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## TREATMENT PREDICTION BIOMARKERS FOR MAJOR DEPRESSIVE DISORDER

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## **History**

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Among mental illnesses, major depressive disorder (MDD) is the leading contributor to the global burden of disease and is associated with a staggering loss of \$210.5 billion per year from disability and impacted productivity (Greenberg et al. 2015). MDD is among the most prevalent of all mental illnesses, with over 16 million Americans experiencing a depressive episode each year (Substance Abuse and Mental Health Services Administration

2013). MDD is highly recurrent, with approximately three out of four depressed individuals experiencing more than one depressive episode (Boland and Keller 2010; Kessler and Wang 2010; Wittchen et al. 2000). It is also difficult to treat, with only one out of three patients having their depression remit after initial treatment (Trivedi et al. 2006; Westen and Morrison 2001), and those in primary care having an even lower remission rate (one out of four) (Vuorilehto et al. 2009).

Understanding the biological mechanisms that underlie depressive pathophysiology, and comprehending how treatments may influence these mechanisms, are key topics for MDD research because they show promise for guiding the development and selection of interventions for improved clinical outcomes. Toward this goal, there has been a growing interest in understanding neural features that predict treatment outcome. The overarching goals of this chapter are to 1) highlight one of the most promising biological predictors of treatment outcome for MDD (pretreatment activity of the rostral anterior cingulate cortex [rACC]); 2) emphasize limitations in the current MDD treatment biomarker literature, including difficulties in predicting treatment-*specific* outcomes, the practicality of using neural biomarkers in clinical practice, and methodological concerns (e.g., small sample size) that have prevented clinical adoption; and 3) provide an overview of what we believe are promising future directions for brain-based prediction of treatment outcomes for MDD.

## **Current Knowledge and Approaches**

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### **ROSTRAL ANTERIOR CINGULATE CORTEX AND THE PREDICTION OF MAJOR DEPRESSIVE DISORDER TREATMENT RESPONSE**

Individual studies have identified a number of clinical and demographic variables that predict relatively worse outcomes from pharmacological and behavioral treatments. These predictors include comorbid psychiatric illness (Carter et al. 2012), general medical conditions (Trivedi et al. 2006), higher levels of depressive symptoms (Trivedi et al. 2006), chronicity of depressive episodes (Souery et al. 2007), anxious depression (Fava et al. 2008), female gender (Trivedi et al. 2006), older age (Fournier et al. 2009), lower socioeconomic status (Jakubovski and Bloch 2014), non-Caucasian race (Trivedi et al. 2006), and less education (Trivedi et al. 2006). Major limitations of these predictors include the failure to replicate in subsequent studies and the limited information these predictors provide regarding the

mechanisms of treatment response (Pizzagalli et al. 2018). Given these limitations, considerable research has focused on biological markers of treatment response.

A particularly promising marker of treatment outcome for MDD is baseline (pretreatment) activity levels within the rostral (i.e., pregenual) rACC (including Brodmann areas 24 and 32). Results from the first study of this marker were published in 1997 and showed that greater baseline (i.e., before pharmacological treatment) activity (as assessed using resting glucose metabolism via positron emission tomography) within the rACC predicted better MDD treatment outcome (Mayberg et al. 1997). This finding has subsequently been replicated across assessment methods, including additional studies that used positron emission tomography and studies that used single-photon emission computerized tomography, source-localized electroencephalography (EEG), or functional magnetic resonance imaging (fMRI). Moreover, this marker was found to predict treatment outcome across a range of treatment modalities for MDD, including antidepressant medication/pharmacology (e.g., selective serotonin reuptake inhibitors [SSRIs], atypical antidepressants, and ketamine), placebo, sleep deprivation, and brain stimulation, including transcranial magnetic stimulation (TMS) (Korb et al. 2011; Pizzagalli 2011; Sikora et al. 2016). While there have been failures to replicate this finding (e.g., Arns et al. 2015; Brody et al. 1999; Little et al. 2005; Teneback et al. 1999) and even reversed findings (predicting response from electroconvulsive therapy (McCormick et al. 2007) and cognitive-behavioral therapy (Konarski et al. 2009; Siegle et al. 2006), further evidence for the robustness of using pretreatment rACC activity for treatment prediction stems from a quantitative meta-analysis of 23 studies which found that this effect was replicated 19 times, with a weighted effect size of 0.918 (Pizzagalli 2011). Moreover, a recent multisite study provided an additional replication of a link between increased pretreatment rACC activity and better treatment response, while addressing several limitations of prior studies including small sample size. Specifically, by assessing 248 depressed outpatients from the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study, the authors showed that rACC activity predicted response to an 8-week administration of sertraline or placebo even when controlling for clinical and demographic variables previously linked to treatment outcome. This provides evidence of the *incremental predictive validity* of rACC activity in a well-characterized large sample (Pizzagalli et al. 2018).

Despite robust evidence that rACC activity predicts outcome to antidepressant therapies, the mechanisms that underlie this predictive relationship are currently unknown. On the basis of a substantial literature that implicates 1) frontocingulate dysfunction in MDD and 2) the rACC as a

core hub within the default mode brain system (Buckner et al. 2008), we have previously theorized that the predictive relationship between rACC activity and improved clinical response may be related to adaptive self-referential processing and improved cognitive control capacities that are related to the modulation of the default mode brain system (Pizzagalli 2011; Pizzagalli et al. 2018). Although speculative, based on evidence that the rACC is involved in inhibiting negative information (Eugène et al. 2010), emotion-related amygdalar activity (Etkin et al. 2006) and emotional biases (Blair et al. 2013), reduced resting rACC activity may index disrupted interplay between the default mode network and frontally mediated cognitive control networks; such disruption might underlie depression-related cognitive processes including chronic repetitive negative self-referential thought (i.e., depressive rumination) and the impaired ability to modulate negative emotions and attentional control (Pizzagalli 2011).

Taken together, there is considerable evidence which indicates that pretreatment rACC activity, measured in a variety of ways, predicts outcomes across a range of treatment modalities. Although not treatment-specific, rACC activity may still prove useful in clinical contexts. For example, one study found that pretreatment rACC activity can be enhanced via cognitive training, which in turn improves antidepressant response to TMS (Li et al. 2014). While promising, further research is necessary to definitively understand the mechanistic role of rACC activity in MDD and in predicting treatment response.

## LIMITATIONS OF BRAIN-BASED TREATMENT PREDICTION FOR MDD

Pretreatment predictors of outcome can be classified as either “prognostic” or “prescriptive” predictors (the latter are also known as *moderators*) (Cohen and DeRubeis 2018). Prognostic predictors refer to a main effect of a predictor variable on treatment outcome. For example, in the above EMBARC study, higher levels of resting rACC theta current density predicted greater depressive symptom improvement *across* treatment conditions (Pizzagalli et al. 2018). That is, there was a main effect of rACC theta power on outcome, but no treatment group-by-rACC theta interaction. In addition, studies have found that higher levels of rACC theta activity predict better treatment outcome to a variety of interventions (e.g., SSRI, sleep deprivation, and TMS). This further suggests that rACC activity is a general (“treatment non-specific”) marker of depression prognosis.

In contrast, a pretreatment variable is considered to be a *prescriptive* predictor if levels of that variable *moderate* treatment-group differences in a clinical outcome (i.e., a significant treatment-group-by-pre-treatment-

variable interaction). Thus, prescriptive variables are more informative for treatment *selection* than ~~are~~ prognostic variables (but see Lorenzo-Luaces et al. 2017). To date, several studies (albeit often using small samples) have provided initial evidence for prescriptive predictors, including behavioral (word fluency; Bruder et al. 2014), electrophysiological (loudness-dependent auditory-evoked potential; Juckel et al. 2007), and neuroimaging (glucose metabolism in the insula; McGrath et al. 2013) variables. While promising, it will be necessary to replicate and extend these findings before we integrate any of these behavioral, EEG, or neuroimaging markers into clinical care for the purpose of informing treatment selection for depressed patients.

Given their associated costs and assessment burden, it will be important to carefully consider the benefit of neuroimaging and/or electrophysiological approaches in real-world clinics. Moreover, additional studies are needed to demonstrate that a given neuroimaging or electrophysiological variable predicts treatment response *over* the contribution of much less expensive and more easily administered self-report and clinician-administered measures (e.g., clinical and demographic characteristics) (Kessler et al. 2017). It is also important to highlight that any single predictor variable may only account for a small amount of outcome variance (Pizzagalli et al. 2018). In this context, multivariable machine learning approaches can be used to incorporate large numbers of baseline variables to model predictive relationships to clinical outcomes. Indeed, several studies have used machine learning to model complex relationships among multivariate sets of prescriptive predictors for the purpose of informing optimal treatment selection (see, e.g., Cohen et al. 2020; DeRubeis et al. 2014; Huibers et al. 2015; Webb et al. 2019).

Sample size is another important consideration in treatment prediction. For example, a recent simulation study provided evidence that the sample size required for adequately powered tests of prescriptive predictors of depression treatment response is substantially larger than those of most published studies (i.e., >300 per treatment group) (Luedtke et al. 2019). It may be possible to increase sample size by pooling data across studies if there is sufficient overlap in predictor and outcome variables. An alternative study design is to leverage naturalistic (i.e., observational) treatment datasets, which may provide substantially larger samples sizes than those in randomized controlled trials (RCTs). In this context, naturalistic datasets must include sufficient baseline assessments of predictors in addition to relevant outcome measures. A major challenge associated with observational datasets is that patients are not randomly assigned to treatment conditions, as they are in RCTs. As a result, treatment groups may differ in baseline patient characteristics. Statistical approaches can be used to address this lim-

itation by balancing treatment groups; for example, by using propensity score matching or weighting approaches (Hirshberg and Zubizarreta 2017; see Kessler et al. 2019).

## **Conclusion and Future Directions**

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MDD is associated with substantial personal and societal burden (Greenberg et al. 2015) and while there are a variety of treatment options, including pharmacological, psychological, and neurostimulation interventions, there are currently no empirically validated approaches for selecting the optimal treatment for individual depressed patients. Instead, treatment selection continues to be largely based on a trial-and-error approach, which typically introduces significant delays in the identification of effective treatments, is often associated with inadequately addressed symptoms (including increased suicidal behaviors), and may contribute to treatment dropout. In this context, the goals of the current chapter were to highlight the promise of neuroimaging-based treatment prediction for MDD and to note several limitations in the current literature, including the limited applicability of biomarkers for predicting which *specific* treatment is best suited for a given individual, the practicality of brain-based clinical approaches, and methodological considerations (e.g., small sample sizes leading to underpowered tests).

Before we can effectively integrate the neuroscience of MDD into clinical practice, it will be necessary to develop new approaches that enable the further incorporation of patient-specific information, which can ultimately be used for patient-specific clinical inference. Toward this objective, several approaches have been gaining momentum in the literature and promise to inform patient-specific psychiatry. For example, as mentioned above, machine learning methods may provide computational leverage by utilizing multiple complex sets of variables to make clinical inferences about specific patients. A growing literature shows that neuroimaging data can be used to differentiate depressed from healthy individuals (e.g., Fu et al. 2008; Mwangi et al. 2012; Sacchet et al. 2015a, 2015b; for review, see Kambeitz et al. 2017), and a similarly promising albeit smaller set of studies provide evidence that machine learning approaches may be useful for treatment prediction (Lee et al. 2018). Recent developments in human brain mapping that provide unprecedented person-specific information may also be useful for the clinical prediction of treatment outcomes in MDD. For example, several methods have been developed that enable the characterization of fMRI-based large-scale functional brain systems at the person-specific level (e.g., Gordon et al. 2017; Wang et al. 2015). Normative approaches

are another new set of methodologies that promise to inform the advancement of empirical treatment prediction. In this context, Dr. Andre Marquand and colleagues have recently pioneered a normative method for the statistically meaningful brain mapping of person-specific features related to psychopathology (Marquand et al. 2016; Wolfers et al. 2018). Such approaches promise to unite patient-specific brain mapping and behavior with treatment selection. Finally, recent developments in “deep phenotyping” (including highly repeated assessments of single individuals) may prove useful for the development of person-specific treatment prediction in psychopathology (Fisher and Boswell 2016; Poldrack et al. 2015).

In conclusion, while brain-based treatment prediction for MDD requires further research, the continued development of increasingly advanced and nuanced brain-based treatment selection shows promise for improving clinical outcomes for the treatment of this burdensome condition.

## KEY POINTS

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- Major depressive disorder (MDD), among the most common of all mental disorders, is particularly difficult to treat, with only one-third of patients remitting after initial treatment. Thus, elucidating the neural mechanisms underlying depression is essential in order to guide improved development and selection of interventions.
- One of the most promising biological predictors of treatment outcome for MDD is pretreatment activity of the rostral anterior cingulate cortex (rACC), measured in numerous ways (e.g., functional magnetic resonance imaging, source-localized electroencephalography) across various treatment modalities (e.g., selective serotonin reuptake inhibitors, transcranial magnetic stimulation, ketamine). However, the precise mechanisms that underlie this relationship are unknown.
- Limitations of MDD treatment biomarker literature includes numerous challenges related to the ability to predict which specific treatment is best suited for each individual, the feasibility of using neural biomarkers in clinical practice, the need for evidence to show that neural biomarkers better predict treatment response compared with less expensive measures, and methodological concerns (i.e., sample size).
- Future directions include developing novel approaches, including machine learning methods that may better help incorporate patient-specific information, in addition to the use of “deep phe-

notyping" for the development of person-specific treatment prediction in psychiatric illness.

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