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Acute Neural Effects of Selective Serotonin Reuptake Inhibitors versus Noradrenaline

Reuptake Inhibitors on Emotion Processing:

Implications for Differential Treatment Efficacy

Tim Outhred^{1,2}

Brittany E. Hawkshead³

Tor D. Wager⁴

Pritha Das^{1,5,6}

Gin S. Malhi^{1,5,6}

Andrew H. Kemp^{1,2,5,6,7*}

¹ Discipline of Psychiatry, Sydney Medical School, University of Sydney, Royal North Shore Hospital NSW 2065, Australia

² SCAN Research and Teaching Unit, School of Psychology, University of Sydney NSW 2006, Australia

³ Department of Psychology, Auburn University, AL 36849, USA

⁴ Department of Psychology and Neuroscience, University of Colorado, CO 80309, USA

⁵ CADE Clinic, Department of Psychiatry, Royal North Shore Hospital NSW 2065, Australia

⁶ Advanced Research and Clinical Highfield Imaging (ARCHI), University of Sydney, Royal North Shore Hospital NSW 2065, Australia

⁷ Hospital Universitário, Universidade de São Paulo, 05508-000 São Paulo SP, Brazil

* Corresponding author: Andrew H Kemp, Centro de Pesquisa Clínica e Epidemiológica, Hospital Universitário, Universidade de São Paulo, Av Lineu Prestes 2565 05508-000 São Paulo SP. Ph. +61 2 9462 9913. Fax. +61 2 9926 4063. Email: andrew.kemp@sydney.edu.au

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Email addresses of each author:

Tim Outhred <tout1075@uni.sydney.edu.au>

Brittany E. Hawkshead <beh0007@tigermail.auburn.edu>

Tor D. Wager <tor.wager@colorado.edu>

Pritha Das <pritha.das@sydney.edu.au>

Gin S. Malhi <gin.malhi@sydney.edu.au>

Andrew H. Kemp <andrew.kemp@sydney.edu.au>

Abstract

Clinical research has demonstrated differential efficacy of selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (NRIs), which may relate to differential acute effects these medications have on emotional brain processes. Here we present findings from a Multi-Level Kernel Density Analysis meta-analysis that integrates and contrasts activations from disparate fMRI studies in order to examine whether single dose SSRIs and NRIs have different effects on emotion processing tasks in healthy participants. Seven SSRI and four NRI studies were eligible for inclusion. SSRIs decreased amygdala responses, suggesting reduced emotional reactivity to emotional stimuli, whereas NRIs increased frontal and medial activation, suggesting increased emotion regulation. As hypothesised, an interaction of antidepressant and task type was found, such that SSRIs modulated amygdaloid-hippocampal, medial and frontal activity during both the presentation of faces and pictures, whereas NRIs only modulated the activation in medial and frontal regions during the presentation of pictures. Findings are interpreted within a novel model of the differential effects of SSRIs and NRIs on emotion processing.

Keywords: antidepressants; SSRI; NRI; serotonin; noradrenalin; emotion; fMRI; Multi-Level Kernel Density Analysis; meta-analysis

Highlights:

- Acute effects of antidepressants may lay the foundation for symptom amelioration.
- Differential acute neural effects may underlie differential treatment efficacy of SSRIs vs NRIs.
- We perform an fMRI meta-analysis to integrate and contrast previous findings.
- We find that SSRIs and NRIs have differential acute neural effects.
- We model the acute neural effects that may underlie the efficacy of SSRIs vs NRIs.

1. Introduction

Affective disorders, including major depressive disorder and generalised anxiety disorder, are debilitating conditions with the greatest worldwide lifetime prevalence of any other DSM-IV disorders (Kessler et al., 2005). A key feature of affective disorders is dysfunctional emotion processing (Beck, 2008; Beck et al., 1979; MacLeod et al., 2002). Recent work has highlighted the early neural effects of antidepressants on emotion processing that may underpin the downstream changes associated with amelioration of symptoms in affective disorders (Harmer et al., 2011; 2009a; Pringle et al., 2011; Roiser et al., 2012). Though both selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (NRIs) appear to alleviate dysfunctional emotion processing (Harmer, 2012), it is generally accepted that SSRIs are more effective than NRIs for treating affective disorders (Cipriani et al., 2009; 2012; Eyding et al., 2010). This differential efficacy may relate to specific neural effects on emotion processing. Functional neuroimaging studies have predominantly examined the impact of either SSRIs or NRIs on different types of emotion processing tasks, highlighting the need to directly contrast the neural effects of these antidepressant medications, taking into account task type. Here, we review the relevant literature, integrating and contrasting these previously reported findings, and then present a quantitative meta-analysis directly contrasting the effects of SSRIs and NRIs on commonly used affective tasks.

Historically, the biological basis for affective disorders was related to impairment in monoaminergic neurotransmitter systems (Belmaker and Agam, 2008; Bunney and Davis, 1965; Schildkraut, 1965). Current neurobiological views also highlight abnormalities in intracellular processes including synaptogenesis and neurogenesis (Belmaker and Agam, 2008) in emotion-related brain regions (Duman and Monteggia, 2006), which are modulated by antidepressant treatment (Castrén, 2004; Duman, 2004; Warner-Schmidt and Duman, 2006). The amygdala (AMY) and prefrontal cortex (PFC) are two regions that are

repeatedly implicated in affective disorders and their treatment due to the roles they play in emotion processing (Davidson, 2002; Davidson and Begley, 2012; Davidson et al., 2002; Lee et al., 2012; Mayberg, 1997; Seminowicz et al., 2004). We define *emotion processing* as a series of processes involving attentional, perceptual, appraisal, and response preparation operations occurring in an individual during salient internal and external events, impacting on the experience of and responses to the events (Gross, 1998; Gross and Thompson, 2007; Scherer, 2000).

During emotion processing, the PFC has a role in appraisal and reappraisal of emotional stimuli (Ochsner and Gross, 2005), thereby playing both a role in the generation and regulation of emotional experiences (Lindquist et al., 2012; Ochsner and Gross, 2005; Wager et al., 2010). The AMY rapidly and reliably responds to salience of emotional stimuli (Luo et al., 2010; Pourtois et al., 2010) and plays a key role in emotional memory (Phelps and LeDoux, 2005). The reciprocal relationship between the PFC and the AMY is apparent during the reappraisal of emotional stimuli (Banks et al., 2007; Wager et al., 2008). A role of the PFC is to attenuate increased AMY activity, allowing for responses to the stimulus to be appropriately regulated (Banks et al., 2007; Wager et al., 2008). Depressed patients display reduced PFC activation and increased AMY activation at rest and during cognitive and emotion processing tasks, suggesting a lack of cortical regulation and inhibition of the AMY (Davidson and Begley, 2012; Mayberg, 2003; Siegle et al., 2007). With antidepressant treatment, these activations are normalised (Arnone et al., 2012; Delaveau et al., 2011; Godlewska et al., 2012). Other brain areas implicated in the mood and anxiety disorders are: the insula, linked to self-awareness and autonomic regulation of emotions (Craig, 2009; Paulus and Stein, 2006); the hippocampus, involved in memory formation, learning, sensitivity to context, and regulation of stress, as well as a major site of neurogenesis (Bellani et al., 2010; Brooks et al., 2012; Heijer et al., 2012); the thalamus, a processing center for sensation and motor regulation, which also plays a role in awareness,

attention, memory, and language (Herrero et al., 2002; Matsumoto et al., 2001); the cingulate cortex, involved in the regulation of both cognitive and emotional processing with functions in directed attention and motivated behaviour (Amiez et al., 2012; Blair et al., 2012; Bush et al., 2000; Etkin et al., 2011); and the superior temporal gyrus (STG), implicated not only in auditory processes, but also in language processing, social cognition, and emotion perception in faces (Bigler et al., 2007; Domínguez-Borràs et al., 2009; Turk-Browne et al., 2010). Furthermore, research on the treatment of affective disorders has demonstrated that treatment restores the function of these regions (e.g., Arce et al., 2007; Korb et al., 2011).

While the precise biological mechanisms of antidepressants remain to be fully understood, recent theory suggests that antidepressants act by changing the way individuals process emotional information. More specifically, antidepressants shift the negativity bias to a more positive one, leading to downstream overall improvements in mood (Harmer et al., 2011; Pringle et al., 2011). While it is generally considered that antidepressant response may take up to four-to-six weeks before a clinical change is apparent, an increasing body of work has examined the ability to predict response to antidepressant medications (Kemp et al., 2008; Pizzagalli, 2011). Research (e.g., Kemp et al., 2004; Kemp and Nathan, 2004; Murphy et al., 2009a; Norbury et al., 2007a; Rawlings et al., 2010) has revealed observable physiological changes occurring within hours of a single dose, suggesting the possibility that differential drug effects may be observed following acute rather than chronic administration of antidepressants prior to noticeable behavioural changes emerging. There is an imperative to better understand the action of different classes of antidepressant medications, especially considering that fewer than 40% achieve clinical remission after the first round of treatment (Kemp et al., 2008; Trivedi, 2006).

1.1 Antidepressants

The most commonly prescribed antidepressants are SSRIs, which act through blocking the reuptake of serotonin (5-HT), increasing the level of 5-HT in the synapses (Depue and Spoont, 1986; Roseboom and Kalin, 2011; Stahl, 1998) leading to downstream changes, including desensitisation of 5-HT autoreceptors, restoration of function in second messenger systems, and transcription of neurotrophic factors, which are believed to occur over a similar timescale to the amelioration of symptoms (see Belmaker and Agam, 2008; Hyman and Nestler, 1996; Pitychoutis et al., 2012; Stahl, 1998). 5-HT cell bodies are located primarily in the raphe nuclei of the reticular formation in the brain stem and serotonergic axons innervate various other regions linked to depression and mood disorders, including the hypothalamus, AMY, basal ganglia, thalamus, hippocampus, cingulate cortex, and PFC (Gillespie et al., 2011; Stahl, 1998). These regions are consistently involved in emotion processing (Kober et al., 2008; Lindquist et al., 2012; Vytal and Hamann, 2010). Indeed, SSRI treatment is associated with the normalisation of activity in these areas (e.g., Di Simplicio et al., 2011; McCabe and Mishor, 2011; Murphy et al., 2009a).

Noradrenergic reuptake inhibitors (NRIs) are another common class of antidepressant that block the reuptake of noradrenaline in the brain. Though downstream effects of NRIs have been examined less extensively than those of SSRIs, NRIs also produce downstream neurotropic effects (First et al., 2012). Noradrenaline (NA) is associated with arousal and alertness, and with other behavioural and physiological effects such as feeding behaviour, blood pressure, heart rate, and mood (Bönisch and Brüss, 2006). NA is also linked to anxiety, cognition, learning, and sleep regulation (Montgomery, 1997). Cell bodies are located in the locus coeruleus (LC) of the brain stem with NA axons projecting widely to regions related to emotion processing (Kober et al., 2008; Lindquist et al., 2012; Vytal and Hamann, 2010); primarily the PFC, but also the AMY, cingulate cortex, and thalamus (Blier, 2001; Brunello et al., 2003; Haenisch and Bönisch, 2011). NRIs have

been reported to increase prefrontal regulation of emotional responses during exposure of emotional stimuli (Norbury et al., 2007a; 2007b).

1.2 Emotional Processing Tasks

In order to examine the effects of antidepressants on emotion processing, functional neuroimaging studies most frequently involve presentation of emotional pictures (IAPS; e.g., Brühl et al., 2011; 2010; Takahashi et al., 2005) or facial expressions (e.g., Anderson et al., 2007; Bigos et al., 2008; Murphy et al., 2009a). While both stimuli types are emotionally potent and illicit many common aspects of emotion processing involved in reactivity and appraisal and regulation (Bleich-Cohen et al., 2006; Britton et al., 2006b; Hariri et al., 2002; Lindquist et al., 2012), there are some differences. Under passive viewing situations, emotional facial expressions illicit more emotion recognition and perceptual processes (Britton et al., 2006b; Frank and Stennett, 2001; Lindquist et al., 2012) and are less likely to elicit emotional experience than emotional pictures (Britton et al., 2006b; Lindquist et al., 2012). Emotionally salient pictures require more elaborated appraisal processes (Britton et al., 2006b; Lindquist et al., 2012), given the relatively more novel and complex stimulus content (Lang et al., 1993; Winston et al., 2003). Emotional pictures tend to be more arousing, and are more likely to elicit explicit emotional responses and experiences than with the perception processes involved in viewing faces (Lang et al., 1993; Lindquist et al., 2012). Under passive viewing conditions, common and differential activations of pictures and faces have been reported (Bleich-Cohen et al., 2006; Britton et al., 2006b; Hariri et al., 2002; Lindquist et al., 2012). While both stimulus sets activate common regions associated with emotion processing including the AMY, hippocampus, ventromedial PFC, and visual cortex, faces elicit more of the components related to basic affective salience and perception, whereas pictures also evoke cognitive appraisal processes that correspond with emotional responses and experiences (Bleich-Cohen et al., 2006; Britton et al., 2006b; Hariri et al., 2002; Lindquist et al., 2012). Therefore, activation of

underlying circuitry is likely to correspond with processes such as emotion perception, reactivity, appraisal and regulation, and experience, rather than with discrete emotion categories or the type of stimulus per se (Kemp et al., in press; Lindquist et al., 2012).

While researchers have suggested that there are common and differential processes and pathways for the processing and regulation of responses to emotional faces versus emotional pictures, the differential impact of specific antidepressants on emotion processing of faces and pictures remains to be examined. While there are many other types of affective tasks that have been employed in functional neuroimaging studies (e.g., mood and anxiety inductions, social feedback/rejection, stress paradigms), only two additional studies have examined responses to single-dose antidepressant administration in healthy subjects. These studies employed tasks other than those with pictures and faces: these are Miskowiak and colleagues study (2007; emotional words) and the Papadatou and colleagues study (2012; emotional memory recall). Studies employing tasks with faces and pictures are therefore the most amenable to meta-analysis as they have been more frequently employed. Including other studies would increase heterogeneity unnecessarily.

1.3 Present Study and Hypotheses

The aim of the present study was to conduct a review and meta-analysis of the effects of acute antidepressant treatment on emotional processing, and examine the specificity of the effects of selective serotonin reuptake inhibitors (SSRIs) and the selective noradrenaline reuptake inhibitors (NRIs) on the processing of facial expressions versus more complex emotional images. It remains unclear as to whether specific classes of antidepressants have different effects on the processing of faces versus images. By enhancing understanding of the manner in which these specific medications act, we may be better able to understand why the clinical efficacy of SSRIs and NRIs differ (Cipriani et al., 2012; 2009; Eyding et al., 2010). Findings will also have implications for the additional utility of the combined serotonin and noradrenaline reuptake inhibitors (Cipriani et al.,

2009) and provide a neurophysiological foundation for personalised medicine in clinical practice.

Our primary hypothesis was that antidepressants would modulate the activity of regions normally associated with emotion processing. Secondly, we hypothesised that there would be an interaction between drug class and task type such that the effect of an antidepressant would depend on the type of task presented. Based on the research (discussed above) linking NA and emotional pictures with responsiveness to novel stimuli and increased arousal, we further predicted that NRIs will modulate activity due to emotional pictures but not faces, while SSRIs will modulate activity in response to both emotional pictures and faces on the basis of their improved efficacy.

2. Methods

2.1. Literature Review and Study Selection

Studies investigating the effects of antidepressants on emotional processing (as measured by functional magnetic resonance imaging) in healthy control subjects published up until April 8, 2013, were identified through a search of published reports in two major databases (Scopus and PubMed), using the terms: “antidepressants” AND (“functional magnetic resonance imaging” OR “fMRI”) AND (“emotion” OR “emotion processing”). Additional studies were then located by searching through the reference sections of those articles. We also searched for any additional publications by the authors of the papers we had already identified to ensure we had an exhaustive list of studies. Published reports were ultimately included if they met the following criteria: (1) they measured blood oxygenation level dependent (BOLD) response (using fMRI) to assess brain activation; (2) they involved healthy, unmedicated adults; (3) the antidepressant tested was either an SSRI or NRI; (4) they reported findings based on a single oral or intravenous dose of an antidepressant; (5) they involved an emotion processing task involving either facial expressions or emotional pictures; (5) activation was assessed using a double-blind placebo controlled experimental

design; (6) they provided standard Talairach or Montreal Neurological Institute (MNI) coordinates, allowing for comparison of findings. Studies were excluded if any participants were considered to be high risk for any psychiatric disorder.

We chose studies evaluating the effects of antidepressants on healthy volunteers to ensure sample homogeneity and avoid issues relating to the cognitive or emotional functioning of study participants as well as the confounding effects of psychological or additional prescribed medications. While meta-analyses and reviews have been conducted on the effects of antidepressants on emotional processing in depressed subjects (Delaveau et al., 2011), no meta-analysis to date has examined the effects of more than one treatment, nor have the acute effects of these antidepressants in healthy controls been examined, and no meta-analysis to date on antidepressants has been published that utilises MKDA, a technique with several methodological advantages (discussed below) over alternatives.

Based on the above criteria, there were nine studies included: five examined SSRIs only (Anderson et al., 2007; Bigos et al., 2008; Del-Ben et al., 2005; Murphy et al., 2009a; Takahashi et al., 2005), two examined NRIs only (Kukolja et al., 2008; Onur et al., 2009), and two examined both SSRIs and NRIs (Brühl et al., 2011; 2010). Task instructions of all studies included in our meta-analysis were for participants to passively view the stimuli. For the studies on faces, emotion categories included angry, fearful, disgusted, surprised, and happy faces, and their combinations used to create an emotional face condition (a combination of positive and negative emotion faces; Bigos et al., 2008) or an aversive face condition (a combination of negative emotion faces; Del-Ben et al., 2005) categories. Emotional face categories were always contrasted against a neutral face category. For studies using picture stimuli, stimuli included negative pictures high in arousal. All IAPS neutral stimuli conditions were low in arousal and were used to contrast the IAPS emotional stimuli. Studies that employed IAPS made attempts to control for content and complexity.

In total, there were seven studies that examined SSRIs and four studies that examined NRIs. There was a total of 152 subjects (103 received SSRI and 49 received NRI), twenty-one individual contrasts (12 SSRIs and 9 NRIs), and 121 unique coordinates (59 SSRIs and 62 NRIs), which were judged to be eligible for inclusion in the final analysis (see Figure 1 for a graphical display of the included coordinates). For each article, coordinates were included in the final analysis if they were considered significant by the criteria specified in the individual study.

2.2 Multilevel Kernel Density Analysis (MKDA)

The ultimate goal of this meta-analysis was to identify the regions in the brain most consistently modulated by emotion processing tasks while subjects were under the effects of a single dose of an antidepressant. Additionally, we were also interested in examining the differential effects of task on activation and whether there were any specific effects relating to the class of antidepressant (SSRI vs NRI). In order to address these objectives, we utilized a Multi-level Kernel Density Analysis (MKDA) to conduct our meta-analysis (Kober and Wager, 2010; Wager et al., 2009). MKDA is a quantitative, coordinate-based approach used in several recently published studies (e.g., Denny et al., 2012; Etkin and Wager, 2007; Kober et al., 2008). The MKDA statistic reflects the number of nominally independent contrast maps (i.e., statistical parametric maps from individual studies) that activate in the vicinity (e.g., within 10 mm) of each voxel in the brain; the null hypothesis is that the activation “blobs” from individual contrast maps are randomly distributed (Kober and Wager, 2010; Wager et al., 2009). Thus, a significant result indicates that more contrast maps activate near a specific voxel than expected by chance (Kober and Wager, 2010; Wager et al., 2009). While there are many meta-analytic methods available in neuroimaging research (Radua and Mataix-Cols, 2012), we selected the MKDA method for a number of reasons. It allows for a nested analysis of the data where multiple coordinates are nested within a contrast. This addresses problems associated with the non-independence of peak

coordinates reported by the same study, and prevents individual studies with a large number of activation peaks from disproportionately contributing to the results. The MKDA also allows the weighting of studies by sample size and effect (fixed vs. random), meaning those studies with a random-effects model and a larger number of participants are given more weight than those with a smaller sample size or fixed-effects model. A third advantage is the summary statistic's clear-cut interpretability: it is simply the proportion of contrasts activating within 10 mm of a given voxel (Kober and Wager, 2010; Wager et al., 2009).

Analyses were performed in MATLAB version 2011b, using the MKDA tool package (Wager, 2008; <http://wagerlab.colorado.edu/files/tools/meta-analysis.html>). Peaks from each study were convolved using a spherical smoothing kernel with a 10 mm radius. Each study was weighted by number of participants (calculated by the square root of the sample size) and type of analysis (where a value of 1.00 was assigned to studies using a random effects model and 0.75 to those with a fixed effects analysis). Contrast maps were weighted by sample size, rather than weighting individual peaks by Z-scores, because Z-scores are inflated in small samples due to low degrees of freedom, and thus are not representative of the true effect sizes (Vul et al., 2009; Yarkoni et al., 2009). MKDA difference analysis was conducted in order to directly contrast the antidepressant and task type conditions. The threshold for statistical significance was determined using a Monte Carlo simulation (5000 iterations) and provided family-wise error (FWE) rate correction for multiple comparisons at $\alpha < .05$ corrected.

2.3 Planned comparisons

In order to evaluate the differential effects of antidepressant class on the two emotional processing tasks, we conducted additional analyses examining the interaction and main effects of each variable. We divided the contrasts included in our database into four distinct groups: SSRI Faces, SSRI Pictures, NRI Faces, and NRI Pictures, and then examined what the effects of each group were when contrasted against one another. This

provided us with an illustration of what the effects of each antidepressant had on the emotional processing of each task type and helped to identify any differences in mode of action. The proportions of contrasts that activated the obtained clusters and 95% confidence intervals obtained from the binomial distribution were calculated (95% CI binomial). This was performed in order to show the consistency of cluster activations within contrasts, thereby providing a measure of confidence in the obtained results.

2.4 Description of selected studies and MKDA analyses

Two MKDA analyses were conducted. For the first analysis, 13 contrasts corresponding to increased activation to emotional stimuli were included (i.e., emotional > neutral stimuli labelled as the *Increased* analysis; see Supplementary Table 1). Within this analysis, the contrasts were further categorised by antidepressant and task type: SSRI Faces = 3, SSRI Pictures = 4, NRI Faces = 3, NRI Pictures = 3. In the second analysis, 8 contrasts corresponding to decreased activation to emotional stimuli were included (i.e., neutral > emotional contrasts labelled as the *Decreased* analysis): SSRI Faces = 4, SSRI Pictures = 1, NRI Faces = 2, NRI Pictures = 1 (see Supplementary Table 2). Rather than assuming increases and decreases are mirror images of each other (Frankenstein et al., 2003), we analysed the consistency of each separately. There was no association between the numbers of contrasts for antidepressant class and task type for the *Increased* analysis ($\tau = .005$, $p = .805$) or the *Decreased* analysis ($\tau = .022$, $p = .693$). Therefore, any differences found between antidepressant classes and tasks types are unlikely to be driven by the different numbers of each type of contrast.

3. Results

3.1 Comparison of task types

For faces, one significant cluster (FWE-corrected level, $p < .05$) of increased activation was observed in the amygdaloid-hippocampal region (69.81% of contrasts activated; 95% CI binomial [24.58, 96.71]), while no significant clusters were observed in

the *Decreased* analysis. For pictures, three significant clusters were observed ($p < .05$; FWE-corrected): two encompassing the right thalamus (66.67% of contrasts activated; 95% CI binomial [25.25, 94.54]) and the third, surrounding the left DLPFC (74.37% of contrasts activated; 95% CI binomial [31.51, 97.28]). No significant clusters of activation were observed in the *Decreased* MKDA analysis. See Table 1 for the complete results.

3.2 Comparison of antidepressant classes

Table 2 displays the results of the MKDA analyses for antidepressant type. The *Increased* MKDA analysis did not identify any significant clusters of increased activation associated with SSRI administration relative to NRIs. However, the *Decreased* analysis revealed an amygdaloid-hippocampal cluster (100% of contrasts activated; 95% CI binomial [47.82, 100]), and indicated that SSRIs decrease activation in this region more than NRIs ($p < .05$; FWE-corrected). At an uncorrected ($p < .01$) level, the *Increased* MKDA analysis identified one cluster encompassing the left MCC, bilateral PCC, and the right thalamus for NRIs (66.67% of contrasts activated; 95% CI binomial [95.67, 22.28]). There were no significant clusters identified for decreased activation due to NRIs.

3.3 Interaction between antidepressant class and task type

The *Increased* MKDA analysis of the 2×2 interaction between antidepressant (SSRI; NRI) and task (faces; pictures) type identified a significant left DLPFC cluster ($p < .05$; FWE-corrected), and, at an uncorrected ($p < .01$) level, the *Decreased* MKDA analysis of the interaction identified a significant cluster including the globus pallidus, thalamus, caudate, putamen, AMY, and uncus. These findings indicate specific regions in which differential effects of antidepressant class are moderated by task type. The *Increased* and *Decreased* interactions and contrast activation proportions are visualised in Figure 2, Panels A and B, respectively. Table 3 displays the results of the interaction as well as follow-up analyses. To summarise the results of the follow-up analyses (relative to NRIs), SSRIs decrease activation to both emotional faces and pictures in the right amygdaloid-hippocampal

region. SSRIs also decrease activation in the left OFC, right STG, and right insula in response to pictures, but increase activation in the right MCC, thalamus, and caudate in response to pictures. In contrast, NRIs decrease activation in response to pictures only (no decreases for faces) when compared with SSRIs, with a significant cluster in the left STG. Finally, NRIs increased activation for pictures in the right thalamus, right STG, left DLPFC, and the left MCC and PCC.

4. Discussion

Here we report on findings obtained from a meta-analysis on the effects of single doses of two classes of antidepressants on emotion processing in healthy participants. Our MKDA analyses demonstrate that antidepressants have acute modulatory effects on emotion processing as measured by fMRI: an important finding considering that clinical change is not observed for up to four-to-six weeks (Kemp et al., 2008; Pizzagalli, 2011). We further determined that the effects of antidepressants are dependent on the antidepressant class and task. In the following discussion, we examine our findings in the context of previous studies and propose a novel model of the acute effects of SSRIs versus NRIs on emotion processing, taking into account different monoaminergic pathways and differential stimulus processing pathways.

4.1 Findings

Our meta-analysis revealed that emotional processing is dependent on task, consistent with previous findings (Bleich-Cohen et al., 2006; Britton et al., 2006b; Hariri et al., 2002; Lindquist et al., 2012). Passive viewing of faces increased activation in the AMY while pictures increased activation of the DLPFC, MCC, and thalamus. These findings are consistent with increased complexity of processing pictorial stimuli (Bleich-Cohen et al., 2006; Britton et al., 2006b; 2006a; Lang et al., 1993; Lindquist et al., 2012; Winston et al., 2003), involving the thalamus and cingulate for attentional direction and sensory integration, and recruitment of frontal cortical structures for increased stimulus appraisal

(Bleich-Cohen et al., 2006; Britton et al., 2006b; Hariri et al., 2002). Consistent with this interpretation, the processing of the emotional content of faces and pictures involves activation across regions involved in attentional, perceptual, and experiential operations, rather than specific activation relating to emotion category or stimulus type (Kemp et al., in press; Lindquist et al., 2012). Critically, we observed that brain function during the processing of emotional faces and pictures is modulated by administration of antidepressants.

Consistent with previous research (see Delaveau et al., 2011) and models of antidepressant action (e.g., Pringle et al., 2011), antidepressants were found to decrease activation of the amygdaloid-hippocampal region and increase the activation of frontal regions during emotion processing. These findings may be attributed to a decrease in emotional reactivity (Balderston et al., 2011; LeDoux, 2007; Patin and Hurlemann, 2011) and an increase in regulatory processes (Grimm et al., 2006; Jung et al., 2008; Ochsner and Gross, 2008), respectively. These combined effects may result in decreased emotional reactivity, thereby helping to reduce affective disturbance in psychiatric populations with chronic administration. Therefore, antidepressants have acute neural effects on the processing of emotional stimuli, which may underpin clinical changes following chronic administration. A major finding obtained in our study is the differential neural effects of the SSRIs and NRIs.

The present study's findings are consistent with current models of neuroaffective disturbance and antidepressant action in psychiatric samples (Mayberg, 2007; 2003; 1997). These models characterize increases in activity of the DLPFC and decreases in amygdaloid-hippocampal activity as a necessary change associated with treatment response and remission from affective disturbance. Notably, these effects are apparent upon acute administration of antidepressants in both healthy samples (present study) and clinical samples (Delaveau et al., 2011). A prior neuroimaging meta-analysis (Delaveau et al., 2011)

on the impact of chronic administration of antidepressants (collapsing across SSRIs, atypical, and SNRIs) on emotion processing (pictures and faces tasks) in patients with MDD reported a similar pattern of effects. Therefore, antidepressants appear to have similar neurophysiological effects in both healthy and clinical samples. Our study further indicates that these effects are presented even after acute administration of antidepressants and that SSRIs and NRIs have differential effects.

Consistent with prior research (e.g., Harmer et al., 2006; Murphy et al., 2009a; Sheline et al., 2001), our meta-analysis demonstrated that SSRIs decrease activation to emotional stimuli in the amygdaloid-hippocampal region. In contrast, NRIs increased activation in the cingulate cortex and thalamus. Interestingly, SSRIs were found to decrease activation in amygdaloid-hippocampal regions when contrasted against NRIs; however, NRIs did not show increased or decreased activation over and above SSRIs in any region. These results suggest that the acute actions of SSRIs on the amygdaloid-hippocampal region reflect reduced early attentional processes to the salience of emotional stimuli, and thus reduced initial reactivity to the stimuli (Luo et al., 2010; Pourtois et al., 2010). In contrast, NRIs modulated the activity of medial regions: the cingulate cortex (involved in the cognitive regulation of emotional processing with functions in directed attention and motivated behaviour (Amiez et al., 2012; Blair et al., 2012; Bush et al., 2000; Etkin et al., 2011) and the thalamus (a processing center for sensation and motor regulation, playing a role in awareness and attention (Herrero et al., 2002; Matsumoto et al., 2001)). We interpret the NRI modulation of these medial regions as highlighting a role for these medications in the alteration of emotional stimuli on attentional load under passive viewing conditions, thereby increasing regulation of emotional processes, rather than attenuating the early reactivity associated with stimulus salience. Indeed, Murphy and colleagues (Murphy et al., 2009b) found that citalopram (SSRI) but not reboxetine (NRI) reduced vigilance towards fearful faces, suggesting that citalopram modified early attentional orienting: decreasing

reactivity. These findings provide further support for the notion that SSRIs may have relatively greater anxiolytic effects than NRIs in treating the mood and anxiety disorders due to reductions in initial emotional reactivity (Pringle et al., 2011). Taken together, these differential findings may underpin increased efficacy and effectiveness of SSRIs relative to NRIs (Cipriani et al., 2012; 2009; Eyding et al., 2010). Our meta-analysis also revealed that the impact of antidepressant medication is dependent on stimulus type.

The interaction between antidepressant and task type suggests that SSRIs and NRIs have differential effects dependent on whether participants are presented with emotional faces or pictures. The locus of this interaction for decreased activity to emotional stimuli was a large cluster encompassing the AMY, caudate, globus pallidus, putamen, thalamus, and uncus. For increased activity, the locus was the DLPFC. When this interaction was further examined, it was demonstrated that SSRIs had effects on both emotional pictures and faces while NRIs impact on responses to emotional pictures only. As SSRIs appear to have more extensive effects on both the amygdaloid-hippocampal region and cortical regions regardless of the stimulus, this may reflect an early indicator—in accordance with clinical findings (Cipriani et al., 2012; 2009; Eyding et al., 2010)—that SSRIs are more effective antidepressants than NRIs.

4.2 Toward a model for the differential effects of 5-HT and NA augmentation on emotion processing

Building on previous models (Harmer et al., 2009a; Pringle et al., 2011), we summarise our findings within a model of the acute effects of serotonin and norepinephrine on emotion processing (see Figure 2, Panel C). We suggest that augmentation of 5-HT impacts on emotional reactivity as well as its regulation, while NA augmentation may be specific to the regulation of responses to complex emotional stimuli. Models of antidepressant action on emotional processing have the potential to elucidate mechanisms underlying drug efficacy (Harmer et al., 2009a; Kemp et al., 2008; Pringle et al., 2011;

Roiser et al., 2012), highlighting the need to further examine the model proposed here. Given that the neurophysiological impacts of antidepressants are further differentiated by the valence of emotional stimuli (see Harmer, 2004; Harmer et al., 2009b; Kemp et al., 2004), consistent with the notion that antidepressants potentiate positive emotion and suppress negative emotion (shifts in emotional bias; Harmer et al., 2009a; Pringle et al., 2011), future modeling should consider the impact of valence of emotional stimuli on SSRI and NRI administration.

4.3 Future Research

The present study demonstrated that differential acute treatment responses to antidepressants may be measured using fMRI. Future research should examine whether these treatment-specific patterns of activation are present in clinical samples, and determine whether these acute treatment responses are able to help predict efficacy of chronic treatment. Once this has been determined, further investigation needs to establish whether early neural modifications in response to a course of treatment will prove more effective than the current practice of waiting four-to-six weeks to then decide whether the course of treatment requires modification. Secondly, future research is needed to examine the impact of SNRIs as compared to SSRIs and NRIs in order to determine the specificity of serotonergic and noradrenergic treatment effects. Further research is also needed on neural responses to positive stimuli in order to further clarify the effects of antidepressants on anhedonia.

4.4 Limitations

The present study has some limitations. First, the number of statistical parametric maps from the eleven examinations of SSRIs and NRIs with a total of 152 subjects on which analyses were conducted may be considered small. However, a similar, recent meta-analysis reported on findings from nine studies and 126 subjects (Delaveau et al., 2011). While some of the results (seven out of the 79 clusters found across all analyses) were

significant at the $p < 0.01$, uncorrected level, our confidence in the obtained findings is reinforced by the consistency of our findings—above chance—across the studies included in the analyses, as shown by the proportions of contrasts found to activate the clusters (Figure 2, Panel B). The confidence in our findings is further increased through our stringent methodological approach of reducing heterogeneity in our analyses by only extracting data from studies on healthy samples and examining tasks with emotional faces and pictures separately, given that responses to emotion processing tasks are heterogeneous depending on the task type (see Bleich-Cohen et al., 2006; Britton et al., 2006b; 2006a; Hariri et al., 2002) and population (e.g., Keedwell et al., 2005).

Secondly, as few studies included positive stimuli in their experimental tasks, our conclusions relate to the neural effects associated with the processing of negative stimuli. We are therefore unable to make any comment on potential differential effects of antidepressants on negative versus positive stimuli. More research in this area will provide the opportunity to examine valence as an additional factor in meta-analysis studies. Nevertheless, our findings demonstrate for the first time that SSRIs and NRIs have differential acute effects on emotion processing. Our findings provide a platform on which future research into specific antidepressant effects on emotion biases may be conducted. Future research on both healthy and clinical samples would further understanding of treatment mechanisms and enable exploration of treatment outcome predictors.

4.5 Conclusion

In conclusion, antidepressants have differential acute effects on emotion processing in healthy participants. Building on previous research, our novel contribution is an illustration of the manner in which different classes of antidepressants have specific acute effects on the processing of emotional faces and pictures. We propose a model of these differential effects on emotion processing, which needs to be further examined in healthy as well as clinical samples. Our findings further suggest the need to consider the impact of

different tasks, along with positive as well as negative valence, in order to determine the early effects of antidepressants on emotion processing. These findings have important implications for better understanding differential clinical efficacy of the SSRI versus the NRI class of antidepressants.

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Figure Captions

Figure 1. Visualisation of the coordinates included in the MKDA analyses. Red and Blue dots differentiate coordinates that are included in the Increased and Decreased MKDA analyses, respectively.

Figure 2. Visualization of the differential acute effects impacts of SSRIs and NRIs emotion processing. Panel A: MKDA analysis of the antidepressant type \times task type interaction showing increased activation cluster of left DLPFC and a decreased activation cluster of the right amygdaloid-hippocampal region. Panel B: Proportions of contrasts found to activate the clusters found in the MKDA analyses across antidepressant type \times task type interaction conditions. Panel C: A model for the differential acute effects of acute 5-HT and NA augmentation on emotion processing, laying the foundation for downstream neuroadaptive effects and symptom amelioration.

Figures and Tables are attached separately.

Figure 1. Color reproduction on web and print.

Figure 2. Colour reproduction on web and print.