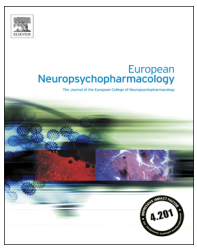
European Neuropsychopharmacology (2013) **23**, 569–580

www.elsevier.com/locate/euroneuro



Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive-compulsive disorder

Marcelo Q. Hoexter[a,b,c,*], Darin D. Dougherty[c], Roseli G. Shavitt[a], Carina C. D'Alcante[a], Fabio L.S. Duran[a], Antonio C. Lopes[a], Juliana B. Diniz[a], Marcelo C. Batistuzzo[a], Karleyton C. Evans[c], Rodrigo A. Bressan[b], Geraldo F. Busatto[a], Euripedes C. Miguel[a]

[a]*Department and Institute of Psychiatry, University of São Paulo Medical School, São Paulo, Brazil*
[b]*Interdisciplinary Laboratory for Clinical Neuroscience (LiNC), Department of Psychiatry, Federal University of São Paulo (UNIFESP), São Paulo, Brazil*
[c]*Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*

Received 14 December 2011; received in revised form 28 June 2012; accepted 30 June 2012

KEYWORDS
OCD;
Neuroimaging;
Gray matter;
Serotonergic reuptake inhibitor;
Cognitive-behavioral therapy

Abstract
Nearly one-third of patients with obsessive–compulsive disorder (OCD) fail to respond to adequate therapeutic approaches such as serotonin reuptake inhibitors and/or cognitive-behavioral therapy (CBT). This study investigated structural magnetic resonance imaging (MRI) correlates as potential pre-treatment brain markers to predict treatment response in treatment-naïve OCD patients randomized between trials of fluoxetine or CBT. Treatment-naïve OCD patients underwent structural MRI scans before randomization to a 12-week clinical trial of either fluoxetine or group-based CBT. Voxel-based morphometry was used to identify correlations between pretreatment regional gray matter volume and changes in symptom severity on the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS). Brain regional correlations of treatment response differed between treatment groups. Notably, symptom improvement in the fluoxetine treatment group (n=14) was significantly correlated with smaller pretreatment gray matter volume within the right middle lateral orbitofrontal cortex (OFC), whereas symptom improvement in the CBT treatment group (n=15) was significantly correlated with larger pretreatment gray matter volume within the right medial prefrontal cortex (mPFC). No significant *a priori* regional correlations of treatment response were identified as common between the two treatment groups when considering the entire sample (n=29). These findings suggest that pretreatment gray matter volumes of distinct brain regions within the lateral OFC

*Corresponding author at: Department and Institute of Psychiatry, University of São Paulo Medical School, Rua Ovídio Pires de Campos 785—3° andar Ala Norte-sala 9 (PROTOC), CEP 05403-010, São Paulo, SP, Brazil. Tel.: +55 11 3069 7896.
E-mail address: mqhoexter@gmail.com (M.Q. Hoexter).

0924-977X/$ - see front matter
http://dx.doi.org/10.1016/j.euroneuro.2012.06.014

and mPFC were differentially correlated to treatment response to fluoxetine versus CBT in OCD patients. This study further implicates the mPFC in the fear/anxiety extinction process and stresses the importance of lateral portions of the OFC in mediating fluoxetine's effectiveness in OCD. Clinical registration information: http://clinicaltrials.gov-NCT00680602.

1. Introduction

Serotonin reuptake inhibitors (SRIs), cognitive-behavioral therapy (CBT) or a combination of both are first line treatments for obsessive–compulsive disorder (OCD) (Koran et al., 2007). However, at least one-third of patients with OCD fails to respond to adequate therapeutic approaches (Mancebo et al., 2006). Therefore, reliable measures to predict which treatment would be more effective in OCD would be of great clinical value. These measures could be used to guide clinical decisions toward the best treatment choice for individuals with OCD (e.g., pharmacotherapy versus CBT).

In this regard, neuroimaging methods have demonstrated some utility for identifying brain patterns predictive of treatment outcome in psychiatric disorders (Evans et al., 2006). There are some neuroimaging treatment studies of mood and anxiety disorders suggesting different mechanisms of action for SRIs and CBT (Benazon et al., 2003; Brody et al., 1998; Gilbert et al., 2000; Hoexter et al., 2012; Martin et al., 2001; Rosenberg et al., 2000). However, given that there are also studies showing similar effects (Baxter et al., 1992; Schwartz et al., 1996), the exact neurobiological underpinnings that predict response to each specific intervention are still not well understood. Brain structures encompassing cortico-subcortical circuits, known to be modulated by serotonergic transmission (el Mansari et al., 1995; Soumier et al., 2009) and implicated in OCD pathophysiology (e.g., orbitofrontal, anterior cingulate and temporolimbic cortices, striatum and thalamus) (Saxena and Rauch, 2000; Valente et al., 2005), are fine candidates. Animal studies have suggested that SRIs were able to modulate serotoninergic neurotransmission earlier in subcortical regions and later in the cerebral cortex (el Mansari et al., 1995). In addition, regions within the medial prefrontal cortex (mPFC), due to their role in fear extinction (Milad et al., 2005; Phelps et al., 2004), should be investigated. More specifically, the mPFC is a key regulatory brain region that participates in the inhibition of conditioned fear responses (thought to underlie some obsessive-compulsive symptoms) and in the mediation of the extinction process of such fear responses (Milad et al., 2005; Phelps et al., 2004). Therefore, this seems a plausible region through which CBT exerts its therapeutic action. The specific mPFC sub-regions that predict fear extinction include the medial orbitofrontal, rostral anterior cingulate and subcallosal cortices (Milad et al., 2005). Moreover, there is evidence showing that successful pharmacological treatments for OCD seems to preferentially exert a subcortical–cortical 'bottom-up' regulation in the brain, whereas CBT seems to elicit cortical–subcortical 'top-down' effects (Derryberry and Tucker, 1992; Goldapple et al., 2004; Tucker et al., 1995).

The majority of the published neuroimaging outcome studies in OCD, using positron emission tomography (PET), have associated pretreatment resting regional metabolism with treatment response (Brody et al., 1998; Evans et al., 2006; Saxena et al., 1999, 2003). The most consistent finding across these studies has been an inverse correlation of pretreatment orbitofrontal cortex metabolism with symptom improvement following SRI exposure (Brody et al., 1998; Saxena et al., 1999). Notably, only one metabolic PET study compared pharmacotherapy and CBT with regard to response prediction. Brody and colleagues showed that lower pretreatment orbitofrontal cortex metabolism correlated with better response to fluoxetine, whereas higher metabolic activity within this region correlated with a better response to CBT (Brody et al., 1998). However, the treatment arms in this study were not randomized, limiting the interpretation of the reported findings. Furthermore, most of the aforementioned studies included patients that had been previously treated with SRIs, an important confounder, which likely contributed to the variability observed across studies. Though metabolic neuroimaging studies have been conducted to evaluate predictors of response in OCD patients with relative success (Brody et al., 1998; Saxena et al., 1999, 2003), morphometrical studies are lacking. This is unfortunate, given that morphometric magnetic resonance imaging (MRI) is widely available, is cheaper, requires no exposure to radiation, and involves a simpler acquisition protocol compared to other neuroimaging methods described above. The heuristic value of using regional brain volumes to predict clinical response has been explored in several studies that investigated other psychiatric disorders such as depression and schizophrenia (Garner et al., 2009; MacQueen, 2009). Thus, the primary aim of the present study is to validate an optimized voxel-based morphometry (VBM) approach to investigate pretreatment structural MRI correlates as potential markers to predict changes in symptom severity in treatment-naïve OCD patients randomized to a clinical trial of either fluoxetine or group-based CBT.

We hypothesized that pretreatment volumetric measures within the principal brain structures implicated in OCD (i.e., orbitofrontal, anterior cingulate and temporolimbic cortices, striatum and thalamus) (Saxena and Rauch, 2000; Valente et al., 2005) would be correlated with subsequent treatment outcome. Specifically, given the effects of serotonin in modulating frontal-subcortical circuits (el Mansari et al., 1995; Soumier et al., 2009) we hypothesized that widespread measurements of gray matter (GM) volume within these territories would be correlated with treatment response to fluoxetine. Conversely, we hypothesized that treatment response to CBT would be correlated with measurements of GM volume within the mPFC, reflecting the primacy of cognitive restructuration and extinction processes attributed to this region (Milad et al., 2005; Phelps et al., 2004).