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Brain Circuit–Derived Biotypes for Treatment Selection in Mood Disorders: A Critical Review and Illustration of a Functional Neuroimaging Tool for Clinical Translation

Evelyn Jiayi Song,

Leonardo Tozzi,

Leanne M. Williams

Stanford Center for Precision Mental Health and Wellness, Psychiatry and Behavioral Sciences, Stanford, California (EJS, LT, LMW); Stanford School of Engineering, Stanford, California (EJS); and Mental Illness Research, Education and Clinical Center of Excellence (MIRECC), VA Palo Alto Health Care System, Palo Alto, California (LMW).

Abstract

Although the lifetime burden due to major depressive disorder is increasing, we lack tools for selecting the most effective treatments for each patient. One-third to one-half of patients with major depressive disorder do not respond to treatment, and we lack strategies for selecting among available treatments or expediting access to new treatment options. This critical review concentrates on functional neuroimaging as a modality of measurement for precision psychiatry. We begin by summarizing the current landscape of how functional neuroimaging–derived circuit predictors can forecast treatment outcomes in depression. Then, we outline the opportunities and challenges in integrating circuit predictors into clinical practice. We highlight one standardized and reproducible approach for quantifying brain circuit function at an individual level, which could serve as a model for clinical translation. We conclude by evaluating the prospects and practicality of employing neuroimaging tools, such as the one that we propose, in routine clinical practice.

Major depressive disorder (MDD) remains a public health crisis worldwide. It is the most prevalent mood disorder and the leading cause of disability (1–3). Economically, it ranks as the most burdensome medical condition by its effects on workplace productivity (4,5). In the United States alone, the disability due to depression exacts an annual cost of $236

Address correspondence to Leanne M. Williams, Ph.D., at leawilliams@stanford.edu.
EJS and LT are joint first authors.

DISCLOSURES

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The dataset for the sample analyzed for the clinical illustration will be made available from the corresponding author upon reasonable request after approval of a proposal. For the antidepressant data, reasonable requests will also require the permission of the study sponsor, Brain Resource Ltd.

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billion (6). The burden of depression has the greatest impact on young people, and the consequences are fatal all too often. Death by suicide has tripled in young people over the past decade (7). The subjective experience of depression spans altered experiences of emotion, body, self, and time that are both highly varied and highly personal (8). We urgently need objective tests that stratify the heterogeneity of depression using measures of underlying processes, thereby facilitating more effective treatment selection (9,10). This critical review focuses on functional neuroimaging as a measurement tool for stratifying depression and predicting treatment outcomes (see Figure 1 for the conceptual framework for this review).

PRECISION MEDICINE IN DEPRESSION

While current treatments have established efficacy on average, as much as one-third to one-half of patients with MDD do not respond to treatment even after multiple attempts (11). New and emerging treatments are available to those for whom multiple conventional therapies have failed [for review, see (12)], but we lack strategies for minimizing attempts using ineffective treatments. Precision medicine applied in psychiatry seeks to address this need.

The precision strategy uses objective testing to personalize treatments for an individual, thereby moving away from the current one-size-fits-all approach. Stratified psychiatry is an intermediate step that aims to parse the heterogeneity of depression into biologically coherent subtypes that implicate different treatment approaches (9,10,13). This strategy seeks to determine which treatment will ameliorate which root cause of the illness. The goal is to quickly rule out ineffective treatments and expedite effective treatments, thereby substantially increasing the number of people who achieve remission with their first treatment.

The focus on measurements is key to precision approaches, paralleling recent advances in other medical fields. As recently as 74 years ago, cardiovascular medicine was limited by a lack of imaging tools such as ultrasound or computed tomography. This prevented quantitative, personalized assessments of the heart’s structure and function in relation to observable symptoms. Today, heart imaging during both rest and stress conditions is the gold standard in patient management.

The shift began in 1948 with the Framingham Heart Study, motivated by U.S. President Franklin D. Roosevelt’s death from cardiovascular disease 3 years prior (14). President Roosevelt died with a blood pressure of 300/190 mm Hg after several unsuccessful treatments had been tried, including salt reduction, digitalis, and phenobarbital. The Framingham study produced standard measurements of vital signs and imaging techniques capable of linking the organ of interest (the heart) to treatments and even prevention. For example, today, echocardiography can be used to identify types of arrhythmias (e.g., too fast, too slow, irregular) and to indicate specific treatments (e.g., pacemaker), or an angiogram can confirm the presence of blockage (e.g., emboli, atherosclerosis) and indicate treatments (e.g., stent).

Its current lack of routine measurements is a challenge for precision psychiatry, in contrast to cardiology. A number of national initiatives have been launched to make progress toward this goal (15–20). These initiatives all include functional magnetic resonance imaging (fMRI), along with other biomarkers. fMRI provides a direct measure of the organ of interest for precision psychiatry—the brain (21). Accumulating evidence indicates that fMRI is promising for stratifying biological subtypes and predicting treatment outcomes in MDD. First, we present an overview of what is known about fMRI-derived circuit predictors of treatment outcomes. Then, we illustrate one approach to clinical translation using a standardized and reproducible method for quantifying brain circuit function in individual participants. Finally, we discuss the potential of neuroimaging tools similar to the one that we describe and the feasibility of implementing them in clinical practice.

PROGRESS IN PREDICTING TREATMENT IN DEPRESSION BASED ON TYPES OF NEURAL CIRCUIT DYSFUNCTION

Over the past 2 decades, fMRI studies that have examined brain regions in the resting state and during tasks have revealed a neural circuit architecture that underpins domain-general and task-related processes, including self-reflection, salience perception, attention, sensorimotor functions, sensory processing, and reactions to emotional stimuli (22–28). Convergent evidence across fMRI studies of MDD has implicated dysfunction across at least 6 large-scale circuits, including the intrinsic default mode, salience, frontoparietal, negative affect, positive affect, and cognitive control circuits (12,21,29).

Several biomarker trials have incorporated fMRI to identify predictive biomarkers of pharmacotherapy outcomes in depression, including PReDicT (Predicting Response to Depression Treatment) (30), EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response in Clinical Care) (31), iSPOT-D (International Study to Predict Optimized Treatment in Depression) (32,33), CAN-BIND (Canadian Biomarker Integration Network in Depression) (34), and NESDA (the Netherlands Study of Depression and Anxiety) (35,36). These trials have focused on identifying fMRI biomarkers to optimize outcomes for first- and second-line antidepressants, and their data are being further pooled (37). Recent trials are using prospective stratification with new drugs for individuals who do not respond to conventional antidepressants. Other trials have focused on transcranial magnetic stimulation (TMS) (38) and on behavioral therapies. Emerging therapeutic areas include deep brain stimulation and rapid-acting exploratory treatments. These areas are important but beyond the scope of the current critical review. We have organized our overview of the findings for circuit predictors of response to antidepressants, behavioral therapy, and TMS by neural circuit. We emphasize commonly used antidepressants but highlight examples of emerging novel antidepressants for which imaging evidence is available.

The Default Mode Circuit

The default mode circuit, more commonly known as the default mode network (DMN), is a prominent task-free circuit implicated in MDD and associated anxiety disorders. Profiles of both intrinsic hyperconnectivity and hypoconnectivity have been observed in depression

(29,39–41). These distinct profiles may reflect different symptoms and predict treatment outcomes. Relatively higher DMN connectivity has been found to predict better outcomes for antidepressants, including escitalopram, sertraline, and venlafaxine (42–44). Higher connectivity between the DMN and the frontoparietal attention circuit (also known as the central executive network) has also been found to predict remission on these antidepressants (42–44). On the other hand, lower pretreatment DMN connectivity identifies patients for whom depression does not remit on these antidepressants, and this pretreatment profile is distinguishable from that of healthy individuals. More localized disruptions within subnetworks of the DMN may inform specific treatment associations. For example, using a patient-level quantification method, hypoconnectivity within posterior nodes of the DMN is associated with response to venflaxine (45). Normalization of the DMN has also been observed after antidepressant treatment in both treatment-naïve depression (46) and late-life depression (47), and changes in this circuit show promise as a long-term treatment biomarker (48). These findings suggest that distinct alterations in DMN connectivity are viable predictive circuit biomarkers for selecting first- and second-line antidepressants.

By contrast, hyperconnectivity within anterior nodes of the DMN, quantified using amplitude fluctuation, has been found to characterize treatment-resistant depression (49). Higher connectivity within the DMN and disrupted connections with prefrontal regions of the attention circuit (or central executive network) have been implicated in response to neuromodulation using TMS in treatment-resistant depression (38,50–52) (Table 1). With regard to emerging therapeutics, zuranolone (SAGE-217), which is currently in phase 3 development for MDD as well as postpartum depression, has been found to modulate resting DMN connectivity by altering GABAergic (gamma-aminobutyric acidergic) excitatory/inhibitory balance (53,54).

The Salience Circuit

Hypoconnectivity of the insula and amygdala within the salience circuit is observed across mood and anxiety disorders, particularly social anxiety and anxious avoidance (21,29). In PReDICT, lower connectivity of the subcallosal cingulate with the insula and ventral frontal regions was associated with remission to escitalopram and treatment failure with cognitive behavioral therapy (55). Complementing these findings, lower salience circuit connectivity has also been shown to predict response to escitalopram as well as sertraline and venlafaxine (45). In NESDA, lower insula connectivity within the salience network has also been identified as a prospective indicator of insufficient response to antidepressants for individuals who are taking multiple medications (36).

The Frontoparietal Attention Circuit

Frontoparietal attention circuit hypoconnectivity has been observed in both depression and anxiety (21,29). Such hypoconnectivity may characterize a distinct biotype of depression with cognitive symptoms and poor behavioral attention, specifically on tasks requiring selective attention (56,57). We lack data about the specific role of attention circuit connectivity in predicting antidepressant medication response. However, as noted above, connectivity of the DMN to specific regions within the frontoparietal circuit are implicated

in response to TMS (38,50–52). Attention circuit hypoconnectivity also predicts response to problem-solving behavioral therapy (45) (Table 1).

The Negative Affect Circuit

When evoked by tasks using negative emotion stimuli, such as facial expressions of threat, heightened amygdala activation and reduced amygdala-prefrontal connectivity have been observed across mood and related anxiety disorders, suggesting a common underlying negative affect circuit disruption (21,29). However, distinct types of amygdala-prefrontal activation predict response to different types of treatment (Table 1). In major depression, amygdala hyperactivation to sad stimuli predicts poor response to venlafaxine (58), and hyperconnectivity of the amygdala and anterior cingulate evoked by fear predicts poor response to selective serotonin reuptake inhibitors (SSRIs) (59) (Table 1). In contrast, relatively lower amygdala activation to fear stimuli has been found to predict a better response to SSRIs (58). Responders to SSRIs have also been characterized by early attenuation of amygdala activation to fear (60,61) and relative normalization of amygdala activity after antidepressant treatment (62–66). Post-treatment amygdala activation has been observed in response to masked fear stimuli and sad stimuli. Dorsal anterior cingulate cortex (ACC) activation to sad stimuli and amygdala and dorsal ACC activation to fear stimuli have been further implicated in response to cognitive behavioral therapy (67) and problem-solving behavior therapy (68), respectively. Emerging treatments targeting mechanisms relevant to negative affect circuitry include BI 1358894, an inhibitor of the transient receptor potential cation channel subfamily C, which reduces activation of the amygdala and insula evoked by negative facial emotion stimuli (69).

The Positive Affect Circuit

Within the positive affect circuit, dysfunction involving corticostriatal reward regions implicates behaviors characteristic of anhedonia (21,29). Reward-related ventral striatal activation has been identified as a differential predictor of response to sertraline versus placebo in the EMBARC trial (70) (Table 1). In CAN-BIND, an early increase in ventral striatal and ACC connectivity from baseline to week 2 was positively correlated with subsequent clinical response to escitalopram (71). The ventral striatum is also a target for selective treatment approaches. Both pramipexole, a selective D_3 receptor antagonist, and aticaprant, a kappa opioid receptor antagonist that stimulates striatal dopamine release, ameliorate anhedonia accompanied by changes in striatal activation evoked by the monetary incentive delay task (72,73). Mechanisms for pramipexole's effect may also involve enhanced reward learning involving the medial orbitofrontal cortex (74).

The Cognitive Control Circuit

During tasks like Go/NoGo that require goal selection and response inhibition, profiles of hypoactivity and hyperactivity, along with poor connectivity, have been observed within the cognitive control circuit. This circuit is defined by the dorsolateral prefrontal cortex, ACC, and connections with dorsal parietal regions (21,29). Hypoactivation of the cognitive control circuit characterizes a distinct cognitive biotype of depression (75) and poor response to SSRIs (76,77) (Table 1). Dorsal ACC activity evoked by a parametric Go/NoGo task has also been identified as a differential predictor of response to the SSRI escitalopram versus

the serotonin and norepinephrine reuptake inhibitor duloxetine (78). Go/NoGo-evoked connectivity of the dorsolateral prefrontal cortex within parietal and other cortical regions also differentially predicts response to SSRIs versus the serotonin and norepinephrine reuptake inhibitor venlafaxine (79).

Assessing Circuit Measures for Aiding Treatment Decisions in Clinical Practice

These imaging trials have established a number of associations between circuits and treatment response that highlight the viability of imaging as a biomarker tool for clinical use. We acknowledge that this synthesis is critical and selective rather than systematic. Table 1 provides a summary comparison of evidence across the circuits covered in this critical review.

In this summary, we have sought to capture the variation in the evidence by treatment and circuit. We have included a subjective preliminary rating of clinical readiness based on the principles of the GRADE (Grading of Recommendations Assessment Development and Evaluation), used by the American Psychiatric Association (80) and the Veterans Affairs, among other organizations (see the Supplement for details).

In the following discussion we provide an illustration of a method for clinical deployment of brain circuit biomarkers; following that is a discussion in which we consider the opportunities and challenges that this presents.

Toward a Functional Neuroimaging Quantification Platform Suited to Clinical Translation

We have established a method for quantifying participant-level brain circuit metrics to facilitate stratification of subgroups and to inform clinical decisions (45) (see Figure 2 and the Supplement for details). The approach to the method, incorporating psychometrics, and quantification of standard scores such as z scores, addresses the need for these characteristics as highlighted by leaders in the field (81).

This standardized image processing method has been applied in clinical samples from controlled trials of antidepressants and problem-solving behavioral therapy, as well as an open-label study of a mechanistically selective treatment. Because these samples were acquired with common imaging sequences and yield standardized outputs, they enable the direct comparison between circuit predictors of each treatment. Table 2 presents a summary of the associations between circuit scores, quantified with the standardized image processing method, and treatment response outcomes.

Predicting Treatment Response Using Participant-Level Circuit Scores

To demonstrate a potential path forward from research into clinical practice, we provide an illustration from the iSPOT-D depression trial. This illustration is intended to outline one practical use of imaging tools in individual patients to prospectively make treatment selections using standard thresholds for circuit dysfunction.

Of the iSPOT-D patients who had pretreatment imaging data, 166 completed treatment (32,33). We generated scores summarizing the function of the 6 brain circuits described above (Figure 2).

Then, we used a receiver operating characteristic (ROC) curve analysis to determine an optimal threshold for circuit score dysfunction to predict treatment response. We calculated the ROC curve using successive standard deviation threshold values (Figure 3). The dependent categorical variable was response defined by an improvement in symptom severity of 50% or more on the Quick Inventory of Depressive Symptomatology (82). Across circuits, a threshold of 0.7 SDs from the reference circuit data mean yielded the highest area under the curve for predicting response (Figure 3).

Next, we untangled the heterogeneity of the sample based on underlying circuit dysfunction when using the threshold of 0.7 SDs. Of the total sample of 199, 90% had a primary dysfunction in one of the 6 circuits (including the 3 conditions for the negative affect circuit) defined by the most extreme global circuit score with a magnitude of at least 0.7 SDs from the reference data. Therefore, using this 0.7 threshold, we assigned clinical participants to a discrete circuit subgroup based on their primary dysfunction. Within the sample, we observed a diverse distribution of primary circuit dysfunctions (Figure 4). This approach shows that case-control studies that average findings across broad diagnostic categories may conflate multiple underlying profiles of circuit dysfunction.

We note that the modal number of additional dysfunctions was one, which is less extreme than the primary dysfunction but still exceeds the 0.7 SD threshold.

We undertook an initial assessment of model performance, comparing a model predicted on circuit dysfunction against one that solely considers symptom severity for predicting treatment response (Figure 5). When we entered our circuit predictors, we found that the area under the curve for the circuit model was 0.75, and balanced accuracy was 71%. Sensitivity was 67%, specificity was 75%, positive predictive value was 73%, and negative predictive value was 69%. By contrast, a null model based only on the baseline Quick Inventory of Depressive Symptomatology exhibited an area under the curve of 0.56, and balanced accuracy was 50%. Sensitivity was 61%, specificity was 39%, positive predictive value was 51%, and negative predictive value was 48%. It is important to note that these predictive models require further validation through external replication.

To assess the clinical utility of the circuit measures for predicting response versus nonresponse, we calculated the number needed to treat (NNT). First, NNT was calculated for the base rate of nonresponse in the sample (53%) compared with the proportion of nonresponse identified by applying the circuit threshold used in the circuit ROC model (80%). We used the following formula: NNT = 1/absolute risk reduction = 1/ (0.80 2 0.53) = 3.70. By convention, we round this value to 4. Second, NNT was calculated for the base rate of response in the sample (47%) compared to the proportion of response identified by applying the circuit threshold used in the circuit ROC model (57%). NNT for response was 10. Consequently, employing the fMRI circuit model for treatment selection prevents one instance of nonresponse for every 10 patients treated. Moreover, this model is capable of identifying an additional nonresponder in every 4 patients, thus enabling these individuals to be fast tracked to an alternative treatment option.

This illustration highlights the potential for using fMRI-derived circuit tools to select antidepressants and improve clinical outcomes. The approach can be expanded by comparing the prediction for different classes of antidepressants and by incorporating additional treatments. It would also be worthwhile to investigate the interaction between circuits and/or the convergence of multiple circuit dysfunctions. Here, we have focused on circuit dysfunction distinguished from the healthy range by a standard deviation threshold. Future analyses are also warranted to examine how circuit variation within the healthy range may combine with circuit dysfunctions outside the healthy range. For example, in autism spectrum disorder, variation in resting-state functional connectivity in the healthy range has been associated with symptoms only when it co-occurs with abnormal connectivity in the DMN (83).

OPPORTUNITIES AND CHALLENGES OF TRANSLATING CIRCUIT PREDICTORS INTO CLINICAL PRACTICE

In this section, we consider translating functional neuroimaging circuit metrics into clinical use. We consider clinical use to encompass precision medicine trials, such as those that target a specific circuit dysfunction or circuit-based subtype of depression and the use of imaging to aid selection of treatments. Currently, one of every three patients achieve remission after the first treatments they try (11). The evidence synthesized in the preceding sections highlights the potential for improving this rate.

A recent systematic review has highlighted the opportunities and challenges for real-world implementation of precision psychiatry (84). Here, we consider the roadmap for translating circuit tools into practice within the context of the GRADE system (see the Supplement). We believe that improving major depression outcomes is an important problem (1–3). According to the Centers for Disease Control and Prevention, suicide was the second leading cause of death among people ages 22 to 44 years in 2020 (85). For two-thirds of individuals, depression is the primary cause of suicide (86). This represents 15,951 young people ages 25 to 44 years who die by suicide each year, comparable to the 19,553 in this age band who die by heart disease (85,87). Functional neuroimaging tools are an opportunity to reduce these fatalities, similar to the way that imaging reduced deaths and morbidity due to heart disease (88).

Regarding the burden of illness, for every employee experiencing depression, an average $15,000/year is lost (89). Depression costs the U.S. economy $210.5 billion/year in absenteeism, reduced productivity, and medical costs (6). For 10 typical patients, the total burden is $150,000. Above, we estimated 40% response to antidepressants, which reduces this burden to $90,000. Based on our NNT of 10, the use of circuit predictors to identify 1 more responder out of 10 could further reduce these costs to $75,000. Our NNT of 4 for nonresponse prediction suggests that this burden could be reduced further if nonresponders were identified earlier for fast tracking to effective treatments.

Regarding values and preferences, major depression is also associated with substantial public stigma that is commonly internalized (90). A survey of providers and patients suggests that brain scans could help alleviate the effects of stigma and self-blame (91).

We made similar observations in our Stanford discovery clinic for neuroscience-informed precision psychiatry. Spontaneous patient feedback indicates that seeing their own brain helps resolve stigma around their experience of major depression, with potential benefits for patient engagement (92). Although there are clearly other approaches to reducing stigma, these results suggest that a validated imaging technology has the potential to mitigate the social burden of depression.

The next GRADE consideration is quality of evidence. As summarized in Table 1, multiple studies meet the criteria of high-quality research defined by their controlled design. Accelerating translation will require large-scale clinical trials with matched reference datasets acquired with standard, clinically applicable sequences, across samples and sites, and using normative reference samples with more adequate sociodemographic representation, to facilitate the clinical interpretation of data similarly to neuropsychological testing (81,93).

Regarding an evaluation of both benefits and harm, we are not aware of a formal evaluation of these factors for fMRI tools in depression treatment prediction. Although fMRI technology is used safely in routine practice, a formal evaluation may be needed.

Of course, there are resource implications. A commonly expressed concern is about the cost of imaging. We can consider costs of testing based on Current Procedural Terminology codes according to the Fair Health Consumer data. For fMRI without contrast or with neurofunctional testing, taking California in the United States as an example, the costs range from $1015 to $1441 out-of-network and $339 to $429 in-network, exclusive of facilities (such as hospital) charges. These costs could be compared to electroencephalogram tests currently available for seizure testing ($693 out-of-network and $583 in-network) and for diagnosing sleep disorders ($1164 out-of-network and $635 in-network), also exclusive of facilities charges. These costs vary globally; in Europe and Australasia, they are most similar to in-network costs. Clearly, these are the direct testing costs, and clinical translation of imaging will also rely on access to quantification systems designed for clinical use, standard equipment, and technical personnel. There is a need for cost-effectiveness analyses of fMRI that consider all contributing factors together with long-term symptom and burden of illness outcomes.

Regarding equity, one key consideration is availability of MRI technology per capita. Figure 6 provides a summary of the availability of 3T MRI scanners per 1 million inhabitants by country (94). It is presented as a total and separately by hospital and ambulatory care facilities. These data for MRI equipment are a close proxy for equipment that is potentially utilized for fMRI in psychiatry. A related challenge will be the management of wait time. There have been relatively few investigations of wait time. In Norway, a register study reported MRI wait times of 8 to 12 weeks (95), and in Canada, a wait time information program reported 15 weeks (96). These wait times may also impact overall psychiatry service wait times, which have been reported as 8 weeks or longer for an inperson visit (97).

The available evidence for acceptability of fMRI tools adds some weight to the consideration of benefits versus risks. Work done through a clinical neuroethics perspective

suggests that there is high receptivity to brain scans for treatment tailoring in major depression (91).

Regarding feasibility, the development of a clinical consensus could facilitate the evaluation of evidence and clinical readiness (98). One approach could be to assemble a group of experts to conduct a synthesis of the perceptions of fMRI tools among psychiatrists and other health care providers, following the lead of pharmacogenomics (99). Methodologically, we need Health Insurance Portability and Accountability Act–compliant fMRI tools that are integrated with the radiological picture archiving and communication system. There is also a need to equip busy practitioners with terminology and training that is suited to integration with current clinical workflows.

CONCLUSIONS

The accumulation of fMRI evidence over the past 2 decades indicates that fMRI measures have utility for informing antidepressant treatment selection. Given the enormous burden due to major depression, there is an urgent need for tools that help identify the most effective treatment for individuals more rapidly. To close the gap between discovery and delivery into practice, there is a need for pragmatic approaches and translational clinics that evaluate fMRI tools for implementation within clinical care settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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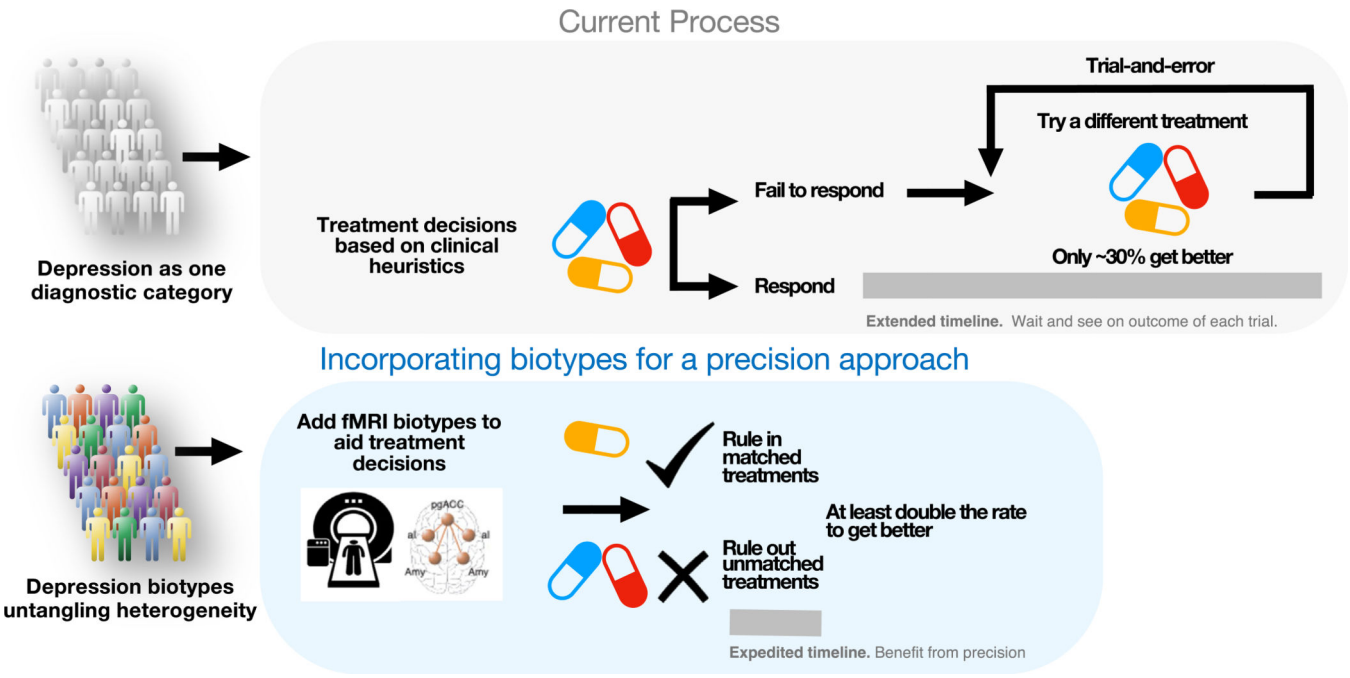

Figure 1.

Conceptual overview. Conceptual overview comparing the current clinical heuristic approach to selection of antidepressants to a precision medicine approach to major depressive disorder in which neural circuit measures are used to identify subtypes (biotypes) of depression and to select treatment based on these biotypes. aI, anterior insula; Amy, amygdala; fMRI, functional magnetic resonance imaging; pgACC, pregenual anterior cingulate cortex.

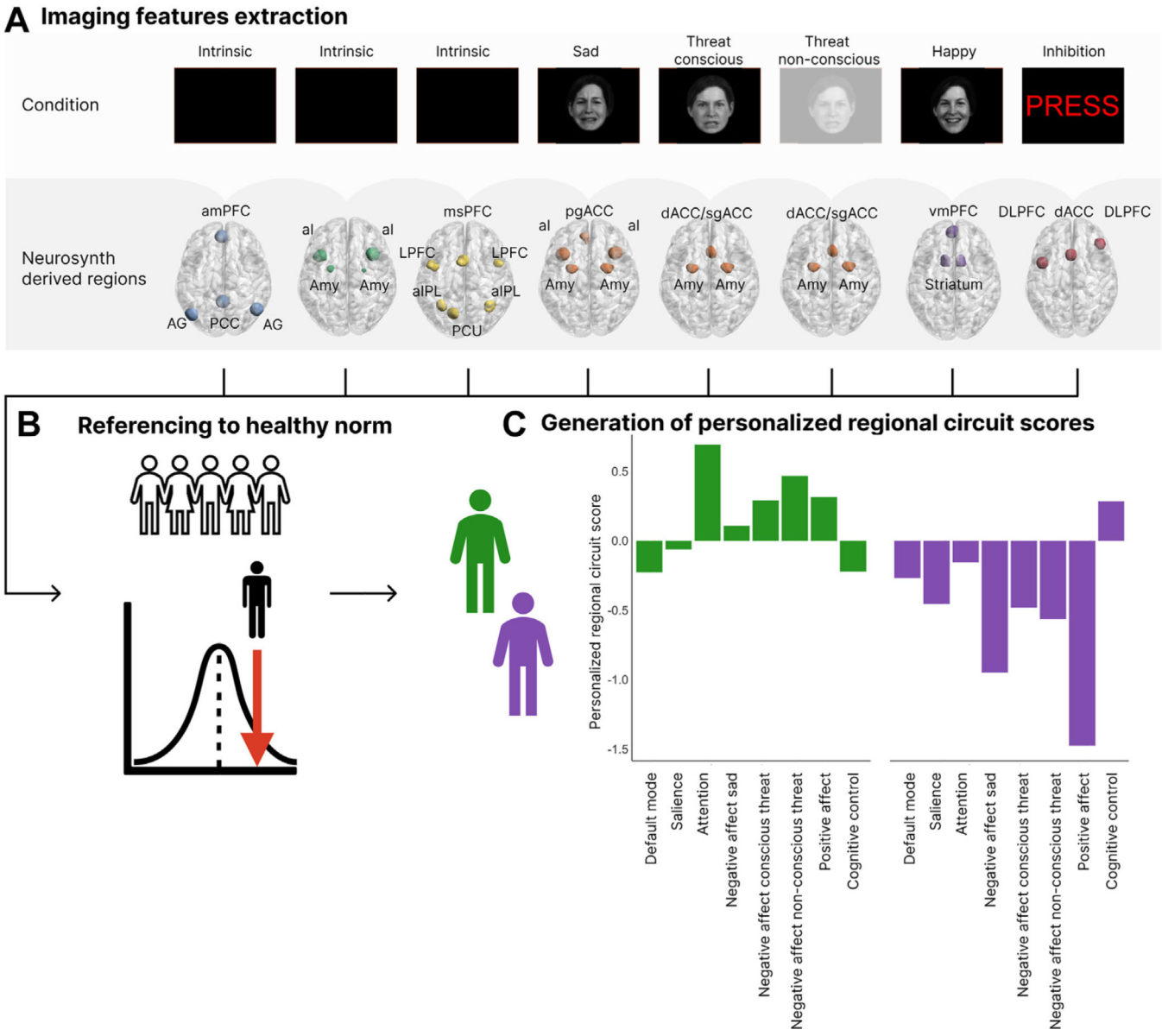

Figure 2.

Overview of the patient-level image processing and analysis pipeline. We derived measures of task-based activation and functional connectivity and task-free connectivity from regions belonging to 6 circuits that have established relevance to depression **(A)**. Default mode, salience, and attention circuits were derived from the task-free periods of the functional magnetic resonance imaging. The task-evoked negative affect circuit is elicited by sad, conscious threat, and nonconscious threat, the positive affect circuit by positive facial emotion and the cognitive control circuit by a Go/NoGo task. The regions of interest comprising each circuit were defined from the meta-analytic database Neurosynth and then refined based on quality control, a set of psychometric criteria, and whether they were implicated in depression. We extracted functional connectivity between circuit regions for task-free circuits and activation and connectivity of regions for task-engaged

circuits (regions shown as sphere, connectivity shown as lines), and these measures were then expressed as standard deviations compared with healthy participants **(B)** to obtain personalized regional circuit scores for each individual **(C)**. AG, angular gyrus; aI, anterior insula; aIPL, anterior inferior parietal lobule; amPFC, anterior medial prefrontal cortex; Amy, amygdala; dACC, dorsal anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; LPFC, lateral prefrontal cortex; msPFC, medial superior prefrontal cortex; PCC, posterior cingulate cortex; PCU, precuneus; pgACC, pregenual anterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex.

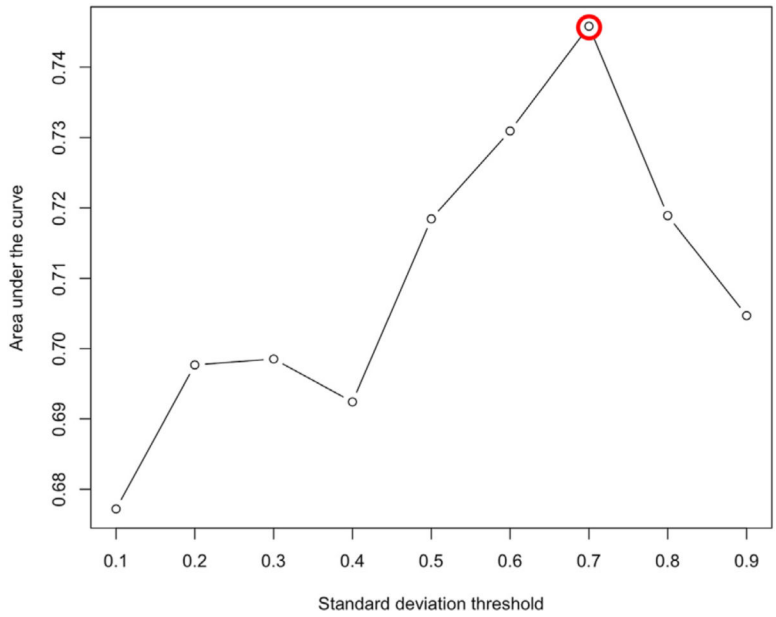

Figure 3.

Illustration of the accuracy calculated by a receiver operating characteristic curve using successive standard deviation threshold values for circuit score dysfunction. The dependent categorical variable was response, with response defined by a decrease of 50% on the Quick Inventory of Depressive Symptomatology. Using this procedure, we found that a threshold of 0.7 SDs from the healthy reference data mean yielded the highest area under the curve for predicting response, as indicated by the red circles.

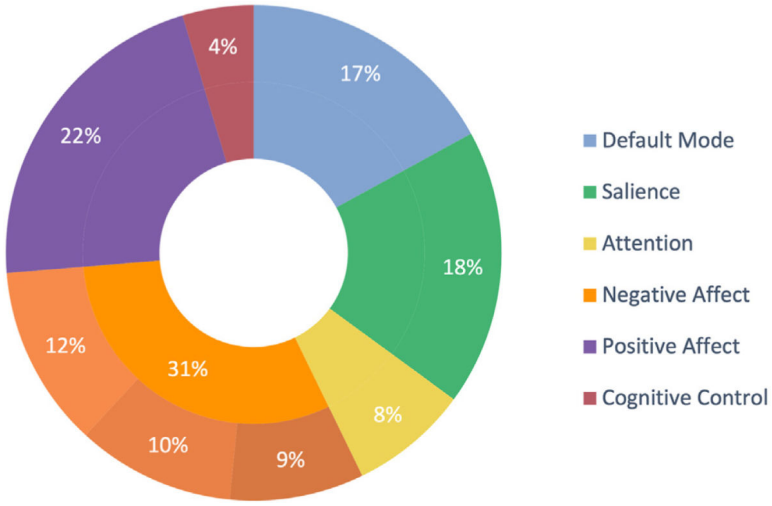

Figure 4.

Distribution of primary circuit dysfunctions. A pie chart showing the distribution of primary circuit dysfunctions for patients with major depressive disorder when dysfunction is defined by a threshold of at least 0.70 SDs from the healthy reference mean. Of the total sample of 199, 181 patients had a primary dysfunction in one of the circuits.

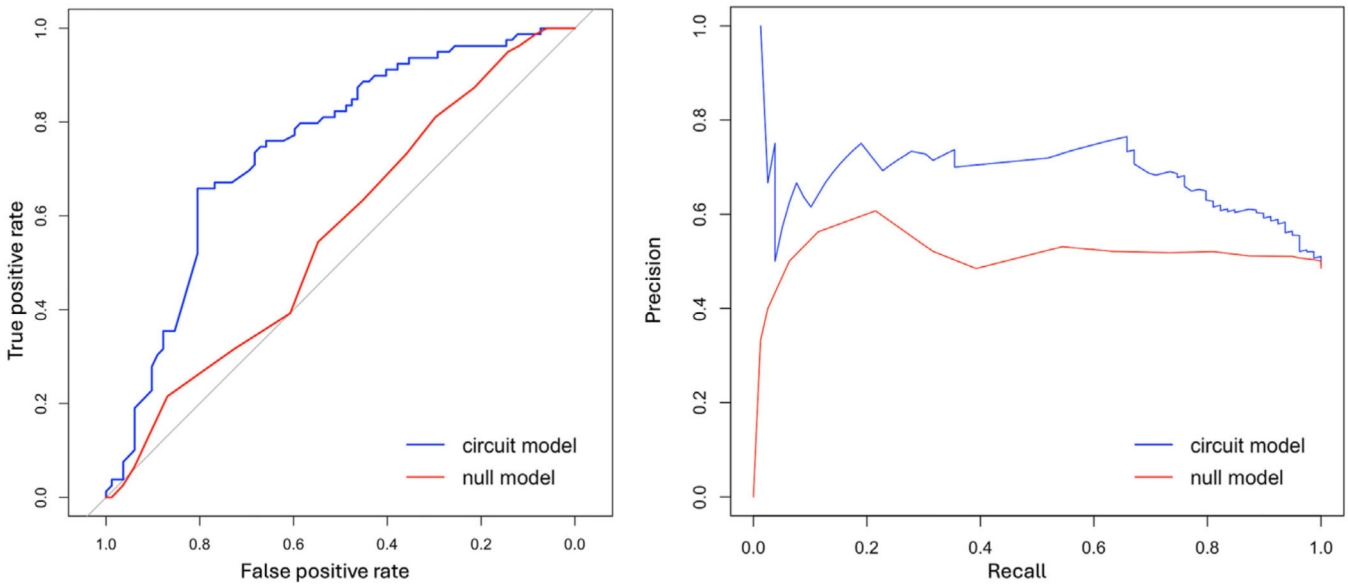

Figure 5.

Circuit model performance in predicting treatment response. Receiver operating characteristic curve comparing the model with circuit score predictors, using a threshold for dysfunction of 0.70 SDs relative to the healthy reference mean (blue) and to a null model based on Quick Inventory of Depressive Symptomatology symptom severity at baseline (red). The area under the curve for the circuit model was 0.75, and balanced accuracy was 71%. For predicting response, sensitivity was 67%, specificity was 75%, the positive predictive value was 73%, and the negative predictive value was 69%. By contrast, a null symptom only model based on the Quick Inventory of Depressive Symptomatology at baseline exhibited an area under the curve of 0.56, and balanced accuracy was 50%. For predicting response, sensitivity was 61%, specificity was 39%, the positive predictive value was 51%, and the negative predictive value was 48%.

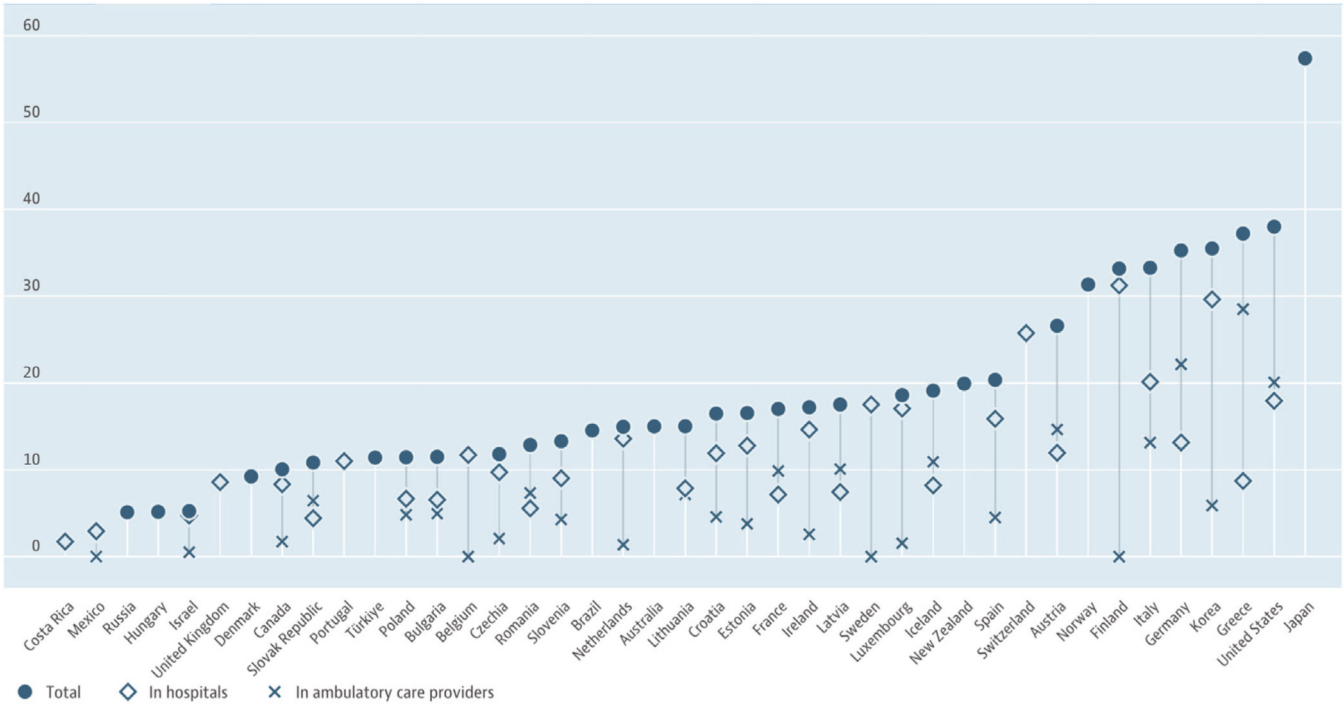

Figure 6.

Magnetic resonance imaging scanner availability per 1 million inhabitants by country. Overview of the availability of magnetic resonance imaging scanners that could be utilized for circuit assessment in depression and in precision psychiatry more broadly by country.

Table 1.

Overview of Evidence and Preliminary Evaluation of Clinical Readiness for 6 Circuits Implicated in Major Depression

Characteristics	Circuit					
	Default Mode	**Salience**	**Attention**[a]	**Negative Affect**	**Positive Affect**[b]	**Cognitive Control**
Task-Free Intrinsic Connectivity	Yes	Yes	Yes	–	–	–
Task-Evoked	–	–	–	Yes	Yes	Yes
Pharmacotherapy Treatment Prediction Using ROI, Seed, and/or Template Methods	Controlled trial (42) Well-designed trials (47,100)	Controlled trial (55) Well-designed trial (36)	Well-designed trial (101)	Controllesssd trials, pretreatment predictor (58,102) Well-designed trial, pretreatment (59) Well-designed trials, early posttreatment (60,61) Well-designed trials, posttreatment (62,63) Meta-analysis (66)	Randomized trial (70)	Randomized trial (70)
Pharmacotherapy Prediction Using Whole-Brain Methods	Controlled trials (43,44,46,48) Well-designed trials (48,103)	–	–	Well-designed trials, posttreatment (64,65,102)		Randomized trial (79) Well-designed trial (78)
Systematic Review	Yes (104,105)	Yes (105)	Yes (105)	Yes (106)	–	–
GRADE Consideration 1: Importance of the Problem	Strong evidence	Strong evidence	Strong evidence	Strong evidence	Strong evidence	Strong evidence
GRADE Consideration 2: Values and Preferences	Strong evidence, particularly for stigma	Strong evidence, particularly for stigma	Strong evidence, particularly for stigma	Strong evidence, particularly for stigma	Strong evidence, particularly for stigma	Strong evidence, particularly for stigma
GRADE Consideration 3: Quality of Evidence	Moderate to strong evidence RCTs Multiple trials Systematic reviews Need to elucidate variation in findings across samples	Moderate evidence RCT Trial Systematic review Need for additional trials	Emerging evidence Trial Systematic review Need for RCT and additional trials	Strong evidence Multiple RCTs Multiple trials Systematic review, highlights amygdala biomarker	Emerging evidence RCT Need additional trials	Emerging to moderate evidence Multiple RCTs Trial Need for additional trials
GRADE Considerations 4–6: Benefit/Harm, Resources, Equity	Need for formal harm/benefit evaluative Need for formal cost-effectiveness analysis	Need for formal harm/benefit evaluation Need for formal cost-effectiveness analysis	Need for formal harm/benefit evaluative Need for formal cost-effectiveness analysis	Need for formal harm/benefit evaluation Need for formal cost-effectiveness analysis	Need for formal harm/benefit evaluative Need for formal cost-effectiveness analysis	Need for formal harm/benefit evaluation Need for formal cost-effectiveness analysis
GRADE Considerations 7–8: Acceptability, Feasibility	Evidence for acceptance (91) Availability of patient-level quantification (45)	Evidence for acceptance (91) Availability of patient-level quantification (45)	Evidence for acceptance (91) Availability of patient-level quantification (45)	Evidence for acceptance (91) Availability of patient-level quantification (45)	Evidence for acceptance (91) Availability of patient-	Evidence for acceptance (91) Availability of patient-level quantification (45)

Characteristics	Circuit					
	Default Mode	Salience	Attention[a]	Negative Affect	Positive Affect[b]	Cognitive Control
					level quantification (45)	

GRADE considerations are based on the Grading of Recommendations Assessment Development and Evaluation (GRADE), used by the American Psychiatric Association (80) (see the Supplement for details).

RCT, randomized controlled trial; ROI, region of interest.

[a] In resting-state functional magnetic resonance imaging, the attention circuit is also commonly referred to as the frontoparietal network and cognitive control network. We use the term attention to distinguish the resting-state circuit from task-evoked cognitive control.

[b] We acknowledge that there are resting-state functional magnetic resonance imaging findings for limbic-frontal connectivity and the positive affect reward circuit (105), which are beyond the scope of the current critical review and synthesis.

Table 2.

Summary of Circuit Biomarkers Quantified at the Individual Participant Level Using the Imaging Pipeline That Generates Standardized Circuit Metrics and That Are Predictive of Antidepressant Treatment Outcomes

Circuit Score Predictors	Treatment Outcome	Statistical Significance[a]	Effect Size[b]	Magnitude of Effect (107)
Task-Free fMRI Data				
Default Mode				
Lower intrinsic connectivity of PCC and AG	Response to venlafaxine (45)	Yes	3.53	Large
Salience				
Lower intrinsic connectivity of insula and amygdala	Response to escitalopram and sertraline (45)	Yes	0.70	Medium
Attention				
Lower intrinsic connectivity of frontal regions	Response to problem-solving therapy (45)	Yes	5.14	Large
Task-Elicited fMRI Data				
Negative Affect				
Higher amygdala activity with lower amygdala-sgACC connectivity for nonconscious threat	Nonresponse to escitalopram and sertraline (45)	Yes	2.82	Large
Lower amygdala activation with higher amygdala-sgACC connectivity for nonconscious threat	Response to venlafaxine (45)	Yes	2.74	Medium
Positive Affect				
Lower vMPFC activity	Response to problem-solving therapy (45)	Yes	4.57	Large
Cognitive Control				
Lower dLPFC activity (76)	Nonresponse to escitalopram sertraline or venlafaxine (76)	Yes	1.33	Medium
	Response to targeted treatment (75)[c]	Yes	2.19	Medium

AG, angular gyrus; dLPFC, dorsal lateral prefrontal cortex; fMRI, functional magnetic resonance imaging; PCC, posterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; vMPFC, ventromedial prefrontal cortex.

[a] Significance of models tested for circuit score prediction over and above baseline severity and demographic variables.

[b] The effect size value reflects the number of SDs increase in log odds of response vs. nonresponse for a 1 SD increase in the circuit predictor.

[c] Guanfacine immediate release is Food and Drug Administration approved for hypertension and used off-label in psychiatry for depression and anxiety.