of the pipeline, the data underwent slice time correction, motion correction, field map-based distortion correction, co-registration and normalisation. fMRIPrep output was subjected to visual quality assessment involving the inspection of the anatomical image segmentation, normalisation of the anatomical image to the MNI152 template, field map correction of the fMRI series and the co-registration of the fMRI series onto the anatomical T1 image. Then, three initial volumes were removed to avoid including data potentially compromised by the initial period of magnetic field stabilisation within the scanner. Any volumes acquired after task end due to manual EPI acquisition stop were also removed. Subsequently, AFNI's *3dBlurToFWHM*, *3dTstat* and *3dcalc* were used for fMRI series smoothing (Gaussian kernel: 6 mm FWHM) and grand mean scaling (Chen et al., 2017) within an MNI space-specific grey matter mask. Whole scans were excluded if more than 20 % of their volumes exceeded framewise displacement of 1.3 mm. Details of within-subject model estimation for the activation and connectivity analyses can be found in our previous publication (Lukow et al., 2024) and in the Supplement.

2.4. Group-level brain activation and connectivity analyses

All brain activation and connectivity analyses were performed twice with two different approaches: 1) once in R 4.4.1 using average activation/connectivity parameters extracted from each ROI (activation: right amygdala, left amygdala, dorsomedial cortex, sgACC, rFFA; connectivity with the dorsomedial cortex: right amygdala, left amygdala, sgACC), and 2) once in AFNI, using the 3D brain activation maps. Baseline analyses were performed with an ANCOVA and follow-up analyses with mixed-effects models. The ROI masks were a) anatomical masks defined through the PickAtlas (Nord et al., 2019, 2017) for, respectively, the right and left amygdala, b) a custom anatomical mask for the sgACC, generated based on probabilistic maps of distinct cyto- and receptor-architectonic features of this region (Nord et al., 2019, 2017) c) a custom mask of a dorsomedial region of interest (referred to hereafter as the dorsal ROI), based on a functional cluster resulting from a threat of shock task analysis in a previous study (Nord et al., 2019) and d) a custom anatomical mask of the rFFA (Nord et al., 2019). ROI masks can be found in the Supplement. In the baseline analyses, group (levels: control/patient), age and sex were entered as between-subject factors (age and sex being covariates of no interest), and emotion as the within-subject factor (levels: happy/fear/neutral). In the follow-up analyses, emotion, group and drug were entered as factors, and the baseline activation/connectivity parameters were entered as an additional covariate of no interest. The mixed-effects approach allowed us to test for the main effect of drug, group and emotion while accounting for a) the crossed nature of the emotion factor (which had three levels at both follow-up and baseline), and b) to accurately test the effect of group and drug on brain activation at follow-up by including baseline as a covariate, which was shown to present the largest power to test treatment effects in randomised paradigms (Assmann et al., 2000; Vickers, 2001). In any analyses containing a within-subject factor (emotion), age was mean-centred prior to analysis.

The baseline analyses in R were performed with the *anova_test()* function from the *rstatix* package (https://cran.r-project.org/web/packages/rstatix/index.html). Any analyses containing within-subject factors included an error term accounting for repeated measures of the emotion factor within subjects. For these analyses, the Greenhouse-Geisser-corrected *p*-value is reported if the sphericity assumption was violated (indicated as p_{GG}); if the assumption was not violated, uncorrected p-value is reported. The follow-up analyses in R were performed with the *lmer()* function from the *lme4* package and the *anova()* function from the *lmerTest* package, to use mixed-effects models and estimate the p-value. Any post-hoc pairwise comparisons were performed with the *pairwise_t_test()* function from the *rstatix* package. For these analyses, the Holm multiple comparison correction was performed if more than one pairwise comparison was required; such *p*-values are clearly indicated as p_{Holm}. Exploratory correlation analyses of GAD-7 scores and follow-up connectivity parameters were performed with the *cor.stat()* function from the *stats* package.

The baseline analyses in AFNI were performed with the *3dMVM* function, whereas the follow-up analyses were performed with the *3dLMEr* function. Statistical thresholding and clustering were performed by: 1) estimating the smoothness of the residuals of the statistical map resulting from *3dMVM* or *3dLMEr*, 2) based on this smoothness, estimating the minimum cluster size with *3dClustSim*, 3) thresholding the statistical map appropriately with *3dClusterize*. In all analyses the statistical threshold applied was the recommended $p = 0.001$ (Colquhoun, 2014) and the cluster threshold extent was estimated for $\alpha = 0.05$ (one-tailed for the F or Chi-square tests, two-tailed for any relevant post-hoc *t*-tests). Result visualisation was performed in AFNI using the recommended approach of highlighting results passing the pre-defined threshold by making them opaque and outlined with a black line, but also presenting sub-threshold results, with opacity decreasing with the statistical significance level (Taylor et al., 2023).

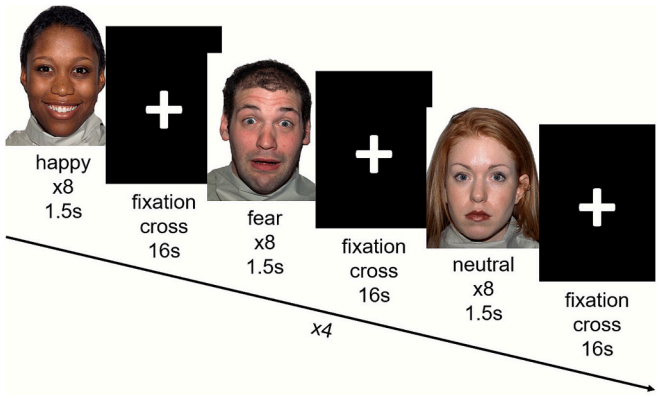

Fig. 1. Schematic of the emotional face processing task. Participants viewed blocks of happy, fearful and neutral faces, separated by a fixation cross. Participants were instructed to label the gender of the faces displayed via button press. There were twelve blocks of stimuli in total, and four of each emotion.

3. Results

3.1. Participants

From the initially recruited 98 HC and 47 ANX participants, 96 HC and 45 ANX participants were included in the baseline analysis. 86 HC participants were included in the follow-up analysis (placebo arm $n =$

40, days of placebo administration mean(SD) = 16.2(2.90) and escitalopram arm $n = 46$, days of escitalopram administration mean(SD) = 15.7(2.70). 42 ANX participants were included in the follow-up analysis (placebo arm $n = 22$, days of placebo administration mean(SD) = 18.6 (12.9) and escitalopram arm $n = 20$, days of escitalopram administration mean(SD) = 14.6(4.1)). Participants taking escitalopram had a shorter average inter-scan interval than the participants taking placebo ($F = 4.0$, $p = 0.048$). The study sample's clinical and demographic information at follow-up is summarized in Table 1, and the information at baseline is summarized in Table S1.

3.1.1. Symptom effects

At time two (controlling for baseline) there was no group*drug interaction in any symptom measures, but ANX participants had greater GAD-7 scores across the drug arms ($F = 7.7$, $p = 0.006$), and PHQ-9 scores were greater post-escitalopram compared to post-placebo across both groups ($F = 4.1$, $p = 0.046$; for more detail, see Supplementary Results).

3.2. Connectivity

We saw a predicted group by drug interaction in bilateral amygdala connectivity with the dorsal ROI at follow-up (right amygdala: $F = 4.2$, $p = 0.04$; left amygdala: $F = 4.7$, $p = 0.03$). However, counter to predictions, a group effect was not present at baseline, and the group by drug interaction at follow-up was driven by *increased* positive coupling between these regions in anxious individuals following escitalopram administration (relative to controls and placebo). Specifically, in both the right and left amygdala there was increased coupling following escitalopram in patients relative to controls (right amygdala: $t = 2.4$, $p = 0.02$; left amygdala: $t = 2.6$, $p = 0.01$) (Fig. 2A,B). In the right amygdala, this was associated with an increase in coupling relative to placebo in the patient group ($t = 2.3$, $p = 0.02$), whereas in the left amygdala this was associated with reduced coupling relative to placebo in the healthy control group ($t = -2.1$, $p = 0.03$) (Fig. 2A,B). A post-hoc combination analysis including both amygdala ROIs and a laterality factor revealed no laterality effect on the drug by group interaction ($F = 0.12$, $p = 0.73$). Of note, this combined post-hoc analysis also indicated that this interaction was driven by connectivity during happy face processing only (drug*group*emotion interaction: $F = 3.3$, $p = 0.037$; see Fig. 2C and the Supplement for full breakdown). Exploratory correlation analyses did not reveal associations between follow-up GAD-7 score and bilateral amygdala connectivity with the dorsal ROI (right amygdala: $r = 0.03$, $p = 0.76$; left amygdala: $r = 0.06$, $p = 0.53$).

Table 1
The study sample's clinical and demographic information after 2–3 weeks of escitalopram or placebo administration. ANX, anxious participants; BDI, The Beck Depression Inventory; GAD-7, Generalised Anxiety Disorder 7; HC, healthy controls; PHQ-9, The Patient Health Questionnaire 9; STAI-S and STAI-T, the State-Trait Anxiety Inventory (state and trait subscales); SD, standard deviation. Missing values were omitted from the comparisons (healthy controls: baseline BDI: 3 participants, baseline GAD-7, PHQ-9, STAI: 1 participant; follow-up BDI: 2 participants, baseline GAD-7, PHQ-9, STAI: 1 participant; anxious participants: baseline BDI: 1 participant).

	HC,ssri (n = 46)	HC,plac (n = 40)	ANX,ssri (*n* = 20)	ANX,plac (*n* = 22)
Sex (% female/male)	73.9/26.1	72.5/27.5	80/20	86.4/13.6
Age	22.9(6.6)	25.2(7.5)	28.3(10.3)	23.5(3.3)
BDI	3.4(4.6)	3.4(3.9)	17.7(10.3)	17.5(11.5)
GAD-7	3.2(4.4)	2.6(2.6)	8.8(5.5)	9.4(6.1)
PHQ-9	3.4(4)	2.1(2)	9.9(7.1)	8(5.5)
STAI-S	32.9(11.2)	32.2(7.9)	45.1(10.9)	50(12.9)
STAI-T	33.6(8)	34.2(7.4)	54.2(5.8)	54(11.3)
Inter-scan interval (days)	15.7(2.7)	16.2(2.9)	14.8(4.2)	18.8(13.2)

3.3. Activation

Contrary to our predictions, we saw no group effect on brain activation at baseline, and no group by drug interaction on brain activation at follow-up in any of our ROIs. However, at follow-up we did see a main effect of drug in the dorsal ROI (mixed-effects model, $F = 6.9$, $p = 0.01$) and sgACC (mixed-effects model, $F = 4.3$, $p = 0.04$), driven by greater activation following escitalopram across groups (dorsal ROI, placebo: mean(SD) = −0.03(0.06), escitalopram: mean(SD) = −0.008(0.07) (Fig. 3A); sgACC, placebo: mean(SD) = −0.04(0.07), escitalopram: mean(SD) = −0.02(0.07)). The same finding was present in the dorsal ROI in the voxel-wise ROI analyses (k = 8, xyz = 8,-37,46) (Fig. 3B), additionally to a main effect of group, with greater activation in the HC than in the ANX group (k = 12, xyz = 4,-27,30). This was not found for the bilateral amygdala or the rFFA (see Supplementary Results).

Additionally, we saw an effect of emotion at baseline on brain activation in the bilateral amygdala and the rFFA (right amygdala: $F = 7.6$, $p < 0.001$, ges = 0.027; left amygdala: $F = 6.26$, $p_{GG} = 0.003$, ges = 0.021; rFFA: $F = 3.76$, $p = 0.025$, ges = 0.008), whereby activation to fearful faces was stronger than to happy faces (right amygdala: $t = 3.0$, $p_{Holm} = 0.007$; left amygdala: $t = 3.1$ $p_{Holm} = 0.005$; rFFA: $t = 2.9$ $p_{Holm} = 0.008$) or neutral faces (right amygdala: $t = 4.7$ $p_{Holm} < 0.0001$; left amygdala: $t = 3.9$ $p_{Holm} = 0.0005$; rFFA: $t = 3.7$ $p_{Holm} = 0.0008$). This was also found in voxel-wise ROI analyses in AFNI (Fig. 3D, Supplementary Results). These effects did not interact with group or drug. All results are comprehensively described and visualized in the Supplementary Results.

4. Discussion

The primary finding from the present study is that 2–3 weeks of escitalopram administration increased bilateral amygdala connectivity with the dorsomedial cortex during emotional face processing in people with anxiety disorders. This was concomitant with an increase in activation in the dorsomedial cortex and the subgenual anterior cingulate cortex, across patients and controls, and was seen in the absence of a significant reduction in anxiety symptoms in either group or associations with anxiety symptoms.

Our primary finding is consistent with the hypothesis that the amygdala-dorsomedial cortex circuit is involved in SSRI treatment. However, contrary to predictions, we found that the connectivity between these regions *increased* in anxious individuals treated with escitalopram for 2–3 weeks. Furthermore, we did not find the expected group effect at baseline. Both findings are inconsistent with the simple hypothesis that elevated dorsomedial cortex coupling with the amygdala may induce amygdala hyperactivity, which would produce elevated anxiety symptoms in anxiety disorders (Carlisi and Robinson, 2018). Altogether, this suggests that while this circuit *is* involved in SSRI treatment, the underlying neural mechanisms may be different than proposed so far.

The lack of group differences in dorsomedial cortex-amygdala coupling at baseline may indicate that an alteration to this circuit is not a robust feature of anxiety disorders. This possibility is supported by the inconsistent results on amygdala-dorsomedial cortex coupling during emotion processing in anxiety disorders, where studies show both increased and decreased coupling in case-control studies (Böhnlein et al., 2021; Cui et al., 2022; Duval et al., 2020; Giménez et al., 2014; Kaldewaij et al., 2019; Reinecke et al., 2015; Robinson et al., 2014; Young et al., 2017). It is plausible that changes in amygdala-dorsomedial cortex coupling are therefore present in some but not all people with anxiety disorders, and may thus represent a non-generalizable feature of anxiety disorders. A larger sample size would be required to detect such inter-individual differences. Nevertheless, our finding of altered connectivity between these regions in anxiety disorders after SSRI administration suggests that this circuit *is* involved in SSRI treatment in this population. This is consistent with

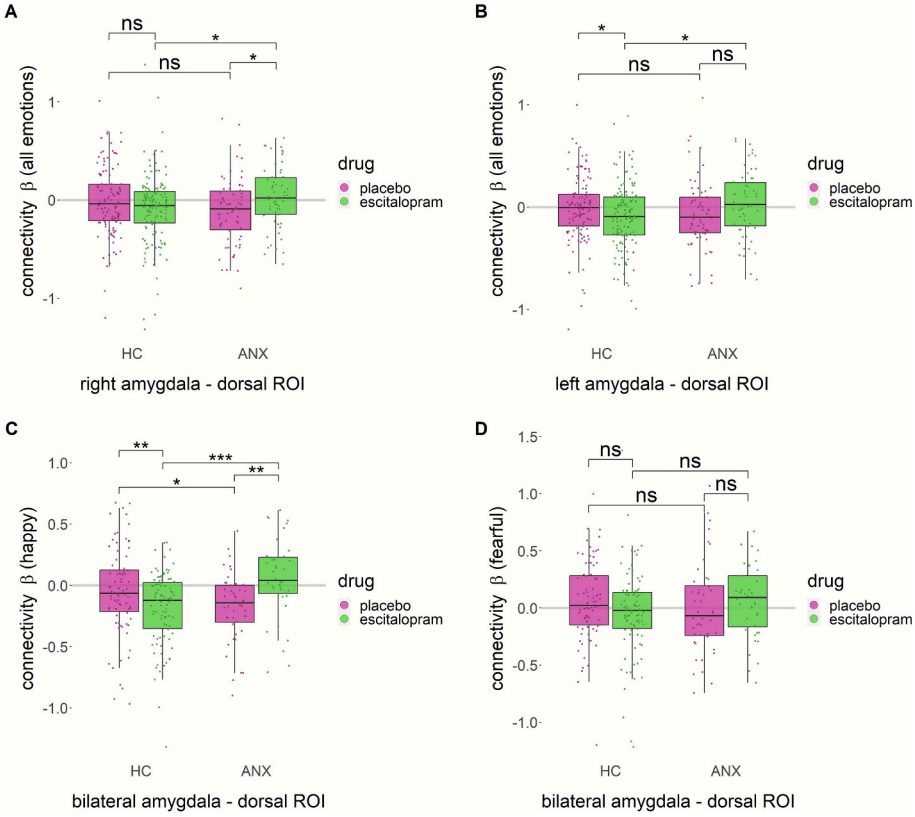

Fig. 2. Group by drug interaction in bilateral amygdala connectivity with the dorsal region of interest (ROI) at follow-up. Increased amygdala connectivity with the dorsal ROI after escitalopram administration in anxious individuals (ANX), relative to healthy controls (HC) in both the right (A) and left (B) amygdala. A *post hoc* combination of the above findings revealed no laterality effect and an additional interaction with emotion driven by increased bilateral amygdala connectivity during happy face processing with the dorsal ROI after escitalopram administration (C) but not fearful face processing (D). *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; ns, not significant.

electroencephalography studies suggesting reduced effective connectivity between cortical and subcortical structures in anxiety disorders (Al-Ezzi et al., 2020). However, it is plausible that the direction of the effect is dependent on task design. Of note, we used a different emotion processing task paradigm in this study relative to our prior experimental medicine studies (e.g., Robinson et al., 2012) because of its better test retest reliability (Nord et al., 2019). Its different type of design (block vs. event-related) may have inadvertently changed the task sensitivity or context. One possibility, therefore, is that the paradigm we used is more sensitive to detecting changes in amygdala-dorsomedial cortex connectivity driven by responses to *happy* rather than to fearful faces. This may have resulted from our relatively simple task paradigm (e.g., not including any anxiogenic or mnemonic manipulations) and the fact that happy faces are identified more accurately than other emotional expressions, especially if displayed briefly like in our paradigm (Calvo and Beltrán, 2013). There is evidence for this in the drug*group*emotion interaction seen in the *post-hoc* bilateral amygdala analysis, which suggests that the SSRI effect was driven by a selective *increase* in response to happy faces in patients. This would not necessarily contradict a reduction in the connectivity to fearful faces with the previously used task paradigm. SSRIs may serve to both reduce a bias towards negative/fearful information alongside increasing a bias towards positive/happy information, and both of these may be driven by a corresponding reduction or increase in amygdala-prefrontal connectivity depending on the stimulus. This is consistent with a previous study showing acute tryptophan depletion to attenuate the bias towards *positively* valenced stimuli in healthy controls (Roiser et al., 2007). Moreover, early change in positive face recognition has been associated with subsequent improvement in depression symptoms (Harmer et al., 2017). These findings are consistent with the model of SSRI action positing neural changes to precede symptom alleviation, with the psychological effects emerging as a result of the pharmacologically altered brain circuits interacting with the environment (Harmer et al., 2017). This may suggest time effects on emotional stimulus processing by SSRIs, whereby changes in positive stimulus processing may be more pronounced earlier in treatment course, and alterations in negative stimulus processing occur in later treatment. In other words, this circuit may serve as an 'amplification' mechanism that is used to augment negative or positive information processing, depending on the context and duration of treatment. A time-dependent shift in the balance towards amplifying positive information, and away from amplifying negative information, could lead to symptom improvement in patients.

Other sources of evidence also suggest that our surprising result may be caused by the duration of our treatment course. Different periods of SSRI administration have been shown to induce opposite behavioural and neural effects. For instance, SSRIs have been shown to increase serotonergic neurotransmission in the amygdala in rodents when given as a single acute dose, but to normalize it over prolonged administration (Bocchio et al., 2016; Burghardt and Bauer, 2013). Acute increases, but chronic decreases in anxiety expression over the course of SSRI administration have been shown both in rodents (Bocchio et al., 2016; Burghardt and Bauer, 2013; Ravinder et al., 2013) and humans (Grillon et al., 2009, 2007). This has also been observed clinically, whereby a short-term anxiety elevation is reported by some patients in the initial days of SSRI treatment ("Recommendations | Social anxiety disorder: recognition, assessment and treatment | Guidance | NICE", n.d.), before the eventual anxiolysis. Although we did not see a change in anxiety symptoms in the anxious group following treatment, it is plausible that our period of drug administration was too short and that escitalopram would eventually reduce the coupling and symptoms if we had provided

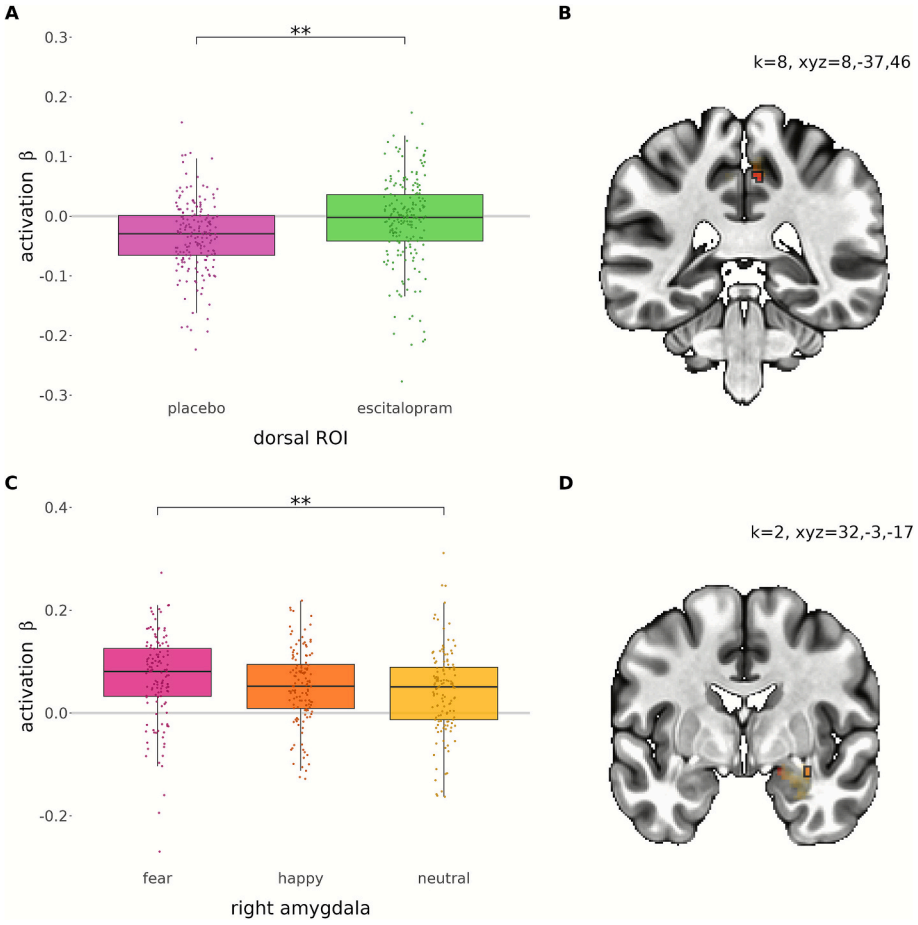

Fig. 3. Main effect of drug and emotion on brain activation during emotional face processing at follow-up. Main effect of drug in the dorsal region of interest (ROI), with greater activation after escitalopram than after placebo administration, assessed with activation parameters (A) and voxel-wise ROI analysis (B). Main effect of emotion in the right amygdala, with greater activation to fearful than to neutral faces assessed with activation parameters (C) and greater activation to fearful than to happy faces assessed with voxel-wise ROI analysis (D). Coordinates are indicated for the largest cluster. Activation clusters passing the pre-defined threshold ($p<0.001$) are indicated with a black outline; voxels not passing threshold are shown with opacity decreasing with the statistical significance level. **, $p < 0.001$.

our participants with a longer course of treatment. Prior work has shown that SSRI treatment with sertraline has an increasingly strong effect on GAD-7 reduction over time between the second and twelfth week of administration in a mixed population of anxiety disorders and depression (Lewis et al., 2019). Although limited, existing evidence suggests that treatment-induced GAD-7 score reductions are large after long-term treatment: the reported effect size was 3.0 after 10 weeks of treatment with sertraline in a small sample of generalised anxiety disorder patients (Christensen et al., 2014), and 1.12 after 48 weeks of any treatment in chronic depression (Hüsing et al., 2019). It is thus plausible that our sample size was not sufficient to detect a decrease in GAD-7 after 2–3 weeks of treatment duration, if the effect size of a reduction in GAD-7 scores was relatively small at this point of treatment. Alternatively, our participants may not have achieved anxiolysis due to an inherent characteristic of our sample. Help-seeking populations have been shown to differ in symptom profiles to community samples (Patel et al., 2022), and greater anxiety severity at baseline has been associated with worse outcomes of treatment with escitalopram (Khoo et al., 2022). However, our sample of anxious individuals had an approximate baseline average GAD-7 score of 13 out of the maximum 21. Thus, our sample would be expected to show a more pronounced improvement in anxiety than a more anxious (and presumably more help-seeking) sample. It is then more likely that our finding was associated with the time-course of drug administration rather than the sample's characteristics. Future, more longitudinal research would help determine the time course of symptom improvement with SSRI treatment and the putatively associated changes in amygdalocortical coupling.

Our second key finding was that dorsomedial and subgenual anterior cingulate cortex (sgACC) activation also increased following 2–3-week escitalopram administration across both patients and controls. This suggests that the reduction in amygdala activation observed after acute SSRI administration may not be sustained during the initial weeks of treatment (Murphy et al., 2009). It is possible that the increase in cortical activation is what drives a short-term increase in anxiety symptoms seen in some patients (Burghardt et al., 2004; Gollan et al., 2012; National Institute for Health and Care Excellence, 2020; Sinclair et al., 2009; Westenberg and Den Boer, 1989). Then again, changes in sgACC recruitment during facial emotion processing could indicate changes in social cognition (Hiser and Koenigs, 2018; Lockwood and Wittmann, 2018) or depressive symptom expression (Arnsten et al., 2023). Accordingly, we saw both sgACC activation increase and an elevation in PHQ-9 scores in participants exposed to escitalopram. Interestingly, we did not see concomitant changes in amygdala activation after escitalopram treatment compared to placebo. It is possible that the SSRI's therapeutic effect is manifested in this task context predominantly through modulation of amygdala connectivity with the cortex, rather than its activation. Alternatively, our sample of anxious individuals may have not been big enough to detect such an effect in this group, since the severe delays in recruitment due to the COVID-19 pandemic reduced the sample size we had initially planned for. For

instance, this resulted in power of 36 % in the right amygdala HC vs ANX comparison after SSRI treatment (estimated post-hoc with G*Power 3.1.9.7 (Erdfelder et al., 2009). Suboptimal sample sizes may have contributed to the inconsistency of results in previous studies of the effects of SSRI administration on brain activation in healthy volunteers (Arce et al., 2008; Harmer et al., 2006; Henry et al., 2013; Maron et al., 2016; McCabe et al., 2010; Norbury et al., 2009; Windischberger et al., 2010). The issue may be compounded by the heterogeneity of clinical samples, which often comprise participants with different diagnoses, which have been shown to present non-identical brain activation patterns (Brühl et al., 2014b; Fonzo and Etkin, 2017; Freitas-Ferrari et al., 2010; Gentili et al., 2016; Goossen et al., 2019; Hattingh et al., 2012; Hilbert et al., 2014; Mochcovitch et al., 2014). This may have also affected our results, as our inclusion criteria permitted a range of anxiety disorders, and comorbid depression and OCD. However, we did not have the power to estimate these potential effects. Further research using larger and more homogeneous samples is required to elucidate these questions.

This study had several strengths and some limitations. Firstly, we employed both a region-wide analysis method (using extracted average activation and connectivity parameters) and a voxel-wise method (in AFNI), allowing us to identify whether our results were generalizable to a whole region of interest or localized to its specific area. Secondly, although we included a larger number of participants than previous studies, due to the COVID-19 pandemic (and associated restrictions in clinical testing), our patient sample was smaller than our healthy control sample, which may have limited our power to detect effects. It is of note that patient recruitment was negatively affected by the COVID-19 pandemic. Finally, our patient sample was recruited from the community rather than directly from mental health services, which may have resulted in the selection of participants with a different symptom profile than help-seeking individuals. It was recently shown that treatment effects of internet-delivered cognitive behavioural therapy may be greater in community samples than in clinical populations (Romijn et al., 2019). Moreover, it was reported that specific symptom profiles may be associated with help-seeking (Patel et al., 2022). Although our study maintained strict clinical criteria through the use of the MINI, the results need to be corroborated in a more explicitly help-seeking sample. This may have interacted with the previously observed lower levels of anxiety in fMRI research participants relative to people taking part in behavioural-only studies (Charpentier et al., 2021). While this may have yielded a lack of group differences, it is noteworthy that there was a significant difference in anxiety symptoms between the groups at baseline. Although it is possible that symptom differences were eventually seen in our samples beyond our trial time (2–3 weeks), unfortunately we did not obtain data from a follow-up period.

In conclusion, we found, counter to our predictions, that 2–3 weeks of SSRI administration may induce an *increase* in amygdala connectivity with the dorsomedial cortex specific to people with anxiety disorders, and an elevation in cortical activation during emotion processing across both healthy individuals and those with anxiety. This indicates that our simple hypothesis of SSRIs inducing a reduction in amygdala-dorsomedial cortex connectivity is incorrect, and the associated brain connectivity may instead increase in the initial weeks of drug administration.

CRediT authorship contribution statement

Paulina B. Lukow: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Millie Lowther:** Writing – review & editing, Project administration, Investigation, Data curation. **Alexandra C. Pike:** Writing – review & editing, Investigation. **Yumeya Yamamori:** Writing – review & editing, Investigation. **Alice V. Chavanne:** Writing – review & editing, Investigation. **Siobhan Gormley:** Writing – review & editing, Investigation. **Jessica Aylward:** Writing – review & editing, Investigation. **Carlos Escalante Vera:** Writing – review & editing, Investigation. **Tayla McCloud:** Writing – review & editing, Investigation. **Talya Goble:** Writing – review & editing, Investigation. **Julia Rodriguez-Sanchez:** Writing – review & editing, Investigation. **Ella W. Tuominen:** Writing – review & editing, Investigation. **Sarah K. Buehler:** Writing – review & editing, Data curation. **Peter Kirk:** Writing – review & editing, Validation. **Oliver J. Robinson:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Oliver J Robinson reports financial support was provided by Medical Research Council. Oliver J Robinson reports equipment, drugs, or supplies were provided by Lundbeck LLC. Oliver J Robinson reports a relationship with Medical Research Council and Roche that includes: funding grants. Alexandra C Pike reports a relationship with Medical Research Council and Roche that includes: travel reimbursement. Oliver J Robinson reports a relationship with PEAK that includes: consulting or advisory. Oliver J Robinson reports a relationship with IESO Digital Health that includes: consulting or advisory. Oliver J Robinson reports a relationship with Roche that includes: consulting or advisory. Oliver J Robinson reports a relationship with Blackthorn Therapeutics Inc. that includes: consulting or advisory. Alexandra C Pike reports a relationship with Wellcome Trust that includes: funding grants. Alexandra C Pike reports a relationship with Academy of Medical Sciences that includes: funding grants. Tayla McCloud reports a relationship with Wellcome Trust that includes: employment. OJR sat on the committee of the British Association for Psychopharmacology until 2022. ACP sits on the Council for the British Association for Psychopharmacology. The other authors declare no competing interests. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2025.120682.

Data availability

The neuroimaging datasets generated and/or analyzed during the

current study are not publicly available due to the protection of participant anonymity but are available from the corresponding author on reasonable request.

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