



Facilitation of emotion regulation with a single dose of escitalopram: A randomized fMRI study



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ABSTRACT

Acute antidepressant administration modulates neural activity consistent with decreases in negative emotion processing bias. However, studies are yet to examine whether treatment facilitates neural activity during reappraisal, an adaptive emotion regulation strategy associated with behavioral treatment response. Here we examine the impact of acute administration on reappraisal of negative stimuli using pharmacofMRI. Thirty-six healthy female participants completed two sessions of fMRI scanning, separated by a one-week washout period. A single dose of the selective serotonin reuptake inhibitor, escitalopram (20 mg) was administered to participants using a double-blind, randomized, placebo-controlled crossover design. When participants were administered escitalopram (relative to a placebo) and asked to reappraise negative emotional stimuli, left amygdala activation was decreased and right inferior frontal gyrus (R IFG) activation was increased. Also observed was a greater negative left amygdala-R IFG functional connectivity when participants were administered escitalopram relative to placebo, and this change in connectivity was associated with reductions in subjective ratings of valence and arousal of negative stimuli. Further analysis revealed connectivity modulation across multiple frontal regions. Results suggest that the acute effect of a commonly prescribed antidepressant may include facilitating the regulation of negative emotional stimuli, providing new important leads for models of antidepressant action.

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1. Introduction

Major depressive disorder and generalized anxiety disorder are associated with high prevalence along with great personal and societal burden (World Health Organization, 2008). Current perspectives suggest that these disabilities are underpinned by cognitive dysfunction which in turn relates to negative emotion processing biases and dysregulation of emotion, particularly in the context of negative emotion (Beck et al., 1979; Beck, 2008; Gotlib

and Joormann, 2010). These dysfunctions can be countered to some extent by employing adaptive emotion regulation strategies, and behavioral studies indicate that reappraisal of negative stimuli results in diminishing affective disorder symptoms (Aldao et al., 2010; Berking and Wupperman, 2012; Cisler and Olatunji, 2012; McRae et al., 2014). Furthermore, behavioral evidence suggests that effective antidepressant treatment facilitates reappraisal (Ehring et al., 2010; Gotlib and Joormann, 2010; Berking and Wupperman, 2012; McRae et al., 2014). However, the neural mechanism underpinning the antidepressant-related facilitatory effects of reappraisal is yet to be examined.

Emotion regulation refers to a diverse set of processes that modulate the manner in which emotions are experienced and expressed (Gross, 1998, 2008). Reappraisal is an emotion regulation strategy that involves reframing a situation or stimulus

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(Gross, 1998; Gross and Thompson, 2007), thereby impacting two interacting, functionally connected neural systems involved in emotion generation and its control (Aron et al., 2004; Ochsner and Gross, 2005; Banks et al., 2007; Goldin et al., 2008). Processes governing the latter have been associated with increased activity within the prefrontal cortex (Aron et al., 2004; Goldin et al., 2008; Ochsner et al., 2012; Buhle et al., 2014), which subsequently decrease limbic activity such as that of the amygdala, associated with emotion generation (Ochsner and Gross, 2005; Banks et al., 2007). These regions are thought to decrease emotional reactivity in an iterative manner, with limbic emotional reactivity continually modified by frontal processes automatically and volitionally (Ochsner and Gross, 2008; Ochsner et al., 2012). Frontal processes are engaged in the appraisal of stimuli and reappraisal; however, the key difference is that reappraisal may be employed to decrease emotional reactivity to negative stimuli (Gross, 1998; Goldin et al., 2008). Key prefrontal cortex regions involved in reappraisal include the right inferior frontal gyrus (R IFG), as well as the dorsomedial, dorsolateral, and ventrolateral regions (Aron et al., 2004; Goldin et al., 2008; Ochsner et al., 2012; Buhle et al., 2014). In order to understand the mechanisms through which antidepressants facilitate reappraisal, it may be beneficial to investigate how the functional connectivity between the amygdala and frontal regions change when an individual reappraises negative emotional stimuli, and how antidepressants modulate this connectivity.

Single doses of antidepressants have been shown to modulate IFG and amygdala activity in healthy participants, enhancing positive emotion processing biases while attenuating negative emotion processing biases (Kemp et al., 2004a; Outhred et al., 2013, 2014b). In order to further understand these changes, more specific neurocognitive processes must be dissected. The facilitation of reappraisal may be one mechanism through which modulation of emotion processing bias with single dose administration can occur. To date, studies remain to determine whether a single dose of an antidepressant is able to sufficiently facilitate reappraisal of negative emotional stimuli resulting in a decrease in neural and behavioral emotional reactivity.

Based on our previous findings (Kemp et al., 2004a; Outhred et al., 2013; 2014b) that single doses of antidepressants modulate L amygdala and R IFG activity, along with findings that reappraisal results in heightened negative connectivity between the amygdala and frontal regions (Ochsner and Gross, 2005; Banks et al., 2007), as well as behavioral findings by others indicating that antidepressants facilitate reappraisal (Ehring et al., 2010; Gotlib and Joormann, 2010; Berking and Wupperman, 2012; McRae et al., 2014), we formed the following predictions. We predicted that the functional connectivity between the L amygdala and R IFG activity would be modulated by escitalopram during reappraisal of negative emotional stimuli, such that decreased L amygdala activity would be associated with increased R IFG activity (i.e., heightened negative connectivity between these regions under escitalopram). In addition to examining this *a priori* hypothesis, we explored functional connectivity changes over broader regions in the frontal cortex in order to examine potential modulation with other regulatory regions. Finally, we predicted that L amygdala-R IFG functional connectivity changes would be reflected in behavioral responses.

2. Methods

2.1. Participants

Thirty-six, right-handed, healthy female participants (mean age=25.08; SD=6.49; range: 18–47) were recruited by

advertisement and completed the study. All participants provided informed consent in accordance with the National Health and Medical Research Council (NHMRC) guidelines (<http://www.nhmrc.gov.au/guidelines/publications/e72>). The Sydney University Human Research Ethics Committee (13901) and the Northern Sydney Central Coast Area Health Service Human Research Ethics Committee (1105-178M) granted ethical approval for this study. Our trial was also registered with the Australian New Zealand Clinical Trials Registry (ANZCTR, available here: <http://www.anzctr.org.au>; ACTRN12611000719932). The trial protocol (including dates, and details on randomization and blinding) is available on the ANZCTR website. Education in number of years ranged from 13 (completed high school) to 23 (completed graduate school). All participants were of Caucasian-European ethno-geographic ancestry. Participants were medication-free (other than hormonal contraceptives), and without physical or psychiatric illness including symptoms of depression (as determined by PHQ-9 scores (Kroenke et al., 2001) and anxiety (as determined by GAD-7 scores (Spitzer et al., 2006)). Participants had no history of previous psychiatric illness or use of psychiatric medication. Participants were also free from self-reported illicit drug use and heavy alcohol use (abstaining for at least 24 hours), smoking, brain injury, neurological disorders, loss of consciousness for longer than five minutes, and contraindications for fMRI scanning. Finally, participants abstained from caffeine on the morning of the experiment and no participant tested positive on pregnancy tests conducted at each session.

2.2. Experimental and emotion regulation task design

All participants were tested under placebo (saccharin) and escitalopram (20 mg; *per os*) conditions using a randomized, double-blind, placebo controlled cross-over design, with a washout period of one week (or five half-lives, $t_{1/2}=26.7$ h; Sogaard et al., 2005), as described previously (Hanson et al., 2013; Kemp et al., 2014; Outhred et al., 2014a, 2014b). The present study reports fMRI findings on the emotion regulation task we employed (an event-related design with reappraisal of negative images). Our previous papers (Outhred et al., 2014a, 2014b) reported on fMRI findings from a basic emotion processing task (a blocked design viewing negative, positive, and neutral images). The emotion regulation task results have not been previously reported. A crossover design approach with manipulation checks, rather than a mixed models approach, was employed, as recommended and discussed previously (Senn, 1988; Senn et al., 2004; Mills et al., 2009). An equal number of participants had either treatment in their first testing session. fMRI during an emotion regulation task was conducted four hours post-treatment to coincide with expected peak pharmacokinetic effects of escitalopram ($t_{max}=3.0 \pm 1.5$ h, Sogaard et al., 2005; mean $t_{max}=4.0$ h, Alphapharm, 2012). An event-related emotion regulation task was constructed based on the emotion regulation task by Goldin et al. (2008). Stimuli were selected from the International Affective Picture System (IAPS; Lang et al., 2008), based on the normed valence and arousal ratings that are provided in the IAPS manual. The task consisted of trials with a 2-second instruction (either 'Think Objectively' or 'Watch') followed by a 4-second high arousal negative IAPS image, a 2-second negative valence rating, a 2-second arousal rating, a 2-second 'Watch' instruction, a 4-second low arousal neutral IAPS image, and a jittered fixation cross (average duration of 4 s; see Supplement for further details on the task administered to participants). The valence and arousal rating scales were on a five-point scale from "0. 'not at all negative/arousing'" to "4. 'overwhelmingly negative/arousing'". During the 'Think Objectively' trials, participants were asked to assume the perspective of a medical professional watching an instructional video, focusing on technical

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