Chapter 15

Brain Imaging and the Prediction of Treatment Outcomes in Mood and Anxiety Disorders

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Neuroimaging for treatment prediction: An advance in personalized medicine

In addition to elucidating the mechanisms of disease, neuroimaging holds another great promise for the mental health field: the ability to predict treatment outcomes. Evidence-based treatments are available for many mental health disorders. However, not all individuals benefit from every treatment. Psychiatric research has begun to focus on the neurobiological factors that predict who will benefit from an intervention by experiencing symptom improvement. This application of neuroimaging is still very much in development, but it has the potential to facilitate a major advance in psychiatry, namely that of personalized care. Personalization of treatment for mental health disorders has been identified as a public health priority [1]. The idea is to select the best therapy for a patient at the beginning of treatment based on a set of patient characteristics that have been shown to be associated with positive outcomes with a given intervention. Those who are well matched for a particular treatment are more likely to stay engaged in the treatment, which will lead to better outcomes [2]. Given the scarcity and expense of available mental health resources, treatment should be conserved so that sufficient resources are available for those who would benefit from a specific type of treatment [3]. Optimally, these efforts will serve to guide treatment development and planning, improve overall response rates, decrease treatment costs, and eventually improve the prognosis of those who suffer from mental illness. In this chapter we review recent advances in application of neuroimaging tools to predict treatment response in patients with internalizing psychological disorders. Following the core themes of *Brain Mapping,* this chapter focuses on describing the brain structures and functions that have been associated with clinically significant response to

psychological and pharmacological treatments in internalizing disorders in addition to the underling research methodology used to investigate such relationships.

2. Internalizing disorders: The focus on mood and anxiety disorders

It is critically important to direct attention towards the study of internalizing problems. Internalizing disorders are associated with significant impairment and distress and they often lead to the development and reoccurrence of debilitating psychiatric illness [4,5]. Based on empirically derived classification models, internalizing disorders are characterized by maladjustment primarily expressed inwardly, as compared to externalizing patterns of behavior where maladjustment is expressed outwardly [6,7]. Although internalizing behavior is increasingly conceptualized as a dimensional construct, treatment research has typically focused on extreme conditions, tending to examine questions regarding internalizing behavior through the lens of discrete psychiatric disorders. Some internalizing disorders, such as Major Depressive Disorder (MDD) and Generalized Anxiety Disorder (GAD), involve negative affect characterized by anxious misery and distress. Other internalizing disorders, including Social Phobia, Specific Phobia, Agoraphobia, and Panic Disorder, involve negative affect associated with activation of the fear system. Obsessive Compulsive Disorder (OCD) has also been characterized as an internalizing disorder [8]. Grouping mental illnesses more broadly along an internalizing dimension is advantageous in a number of ways. Namely, this approach accounts for the high rates of comorbidity between internalizing disorders and it groups problems that share commonalities in pathophysiology and genetic variance [7]. For example, internalizing problems are centrally implicated in the threat response system and involve abnormalities in fronto-limbic brain circuitry. This chapter focuses on the most commonly exhibited internalized disorders, namely MDD and Anxiety Disorders [9].

3. Available treatments for major depressive disorder and anxiety disorders

The past two decades have shown significant advances in the development and refinement of treatments available to those who suffer from internalizing problems. Validated, evidence-based treatments (EBTs) are now available for treating the classes of internalizing problems discussed here, including specific mood and anxiety disorders. The commonalities in the EBTs for these classes of problems are considerable. Validated treatments include medication and/or psychotherapy [10-12].

In MDD, first-line treatments that are currently offered include antidepressant medications and psychotherapy. Regarding antidepressants, the first options are typically those that impact the monoamine neurotransmitters, such as the selective serotonin reuptake inhibitors (SSRIs). Second-line medication treatments impact other neurotransmitters such as dopamine or norepinephrine, and some impact serotonin by alternate mechanisms. Regarding psycho-therapies, empirically validated interventions include cognitive behavioral therapy (CBT) and

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interpersonal therapy (IPT). For patients that do not respond to either or a combination of these treatments, additional options are considered including electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS).

Similarly for anxiety disorders, antidepressant medications and behavioral therapies, including CBT, are frequently the treatments of choice. While CBT in MDD primarily aims to change behavior by altering distorted cognitions, forms of CBT in the context of anxiety disorders employ the use of exposure techniques, where individuals face feared stimuli until their fear response naturally declines. Anxiolytics (e.g., benzodiazepines) are also used to mitigate acute symptoms of anxiety and are employed for short-term treatment of anxiety in more extreme cases [13].

Unfortunately, even when treatments are delivered under ideal circumstances, 30-60% patients with depressive and anxiety disorders who are treated are not likely to achieve remission with their first treatment [14-17]. Therefore, there is a great need for the identification of biological markers that predict which interventions would work and for whom, thus helping guide clinicians in selecting a treatment with the greatest potential to provide effective symptom management.

4. Brain mapping methodologies employed to assess structural and functional predictors of treatment response

Several different types of neuroimaging techniques have been developed and increasingly employed in the context of psychiatric research. Research studies that have investigated neurobiological predictors of treatment response have relied on the use of structural and functional brain imaging technologies. In structural magnetic resonance imaging (MRI), a non-invasive imaging technique, both whole brain and individual structure volumes are examined. Researchers use this methodology to examine anatomical detail, localize individual brain regions and to identify brain pathology. Functional MRI (fMRI) methodology provides useful temporal information about brain function by measuring the blood-oxygen-level-dependent (BOLD) contrast, where changes in energy between oxygenated and deoxygenated blood within the brain across time are examined to assess neural functioning within specific task constraints. Additional functional imaging methods employed in the context of treatment prediction research include positron emission tomography (PET) and single-photon emission computed tomography (SPECT). These procedures are considered invasive procedures in that they use radioactive substances in order to generate contrasts that assess brain blood flow, blood perfusion, and glucose metabolism as an indirect measure of neural activity. This wide array of brain imaging techniques has been used to assess which brain structures and functions prior to treatment predict treatment response in individuals diagnosed with Major Depressive Disorder and Anxiety Disorders.

5. Major depressive disorder

Major Depressive Disorder is a prevalent and debilitating disorder that is a leading cause of disability worldwide [18]. MDD often starts in adolescence and places youth at risk for

morbidity and mortality across the lifespan. The negative outcomes associated with MDD affect all aspects of life: personal, social, and academic functioning, and may result in chronic suffering and early death. The prognosis for depression is particularly poor when the problems are evident early on in development [19-21]. While a broader array of mood disorders (e.g., Dsythymic Disorder) may be relevant to include here, this chapter focuses on MDD because most of the predictive literature has focused on adults diagnosed with this disorder. fMRI, PET, SPECT and volumetric imaging have been used to examine predictive biomarkers of treatment response in MDD. Since a majority of findings have implicated subregions of the anterior cingulate cortex (ACC), we begin by reviewing these regions and then extend to other parts of the brain that have been implicated through various modalities as predictive of treatment response.

5.1. The anterior cingulate cortex

Many imaging studies have now implicated the pregenual ACC as a key area differentiating responders from nonresponders for a variety of psychiatric treatments. For the most part, as suggested in a meta-analysis of 23 studies of adults with MDD using various modalities and treatments [22], elevated activity or metabolism in the pregenual ACC at baseline is generally predictive of a positive response to treatment. For example, Fu and colleagues [23] reported that at baseline, increased activity in the ACC was associated with a positive treatment response to CBT. Similarly, elevated resting activity of the pregenual ACC "confers better treatment outcomes by fostering adaptive self-referential processing and by helping to recalibrate cingulate regions implicated in cognitive control" [22].

Careful attention should be paid to the problem of inconsistencies across studies. For instance, as Pizagalli [22] noted, four of the studies in his meta-analysis showed that pregenual ACC predicted non-response to paroxetine [24], venlafaxine, CBT [25], and ECT [26] as measured by PET and non-response to repetitive transcranial magnetic stimulation (rTMS) as measured by SPECT [27]. Part of the inconsistency may be due to error in the assessment. Specifically, low resolution in fMRI acquisition may interfere with the ability to pinpoint exactly which areas predict treatment response versus non-response. For example, a PET study showed that pretreatment hypermetabolism at the interface between pregenual and subgenual ACC was notable in non-responders in comparison to responders [25]. Indeed, in contrast to pregenual ACC findings, it appears that the subgenual region of the ACC is associated with the opposite pattern, where some studies have suggested that increased resting metabolism or activation predicts treatment resistance [25,28,29]. In an fMRI study, hyperactivity of the subgenual ACC in response to emotional stimuli was associated with poor response to 16 sessions of CBT in 14 adults with MDD [28]. This group replicated their finding in a second, larger sample of 49 patients with MDD, finding that individuals with the lowest pretreatment sustained subgenual ACC reactivity in response to negative words displayed the most improvement after cognitive therapy [29]. Such work focusing on the subgenual ACC has contributed to current models in which this region has become one of the targets of deep-brain stimulation for patients with treatment-refractory MDD [30]. Figure 1 provides an illustration of various divisions within the ACC, including pregenual and subgenual regions.

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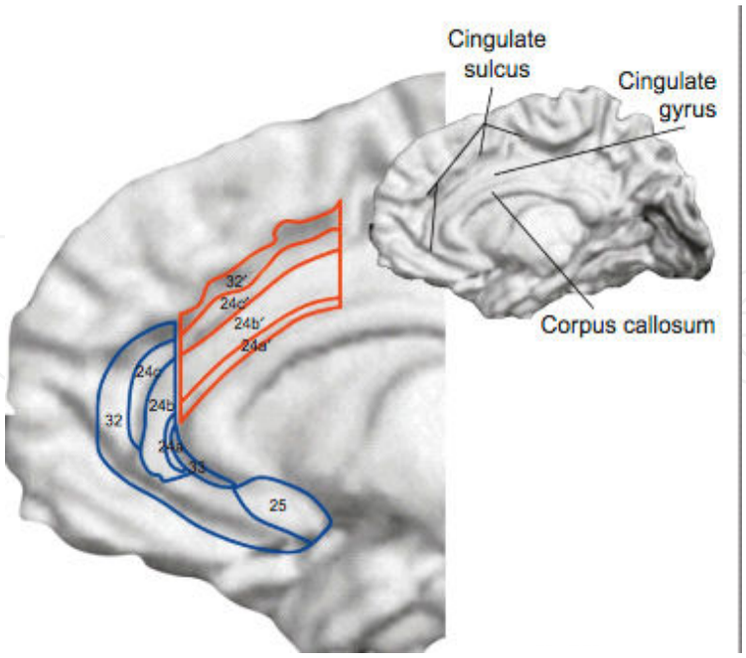

Figure 1. This figure illustrates the anatomical locations of divisions within the anterior cingulate cortex (ACC). A reconstructed MRI of the medial surface of the right hemisphere of the brain depicts the ACC (sulcus and gyrus) in relation to the underlying corpus callosum (upper right). Cytoarchitecture and functional differences have distinguished cognitive (red) and affective (blue) divisions of the ACC (left; 31). Better treatment response to pharmacological and psychological therapies in MDD has been associated with activity within the affective division of the ACC, namely increased pre-treatment activity in the pregenual ACC (includes Brodmann Area BA32 and inferior portions of BA24] and decreased activity in the subgenual ACC (BA25 and caudal portions of BA32 and BA 24). The subgenual ACC has been identified as a target for deep-brain stimulation in patients with treatment resistant MDD [30]. Reprinted and adapted from *Trends in Cognitive Sciences*, volume 4[6], Bush, G., Luu, P., & Posner, M.I., Cognitive and emotional influences in anterior cingulate cortex, pages 215-222, Copyright (2000), with permission from Elsevier [32].

5.2. Broader fronto-limbic brain regions

Not all imaging studies have pointed only to the pregenual and subgenual ACC as an important predictor of treatment response in MDD. Using a variety of methodological approaches, a growing number of studies have implicated a range of brain regions that are broadly associated with fronto-limbic circuitry. One fMRI study using an emotion-processing task before treatment with antidepressant medications (mirtazapine or venlafaxine) showed that at baseline, patients had higher activation in the dorsal/medial prefrontal cortex (PFC), posterior cingulate cortex and superior frontal gyrus. Furthermore, pre-treatment activations in caudate and insula were associated with successful treatment [33]. In an fMRI study that focused on anhedonia [34], patients with lower ventral/lateral PFC activation during cognitive reappraisal (suppression) of positive emotion at baseline had greater rates of improvement in anhedonia after 8 weeks of treatment with an antidepressant, specifically venlafaxine extended release or fluoxetine. Another study employing fMRI reported that with treatment using various antidepressants, greater right visual cortex and right subgenual ACC responses to sad stimuli, but not happy stimuli, were associated with a good clinical outcome in the early stages of treatment [35]. Similar to the findings reported by Light and colleagues [34], greater ventral/lateral PFC responses to

either happy or sad faces were associated with a relatively poor outcome [35]. A recent rTMS study found that greater symptom improvement was significantly correlated with smaller deactivations at baseline in the ACC, the left medial orbitofrontal and the right middle frontal cortices, but larger activations in the putamen [36]. Using SPECT, responders to rTMS had greater perfusions in the left medial and bilateral superior frontal cortices (BA10), the left uncus/parahippocampal cortex (BA20/BA35] and the right thalamus [37]. In a PET study in adults with late-onset MDD, 34 patients remitted and 13 did not after treatment with antidepressants for 12 weeks. Left anterior fronto-cerebellar perfusion ratio had a global predictive power of 87% [38]. Analyzing this variable together with the baseline variables age of onset and duration of index episode, the predictive power of the model rose to 94% [38].

A few studies have reported on anatomical differences that have predicted MDD treatment response in broader front-limbic brain regions. Chen and colleagues [39] found that increased grey matter volumes in ACC, insula, and right tempro-parietal cortex was associated with faster rates of symptom improvement with fluoxetine. A recent study found that smaller left hippocampal volumes predicted better treatment response to six weeks of daily rTMS in adults with treatment-refractory depression; however, the significance for this prediction was only a trend [40]. If volumetric predictors could be established, these would be useful in comparison to other imaging techniques (e.g., PET, SPECT), as this type of imaging acquisition is relatively easy, safe and is consistent in analysis across sites. Like other modalities, however, the extant data are from cross-sectional studies, so it is unclear whether any differences relate to pre-existing processes or to scarring from disease exposure.

5.3. Serotonin systems

Since most medication treatments focus on serotonin, a reasonable approach is to examine how either serotonin binding or brain regions associated with serotonin production might be relevant to treatment response. A SPECT study that examined serotonin binding availability found that higher pretreatment diencephalic serotonin availability significantly predicted better treatment response to 4 weeks of paroxetine [41]. Miller and colleagues [42] used PET to assess serotonin transporter (5-HTT) binding in 19 currently depressed subjects with MDD who received naturalistic antidepressant treatment for one year. They found that non-remitters had lower 5-HTT binding than controls in midbrain, amygdala, and ACC (sub-region not specified). Remitters did not differ significantly from controls or non-remitters in 5-HTT binding. Assessment of baseline 5-HTT binding as a predictor of remission status was suggestive but not significant. In a PET study of adults with MDD who received community-based monoaminergic anti-depressant treatments by their physician, Milak and colleagues [43] reported that treatment remitters had lower activity in the region of the midbrain where monoaminergic nuclei are located prior to treatment, and that degree of improvement correlated with pretreatment midbrain activity.

5.4. Major depressive disorder summary

Studies investigating neurobiological predictors of treatment response in MDD have primarily focused on adults with the illness. The most replicated findings implicate regions within the

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ACC as being particularly salient indicators of treatment outcome. Specifically, increased activity in areas within the ACC, namely the pregenual ACC, may be particularly predictive of improved outcome following both psychological and pharmacological intervention whereas hyperactivity in the subgenual ACC may be associated with poorer treatment response. In addition, pre-treatment serotonergic binding appears predict response to antidepressant therapy in adults with MDD. Other studies have linked structural and functional differences to pharmacological and psychological treatment response, but findings differ significantly as a function of the type of imaging modality employed (e.g., fMRI task based paradigm, PET). See Figure 2.

Cognitive Behavioral Therapy
Increased pregenual ACC activity *Decreased* subgenual ACC activity
Anti-depressant Medications
Increased: • ACC, insula, and right tempro-parietal cortex grey matter volumes • pregenual ACC activity and metabolism • dorsal/medial PFC, posterior cingulate cortex, superior frontal gyrus, caudate, and insula activity in response to emotional stimuli • diencephalic serotonin availability *Decreased* • ventral/lateral PFC activity when viewing happy and sad faces
Repetitive Transcranial Magnetic Stimulation
Increased: • putamen activity • perfusion in left medial frontal cortex, superior frontal cortex, left uncus/parahippocampal cortex, and right thalamus *Decreased:* • activity in ACC regions, left-medial OFC, and right middle frontal cortex

Figure 2. Summary of pre-treatment neuroimaging findings that have been associated with positive responses to Cognitive-Behavioral Therapy (CBT), repetitive transcranial magnetic stimulation (rTMS), and various anti-depressant medication treatments in MDD.

6. Anxiety disorders

Several distinct types of anxiety disorders have been recognized in the field of psychiatry and delineated within the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). Three will be discussed here, namely Obsessive Compulsive Disorder (OCD), General Anxiety Disorder (GAD), and Social Anxiety Disorder (SAD). Some initial headway is being made using neuroimaging to attempt to identify who will respond to which type of intervention for these disorders.

6.1. Obsessive compulsive disorder

OCD is a significantly impairing mental illness associated with debilitating cycles of persistent anxiety-provoking thoughts, impulses or images that are accompanied by repetitive behaviors aimed at counteracting anxiety [44]. For example, an individual may have constant and intrusive thoughts that surfaces that he or she comes in contact with are dirty or have germs. These thoughts are experienced as extremely distressing to the individual, who as a result, engages in compulsive behavior (e.g., repetitive hand washing) to prevent or alleviate fear associated with the content of obsessive thoughts (e.g., contamination).

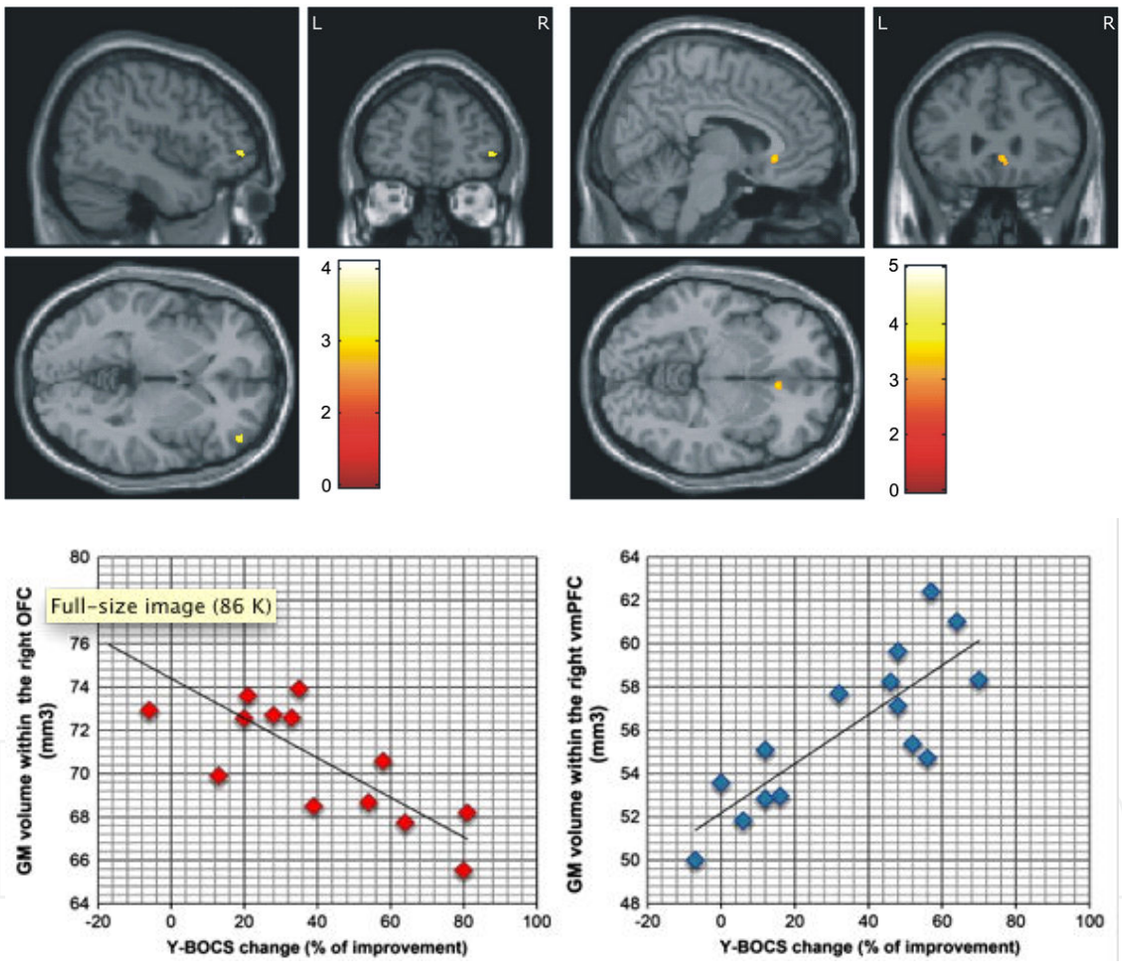

Figure 3. *Top:* Loci of significant correlations between pretreatment gray matter volume and subsequent response to Fluoxetine (top left) and CBT (top right). *Bottom left*: negative statistically significant correlation between pretreatment gray matter volume within the right middle lateral orbitofrontal cortex and improvements in OCD severity (measured by the Yale-Brown Obsessive Compulsive Scale: Y–BOCS) following treatment with fluoxetine. *Bottom right*: positive statistically significant correlation between pretreatment gray matter volume within the right medial prefrontal cortex, (subgenual anterior cingulate cortex) and Y–BOCS improvement following treatment with CBT. Reprinted and adapted from *European Neuropsychopharmacology*, published online, Hoexter et al., Differential prefrontal gray matter correlates of treatment response to fluoxetine or cognitive-behavioral therapy in obsessive–compulsive disorder, pages 1-12, Copyright (2012), with permission from Elsevier [45].

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One study to date has investigated structural predictors of treatment response in OCD. Hoexter and colleagues [45] recruited thirty-eight treatment naive individuals with a primary diagnosis of OCD and randomized them to receive either 12 weeks of treatment with fluoxetine or 12 weekly sessions of group CBT. Specifically interested in structural prognostic indicators of treatment response, Hoexter et al. [45] found that smaller grey matter volumes prior to treatment initiation in the right middle lateral orbital frontal cortex (OFC) predicted a decrease in OCD symptoms following pharmacological intervention whereas greater grey matter volumes in the medial prefrontal cortex predicted better response following CBT (Figure 3). This study suggests that improvement via pharmacologic and psychological approaches in OCD may occur via different mechanisms.

Numerous functional imaging studies, primarily using PET imaging, have also investigated biological prognostic indicators in OCD. Brody and colleagues [46] showed that decreased metabolic activity in the orbitofrontal cortex (OFC) was associated with better outcomes with fluoxetine treatment whereas as increased metabolism in the same region predicted improvement following cognitive behavioral therapy (CBT). However, it is important to note that, unlike the Hoexter et al. [45] study above, treatment designation in this study was not randomized. Similar to Brody et al. [46], Saxena et al. [47] found an inverse relationship between OFC glucose metabolism using PET and response to 8-12 weeks of SSRI (paroxetine) treatment in 20 OCD outpatients. These negative correlations between regional OFC glucose metabolism and treatment response appear to be present in adults with childhood onset OCD [48]. In a symptoms provocation study, where individuals with contamination-related OCD were exposed to neutral and contamination specific stimuli, lower regional cerebral flood flow (rCBF) measured by PET in the OFC and higher pre-treatment rCBF in the bilateral posterior cinglate cortex (PCC) predicted better symptom reduction after a 12-week open trial of fluvoxamine [49]. The relationship between rCBF and treatment outcome was present in response to both OCD-related and neutral stimuli, suggesting that activity in the OFC and PCC exist independent of OCD-salient cues. Using a functional MRI paradigm that evoked OCD symptoms by displaying salient illness-related words, BOLD response in the right cerebellum and left superior temporal gyrus (STG) positively correlated with improvements in OCD symptoms following 12 weeks of SSRI (fluvoxamine) pharmacotherapy [50].

Given that SSRI medications have been shown to be effective in both OCD and MDD, Saxena et al. [47] examined whether pretreatment brain activity would differentially predict response to pharmacotherapy in these two different patient groups. 27 individuals with OCD and 27 with MDD underwent PET to measure cerebral glucose metabolism prior to paroxetine treatment. These researchers concluded that OCD symptom improvement was related to increased pretreatment metabolism in the right caudate nucleus whereas decreased depression symptoms were predicted by low amygdala and thalamus but increased medial prefrontal and ACC metabolism prior to treatment. This study, in particular, suggests that treatment with SRIs may improve OCD and MDD pathology by its impact at different brain sites.

Using SPECT imaging, investigators have examined neurochemical transporters as predictors of response to medication treatments in OCD. Specifically, Zitteral et al. [51] found that serotonin transporter (SERT) availability in thalamic and hypothalamic brain regions predict-

ed better treatment outcomes following 14 weeks of sertraline (an SSRI) administration in a homogenous sample of OCD patients with behavioral checking compulsions. It is important to note that SERT availability has been associated with OCD symptom severity in previous studies [51,52], suggesting that individuals with higher transporter availability may be more likely to respond favorably to SSRIs as their serotonin system is less impaired prior to beginning intervention. Another SPECT study prior to 12 weeks of treatment with Inositol, a chemical precursor of second messengers in critical brain signaling pathways, found that higher blood perfusion in the left medial prefrontal regions differentiated OCD responders from nonresponders [53] and regional cerebral blood flow (rCBF) in cerebellar regions in addition to whole brain tracer uptake has also been shown to be elevated in OCD responders compared to nonresponders prior to beginning an open label trial of fluvoxamine [54].

6.2. Generalized anxiety disorder

GAD is a chronic and prevalent disorder characterized by frequent and excessive worry that is difficult to control [55]. This worry lasts for a minimum of six months and is associated with somatic and cognitive difficulties (e.g., fatigue, concentration problems), significant role impairment [44] and suicide [56].

To date, two known studies have investigated predictors of treatment response and non-response in GAD, both involving the use of fMRI methodology. Nitschke et al. [57] looked at brain reactivity to anticipatory cues of neutral and adverse stimuli (e.g., attack scenes vs. household items) in adults with GAD and examined how individual responses to these cues predicted outcome following an 8-week open label trial of venlafaxine, a type of selective serotonin and norepinephrine reuptake inhibitor (SNRI). Reminiscent of what has been found in the depression literature as discussed above, Nitschke et al. [57] found that activity in the pregenual ACC in response to anticipatory aversive and neutral cues predicted better outcomes. Specifically, individuals with hyperresponsivity in the pregenual ACC showed greater response to treatment measured by decreases in self-reported anxiety symptoms. The pregenual ACC is thought to play a role in the detection and resolution of emotional conflict [58] and thus Nitschke et al. [57] have proposed that individuals with greater pretreatment activity in this area may be better able to engage top-down control and regulate emotions when given treatment.

In the same participant pool, Whalen et al. [59] examined whether response to an emotional faces task could predict response following venlafaxine treatment in GAD. They specifically examined reactivity in the amygdala and rostral region of the ACC, as these areas have been found to be functionally related and relevant to the study of visually presented expressions of emotions [60]. Results from this study showed that increased reactivity in the rostral ACC and decreased reactivity in the amygdala when viewing fearful faces was related to improved outcomes after the 8-week medication trial (similarly measured by self-reported anxiety symptoms).

Since all participants were free from comorbid diagnoses, findings in these two studies cannot be accounted for by any other axis I disorder. In addition, results persisted after controlling for current depressive symptoms, further strengthening the conclusion that activity in these

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brain areas specifically predict GAD treatment outcome. However, the overlap in findings observed between studies in GAD and MDD, where activity in the pregenual ACC is implicated as a predictor of treatment response, may highlight the commonality in the underlying mechanisms of these disorders, which are commonly co-morbid. Future studies employing randomized, placebo controlled designs will need to be conducted in order to ensure that findings described above predict improvement with venlafaxine, not simply improvement in general.

6.3. Social anxiety disorder

SAD is characterized by intense fear of being in social situations in which judgment or embarrassment may occur. Age of onset in SAD is typically during mid-teen years, where symptoms tend to follow a long, protracted course of illness that often goes untreated [61].

Two known studies have investigated neuroimaging predictors of treatment outcome in SAD following psychotherapy interventions. Nine patients diagnosed with SAD underwent PET imaging using dopamine agonist ligands to examine dopamine function prior to 15 weeks of CBT [62]. The study found that reduced dopamine D2 receptor binding in the medial prefrontal cortex and the hippocampus prior to treatment predicted greater changes in self-reported social anxiety symptoms after CBT.

Employing fMRI methodology, Doehrmann et al. [63] investigated functional brain activity in response to emotional faces and scenes. Using whole-brain regression analyses, Doehrmann and colleagues found that BOLD response to angry vs. neutral faces in right occiptotemporal brain areas predicted better response to CBT, especially in initially more severe patients. This was true even when accounting for possible confounding effects of depressive co-morbidity. Researchers purport that predictive activity to faces over emotional non-face scenes is consistent with the social nature of SAD. While connectivity between higher-order visual and emotion processing areas has been shown to be altered in SAD, the authors note that further research is needed to elucidate the how the relationship between pretreatment activity in occiptotemporal brains relates to altered activity in limbic brain regions identified in other areas of research.

6.4. Anxiety disorder summary

Within the class of anxiety disorders, neuroimaging outcome prediction studies have, thus far, focused mostly on OCD. Findings implicate the OFC as being especially important in regards to predicting outcomes following pharmacological and psychological interventions in this disorder; however, areas of the PFC, ACC, caudate, cerebellum and STG in addition to serotonin system functioning may be salient predictors of treatment response in OCD as well. Research in GAD and SAD is still in its infancy; however, initial studies suggest that activity in the ACC may differentiate individual response to medication treatment in GAD whereas D2 receptor binding in the prefrontal cortex and hippocampus can be used to predict better social anxiety outcomes following psychological intervention. (Figure 4).

Obsessive-Compulsive Disorder
Cognitive Behavioral Therapy: • larger grey matter volumes in medial PFC • increased metabolism in OFC *Pharmacotherapy:* • smaller grey matter volumes in right middle lateral OFC • decreased metabolic activity in OFC • increased right caudate nucleus metabolism • SERT availability in thalamic and hypothalamic brain regions • lower regional cerebral flood flow in OFC and higher regional cerebral flood flow in bilateral posterior cinglate cortex in response to symptom provocation • increased right cerebellum and left STG activity to illness-related words
Generalized Anxiety Disorder
Pharmacotherapy: • hyperactivity in the pregenual ACC in response to anticipation of aversive and neutral stimuli • increased activity in the rostral ACC and decreased amygdala activity when viewing fearful faces
Social Anxiety Disorder
Cognitive Behavioral Therapy: • reduced dopamine D2 receptor binding in medial PFC and hippocampus • increased activity in right occiptotemporal brain areas in response to response to angry vs. neutral faces

Figure 4. Summary of pre-treatment neuroimaging findings that have been associated with positive responses to either Cognitive-Behavioral Therapy or anti-depressant medication treatments in anxiety disorders. *(PFC=prefrontal cortex, OFC=orbital frontal cortex, SERT=serotonin transporter, STG=superior temporal gyrus, ACC=anterior cingulate cortex).*

7. Conclusions and future clinical applications

Internalizing disorders are serious and often debilitating problems associated with significant impairment and individual suffering. While pharmacological and psychological interventions show some efficacy in the treatment of MDD and anxiety disorders, more precise personalized care is needed in order to improve overall treatment outcomes and to reduce the cost of psychiatric interventions. While this avenue of research is in its infancy, the use of imaging methods to identify neurobiological markers that predict treatment outcome holds the potential to further advance the field of personalized psychiatry and may eventually help guide clinicians towards the selection of treatments that have the highest likelihood of improving individuals patients' symptoms.

Advanced technologies have greatly facilitated efforts to examine anomalies in neural structure and function over the past decade. The findings in MDD show that regions of the anterior cingulate cortex have most reliably been identified as areas differentiating treatment responders from non-responders. Studies aimed at examining predictors of treatment outcome

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in anxiety disorders have primarily focused on OCD, most frequently implicating the orbital frontal cortex. Treatment predication research in other anxiety disorders, such as GAD and SAD is beginning to receive more attention.

While the research reviewed above provides an initial foundation for future research to advance personalized psychiatric care, several points need to be highlighted when considering these treatment studies. Most of the studies to date have reported results on small samples with uncontrolled treatment delivery, assessing imaging in the context of either a naturalistic and community-based treatment, or in the setting of a trial that compared different treatments but then examined effects after treatment arms were collapsed. While the field is currently limited in that large-scale treatment studies that involve comprehensive neurobiological assessments are highly labor intensive and are rarely feasible (for a noted exception see Dunlop et al. [64], next steps will require larger, more diverse samples and controlled treatment delivery to more accurately and reliably assess prediction across interventions.

Most research to date has been conducted in adult samples with little research examining biological predictors of treatment response in younger populations. It will be particularly important for future research to identify predictors of treatment response for children and adolescents suffering from anxiety and depression given that neurobiological factors associated with treatment outcomes may differ across development, early onset is a negative prognostic indicator of future problems and plasticity in key neural networks may be amenable to alteration during this period in development [20,65]. Furthermore, with the exception of symptom severity [20,66,67], younger age [67] and positive family history [68], few psychosocial indexes have consistently identified who responds favorably to an intervention [69], and very little is known as to which variables differentially predict response across types of interventions. Recent work has taken initial steps towards using brain imaging methods to identify biological markers for use in tailoring treatment for adolescent depression. In the only study to date that has published data on predictive imaging for adolescent depression, Forbes et al. [70] examined reward-related brain functioning in adolescent MDD before treatment with either CBT (n=7) or CBT plus a selective serotonin reuptake inhibitor (n=6). Due to the small number, the treatment arms were combined. Greater striatal activity during reward outcome predicted higher general severity after treatment, whereas greater striatal activation during reward anticipation predicted lower anxiety after treatment.

Inclusion of broader populations characterized as suffering from internalizing disorders may provide additional insights into relevant brain mechanisms for prevention. As previously mentioned, internalizing disorders have high rates of co-morbidity with one another, and although research to date has focused on depression and anxiety disorders, future research may be needed to delineate the biological underpinnings that account for such overlap. This work may help us refine particular psychological and pharmacological treatments. Similarly, expanding prediction studies to include internalizing problems outside of those classified as mood or anxiety disorders are also needed. Particularly, Eating Disorders have been characterized as belonging to the internalizing construct [71]; however, while imaging research has begun to characterize the neurobiological underpinnings of Eating Disorders [72-75], research has yet to examine neurobiological predictors of treatment response in this population.

While research reviewed above employed the use of fMRI, PET, and SPECT imaging techniques, the study of predictive biomarkers of treatment outcome should be expanded with the use of other neuroimaging methods. For example, the use of spectroscopy would provide evidence of pretreatment chemical and metabolite profiles predictive of treatment outcome. Similarly, resting state fMRI methods might be particularly useful, potentially elucidating our understanding of how different patterns of functional connectivity within and between neural circuits relate to treatment outcome or treatment resistance. In addition, it is expected that future research will increasingly employ the use of multi-modal approaches in predictive treatment research, helping to identify other biological markers not capable of being assessed via neuroimaging techniques. For example, current efforts are underway to more definitively assess biological markers for treatment response across treatments in adults with MDD (CBT, duloxetine, escitalopram) using multi-modal techniques including resting fMRI, neuroendocrine assessments, immune markers and measures of gene expression [64]. Additionally, neurobiological predictors of treatment response that have been identified thus far are not sufficiently strong enough nor have they been sufficiently replicated to warrant changes in clinical decision making at this juncture. Perhaps and understanding of broader brain networks will be enhanced by profiling numerous brain functions and structures that, in compilation, will more aptly predict treatment response.

An exciting advance that has the potential to improve personalized care is recent work incorporating machine-learning approaches to classify groups—disease versus no disease, or responders versus non-responders. Machine learning approaches are "brain reading" or "brain decoding" methods. Instead of analyzing the brain voxel by voxel, data from groups of voxels are used to train a computer program to distinguish different classes of data (e.g., treatment responders from treatment non-responders) and provide maps which indicate the levels by which different brain regions are accurately involved in the classification [76]. In a study that analyzed grey and white matter volumes, using a support vector machine (SVM) approach, Gong and colleagues [77] showed they were able to predict response versus non-response based on gray matter with 70% accuracy and based on white matter with 65% accuracy. Another study that used SVM measured responses to sad faces with fMRI before CBT in 16 unmedicated depressed adults. Brain regions implicated in clinical remission included ACC, superior and middle frontal cortices, paracentral cortex, superior parietal cortex, precuneus, and cerebellum, with 71% sensitivity and 86% specificity of response prediction [78]. A third SVM study found that the pattern of brain activity during sad facial processing correctly classified patients' clinical response at baseline, prior to the initiation of treatment, at trend levels of significance [23]. SVM approaches are still new in the field and the value of such non-traditional statistical approaches still needs to be weighed.

Practical constraints must be considered as future efforts aim to translate knowledge of neurobiological predictors of treatment response into clinical practice. In addition to providing reliable data with high sensitivity and specificity, ideally a biomarker would be low in cost, easy to collect and simple to analyze [79]. It is possible that these approaches could be mechanized sufficiently to reduce costs and increase feasibility so that one day, routine clinical assessment will include the collection of data via neuroimaging technology [80]. For example, if activity in the ACC remains

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a robust predictor of treatment response in larger controlled studies, one potential implication of this type of research could be that individual patients presenting with MDD may undergo an MRI to measure pregenual and subgenual ACC activity, which could in turn be used to guide whether the individual is referred for Cognitive Behavioral Therapy or pharmacotherapy. Currently, such an approach is likely cost prohibitive and may not be sufficiently feasible given the constraints of data acquisition, preprocessing and analysis. Alternatively, once neuroimaging markers that predict treatment outcome are well established, neuroimaging technology used to identify brain regions and functions associated with treatment outcome may be used to aid in the development or refinement of proxy biomarkers, such as neuropsychological functioning or serum markers, that could feasibly measure prediction and be disseminated for wide-spread application of personalized psychiatric care.

Here we have focused on neurobiological factors that can be measured at baseline to predict treatment. However, increased understanding of what aspects of neurobiological factors change over the course of treatment may also serve to enhance our understanding of the pathophysiology of internalizing problems and aid in identifying neurobiological factors that are likely to predict treatment outcomes. A recent review of the literature on changes with treatment concludes that a functional normalization of the fear network occurs with recovery across treatments [81]. Specifically, evidence suggests that both psychotherapy and psychopharmacology each in specific ways result in normalization of activity in the target structures (respectively, "top-down" and "bottom-up" effects). Methodologies that capitalize on considering both prediction of and change associated with treatment outcomes are needed.

Advanced techniques, such as those used in neuroimaging research, offer tremendous benefit to our society in that they provide the capability to improve our understanding of the pathophysiology underlying internalizing problems and may eventually offer guidance in regards to treatment selection, allowing providers to choose only those treatments that are most likely to be maximally effective for a given individual. This area of research is still developing. The concept of neural network medicine envisions a time to come when treatments will be used to target a neural network rather than simply components within the network. While personalized medicine in psychiatry is still at an early stage, "it has a very promising future" (Costa e Silva, in press).

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