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Anxiety, Obsessive Compulsive, and Related Disorders (B Brennan and D Dougherty, Section Editors)

The Potential Use of Neuroimaging Biomarkers in the Treatment of Obsessive-Compulsive Disorder

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Opinion statement

Predicting treatment outcome in obsessive-compulsive disorder (OCD) has become an important research priority given the prevalence and disability associated with the disorder and the fact that different effective treatments exist. Here, we summarize recent studies that have used neuroimaging to predict treatment outcome across three different treatment modalities: psychological treatment (exposure and response prevention), medication, and neurosurgery. Although several neural baseline variables have been shown to predict treatment outcome in OCD, results are so far not conclusive. We highlight some limitations from the current literature and offer some conceptual and methodological suggestions for future research.

Introduction

Cognitive-behavior therapy (CBT) consisting of exposure with response prevention (EX/RP), selective serotonin reuptake inhibitors (SSRIs), and their combination are recommended as first-line treatments for patients with

obsessive-compulsive disorder (OCD) [1, 2]. Adding antipsychotics may also be effective for some patients who do not respond to SSRIs [3–5]. When these options fail, there is some preliminary evidence for other medications either as monotherapy (e.g., mirtazapine) or in combination with SSRIs (e.g., memantine), as well as other psychotherapies (e.g., cognitive therapy, acceptance, and commitment therapy) [6]. Some patients who do not benefit from any of these options may benefit from neurosurgical approaches [1]. Given the high prevalence and disability associated with OCD, knowing in advance who will/will not benefit from these treatments is of the utmost importance from a scientific, humane (to avoid unnecessary suffering), and public health (for example, in terms of cost-effectiveness) perspective.

Although the interest in finding outcome predictors for psychiatric treatments is old, with the plethora of neuroimaging studies conducted in recent years, there have been new hopes that we could be close to identifying brain-based "neural signatures" as treatment predictors. This is a line of research that has had recent success in depression [7•].

Two main research strategies have been used when relating neuroimaging variables to treatment outcome [8]. Some studies have focused on pretreatment to posttreatment neural changes (*treatment mechanism studies*). Although these studies refer to "treatment predictors," they look actually at *correlates of outcome* (not true predictors), because the changes can be observed only after the outcome is known [7•]. Here, we will focus on t*reatment outcome prediction* studies, which look at neural baseline variables as predictors of treatment outcome. We will briefly review studies looking at neuroimaging variables as a predictor of treatment outcome in OCD, according to treatment modality (EX/RP, medication, and neurosurgery) and highlight some recent work. Except when noted, all studies reviewed have been conducted in adult outpatients, using individually delivered EX/RP, and the measure of treatment outcome was a change in OCD symptom severity from pretreatment to posttreatment, as measured by the Yale-Brown Obsessive-Compulsive Scale [9]. We also will highlight some limitations of research in this area. Finally, we will offer some suggestions for future studies.

Neuroimaging predictors of EX/RP outcomes

OCD was one of the first mental disorders in which neuroimaging variables were used to predict the outcome of psychological treatment. In a seminal study using 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), Brody and colleagues found that higher activity in the left orbitofrontal cortex (OFC) predicted better EX/RP outcome in OCD ($n = 18$) [10]. Since then, more than 20 studies on neuroimaging and psychological treatment (mainly EX/RP) in OCD have been published. Most often, these were *treatment mechanism studies* (reviewed in [11•]). The literature on treatment predictors is more limited and some of the key recent papers are reviewed below.

Using structural neuroimaging, Hoexter and colleagues found that greater gray matter in the subgenual anterior cingulate cortex (sgACC) is associated with better outcome in unmedicated patients ($n = 15$) receiving group-delivered EX/RP [12]. Another recent study by Fullana and colleagues found that less cortical thickness of the rostral anterior cingulate cortex (rACC) is associated with better EX/RP outcome in medicated patients ($n = 74$) [13].

Studies using single-photon emission computed tomography (SPECT) or functional magnetic resonance imaging (fMRI) at rest have found that greater activity in the orbitofrontal cortex (OFC) predicts a better EX/RP outcome, but this has not been always replicated (reviewed in [14•]). A recent fMRI study by Olatunji and colleagues found that a higher activity during symptom provocation in several brain areas (including the anterior temporal cortex, ventromedial prefrontal cortex, posterior cingulate cortex, uncus, amygdala, and insula) was associated with a better EX/RP outcome in OCD medicated patients (mostly inpatients; $n = 12$) with contamination symptoms [15•]. The authors

interpreted these results as support to the idea that a heightened processing ("fear activation") of emotional information during symptom provocation in OCD may predict greater EX/RP treatment effects.

A few magnetic resonance spectroscopy (MRS) studies have also been conducted (see [16] for a review). For example, using proton MRS, Zurowki and colleagues found that the concentration of (myo)inositol in the OFC predicted a worse EX/RP outcome in unmedicated patients ($n = 20$) [17].

Finally, in a recent resting-state functional connectivity (r-s fc) study, Göttlich and colleagues found that the degree centrality (a marker for altered connectivity) of the right basolateral amygdala (BLA) was positively correlated with EX/RP outcome in unmedicated patients with OCD ($n = 17$) [18•]. Using r-s fc, we have also recently found that the connectivity between the BLA and the medial prefrontal cortex (mPFC) predicts a worse EX/RP outcome in drug-resistant OCD patients ($n = 73$) [Fullana et al., in preparation].

Neuroimaging predictors of medication outcomes

Swedo and colleagues were among the first to test whether neuroimaging could predict the outcome of drug treatment in OCD. Using FDG-PET, these authors showed that a lower activity in the right ACC and right OFC was associated with a positive response (>40 % symptom reduction) in OCD patients ($n = 18$) receiving clomipramine, a nonselective serotonin reuptake inhibitor [19]. Since then, several studies using different neuroimaging techniques (FDG-PET, SPECT, and fMRI) and a variety of SSRIs (e.g., paroxetine, sertraline, and fluvoxamine) have been conducted (reviewed in [8] and [14•]). These studies have mainly implicated the anterior cingulate cortex (ACC) and the OFC in the response to medication, with most studies showing that less pretreatment activity in either brain region predicts a better response to medication in OCD. Only one study so far has looked at possible neuroimaging predictors of antipsychotic augmentation in OCD. Using FDG-PET, Buchsbaum and colleagues found that a lower activity in the striatum (without specification of nuclei) and a higher activity in the ACC were associated with a better response to risperidone augmentation in OCD patients ($n = 15$) not responding to SSRIs [20].

Neuroimaging predictors of neurosurgery outcomes

Different types of stereotactic surgical lesions, including dorsal anterior cingulotomy and anterior capsulotomy, have been used for years to treat selected patients with severe and treatment-refractory OCD. Knowing if a patient will respond to a treatment before using such invasive procedures would be an important step in improving OCD treatment algorithms. Given that this is a highly selected population, relatively few studies have been conducted. Using FDG-PET, Rauch and colleagues found that activity in the posterior cingulate cortex was positively associated with response (>25 % reduction in YBOCS presurgery to postsurgery) 6 months after anterior cingulotomy in 11 OCD patients [21]. More recently, using structural neuroimaging, Banks and colleagues found that less gray matter in the right ACC was associated with a positive treatment response (defined as >35 % reduction in YBOCS presurgery to postsurgery) in 15 OCD patients who underwent dorsal anterior cingulotomy [22•]. In this study, a greater white matter connectivity (as

measured with diffusion tensor imaging) between the right dACC and several brain regions (caudate, putamen, pallidum, thalamus, and hippocampus) also predicted a positive treatment response.

Different predictors for different treatments?

Once the feasibility of predicting treatment outcome using neuroimaging has been established, an important question is whether different predictors exist for different treatments.

Few studies to date have tried to answer this question in OCD. Using FDG-PET, Brody and colleagues found that a higher activity in the left OFC predicted a better outcome with EX/RP, whereas a lower activity in the same brain area predicted a better outcome with fluoxetine ($n = 27$) [10]. Using structural neuroimaging, Hoexter and colleagues found that less gray matter in the ventrolateral PFC predicted a better outcome with fluoxetine whereas more gray matter in the sgACC predicted a better outcome with EX/RP ($n = 29$) [12]. A recent review of PET and SPECT studies suggested that pretreatment activity in the OFC and ACC may be the best way to differentiate between medication and EX/RP responders, with high activity predicting a better response to medication and low activity predicting a better response to EX/RP [14•].

Limitations from research so far

Most studies using neuroimaging to predict treatment outcome in OCD have significant limitations. One limitation is sample size: most studies have included less than 30 participants. Another limitation is that most studies have included patients with comorbid disorders. Although in the "real-world" comorbidity in OCD is the rule rather than the exception, this may have a significant effect on the results of neuroimaging studies.

There are also some limitations that are specific to some treatment modalities. For example, many studies looking at predictors of EX/RP and all neurosurgery studies have included patients on medication. Although this is close to clinical reality (and most often unavoidable in the case of neurosurgery), it is difficult to draw firm conclusions from these studies given the likely effects of medication on the neural circuits studied. In addition, in the EX/RP studies, the EX/RP procedures differ across studies (as regards number/frequency of sessions, experience of therapists, compliance with "homework," etc.).

Methodological aspects specifically related to neuroimaging also limit our interpretation of the findings. These include the low (or sometimes unknown) reliability of some neuroimaging measures (see [8]) or the use of the same dataset for the selection and validation of predictors [23]. Ideally, predictors established in one sample should be validated in another (independent) sample (see [24] for an example in MDD). However, few neuroimaging treatment-prediction studies in OCD have followed this strategy (but see [25•] for an exception).

Moreover, many studies have used regions of interest (ROI) analyses focusing on particular brain regions. For example, the first OCD studies on neuroimaging treatment predictors focused on cortico-striatal areas given its putative relevance in the pathophysiology the disorder whereas more recent studies have focused on the amygdala or the ventromedial prefrontal cortex, following a renewed interest on these areas in OCD [26]. Although ROI

approaches are well established, they increase the vulnerability to type II errors (failing to detect significant results outside the predetermined ROIs) [27].

Finally, it is also important to note that most of the data we have so far on outcome prediction using neuroimaging in OCD comes from secondary analyses. For example, few studies were designed initially and specifically to look for neuroimaging predictors of (different) treatments for OCD.

Where to go next

An important conceptual issue in the area of neuroimaging predictors of treatment in mental health is whether we should look for predictors that are disorder-specific or treatment-specific (or both). In the case of OCD, one may guess that cortico-striatal abnormalities may predict the outcome of treatment, given the likely involvement of those abnormalities in the disorder. However, treatments *may not* work by directly correcting a pathogenic process but through other means. For example, CBT treatments (including EX/RP) may work by improving fear extinction. Therefore, activity (or structural variability) in "fear extinction areas" such as the prefrontal cortex or limbic system (see [26]) rather than in cortico-striatal regions may predict treatment outcome in EX/RP for OCD (and more generally, in exposure therapy for fear-related disorders).

Alternatively, EX/RP in OCD may "work" by increasing the inhibition capacities of the individual, which may be associated with activity/variability in *other* brain areas such as the supplementary motor area (see [28]). Unfortunately, we do not have sufficient knowledge on how CBT works at the neural level to make such specific predictions and a similar argument can be made for drug or neurosurgical treatments. As stated before, it seems that comparing different types of treatment (e.g., medication versus EX/RP) has a good potential to inform the field.

Conclusion

The ultimate goal of identifying predictors (including neuroimaging) of treatment outcome is to individualize therapy, i.e., to determine which treatment is going to be more/less successful for a particular patient. However, research on predictors in OCD (and in fact, in most mental disorders) is often conducted at the group (not at the single-subject) level. In recent years, new statistical approaches have been developed, which may help change this trend. These include random forest models (see [29•], for an example in generalized anxiety disorder and social anxiety disorder (SAD)) or support vector machine models (see [30] for an example in SAD). These analyses methods have, to our knowledge, not been applied to predict outcome using neuroimaging in OCD.

Another important issue is to what extent a "new" treatment predictor (e.g., a neural variable) has incremental explanatory power compared to other known predictors. If neural predictors are to be used in clinical practice, it is important to show that they predict the response to treatment *over and above* other more easy-to-collect measures (see [24] or [31] for examples of these approaches in MDD and SAD). For example, in our recent rs-fc study [Fullana et al., in preparation], we were able to show that a measure of BLA-mPFC connectivity was a significant predictor of EX/RP outcome *over and above* baseline OCD severity, which has been associated with negative EX/RP outcome in some studies [32].

Finally, it will be important in the future to know whether different neuroimaging measures (e.g., fMRI and morphometric measures) can be combined to explain nonoverlapping variability and therefore to improve prediction in treatment outcome. An example of this strategy, where cortical thickness and r-s f-c measures were combined can be found in our recent work [Fullana et al., in preparation].

Compliance with Ethical Standards

Conflict of Interest

Miquel A. Fullana declares no conflict of interest.

H. Blair Simpson reports royalties from UpToDate, Inc., other from Cambridge University Press, outside the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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