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Effects of Escitalopram Administration on Face Processing in Intermittent Explosive Disorder: An fMRI Study

Henk Cremers*[,1], Royce Lee[1], Sarah Keedy[1], K Luan Phan[2] and Emil Coccaro[1]

[1]Biological Science Division, Department of Psychiatry, University of Chicago, Chicago, IL, USA; [2]Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

The neurobiological underpinnings of intermittent explosive disorder (IED) are traditionally linked to deficiencies in the serotonergic system. In this study, we investigated the effects of escitalopram, a selective serotonin reuptake inhibitor (SSRI), on brain activation during face processing. We expected that escitalopram would reduce amygdala activity in IED and in addition, we explored the effect in other social–emotional-related brain regions. A total of 17 subjects with current IED and 14 healthy controls participated in a randomized, double-blind, placebo-controlled, counterbalanced fMRI face processing study. The analysis focused on the faces compared to a fixation baseline contrast, and a factorial model with *Group* as between-subject and *Drug* as within-subject factor was tested. *Group* × *Drug* interaction effects were found in the amygdala (small volume corrected) and the left temporal parietal junction (TPJ; whole-brain corrected). Escitalopram increased amygdala activation in controls, but surprisingly not in IED. However, the TPJ showed increased activity in IED on escitalopram compared with placebo. The TPJ is associated with social–cognitive processes, such as perspective taking and empathy. The TPJ findings suggest that SSRI administration may reduce aggressive tendencies towards other people by enhancing these social–cognitive processes. Future research should further elucidate the long-term effects of SSRIs on various social–emotional tasks in IED.

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INTRODUCTION

Intermittent explosive disorder (IED) is characterized by the expression of recurrent, problematic impulsive aggressive behavior (Coccaro, 2000). The degree of aggressiveness expressed during the episodes is grossly out of proportion to any precipitating psychosocial stress. IED affects 5–7% of the US population, and is often but not necessarily comorbid with mood, anxiety, substance use, and personality disorders (Coccaro, 2012).

The neurobiological underpinnings of aggression are traditionally linked to deficiencies in the serotonergic system (5-HT; Coccaro, 1989, 2000, 2012; Lesch and Merschdorf, 2000). For instance, a negative correlation between an indicator for 5-HT transporter binding and aggression was found in personality disorder patients with IED (Coccaro *et al*, 2010; Coccaro, 2012) and IED patients show reduced 5-HT transporter availability in the anterior cingulate cortex (Frankle *et al*, 2005). Moreover, males with IED tend to increase intensity ratings of angry faces after tryptophan depletion that *reduces* 5-HT availability (Lee *et al*, 2012). Conversely, fluoxetine (a selective serotonin reuptake inhibitor (SSRI) that *increases* 5-HT availability) was shown to reduce impulsive aggressive behavior in patients with personality disorders and comorbid IED (Coccaro *et al*, 2009). Two studies in other aggressive populations (Silva *et al*, 2010; George *et al*, 2011) replicated this finding. However, despite the evidence for the central role of 5-HT, it is unknown how SSRI administration affects the neural mechanism of IED.

In an fMRI study on face processing, Coccaro *et al* (2007) found a stronger amygdala response to angry faces in IED compared with controls, and a correlation between amygdala activation and a life history of aggression. Moreover, IED patients showed less amygdala–orbitofrontal cortex connectivity than controls, suggesting reduced regulatory control of the prefrontal cortex. Previous work already showed that IED patients make disadvantageous choices on the Iowa gambling task, hinting at the possibility of disrupted prefrontal functioning (Best *et al*, 2002). The limited available research on the neural systems underlying IED so far thus points at a disrupted amygdala–prefrontal circuitry, yet a complex disorder like IED undoubtedly involves an even broader network of brain regions. A study on multicomponent cognitive behavioral therapy, consisting of coping skill training and cognitive restructuring, showed effectiveness in reducing aggressive symptoms (McCloskey *et al*, 2008). Such finding hints at the possible underlying involvement of social–cognitive (eg, empathy) and regulatory processes and related brain networks in IED.

*Correspondence: Dr H Cremers, Department of Psychiatry, University of Chicago, MC 3077, 5841 South Maryland Avenue, L-602, Chicago, IL 60637, USA, Tel: +1 773 834 4645,
E-mail: hcremers@yoda.bsd.uchicago.edu
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In this study, we investigate the effects of escitalopram (an SSRI) on the neural mechanisms in IED when viewing faces. Research has mostly shown that, in controls, a single-dose or short-term administration of citalopram reduces amygdala activity (Del-Ben *et al*, 2005; Harmer *et al*, 2006; Anderson *et al*, 2007; Murphy *et al*, 2009; Windischberger *et al*, 2010), although increases have also been found (Bigos *et al*, 2008). We hypothesize that escitalopram will lower amygdala activity in IED. In addition, we explore the effects of escitalopram on other regions involved in social–emotional processing.

MATERIALS AND METHODS

Participants

A total of 31 subjects completed this study and were included in the analysis. All subjects were right-handed and had normal or corrected-to-normal vision. Groups were matched on age and gender (Table 1). In all, 17 subjects met DSM-5 criteria for current IED and 14 subjects met inclusion/exclusion criteria as a healthy control. Healthy controls had no current or past history of any psychiatric or personality disorder and none had a first-degree relative with documented history of any psychiatric disorder. Six other subjects were excluded from the analysis: three completed the first session only, one had a brain cyst, and two subjects had poor-quality fMRI data (excessive head motion or spikes, determined by visual inspection and with artifact detection software: www.nitrc.org/projects/artifact_detect). Subjects were recruited through advertisements in the community. All subjects gave written informed consent. The study was approved by our institutional review board.

Diagnostic Assessment

Diagnoses were made using information from: (1) the Structured Clinical Interview for DSM Diagnoses (SCID-IV; First *et al*, 1997) for syndromal disorders and the Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP; Pfohl *et al*, 1997); (2) clinical interview by a research psychiatrist; and (3) review of all other available clinical data. Final diagnoses were assigned by team best-estimate consensus procedures involving research psychiatrists and clinical psychologists as previously described (Coccaro *et al*, 2014). Subjects with a current history of a substance use disorder or of a life history of bipolar disorder, schizophrenia (or other psychotic disorder), or mental retardation were excluded from study. Medical health of all subjects was documented by medical history and examination, and urine screen for illicit drugs. Supplementary Table S1 lists the current and life-time comorbidity of all IED participants.

Assessment of Aggression, Impulsivity, and Psychopathic Personality

Aggression was assessed with the Aggression score from the Life History of Aggression (LHA; Coccaro *et al*, 1997) that assesses history of actual aggressive behavior. Impulsivity was assessed using the Life History of Impulsive Behavior (LHIB; Coccaro and Schmidt-Kaplan, 2012) that assesses history of actual impulsive behavior, and the Barratt Impulsiveness Scale (BIS-11; Barratt, 1965) that assesses impulsive tendencies as a personality trait. The Psychopathy Checklist Screening Version (PCL-SV; Hart *et al*, 1995) was used to assess for presence of Psychopathic Personality (PP) using a threshold of PCL-SV score ≥ 13.

Table 1 Participant Characteristics

	Controls mean (SD)	IED mean (SD)		
Characteristic			*T*	*P*
Age	36.07 (9.1)	32.53 (9.5)	1.0	0.3
Gender	8 M/6 F	10 M/7 F		
LHA–self	5.1 (3.0)	21.9 (6.6)	8.8	<0.001
LHA–clinical	3.8 (2.9)	23.8 (7.7)	9.1	<0.001
LHIB	16.28 (9.34)	51.05 (18.68)	6.3	<0.001
PCL_total	0.78 (0.69)	9.1 (5.9)	5.19	<0.001
BIS	51.7 (8.3)	69.5 (14.8)	3.90	<0.001

Abbreviations: BIS, Barratt Impulsivity Scale; LHA, Lifetime History of Aggression; LHIB, Lifetime History of Impulsive Behavior; PCL-SV, Psychopathy Checklist-Screening Version.

Study Design

A randomized, double-blind, placebo-controlled, counterbalanced design was used. Either placebo or escitalopram (0.375 mg/kg; typically $\sim$30 mg per subject) was administered orally 2 to 3 h before the MR scans. This timing was right after the time of peak neuroendocrine response to escitalopram and right before the time of peak plasma concentration of escitalopram. Participants verbally rated their mood state on a scale ranging from 0 (= not at all) to 9 (= extremely) for happy, angry, sad, fear, calm, and irritable. There was an interval of $\sim$1 to 2 weeks between scan sessions ($M = 12.1$ days, SEM = 1.9, range: 5–57 days).

The paradigm involved the explicit emotional valence recognition of facial expressions in a block-related fMRI design. Stimuli consisted of black and white photographs of human facial expressions from both the Penn Emotion Recognition task faces (Gur *et al*, 2002) and the Ekman faces (Ekman and Friesen, 1976). The task consisted of two functional runs, where each run included 14 blocks of 20 s duration. Within each run, blocks of different emotional expression were presented twice: angry (A), fearful (F), and neutral (N). One block consisted of pictures of a radio (as a visual control condition), and these blocks were interspersed with fixation-cross control blocks. Each block consisted of 5 trials of 1 face stimulus type (A, F, N) presented for 4 s each. Each stimulus was presented once. The face stimuli were counterbalanced for gender (male and female). Each set of face stimuli was randomly ordered within their respective blocks, and blocks were randomly ordered within each functional run as well as across the two functional runs. During the presentation of each face stimulus, subjects identified the valence (positive, negative, neutral) expressed on each face via right-hand button press.

Functional MRI Data Acquisition

The fMRI data were acquired using a Philips Achieva Quasar 3T MRI scanner at the Brain Research Imaging Center at the University of Chicago. A structural MRI was obtained with a T1-weighted gradient-echo sequence (301 sagittal slices, repetition time/TR = 7.1ms, echo time/TE = 3.4 ms; flip angle/FA = 8°, field of view/FOV = 250 × 250 mm, slice thickness = 0.6 mm). The fMRI images were obtained with high-field functional MRI utilizing T2*-weighted gradient-echo echo planar imaging (EPI) sensitive to the BOLD (blood oxygenation level dependent) signal (TE = 25 ms, TR = 2000 ms, FA = 80°, FOV = 230 × 230 mm, 30 4 mm axial slices approximately parallel to the AC–PC line, 0.5 mm slice gap).

Statistical Analysis

Behavioral and self-report data. Accuracy (percentage) and Reaction Time (ms) data were analyzed in a repeated-measure ANOVA, with group as between-subject and *Drug* (escitalopram/placebo) and *Emotion* (Anger/Fear/Neutral) as within-subject variables. Subjective mood ratings were analyzed separately per emotion (happy, angry, sad, fear, calm, and irritable) with the within-subject factors *Time* (before and after administration, +105 min) and *Drug* and between-subject factor *Group*.

Functional MRI

Preprocessing. The preprocessing started with skull stripping of the structural images using BET (Smith, 2002) and subsequent preprocessing was carried out in SPM8 (Wellcome Department of Cognitive Neurology, London; www.fil.ion.ucl.ac.uk/spm); the EPIs were realigned to correct for head motion, the structural image co-registered to the mean EPI image and segmented and normalized to MNI space, EPI images were normalized to the MNI space, and a Gaussian spatial smoothing kernel of 6 mm FWHM was applied.

Statistics. The subject-level statistical analyses were performed within the general linear model framework (Friston *et al*, 1994) implemented in SPM8. The preprocessed images were filtered using a 128-s high-pass filter. The regression model consisted of each stimulus type convolved with the canonical hemodynamic response function as well as six motion parameters to correct for residual motion effects. Statistical parametric maps (SPMs) were produced from linear contrasts of interest: each face category *versus* baseline (eg, angry > fixation) and all faces > fixation. We opted for this latter contrast to use in the group-level analyses for several reasons: (1) because of the application of high-pass filtering, condition (face expression)-specific effects are partly removed; (2) amygdala activation to the 'neutral' expressionless faces have been shown to also activate the amygdala to the same extent as emotional faces (Fitzgerald *et al*, 2006); and (3) IED subjects have been shown to mislabel 'neutral' faces as conveying negative emotions (Best *et al*, 2002).

To test whole-brain voxel-wise effects, a full-factorial model was set up in SPM. We investigated the overall effect of face processing (regardless of group or drug, using a voxel-wise FWE rate of $P<0.05$), main effect of *Group*, and main effect of *Drug* and *Group* × *Drug* interaction. The false positive rate for these tests was controlled by applying an initial cluster threshold of $P<0.001$, cluster size >10 voxels, and a cluster-level family-wise error (FWE) rate of $P<0.05$. Although the focus is on the 'all faces > baseline' contrast, in order to consider possible emotion-specific effects, the contrast estimates for each emotion separately were also extracted and included in a new model with *Emotion* as an additional within-subject factor, and reported when showing a significant interaction effect with *Group* and *Drug*. For the hypothesis regarding an interaction effect in the amygdala, an initial uncorrected $P<0.005$, cluster size >5 voxels was applied, as well as a small-volume, cluster-level FWE rate of $P<0.05$ (amygdala was defined using the Harvard-Oxford subcortical Atlas 70% probability for the amygdala, implemented in FSL; Smith *et al*, 2004).

Brain–behavioral correlations. Correlational analyses were performed to test whether parameter estimates of significant clusters for faces > baseline contrast (*Group* × *Drug* interaction) were linearly related to behavioral measures of aggression (LHA), psychopathy (PCL), and impulsivity (BIS-11 and LHIB).

Decoding analysis. In order to aid the interpretation of the whole-brain voxel-wise analysis, we applied a novel method to 'decode' significant clusters using Neurosynth (Yarkoni *et al*, 2011). This method essentially correlates an input image with reverse inference maps related to a topic (ie, a map of the probability per voxel of being active given a certain topic, cf. Chang *et al*, 2012). The analysis provides an automatic 'interpretation of the involvement' of an input image (for instance, a specific brain region or a contrast image of different conditions) in a certain a topic (eg, 'emotion'). The analysis was restricted to a set of 140 latent topics as presented in Poldrack *et al* (2012).

RESULTS

Self-Report Mood Ratings

The self-report showed that controls overall rated themselves as higher on happiness ($F(1,28)=13.8$, $P=0.001$) and calmness ($F(1,28)=7.4$, $P=0.011$) compared to IED, but not on any of the other emotions (all $P>0.15$). No significant *Group* × *Drug* × *Time* interaction effects were found (all $P>0.08$).

Behavioral Results

Accuracy during the emotion detection was high overall (>78%), and a significant main effect of *Emotion* was observed ($F(2,58)=4.45$, $P=0.016$; neutral (mean (SE), 78% (3.6%); fear, 87% (3.1%); anger, 84% (2.9%); both fear > neutral and fear > anger, $P<0.05$) but no other main or interaction effects were found (all $P>0.05$). Reaction time data showed a similar pattern: a significant main effect of *Emotion* ($F(2,56)=9.53$, $P=0.001$). Reaction times for neutral faces were higher than anger or fear (neutral, 1233 (33.0); fear, 1100.0 (43.4); anger, 1134.91 (39.3); both fear > neutral and anger > neutral, $P<0.01$). No other significant main or interaction effects were found.

Table 2 Whole-Brain Results for the Faces > Fixation Contrast

Cluster size (voxels)	Peak *T*-value	Peak *P*-value	FWE *P*-value	Coordinates *x*	*y*	*z*	
Overall							
12584	**17.96**	**<0.0001**	**<0.001**	**40**	**−46**	**−28**	**Occipital fusiform cortex**
136	**11.28**	**<0.0001**	**<0.001**	**−22**	**−32**	**−8**	**Left hippocampus**
1677	**10.79**	**<0.0001**	**<0.001**	**−52**	**30**	**10**	**Inferior frontal gyrus**
360	**10.57**	**<0.0001**	**<0.001**	**32**	**−10**	**−22**	**Right hippocampus/amygdala**
111	**9.89**	**<0.0001**	**<0.001**	**24**	**−30**	**−6**	**Right hippocampus**
533	**9.52**	**<0.0001**	**<0.001**	**56**	**32**	**10**	**Inferior frontal gyrus**
222	**8.31**	**<0.0001**	**<0.001**	**−18**	**−6**	**−16**	**Left amygdala**
63	**7.42**	**<0.0001**	**<0.001**	**6**	**58**	**18**	**Frontal pole**
89	**6.84**	**<0.0001**	**0.001**	**−10**	**26**	**62**	**Superior frontal gyrus**
16	**6.53**	**<0.0001**	**0.004**	**−2**	**−60**	**−42**	**Cerebellum**
14	**6.43**	**<0.0001**	**0.006**	**34**	**−10**	**−40**	**Temporal fusiform cortex**
15	**6.33**	**<0.0001**	**0.009**	**−4**	**54**	**30**	**Superior frontal gyrus**
Group							
		CON > IED					
44	4.01	0.00009	0.352	44	−64	32	Occipital gyrus
14	3.63	0.00030	0.995	−28	−64	46	Parietal cortex
17	3.61	0.00032	0.98	−44	46	10	Frontal pole
		IED > CON, no difference					
Drug							
		CIT > PLC					
63	4.18	0.00005	0.115	10	−82	−44	Cerebellum
34	4.13	0.00006	0.598	10	−52	−38	Cerebellum
10	3.59	0.00034	1	−26	56	−20	Frontal pole
		PLC > CIT, no difference					
Group × Drug							
37	4.31	0.00003	0.515	−22	−82	52	Occipital cortex
92	**4.29**	**0.00003**	**0.022**	**−48**	**−48**	**18**	**Temporal parietal junction**
29	4.17	0.00005	0.742	−60	24	14	Inferior frontal gyrus
46	4.13	0.00006	0.314	−4	−82	54	Occipital cortex
11	3.87	0.00014	0.99	12	0	16	Caudate
11	3.73	0.00022	0.99	−34	22	−24	Orbital frontal cortex
32	3.68	0.00026	0.655	−46	−60	18	Angular gyrus
11	3.46	0.00050	0.99	38	−40	−50	Cerebellum

Overall effect across the two groups and drugs conditions are FWE voxel-wise corrected $P<0.05$. For the main effect of *Group* (Controls > IED and IED > controls), *Drug* (CIT > PLC, and PLC > CIT), and *Group* × *Drug* Interaction, clusters that met a $P<0.001$ uncorrected, cluster size > 10 voxels criterion are presented for descriptive purposes, and clusters are printed in bold that met a whole-brain FWE cluster corrected $P<0.05$ threshold.

fMRI Results

Whole-brain analyses on the faces > baseline contrast showed a significant *main effect* in several well-known face processing regions: visual cortex, bilateral amygdala/hippocampus, superior temporal gyrus, and inferior frontal gyrus (see Table 2). No significant cluster-corrected effects of the factors *Group* or *Drug* were found (all $P<0.001$ uncorrected, *cluster size* > 10 voxels, results are reported in Table 2). The *Group* × *Drug* interaction test revealed an effect in the left temporal parietal junction (TPJ; see Figure 1). The decoding (Neurosynth) analysis showed that the two latent topics that are most strongly linked to the TPJ were related to 'social cognition' and 'moral beliefs' (see Supplementary Table S2 for the complete list of results). The region of interest analysis of the amygdala revealed a *Group* × *Drug* interaction

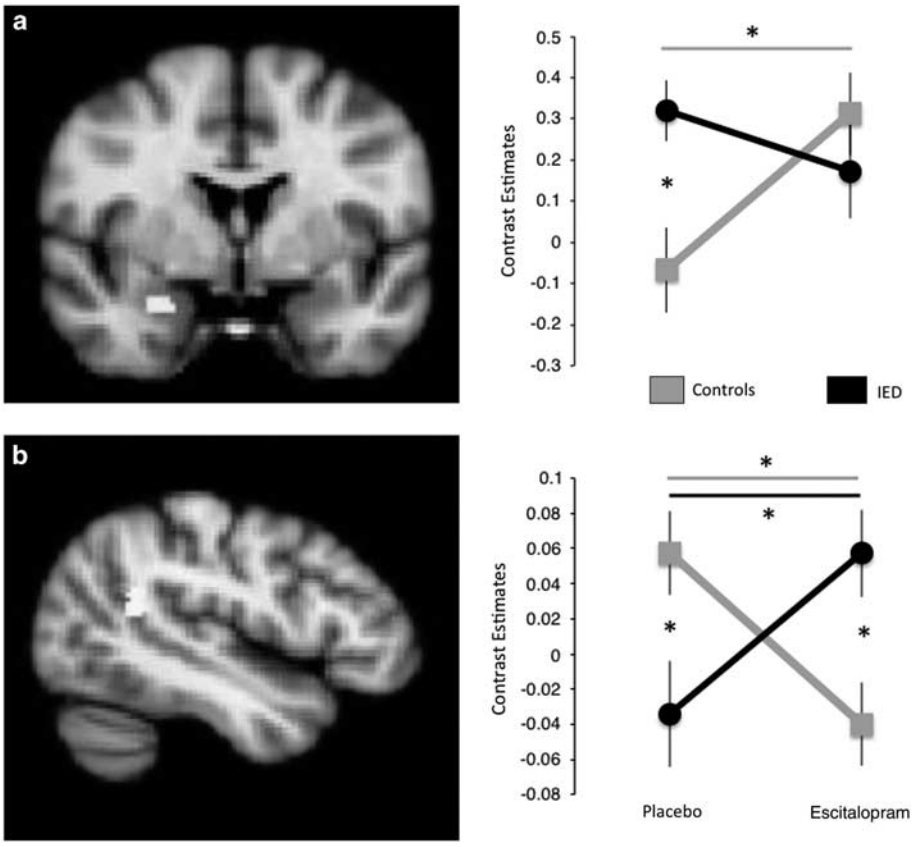

Figure 1 *Group* × *Drug* interaction effects. (a) Right amygdala, small volume corrected. (b) Left temporal parietal junction. Error bars are SEM (radiological convention; left is right, right is left). **Post hoc* pairwise *t*-test $P<0.05$ (between-group effect per drug condition, or within-group change because of drug condition).

effect, small-volume, cluster-level FWE $P<0.05$ (x, y, $z=30/0/-22$, *cluster size* = 20 voxels, $P_{unc}=0.001$). No significant correlations were observed between the amygdala or TPJ (contrast estimates for citalopram > placebo and placebo only) and behavioral measures of aggression, psychopathy, and impulsivity.

DISCUSSION

In this study, we investigated how a selective serotonin reuptake inhibitor, escitalopram, affects the neural mechanisms of social–emotional processing in IED. We found that escitalopram increased amygdala activity during social–emotional processing in controls, but surprisingly not in IED. In addition to the amygdala results, we also found a strong and intriguing effect in the TPJ: the IED group displayed increased activity on escitalopram (relative to placebo) compared with healthy controls. This finding is of great interest, as the TPJ is associated with social–cognitive processes, such as perspective taking and empathy (Van Overwalle and Baetens, 2009), and the decoding analysis confirmed the relatively specific involvement of the TPJ in such social–cognitive processes. Therefore, in addition to dysfunctional amygdala–prefrontal circuitry (Coccaro *et al*, 2007), our findings suggest that the TPJ is also a potentially important brain region involved in IED and escitalopram may reduce aggressive tendencies toward others in IED by enhancing social–cognitive processing, rather than affecting the primary salience response of the amygdala.

The amygdala is perhaps the most well-established region in face processing (Morris *et al*, 1998; Vuilleumier *et al*, 2001; Fusar-Poli *et al*, 2009) and a main target of dorsal raphe nucleus serotonergic projections (Maier *et al*, 2006; Asan *et al*, 2013). Previously, IED was found to be associated with a dysbalance in amygdala and OFC activity during threatening face processing (Coccaro *et al*, 2007). Contrary to our expectations, here we did not find evidence that citalopram decreases amygdala activation in IED. Moreover, although the results in controls (escitalopram increases amygdala activation) are in line with a prior report (Bigos *et al*, 2008), some studies did not observe an effect of citalopram on amygdala activity (Brühl *et al*, 2010; Henry *et al*, 2013) and several other single-dose and short-term citalopram administration studies found amygdala decreases (Del-Ben *et al*, 2005; Harmer *et al*, 2006; Anderson *et al*, 2007; Arce *et al*, 2008; Murphy *et al*, 2009; Windischberger *et al*, 2010). Although it is possible that our results in controls are perhaps due to sampling error (see Limitations section), several other methodological issues in citalopram administration studies also need to be considered. The citalopram fMRI studies differ substantially on potentially interacting factors like administration method (oral or intravenous), design (within or between subjects), duration of the drug administration (eg, a single dose or a daily intake for several days), dose, task (eg, block design or event related, masked

stimuli or unmasked stimuli), and task contrast (eg, comparing faces with a low-level baseline or emotion-specific effects such as fear > happy). Hence, any of these factors could turn out to be a major determinant on itself or interact with other factors in the effect that citalopram has on amygdala activity and social–emotion processing; a topic that deserves systematic investigation. Specifically, given the delay in SSRI effectiveness (Harmer *et al*, 2009), the difference between single-dose, short-term (eg, 1 week), and long-lasting effects (months) of SSRIs on brain systems seems crucial and, ideally, future research should also address long-term effects of SSRI on amygdala functioning in IED.

Serotonin is widely distributed in the brain (Cools *et al*, 2008) and linked to a variety of cognitive functions related to aversive processing (Cools *et al*, 2008; Dayan and Huys, 2009). In addition, serotonin dysfunction affects social cognition and behavior; for instance, animal research has shown that serotonin suppresses reactive aggression and promotes affiliate actions linked to social status in primates (Dayan and Huys, 2009). Moreover, human research has shown that tryptophan depletion (that decreases 5-HT availability) reduces cooperative behavior in a prisoner's dilemma game (Wood *et al*, 2006), whereas citalopram administration made subjects more likely to judge harmful actions as forbidden (Crockett *et al*, 2010) and enhanced reward sensitivity to facial expressions of a social partner (Tse *et al*, 2014). FMRI studies have found that citalopram reduces negative self-referential processing in depressed patients by enhancing medial PFC activity (Di Simplicio *et al*, 2012), and normalizes resting-state connectivity with the dorsal medial PFC (McCabe *et al*, 2011). Given the variety of lines of evidence on the link between social–cognition and serotonin, it is worth considering this a potential therapeutic mechanism, perhaps even more so than through amygdala-based emotional salience processing. It is important to point out that beyond serotonin, (impulsive) aggression is related to a number of neurotransmitter and neuropeptide systems, including dopamine, GABA, norepinephrine, vasopressin, and oxytocin (Yanowitch and Coccaro, 2011) that can be additional useful targets for pharmacological studies and treatment.

The meta-analytic decoding results of the TPJ revealed a relatively specific involvement with social–cognition. This notion is further underscored by a transcranial direct current stimulation study showing that TPJ stimulation increased perspective taking (Santiesteban *et al*, 2012). The link between TPJ functioning and social–cognitive processes in IED moreover fits with deficiencies in the neural mechanisms of social–cognitive functioning during perspective taking, empathy, and theory-of-mind tasks in psychopathy (Anderson and Kiehl, 2012; Blair and Lee, 2013; Decety *et al*, 2013a) that is also clearly characterized by aggressive behavior, although to a larger extend premeditated rather than impulsive. It is of note however that the current sample scored substantially lower on the PCL than the cutoff for psychopathology (Decety *et al*, 2013b) and more research is needed to further investigate the differences and similarities in the neural mechanism of social–cognitive functioning between IED and psychopathy.

Citalopram is an often-prescribed drug for not only depression (Cipriani *et al*, 2009) but also various other disorders like PTSD (Hetrick *et al*, 2010) and OCD (Soomro *et al*, 2008). To understand the potential efficiency of a drug, it is important to uncover its neural mechanism of action. Previous work has shown reasonable effectiveness of another SSRI, fluoxetine, in treating IED (Coccaro *et al*, 2009), and hence the current findings indicate a potential neural mechanism for SSRI functioning. The results suggest that escitalopram may affect the neural mechanisms of social–emotional and social–cognitive processes. Our findings aid in the understanding of the mechanisms of treatment efficiency obtained from multicomponent cognitive behavioral therapy (McCloskey *et al*, 2008). However, the effectiveness of escitalopram for IED treatment, and a detailed mechanistic model, will ultimately have to be tested in large randomized controlled trials.

LIMITATIONS

In addition to the above-mentioned methodological consideration with respect to the amygdala findings, there are some other limitations of this study and the findings that need to be taken into account. For instance, it has been found that the test–retest reliability of the influence of citalopram administration on amygdala activity is low (Klomp *et al*, 2013), perhaps because of the relatively low test–retest reliability of amygdala activity to emotional faces in general (Plichta *et al*, 2012). Another critical consideration, as with many studies in the field of clinical fMRI, is the small sample size of this study that negatively affects the reliability of the findings (Button *et al*, 2013; Yarkoni, 2009).

CONCLUSIONS

This study's findings suggest that escitalopram may enhance social–emotional functioning in IED, and hence provide insight into potential therapeutic mechanisms. Future research should further elucidate the long-term effects of SSRIs on various social–cognitive tasks in IED.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)