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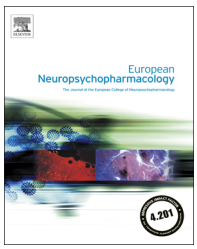

Functional effects of chronic paroxetine versus placebo on the fear, stress and anxiety brain circuit in Social Anxiety Disorder: Initial validation of an imaging protocol for drug discovery

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Abstract
Recent studies suggest that pharmacologic effects of anxiolytic agents can be mapped as functional changes in the fear, stress and anxiety brain circuit. In this work we investigated the effects of a standard treatment, paroxetine (20 mg/day), in subjects with Social Anxiety Disorder (SAD) versus placebo using different fMRI paradigms. The fMRI sessions, performed before and after the treatment, consisted of a public exposition of recorded performance task (PERPT), an emotional face processing task (EFPT) and a 6-min resting state followed by an off-scanner public speaking test. Paroxetine significantly improved the clinical conditions of SAD patients (n=17) vs. placebo (n=16) as measured with Clinical Global Inventory – Improvement (CGI-I) while no change was seen when using Liebowitz Social Anxiety Scale, as expected given the small size of the study population. Paroxetine reduced the activation of insula, thalamus

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and subgenual/anterior cingulate cortex (ACC) in PERPT. Resting-state fMRI assessment using Independent Component Analysis indicated that paroxetine reduced functional connectivity in insula, thalamus and ACC when compared with placebo. Both paradigms showed significant correlation with CGI-I in rostral prefrontal cortex. Conversely, paroxetine compared to placebo produced activation of right amygdala and bilateral insula and no effects in ACC when tested with EFPT. No treatment effects on distress scores were observed in the off-scanner Public Speaking Test. Overall this study supports the use of fMRI as sensitive approach to explore the neurobiological substrate of the effects of pharmacologic treatments and, in particular, of resting state fMRI given its simplicity and task independence.

1. Introduction

Anxiety Disorders are among the most common mental disorders whose societal cost is calling for novel and more effective treatments (Wittchen et al., 2011). A recognised obstacle in the development of novel treatment is the high rate of failure due to lack of clinical efficacy. The current standard clinical measurements of treatment effects generally require large study populations (i.e., hundred subjects) due to their limited effect size (Hedges et al., 2009). The introduction of novel paradigms driven by technological innovation and better knowledge of the disease could reduce cost and the number of subjects enroled in the study. Recent advancements in human functional magnetic resonance imaging (fMRI) based on blood oxygenation level dependent (BOLD) signals indicate the possibility to explore its use as a novel paradigm in drug discovery (Valenzuela et al., 2011).

Functional imaging studies in Anxiety Disorders have focused on measuring the response to emotional or stressful stimuli as BOLD activation level in the amygdala, a brain region classically considered one of the most representative structures of an extended circuit that processes fear, stress and anxiety (Thomas et al., 2001; Phan et al., 2006; Etkin and Wager, 2007; Shin and Liberzon, 2010). Amygdala was described as over-responsive when subjects with either high trait anxiety or diagnosis of Anxiety Disorders were exposed to stressful or negative emotional stimuli (Furmark et al., 2005; Phan et al., 2006; Etkin and Wager, 2007). This over-responsiveness of amygdala was suggested to reflect a disease-related susceptibility, participating to the symptom generation and possibly to the mood congruent bias in processing emotional stimuli observed in Anxiety and Mood Disorders (Thomas et al., 2001; Fu et al., 2004; Etkin and Wager, 2007; Phan et al., 2006). This view led to the proposal that a pharmacologic agent attenuating amygdala hyper-responsiveness would be also an effective treatment for clinical anxiety. Promising findings were obtained using standard therapeutics, such as benzodiazepine (Paulus et al., 2005; Wollweber et al., 2010), pregabaling (Aupperle et al., 2011) and serotonin re-uptake inhibitors (SSRIs) (Furmark et al., 2005; Harmer et al., 2006; Simmons et al., 2009; Schneier et al., 2011; Godlewska et al., 2011). However, amygdala over-responsiveness was not always observed in Anxiety Disorders (Marsh et al., 2008, Whalen et al., 2008) and per se may not be the most appropriate endpoint for pharmacologic studies. For example, a lower or equal, and not higher, amygdala response to negative emotional stimuli was observed in subjects with Anxiety Disorders (Phan et al., 2006; Marsh et al., 2008); and a higher, and not lower, activation to emotionally neutral stimuli were reported (Britton et al., 2010; Cooney et al., 2006), while no effects of amygdala response was found using agomelatine, a novel effective anxiolytic/antidepressant treatment (Lees et al., 2010). These observations suggested the engagement of regulatory processes generated in other components of the fear, stress and anxiety circuit, e.g., the prefrontal cortex (PFC) and anterior cingulate cortex (ACC), areas associated with cognitive appraisal and top-down emotion regulation (Etkin et al., 2006; Goldin et al., 2009; Blair et al., 2011). Another brain region involved in processing interoceptive signals, the insula, was proposed as critical mediator of anxiety (Paulus and Stein, 2006). This simple and attractive view, i.e., focusing on a single brain area, has recently lost ground in respect to the connectivity approach, where the interplay between circuits is conceived as the main substrate of behaviour and symptom generation (Valenzuela et al., 2011; Tromp et al., 2012). According to this model functional impairment of different components of a circuit can generate similar dysfunctional outcomes.

All this background information was used to design an fMRI study to explore novel putative anxiolytic treatments. We attempt an initial validation using paroxetine, a standard SSRI treatment which is particularly effective in subjects with diagnosis of Social Anxiety Disorder (SAD). SAD is a common Anxiety Disorder characterised by heightened fear and avoidance of social situations (APA, 2000). Clinical effects of pharmacologic treatments are generally assessed using the Liebowitz Social Anxiety Scale (LSA) and the Clinical Global Impression-Improvement scale (CGI-I) scales, known to generate similar in effect size (around 0.4) in spite of different psychometric properties (Hedges et al., 2009). Previous studies were dedicated to assess challenge-induced brain activity in SAD patients by exposing them to mildly-arousing tasks involving socially salient stimuli, e.g., human faces expressing emotions (Cooney et al., 2006; Phan et al., 2006; Pujol et al., 2009; Schneier et al., 2011), or distress-provoking highly-arousing tasks, e.g., performing a speech in front of an audience (Furmark et al., 2005; Lorberbaum et al., 2004) or being exposed to social threat (Giménez et al., 2012).

In the present study we explore various fMRI paradigms known to generate different levels of arousal and distress. We included the emotional face processing task (EFPT), a widely used procedure developed by Hariri et al. (2002)