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Review

Acute neural effects of selective serotonin reuptake inhibitors versus noradrenaline reuptake inhibitors on emotion processing: Implications for differential treatment efficacy

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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.

Contents

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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; den Heijer et al., 2012); the thalamus, a processing centre 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 coruleus (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,b).

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., 2010, 2011; 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 repute 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., 2009, 2012; 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

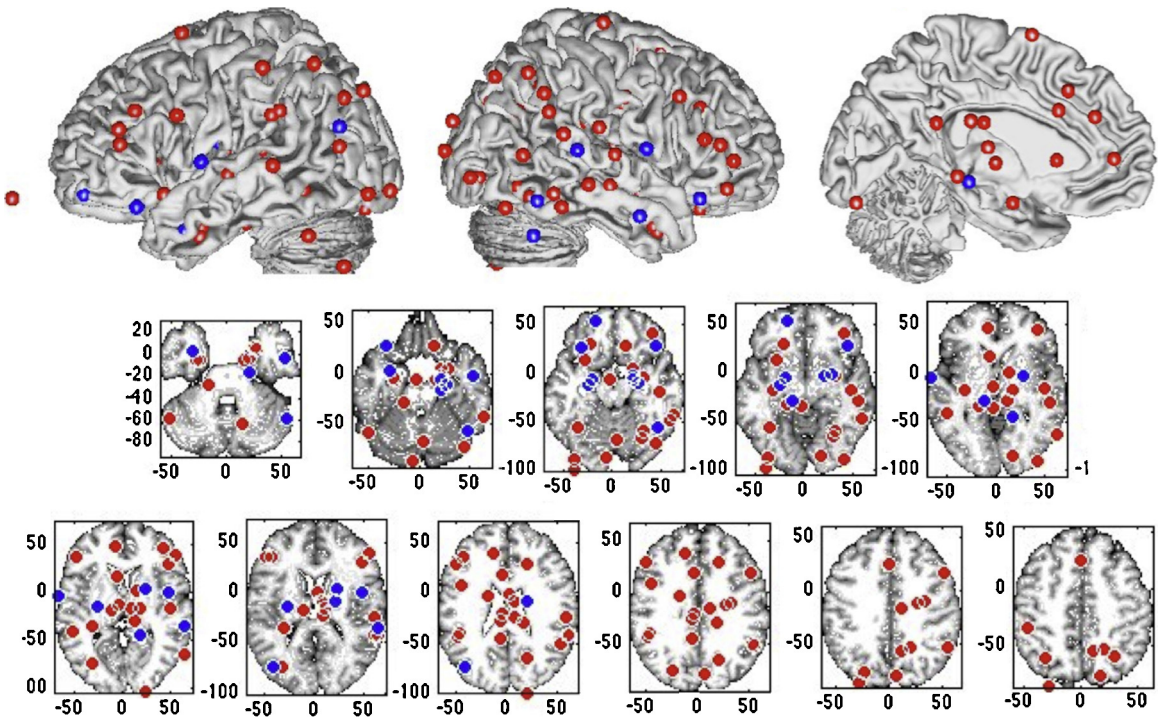

Fig. 1. Visualisation of the coordinates included in the MKDA analyses. Red and Blue dots differentiate coordinates that are included in the Increased and Decreased MKDA analyses, respectively.

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; (3) they reported findings based on a single oral or intravenous dose of an antidepressant; (4) 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 Multi-Level Kernel Density Analysis (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., 2010, 2011). 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 81 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 Fig. 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. Multi-Level 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 utilised 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

Table 1
MKDA results of effects by task.

Contrast	Region	BA	MNI coordinates			Voxels	Maxstat.
			X	*Y*	*Z*		
Faces							
Increased	R. AMY		24	0	−24	91	1.11
	R. uncus		22	0	−28	47	
	R. AMY		26	0	−20	44	
Decreased	*n.s.*						
Pictures							
Increased	R. thalamus		8	−8	16	3	1.07
	R. thalamus		8	−16	20	8	1.16
	L. DLPFC	46/48	−46	32	28	39	0.91
Decreased	*n.s.*						
Faces > Pictures							
Increased	R. AMY		24	0	−24	91	1.11
	R. uncus		22	0	−28	47	
	R. AMY		26	0	−20	44	
Decreased	*n.s.*						
Pictures > Faces							
Increased	R. thalamus		8	−8	16	3	1.07
	R. thalamus		8	−16	20	8	1.16
	L. DLPFC	45/46	−46	32	28	39	0.91
	R. MCC	23	10	−12	30	62	0.26
Decreased	*n.s.*						

Note: Coordinates denote point of most consistent peak activation across clusters and subclusters; all clusters are significant at $p < .05$, FWE corrected; *n.s.*: no significant clusters; BA: Brodmann's Area; Voxels: number of voxels in cluster; Maxstat.: maximum statistic value; AMY: amygdala, DLPFC: dorsolateral prefrontal cortex, MCC: middle cingulate cortex.

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.

Table 2
MKDA results of effects by antidepressant type.

Contrast	Region	BA	MNI Coordinates			Voxels	Maxstat.
			X	*Y*	*Z*		
SSRI							
Increased	*n.s.*						
Decreased	R. amygdaloid-hippocampal		24	−8	−18	317	1.64
	→		24	−6	−24	88	
	→		24	−8	−16	229	
NRI							
Increased	L. MCC	23	4	−28	18	2696	0.65**
	L. PCC						
	R. PCC						
	R. thalamus						
Decreased	*n.s.*						
SSRI > NRI							
Increased	*n.s.*						
Decreased	R. amygdaloid-hippocampal		24	−8	−18	317	1.64
	→		24	−6	−24	88	
	→		24	−8	−16	229	
NRI > SSRI							
Increased	*n.s.*						
Decreased	*n.s.*						

Note: Coordinates denote point of most consistent peak activation across clusters and subclusters; *n.s.*: no significant clusters; $p < .05$, FWE corrected unless otherwise noted; BA: Brodmann's Area; Voxels: number of voxels in cluster; Maxstat.: maximum statistic value; MCC: middle cingulate cortex, PCC: posterior cingulate cortex.
** $p < 0.01$, uncorrected.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2013.07.010.

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 Fig. 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.,

Table 3
MKDA results of interaction effect and follow-up comparisons.

Contrast	Region	BA	MNI Coordinates			Voxels	Maxstat.
			X	*Y*	*Z*		
Interaction							
Increased	L. DLPFC	45/46	−44	36	18	201	1.13
	→		−42	36	16	83	
	→		−46	32	20	64	
	→		−46	40	20	54	
Decreased	R. global pallidus		20	0	2	1028	0.57**
	R. thalamus						
	R. caudate						
	R. putamen						
	R. amygdala						
	R. uncus						
SSRI							
Pictures							
Increased	R. MCC	23	18	−30	22	406	0.51
	R. thalamus		16	−30	18	125	
	→		16	−36	24	74	
	→		16	−24	24	87	
	→		20	−30	26	120	
	R. thalamus		8	−10	24	400	0.74
	→		8	−12	18	80	
	→		6	−6	24	117	
	R. caudate		14	−8	24	101	
	R. MCC		8	−12	28	102	
Decreased	R. amygdaloid-hippocampal		26	−8	−16	1365	1.07
	→		20	−16	−30	165	
	→	28	30	−12	−24	172	
	→		22	−20	−24	193	
	→		22	−6	−22	150	
	→		28	−6	−12	341	
	R. claustrum/putamen		34	−2	−4	113	
	R. insula		26	−2	0	231	
	L. frontal inf. orbital	11/47	−32	28	−16	515	1.07
	→		−32	28	−22	130	
	→		−32	22	−14	132	
	→		−26	28	−16	92	
	→		−34	32	−14	161	
	L. amygdaloid-hippocampal		−24	−12	−14	515	1.07
	→		−24	−12	−20	130	
	→		−24	−18	−12	132	
	→		−18	−12	−14	92	
	L. AMY		−26	−8	−12	161	
	R. STG	22/42	64	−36	10	485	1.07
	→		64	−36	4	127	
	→		64	−42	12	132	
	→		68	−32	10	83	
	→		60	−34	14	143	
	R. insula/rolandic operculum	48	48	0	10	512	1.07
	→		48	0	4	130	
	→		48	−6	12	129	
	→		54	0	10	92	
	→		46	4	12	161	
Faces							
Increased	*n.s.*						
Decreased	R. amygdaloid-hippocampal		20	−4	−12	134	0.57
	R. globus pallidus		22	−2	−2	1406	0.34**
	R. thalamus						
	R. caudate						
	R. putamen						
Pictures > Faces							
Increased	R. MCC	23	18	−30	22	406	0.51
	→		16	−30	18	125	
	→		16	−36	24	74	
	→		16	−24	24	87	
	→		20	−30	26	120	
	R. thalamus		8	−10	24	400	0.74
	→		8	−12	18	80	
	→		6	−6	24	117	
	R. caudate		14	−8	24	101	
	R. MCC		8	−12	28	102	
Decreased	R. amygdaloid-hippocampal		28	−14	−16	853	1.07
	→		20	−16	−30	171	
	→		30	−12	−26	105	
	→		20	−20	−24	143	

Table 3 (*Continued*)

Contrast	Region	BA	MNI Coordinates			Voxels	Maxstat.
			X	*Y*	*Z*		
	→		32	−4	−18	33	
	→		28	−16	−18	123	
	→		32	−6	−6	86	
	→		30	4	−4	100	
	→		26	−8	0	40	
	→		32	−2	2	52	
	L. frontal inf. orbital	11/47	−32	28	−16	515	1.07
	→		−32	28	−22	130	
	→		−32	22	−14	132	
	→		−26	28	−16	92	
	→		−34	32	−14	161	
	L. amygdaloid-hippocampal		−26	−14	−16	303	1.07
	→		−26	−12	−18	153	
	→		−26	−16	−12	150	
	R. STG	22/42	64	−36	10	485	1.07
	→		64	−36	4	127	
	→		64	−42	12	132	
	→		68	−32	10	83	
	→		60	−34	14	143	
	R. insula/rolandic operculum	48	48	0	10	512	1.07
	→		48	0	4	130	
	→		48	−6	12	129	
	→		54	0	10	92	
	→		46	4	12	161	
Faces > Pictures							
Increased	*n.s.*						
Decreased	R. amygdaloid-hippocampal		18	−4	−14	76	0.57
	→		18	−2	−14	59	
	→		20	−8	−10	17	
NRI							
Pictures							
Increased	R. thalamus		16	−24	4	22	0.65
	→		16	−24	2	11	
	→		14	−22	4	11	
	R. STG	22/42	62	−42	18	365	0.65
	→		62	−46	16	146	
	→		62	−40	20	219	
	L. DLPFC	45/46	−42	36	22	505	0.65
	→		−44	38	18	179	
	→		−44	30	22	88	
	→		−36	38	22	90	
	→		−44	36	28	148	
	L. MCC	23	−4	−24	26	246	0.65
	→		−6	−24	24	114	
	→		−2	−24	28	132	
	L. PCC	23/31	−6	−36	24	2	0.65
	L. MCC	24	−2	20	36	96	0.65
	→		0	22	36	50	
	→		−4	20	38	46	
	R. thalamus		6	−28	16	2426	0.33**
Decreased	L. STG	48	−64	−4	6	374	0.97
	→		−64	−4	0	98	
	→		−66	−10	6	94	
	→		−60	−4	6	92	
	→		−66	−2	10	90	
Faces							
Increased	*n.s.*						
Decreased	*n.s.*						
Pictures > Faces							
Increased	R. thalamus		16	−24	4	22	0.65
	→		16	−24	2	11	
	→		14	−22	4	11	
	R. STG	22/42	62	−42	18	365	0.65
	→		62	−46	16	146	
	→		62	−40	20	219	
	L. DLPFC	45/46	−42	36	22	505	0.65
	→		−44	38	18	179	
	→		−44	30	22	88	
	→		−36	38	22	90	
	→		−44	36	28	148	
	L. MCC	23	−4	−24	26	246	0.65
	→		−6	−24	24	114	
	→		−2	−24	28	132	
	L. PCC	23/31	−6	−36	24	2	0.65
	L. MCC	24	−2	20	36	96	0.65

Table 3 (*Continued*)

Contrast	Region	BA	MNI Coordinates			Voxels	Maxstat.
			X	*Y*	*Z*		
	→		0	22	36	50	
	→		−4	20	38	46	
	R. thalamus		6	−28	16	2426	0.33**
Decreased	L. STG	48	−64	−4	6	374	0.97
	→		−64	−4	0	98	
	→		−66	−10	6	94	
	→		−60	−4	6	92	
	→		−66	−2	10	90	
Faces > Pictures							
Increased	*n.s.*						
Decreased	*n.s.*						
Pictures							
SSRI > NRI							
Increased	R. MCC	23/32	20	−32	22	251	0.51
	→		20	−34	20	132	
	→		22	−26	22	73	
	→		16	−30	28	46	
	R. thalamus		10	−10	24	290	0.74
	→		8	−12	20	80	
	→		14	−8	24	101	
	R. MCC	23	8	−8	28	109	
Decreased	R. amygdaloid-hippocampal		26	−8	−16	1365	1.07
	→		20	−16	−30	165	
	→		30	−12	−24	172	
	→		22	−20	−24	193	
	→		22	−6	−22	150	
	→		28	−6	−12	341	
	→		34	−2	−4	113	
	→		26	−2	0	231	
	L. frontal inf. orbital	11/47	−32	28	−16	515	1.07
	→		−32	28	−22	130	
	→		−32	22	−14	132	
	→		−26	28	−16	92	
	→		−34	32	−14	161	
	L. amygdaloid-hippocampal		−24	−12	−14	515	1.07
	→		−24	−12	−20	130	
	→		−24	−18	−12	132	
	→		−18	−12	−14	92	
	→		−26	−8	−12	161	
	R. STG	22/42	64	−36	10	485	1.07
	→		64	−36	4	127	
	→		64	−42	12	132	
	→		68	−32	10	83	
	→		60	−34	14	143	
	R. insula/rolandic operculum	48	48	0	10	512	1.07
	→		48	0	4	130	
	→		48	−6	12	129	
	→		54	0	10	92	
	→		46	4	12	161	
NRI > SSRI							
Increased	R. thalamus		16	−24	2	20	0.65
	R. STG	22/42	62	−42	18	365	0.65
	→		62	−46	16	146	
	→		62	−40	20	219	
	L. DLPFC	45/46	−42	36	22	461	0.65
	→		−44	38	18	179	
	→		−42	30	22	73	
	→		−36	38	22	90	
	→		−42	38	26	119	
	L. MCC	23	−4	−24	26	236	0.65
	→		−6	−24	24	106	
	→		−2	−24	28	130	
	L. PCC	23/31	−6	−36	24	2	0.65
	L. MCC	24	−2	20	36	96	0.65
	→		0	22	36	50	
	→		−4	20	38	46	
Decreased	L. STG	48	−64	−4	6	374	0.97
	→		−64	−4	0	98	
	→		−66	−10	6	94	
	→		−60	−4	6	92	
	→		−66	−2	10	90	

Table 3 (*Continued*)

Contrast	Region	BA	MNI Coordinates			Voxels	Maxstat.
			X	*Y*	*Z*		
Faces							
SSRI > NRI							
Increased	*n.s.*						
Decreased	R. amygdaloid-hippocampal		20	−4	−12	134	0.57
	R. globus pallidus		22	−2	−2	1406	0.34**
	R. thalamus						
	R. caudate						
	R. putamen						
NRI > SSRI							
Increased	*n.s.*						
Decreased	*n.s.*						
SSRI Pictures > NRI Faces							
Increased	R. MCC		18	−30	22	400	0.51
	R. thalamus		16	−30	18	125	
	→		16	−36	24	74	
	→		16	−24	24	81	
	→		20	−30	26	120	
	R. thalamus		8	−8	22	331	0.74
	→		8	−12	20	89	
	→		6	−6	22	106	
	→		14	−8	24	85	
	R. MCC		4	−10	28	51	
Decreased	R. amygdaloid-hippocampal		26	−8	−16	1365	1.07
	→		20	−16	−30	165	
	→		30	−12	−24	172	
	→		22	−20	−24	193	
	→		22	−6	−22	150	
	→		28	−6	−12	341	
	R. claustrum/putamen		34	−2	−4	113	
	R. insula		26	−2	0	231	
	L. frontal inf. orbital	11/47	−32	28	−16	515	1.07
	→		−32	28	−22	130	
	→		−32	22	−14	132	
	→		−26	28	−16	92	
	→		−34	32	−14	161	
	L. amygdaloid-hippocampal		−24	−12	−14	515	1.07
	→		−24	−12	−20	130	
	→		−24	−18	−12	132	
	→		−18	−12	−14	92	
	L. AMY		−26	−8	−12	161	
	R. STG	22/42	64	−36	10	485	1.07
	→		64	−36	4	127	
	→		64	−42	12	132	
	→		68	−32	10	83	
	→		60	−34	14	143	
	R. insula/rolandic operculum	48	48	0	10	512	1.07
	→		48	0	4	130	
	→		48	−6	12	129	
	→		54	0	10	92	
	→		46	4	12	161	
NRI Pictures > SSRI Faces							
Increased	R. thalamus		16	−24	4	22	0.65
	→		16	−24	2	11	
	→		14	−22	4	11	
	R. STG	22/42	62	−42	18	365	0.65
	→		62	−46	16	146	
	→		62	−40	20	219	
	L. DLPFC	45/46	−40	36	24	299	0.65
	→		−36	38	20	87	
	→		−40	32	26	91	
	→		−42	40	26	121	
	L. MCC	23	−4	−24	26	246	0.65
	→		−6	−24	24	114	
	→		−2	−24	28	132	
	L. PCC	23/31	−6	−36	24	2	0.65
	L. MCC	24	−2	20	36	96	0.65
	→		0	22	36	50	
	→		−4	20	38	46	
Decreased	L. STG	48	−64	−4	6	374	0.97
	→		−64	−4	0	98	
	→		−66	−10	6	94	
	→		−60	−4	6	92	
	→		−66	−2	10	90	

Table 3 (*Continued*)

Contrast	Region	BA	MNI Coordinates			Voxels	Maxstat.
			X	*Y*	*Z*		
NRI Faces > SSRI Pictures							
Increased	*n.s.*						
Decreased	*n.s.*						
SSRI Faces > NRI Pictures							
Increased	*n.s.*						
Decreased	R. amygdaloid-hippocampal		20	−4	−12	134	0.57
	R. globus pallidus		22	−2	−2	1406	0.34**
	R. thalamus						
	R. caudate						
	R. putamen						

Note: Coordinates denote point of most consistent peak activation across clusters and subclusters; *n.s.*: no significant clusters; $p < .05$, FWE corrected unless otherwise noted; BA: Brodmann's Area; Voxels: number of voxels in cluster; Maxstat.: maximum statistic value; DLPFC: dorsolateral prefrontal cortex, MCC: middle cingulate cortex, AMY: amygdala, STG: superior temporal gyrus.

** $p < 0.01$, uncorrected.

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., 2006a,b; 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

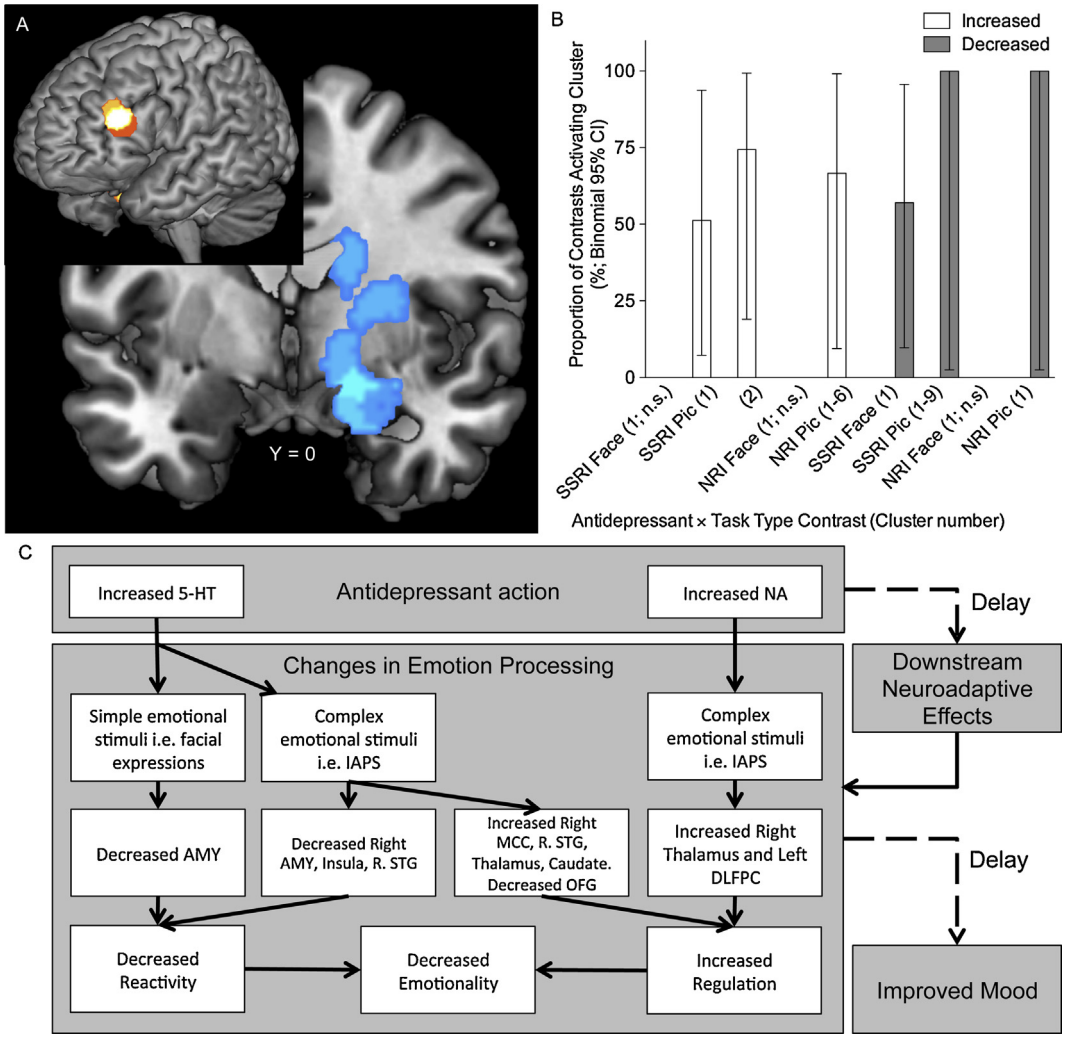

Fig. 2. Visualisation of the differential acute effects impacts of SSRIs and NRIs emotion processing. Panel A: MKDA analysis of the antidepressant type × task type interaction showing increased activation cluster of left DLPFC and a decreased activation cluster of the right amygdaloid-hippocampal region. Panel B: Proportions of contrasts found to activate the clusters found in the MKDA analyses across antidepressant type × 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.

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, 1997, 2003, 2007). These models characterise 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 centre 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., 2009, 2012; 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., 2009, 2012; Eyding et al., 2010)—that SSRIs are more effective antidepressants than NRIs.

4.2. Towards 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 Fig. 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 modelling 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 (Fig. 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., 2006a,b; 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.

5. 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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References

Amiez, C., Sallet, J., Procyk, E., Petrides, M., 2012. Modulation of feedback related activity in the rostral anterior cingulate cortex during trial and error exploration. NeuroImage 63, 1078–1090.

Anderson, I.M., Del-Ben, C.M., McKie, S., Richardson, P., Williams, S.R., Elliott, R., Deakin, J.F.W., 2007. Citalopram modulation of neuronal responses to aversive face emotions: a functional MRI study. Neuroreport 18, 1351–1355.

Arce, E., Simmons, A.N., Lovero, K.L., Stein, M.B., Paulus, M.P., 2007. Escitalopram effects on insula and amygdala BOLD activation during emotional processing. Psychopharmacology 196, 661–672.

Arnone, D., McKie, S., Elliott, R., Thomas, E.J., Downey, D., Juhasz, G., Williams, S.R., Deakin, J.F.W., Anderson, I.M., 2012. Increased amygdala responses to sad but not fearful faces in major depression: relation to mood state and pharmacological treatment. American Journal of Psychiatry 169, 841–850.

Balderston, N.L., Schultz, D.H., Helmstetter, F.J., 2011. The human amygdala plays a stimulus specific role in the detection of novelty. NeuroImage 55, 1889–1898.

Banks, S.J., Eddy, K.T., Angstadt, M., Nathan, P.J., Phan, K.L., 2007. Amygdala frontal connectivity during emotion regulation. Social Cognitive and Affective Neuroscience 2, 303–312.

Beck, A.T., 2008. The evolution of the cognitive model of depression and its neurobiological correlates. American Journal of Psychiatry 165, 969–977.

Beck, A.T., Rush, A.J., Shaw, B.F., Emery, G., 1979. Cognitive Therapy of Depression. The Guilford Press, New York.

Bellani, M., Baiano, M., Brambilla, P., 2010. Brain anatomy of major depression. I. Focus on hippocampus. Epidemiologia e Psichiatria Sociale 19, 298–301.

Belmaker, R.H., Agam, G., 2008. Major depressive disorder. New England Journal of Medicine 358, 55–68.

Bigler, E.D., Mortensen, S., Neeley, E.S., Ozonoff, S., Krasny, L., Johnson, M., Lu, J., Provencal, S.L., McMahon, W., Lainhart, J.E., 2007. Superior temporal gyrus, language function, and autism. Developmental Neuropsychology 31, 217–238.

Bigos, K.L., Pollock, B.G., Aizenstein, H.J., Fisher, P.M., Bies, R.R., Hariri, A.R., 2008. Acute 5-HT reuptake blockade potentiates human amygdala reactivity. Neuropsychopharmacology 33, 3221–3225.

Blair, K.S., Geraci, M., Smith, B.W., Hollon, N., Devido, J., Otero, M., Blair, J.R., Pine, D.S., 2012. Reduced dorsal anterior cingulate cortical activity during emotional regulation and top-down attentional control in generalized social phobia, generalized anxiety disorder, and comorbid generalized social phobia/generalized anxiety disorder. Biological Psychiatry 72, 476–482.

Bleich-Cohen, M., Mintz, M., Pianka, P., Andelman, F., Rotshtein, P., Hendler, T., 2006. Differential stimuli and task effects in the amygdala and sensory areas. Neuroreport 17, 1391–1395.

Blier, P., 2001. Crosstalk between the norepinephrine and serotonin systems and its role in the antidepressant response. Journal of Psychiatry and Neuroscience 26 (Suppl.), S3–S10.

Bönisch, H., Brüss, M., 2006. The norepinephrine transporter in physiology and disease. In: Handbook of Experimental Pharmacology., pp. 485–524.

Britton, J.C., Phan, K.L., Taylor, S.F., Welsh, R.C., Berridge, K.C., Liberzon, I., 2006a. Neural correlates of social and nonsocial emotions: an fMRI study. NeuroImage 31, 397–409.

Britton, J.C., Taylor, S.F., Sudheimer, K.D., Liberzon, I., 2006b. Facial expressions and complex IAPS pictures: common and differential networks. NeuroImage 31, 906–919.

Brooks, S.J., Savov, V., Allzén, E., Benedict, C., Fredriksson, R., Schiöth, H.B., 2012. Exposure to subliminal arousing stimuli induces robust activation in the amygdala, hippocampus, anterior cingulate, insular cortex and primary visual cortex: a systematic meta-analysis of fMRI studies. NeuroImage 59, 2962–2973.

Brühl, A.B., Kaffenberger, T., Herwig, U., 2010. Serotonergic and noradrenergic modulation of emotion processing by single dose antidepressants. Neuropsychopharmacology 35, 521–533.

Brühl, A.B., Jäncke, L., Herwig, U., 2011. Differential modulation of emotion processing brain regions by noradrenergic and serotonergic antidepressants. Psychopharmacology 216, 389–399.

Brunello, N., Blier, P., Judd, L.L., Mendlewicz, J., Nelson, C.J., Souery, D., Zohar, J., Racagni, G., 2003. Noradrenaline in mood and anxiety disorders: basic and clinical studies. International Clinical Psychopharmacology 18, 191–202.

Bunney, W.E., Davis, J.M., 1965. Norepinephrine in depressive reactions. A review. Archives of General Psychiatry 13, 483–494.

Bush, G., Luu, P., Posner, M., 2000. Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences 4, 215–222.

Castrén, E., 2004. Neurotrophic effects of antidepressant drugs. Current Opinion in Pharmacology 4, 58–64.

Cipriani, A., Furukawa, T.A., Salanti, G., Geddes, J.R., Higgins, J.P., Churchill, R., Watanabe, N., Nakagawa, A., Omori, I.M., McGuire, H., Tansella, M., Barbui, C., 2009. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 373, 746–758.

Cipriani, A., Purgato, M., Furukawa, T.A., Trespidi, C., Imperadore, G., Signoretti, A., Churchill, R., Watanabe, N., Barbui, C., 2012. Citalopram versus other antidepressive agents for depression. Cochrane Database of Systematic Reviews 7, CD006534.

Craig, A.D.B., 2009. How do you feel—now? The anterior insula and human awareness. Nature Reviews Neuroscience 10, 59–70.

Davidson, R.J., 2002. Anxiety and affective style: role of prefrontal cortex and amygdala. Biological Psychiatry 51, 68–80.

Davidson, R.J., Begley, S., 2012. The brain basis of emotional style. In: The Emotional Life of Your Brain. Hodder & Stoughton, London, UK, pp. 67–90.

Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Putnam, K., 2002. Depression: perspectives from affective neuroscience. Annual Review of Psychology 53, 545–574.

Delaveau, P., Jabourian, M., Lemogne, C., Guionnet, S., Bergouignan, L., Fossati, P., 2011. Brain effects of antidepressants in major depression: a meta-analysis of emotional processing studies. Journal of Affective Disorders 130, 66–74.

Del-Ben, C.M., Deakin, J.F.W., McKie, S., Delvai, N.A., Williams, S.R., Elliott, R., Dolan, M., Anderson, I.M., 2005. The effect of citalopram pretreatment on neuronal responses to neuropsychological tasks in normal volunteers: an FMRI study. Neuropsychopharmacology 30, 1724–1734.

Denny, B.T., Kober, H., Wager, T.D., Ochsner, K.N., 2012. A meta-analysis of functional neuroimaging studies of self- and other judgments reveals a spatial gradient for mentalizing in medial prefrontal cortex. Journal of Cognitive Neuroscience 24, 1742–1752.

Depue, R.A., Spoont, M.R., 1986. Conceptualizing a serotonin trait. A behavioral dimension of constraint. Annals of the New York Academy of Sciences 487, 47–62.

Di Simplicio, M., Norbury, R., Harmer, C.J., 2011. Short-term antidepressant administration reduces negative self-referential processing in the medial prefrontal cortex in subjects at risk for depression. Molecular Psychiatry 17, 503–510.
Domínguez-Borràs, J., Trautmann, S.-A., Erhard, P., Fehr, T., Herrmann, M., Escera, C., 2009. Emotional context enhances auditory novelty processing in superior temporal gyrus. Cerebral Cortex 19, 1521–1529.
Duman, R.S., 2004. Depression: a case of neuronal life and death? Biological Psychiatry 56, 140–145.
Duman, R.S., Monteggia, L.M., 2006. A neurotrophic model for stress-related mood disorders. Biological Psychiatry 59, 1116–1127.
Etkin, A., Wager, T.D., 2007. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. American Journal of Psychiatry 164, 1476–1488.
Etkin, A., Egner, T., Kalisch, R., 2011. Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in Cognitive Sciences 15, 85–93.
Eyding, D., Lelgemann, M., Grouven, U., Härter, M., Kromp, M., Kaiser, T., Kerekes, M.F., Gerken, M., Wieseler, B., 2010. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. BMJ 341, 4737.
First, M., Gil-Ad, I., Taler, M., Tarasenko, I., Novak, N., Weizman, A., 2012. The effects of reboxetine treatment on depression-like behavior, brain neurotrophins, and ERK expression in rats exposed to chronic mild stress. Journal of Molecular Neuroscience, 1–10.
Frank, M.G., Stennett, J., 2001. The forced-choice paradigm and the perception of facial expressions of emotion. Journal of Personality and Social Psychology 80, 75–85.
Frankenstein, U., Wennerberg, A., Richter, W., Bernstein, C., Morden, D., Rémy, F., Mcintyre, M., 2003. Activation and deactivation in blood oxygenation level dependent functional magnetic resonance imaging. Concepts in Magnetic Resonance: Part A 16A, 63–70.
Gillespie, C.F., Garlow, S., Binder, E.B., Schatzberg, A.F., Nemeroff, C.B., 2011. Neurobiology of mood disorders. In: Schatzberg, A.F., Nemeroff, C.B. (Eds.), The American Psychiatric Publishing Textbook of Psychopharmacology. American Psychiatric Publishing, Inc., Arlington, VA.
Godlewska, B.R., Norbury, R., Selvaraj, S., Cowen, P.J., Harmer, C.J., 2012. Short-term SSRI treatment normalises amygdala hyperactivity in depressed patients. Psychological Medicine 42, 1–9.
Grimm, S., Schmidt, C.F., Bermpohl, F., Heinzel, A., Dahlem, Y., Wyss, M., Hell, D., Boesiger, P., Boeker, H., Northoff, G., 2006. Segregated neural representation of distinct emotion dimensions in the prefrontal cortex—an fMRI study. NeuroImage 30, 325–340.
Gross, J.J., 1998. Antecedent- and response-focused emotion regulation: divergent consequences for experience, expression, and physiology. Journal of Personality and Social Psychology 74, 224–237.
Gross, J.J., Thompson, R.A., 2007. Emotion regulation: conceptual foundations. In: Gross, J.J. (Ed.), Handbook of Emotion Regulation. The Guilford Press, New York, pp. 3–24.
Haenisch, B., Bönisch, H., 2011. Depression and antidepressants: insights from knockout of dopamine, serotonin or noradrenaline re-uptake transporters. Pharmacology & Therapeutics 129, 352–368.
Hariri, A.R., Tessitore, A., Mattay, V.S., Fera, F., Weinberger, D.R., 2002. The amygdala response to emotional stimuli: a comparison of faces and scenes. NeuroImage 17, 317–323.
Harmer, C.J., 2004. Increased positive versus negative affective perception and memory in healthy volunteers following selective serotonin and norepinephrine reuptake inhibition. American Journal of Psychiatry 161, 1256–1263.
Harmer, C.J., 2012. Emotional processing and antidepressant action. Current Topics in Behavioral Neurosciences 14, 209–222.
Harmer, C.J., Mackay, C.E., Reid, C.B., Cowen, P.J., Goodwin, G.M., 2006. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. Biological Psychiatry 59, 816–820.
Harmer, C.J., Goodwin, G.M., Cowen, P.J., 2009a. Why do antidepressants take so long to work? A cognitive neuropsychological model of antidepressant drug action. British Journal of Psychiatry 195, 102–108.
Harmer, C.J., O'Sullivan, U., Favaron, E., Massey-Chase, R., Ayres, R., Reinecke, A., Goodwin, G.M., Cowen, P.J., 2009b. Effect of acute antidepressant administration on negative affective bias in depressed patients. American Journal of Psychiatry 166, 1178–1184.
Harmer, C.J., Cowen, P.J., Goodwin, G.M., 2011. Efficacy markers in depression. Journal of Psychopharmacology 25, 1148–1158.
den Heijer, T., van der Lijn, F., Vernooij, M.W., de Groot, M., Koudstaal, P.J., der van Lugt, A., Krestin, G.P., Hofman, A., Niessen, W.J., Breteler, M.M.B., 2012. Structural and diffusion MRI measures of the hippocampus and memory performance. NeuroImage 63, 1782–1789.
Herrero, M.-T., Barcia, C., Navarro, J.M., 2002. Functional anatomy of thalamus and basal ganglia. Childs Nervous System 18, 386–404.
Hyman, S.E., Nestler, E.J., 1996. Initiation and adaptation: a paradigm for understanding psychotropic drug action. American Journal of Psychiatry 153, 151–162.
Jung, Y.-C., Park, H.-J., Kim, J.-J., Chun, J.W., Kim, H.S., Kim, N.W., Son, S.J., Oh, M.-G., Lee, J.D., 2008. Reciprocal activation of the orbitofrontal cortex and the ventrolateral prefrontal cortex in processing ambivalent stimuli. Brain Research 1246, 136–143.
Keedwell, P.A., Andrew, C., Williams, S.C.R., Brammer, M.J., Phillips, M.L., 2005. A double dissociation of ventromedial prefrontal cortical responses to sad and happy stimuli in depressed and healthy individuals. Biological Psychiatry 58, 495–503.
Kemp, A.H., Nathan, P.J., 2004. Acute augmentation of serotonin suppresses cardiovascular responses to emotional valence. International Journal of Neuropsychopharmacology 7, 65–70.
Kemp, A.H., Gray, M.A., Silberstein, R.B., Armstrong, S.M., Nathan, P.J., 2004. Augmentation of serotonin enhances pleasant and suppresses unpleasant cortical electrophysiological responses to visual emotional stimuli in humans. NeuroImage 22, 1084–1096.
Kemp, A.H., Gordon, E., Rush, A.J., Williams, L.M., 2008. Improving the prediction of treatment response in depression: integration of clinical, cognitive, psychophysiological, neuroimaging, and genetic measures. CNS Spectrums 13, 1066–1086 (quiz 1087-8).
Kemp, A.H., Krygier, J., Harmon-Jones, E., 2013. Neuroscientific perspectives of emotion. In: Calvo, R.A., D'Mello, S.K., Gratch, J., Kappas, A. (Eds.), Handbook of Affective Computing. Oxford University Press, Oxford (in press).
Kessler, R.C., Chiu, W.T., Demler, O., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. Archives of General Psychiatry 62, 617–627.
Kober, H., Wager, T.D., 2010. Meta-analysis of neuroimaging data. Wiley Interdisciplinary Reviews: Cognitive Science 1, 293–300.
Kober, H., Barrett, L.F., Joseph, J., Bliss-Moreau, E., Lindquist, K., Wager, T.D., 2008. Functional grouping and cortical–subcortical interactions in emotion: a meta-analysis of neuroimaging studies. NeuroImage 42, 998–1031.
Korb, A.S., Hunter, A.M., Cook, I.A., Leuchter, A.F., 2011. Rostral anterior cingulate cortex activity and early symptom improvement during treatment for major depressive disorder. Psychiatry Research 192, 188–194.
Kukolja, J., Schläpfer, T.E., Keysers, C., Klingmüller, D., Maier, W., Fink, G.R., Hurlemann, R., 2008. Modeling a negative response bias in the human amygdala by noradrenergic–glucocorticoid interactions. Journal of Neuroscience 28, 12868–12876.
Lang, P.J., Greenwald, M.K., Bradley, M.M., Hamm, A.O., 1993. Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology 30, 261–273.
LeDoux, J., 2007. The amygdala. Current Biology 17, R868–R874.
Lee, H., Heller, A.S., van Reekum, C.M., Nelson, B., Davidson, R.J., 2012. Amygdala-prefrontal coupling underlies individual differences in emotion regulation. NeuroImage 62, 1575–1581.
Lindquist, K.A., Wager, T.D., Kober, H., Bliss-Moreau, E., Barrett, L.F., 2012. The brain basis of emotion: a meta-analytic review. Behavioral and Brain Sciences 35, 121–143.
Luo, Q., Holroyd, T., Majestic, C., Cheng, X., Schechter, J., Blair, R.J., 2010. Emotional automaticity is a matter of timing. Journal of Neuroscience 30, 5825–5829.
MacLeod, C., Rutherford, E., Campbell, L., Ebsworthy, G., Holker, L., 2002. Selective attention and emotional vulnerability: assessing the causal basis of their association through the experimental manipulation of attentional bias. Journal of Abnormal Psychology 111, 107–123.
Matsumoto, N., Minamimoto, T., Graybiel, A.M., Kimura, M., 2001. Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events. Journal of Neurophysiology 85, 960–976.
Mayberg, H.S., 1997. Limbic-cortical dysregulation: a proposed model of depression. Journal of Neuropsychiatry and Clinical Neurosciences 9, 471–481.
Mayberg, H.S., 2003. Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. British Medical Bulletin 65, 193–207.
Mayberg, H.S., 2007. Defining the neural circuitry of depression: toward a new nosology with therapeutic implications. Biological Psychiatry 61, 729–730.
McCabe, C., Mishor, Z., 2011. Antidepressant medications reduce subcortical–cortical resting-state functional connectivity in healthy volunteers. NeuroImage 57, 1317–1323.
Miskowiak, K., Papadatou-Pastou, M., Cowen, P.J., Goodwin, G.M., Norbury, R., Harmer, C.J., 2007. Single dose antidepressant administration modulates the neural processing of self-referent personality trait words. NeuroImage 37, 904–911.
Montgomery, S.A., 1997. Reboxetine: additional benefits to the depressed patient. Journal of Psychopharmacology 11, S9–S15.
Murphy, S.E., Norbury, R., O'Sullivan, U., Cowen, P.J., Harmer, C.J., 2009a. Effect of a single dose of citalopram on amygdala response to emotional faces. British Journal of Psychiatry 194, 535–540.
Murphy, S.E., Yiend, J., Lester, K.J., Cowen, P.J., Harmer, C.J., 2009b. Short-term serotonergic but not noradrenergic antidepressant administration reduces attentional vigilance to threat in healthy volunteers. International Journal of Neuropsychopharmacology 12, 169–179.
Norbury, R., Mackay, C.E., Cowen, P.J., Goodwin, G.M., Harmer, C.J., 2007a. The effects of reboxetine on emotional processing in healthy volunteers: an fMRI study. Molecular Psychiatry 13, 1011–1020.
Norbury, R., Mackay, C.E., Cowen, P.J., Goodwin, G.M., Harmer, C.J., 2007b. Short-term antidepressant treatment and facial processing. Functional magnetic resonance imaging study. British Journal of Psychiatry 190, 531–532.
Ochsner, K.N., Gross, J.J., 2005. The cognitive control of emotion. Trends in Cognitive Sciences 9, 242–249.
Ochsner, K.N., Gross, J.J., 2008. Cognitive emotion regulation: insights from social cognitive and affective neuroscience. Current Directions in Psychological Science 17, 153–158.

Onur, O.A., Walter, H., Schlaepfer, T.E., Rehme, A.K., Schmidt, C., Keysers, C., Maier, W., Hurlemann, R., 2009. Noradrenergic enhancement of amygdala responses to fear. Social Cognitive and Affective Neuroscience 4, 119–126.
Papadatou-Pastou, M., Miskowiak, K.W., Williams, J.M.G., Harmer, C.J., Reinecke, A., 2012. Acute antidepressant drug administration and autobiographical memory recall: a functional magnetic resonance imaging study. Experimental and Clinical Psychopharmacology 50, 364–372.
Patin, A., Hurlemann, R., 2011. Modulating amygdala responses to emotion: evidence from pharmacological fMRI. Neuropsychologia 49, 706–717.
Paulus, M.P., Stein, M.B., 2006. An insular view of anxiety. Biological Psychiatry 60, 383–387.
Phelps, E.A., LeDoux, J.E., 2005. Contributions of the amygdala to emotion processing: from animal models to human behavior. Neuron 48, 175–187.
Pitychoutis, P.M., Dalla, C., Sideris, A.C., Tsonis, P.A., Papadopoulou-Daifoti, Z., 2012. 5-HT(1A), 5-HT(2A), and 5-HT(2C) receptor mRNA modulation by antidepressant treatment in the chronic mild stress model of depression: sex differences exposed. Neuroscience 210, 152–167.
Pizzagalli, D.A., 2011. Frontocingulate dysfunction in depression: toward biomarkers of treatment response. Neuropsychopharmacology 36, 183–206.
Pourtois, G., Spinelli, L., Seeck, M., Vuilleumier, P., 2010. Temporal precedence of emotion over attention modulations in the lateral amygdala: intracranial ERP evidence from a patient with temporal lobe epilepsy. Cognitive, Affective, & Behavioral Neuroscience 10, 83–93.
Pringle, A., Browning, M., Cowen, P.J., Harmer, C.J., 2011. A cognitive neuropsychological model of antidepressant drug action. Progress in Neuro-Psychopharmacology and Biological Psychiatry 35, 1586–1592.
Radua, J., Mataix-Cols, D., 2012. Meta-analytic methods for neuroimaging data explained. Biology of Mood & Anxiety Disorders 2, 1–11.
Rawlings, N.B., Norbury, R., Cowen, P.J., Harmer, C.J., 2010. A single dose of mirtazapine modulates neural responses to emotional faces in healthy people. Psychopharmacology 212, 625–634.
Roiser, J.P., Elliott, R., Sahakian, B.J., 2012. Cognitive mechanisms of treatment in depression. Neuropsychopharmacology 37, 117–136.
Roseboom, P.H., Kalin, N.H., 2011. Citalopram and S-Citalopram. In: Schatzberg, A.F., Nemeroff, C.B. (Eds.), The American Psychiatric Publishing Textbook of Psychopharmacology. American Psychiatric Publishing, Inc., Arlington, VA, pp. 363–387.
Scherer, K.R., 2000. Psychological models of emotion. In: Borod, J. (Ed.), The Neuropsychology of Emotion. Oxford University Press, New York, pp. 137–162.
Schildkraut, J.J., 1965. The catecholamine hypothesis of affective disorders: a review of supporting evidence. American Journal of Psychiatry 122, 509–522.
Seminowicz, D.A., Mayberg, H.S., McIntosh, A.R., Goldapple, K., Kennedy, S., Segal, Z., Rafi-Tari, S., 2004. Limbic-frontal circuitry in major depression: a path modeling metanalysis. NeuroImage 22, 409–418.
Sheline, Y.I., Barch, D.M., Donnelly, J.M., Ollinger, J.M., Snyder, A.Z., Mintun, M.A., 2001. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biological Psychiatry 50, 651–658.
Siegle, G.J., Thompson, W., Carter, C.S., Steinhauer, S.R., Thase, M.E., 2007. Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. Biological Psychiatry 61, 198–209.
Stahl, S.M., 1998. Mechanism of action of serotonin selective reuptake inhibitors. Journal of Affective Disorders 51, 215–235.
Takahashi, H., Yahata, N., Koeda, M., Takano, A., Asai, K., Suhara, T., Okubo, Y., 2005. Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. NeuroImage 27, 991–1001.
Trivedi, M.H., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. American Journal of Psychiatry 163, 28–40.
Turk-Browne, N.B., Norman-Haignere, S.V., McCarthy, G., 2010. Face-specific resting functional connectivity between the fusiform gyrus and posterior superior temporal sulcus. Frontiers in Human Neuroscience 4, 176.
Vul, E., Harris, C., Winkielman, P., Pashler, H., 2009. Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. Perspectives on Psychological Science 4, 274–290.
Vytal, K., Hamann, S., 2010. Neuroimaging support for discrete neural correlates of basic emotions: a voxel-based meta-analysis. Journal of Cognitive Neuroscience 22, 2864–2885.
Wager, T.D., 2008. Multilevel Kernel Density Analysis version 1.0. University of Colorado.
Wager, T.D., Davidson, M.L., Hughes, B.L., Lindquist, M.A., Ochsner, K.N., 2008. Prefrontal–subcortical pathways mediating successful emotion regulation. Neuron 59, 1037–1050.
Wager, T.D., Lindquist, M.A., Nichols, T.E., Kober, H., Van Snellenberg, J.X., 2009. Evaluating the consistency and specificity of neuroimaging data using meta-analysis. NeuroImage 45, S210–S221.
Wager, T.D., Barrett, L., Bliss-Moreau, E., 2010. The neuroimaging of emotion. In: Handbook of Emotions. The Guilford Press, New York.
Warner-Schmidt, J.L., Duman, R.S., 2006. Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. Hippocampus 16, 239–249.
Winston, J.S., O'Doherty, J., Dolan, R.J., 2003. Common and distinct neural responses during direct and incidental processing of multiple facial emotions. NeuroImage 20, 84–97.
Yarkoni, T., Barch, D.M., Gray, J.R., Conturo, T.E., Braver, T.S., 2009. BOLD correlates of trial-by-trial reaction time variability in gray and white matter: a multi-study fMRI analysis. PLoS ONE 4, e4257.