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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