Neuroimaging-based biomarkers for treatment selection in major depressive disorder

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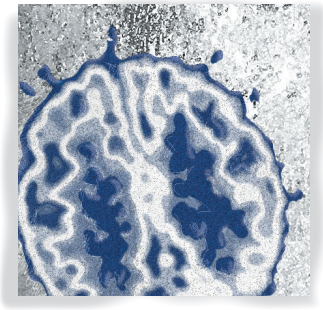

The use of neuroimaging approaches to identify likely treatment outcomes in patients with major depressive disorder is developing rapidly. Emerging work suggests that resting state pretreatment metabolic activity in the fronto-insular cortex may distinguish between patients likely to respond to psychotherapy or medication and may function as a treatment-selection biomarker. In contrast, high metabolic activity in the subgenual anterior cingulate cortex may be predictive of poor outcomes to both medication and psychotherapy, suggesting that nonstandard treatments may be pursued earlier in the treatment course. Although these findings will require replication before clinical adoption, they provide preliminary support for the concept that brain states can be measured and applied to the selection of a specific treatment most likely to be beneficial for an individual patient.

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Introduction

A leading goal in medical research is to improve the selection of particular treatments most likely to benefit individual patients. Matching individual patients to a specific treatment based on the individual's particular characteristics is called "personalized medicine" or "precision medicine."[1] By using individual characteristics to select the optimal intervention for a given patient from the outset of treatment, costs and side effects should be reduced and outcomes improved. This approach is distinctly different from the practice of selecting treatments based on clinical trial outcomes, in which the "average" improvement in the sample is used to identify efficacious treatments.

Personalized medicine has made major strides in the treatment of a growing number of medical conditions including infectious disease, cancer, and most recently, cystic fibrosis. Notable is the high impact in the treatment of breast cancer; distinguishing between tumors with and without high estrogen or epidural growth factor receptor expression is used to select specific chemotherapeutic agents, such as tamoxifen and trastuzumab, and even to avoid certain agents or their combination when certain combinations of receptors are present.[2] Ideally, identification of such specific

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Selected abbreviations and acronyms

CBT	*cognitive behavior therapy*
CEN	*central executive network*
DLPFC	*dorsolateral prefrontal cortex*
DMN	*default mode network*
ECT	*electroconvulsive therapy*
HDRS	*Hamilton Depression Rating Scale*
MDD	*major depressive disorder*
mPFC	*medial prefrontal cortex*
PCC	*posterior cingulate cortex*
PET	*positron emission tomography*
rAI	*right anterior insula*
rTMS	*repetitive transcranial magnetic stimulation*
SCC	*subcallosal cingulate cortex*
SN	*salience network*
TSB	*treatment selection biomarker*

treatments stems from an understanding of the various pathophysiologies contributing to a disease. This personalized medicine approach is particularly important for diseases defined by syndromes, for which multiple etiopathological mechanisms are believed to produce a similar clinical phenotype. Major depressive disorder (MDD) is a classic example of such a heterogeneous syndrome. Unfortunately, extensive research efforts aiming to subcategorize MDD have thus far failed to identify reliable and distinct pathophysiologies. The problem is particularly pressing for MDD, given its prevalence and status as a leading cause of disability around the world.[3]

Defining the imaging signature of the depressed brain

Major depressive episodes occur in both MDD and bipolar disorder. As bipolar disorder has distinct neuroimaging characteristics that distinguish it from MDD,[4,5] in this paper we limit our focus to MDD. Among the most consistent findings present in MDD patients compared with healthy controls are "hypofrontality" (reduced metabolism) of the dorsolateral prefrontal cortex (DLPFC) and increased activity in limbic regions, such as the amygdala and insula.[6] Hyperactivity of the subcallosal cingulate cortex (SCC) is another replicated finding. However, a major caveat to such comparisons is that they are based on the average activity of the MDD sample compared with the controls and thus may mask important heterogeneity within MDD subjects.[7] Indeed, some studies have found increased activity in the DLPFC, suggesting that different subgroups of patients may neurologically adapt to the depressive illness in divergent ways.[8,9] Another commonly reported finding, reduced hippocampal volume in MDD patients, may also arise from averaging effects.[10] Although a subgroup of MDD patients may demonstrate reduced hippocampal volumes, there is currently no biological reason to expect MDD patients to have increased volumes compared with controls. Thus, significant average volume differences between the MDD and control patients may be identified, even though the finding is driven only by those individuals with reduced volumes. Here again the heterogeneity of the sample is masked by use of a sample average measure.

Original efforts to improve MDD treatment employed the classic medical approach of defining the disease pathology, with the aim of developing treatments that would specifically target the identified pathophysiologic process. The first of these approaches was the dexamethasone suppression test,[11] followed by identification of a broad array of putative endophenotypes.[12] Most recently, the pathophysiologic role of inflammation has been recognized as a potential contributor to depressive illness,[13] and the inclusion of patients with high levels of inflammation may confound results from studies examining neuroimaging or other predictors of treatment outcomes.[14] Unfortunately, to date, none of the putative pathophysiologic indices have resulted in a replicated measure that can be used to select a specific treatment for an individual patient. In neuroimaging, efforts have been made to associate specific symptom clusters with neuroimaging signatures.[15] Other investigators have narrowed their focus to core symptom constructs that comprise MDD, rather than MDD as a whole syndrome. Examples of these symptom constructs include anhedonia, reward processing, and emotion regulation.[16,17] By selecting for a more homogenous sample of subjects who share a core symptom construct, researchers hope to better identify the neural circuitry underlying those constructs. However, such approaches can supply only a partial understanding of a patient experiencing a full syndromal major depressive episode, and thus the clinical application of these approaches for treatment selection may be limited.

Network models of major depressive disorder

Neuroimaging studies of MDD are increasingly focused on aberrant function within intrinsically connected networks that seem to mediate specific categories of mental activity. Although there is some divergence between studies in defining all the regions contributing to each network, the broad constructs are generally consistent. One such network is the default mode network (DMN), which includes the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), inferior parietal cortex, and medial temporal lobe, and is most active during self-referential processing.[18,19] Compared with healthy controls, MDD patients demonstrate changes in activity of the DMN both at rest[18] and when engaged in an external task, particularly during tasks that involve processing negative information.[20]

Another well-characterized network is the central executive network (CEN), comprised primarily of the DLPFC and posterior parietal cortices. The CEN is engaged during externally oriented and goal-directed tasks requiring working memory and planning.[21] The ventrolateral PFC and anterior insula (also referred to as the fronto-insular cortex), along with the dorsal anterior cingulate cortex (ACC), are key components of the salience network (SN), which functions to monitor for and orient to potentially relevant internal and external stimuli.[21] Although some researchers associate the insular cortex with the DMN,[22] others have identified the fronto-insular cortex as a key node in switching between the predominantly self-referentially focused DMN and the external task-focused CEN or task-positive networks.[23-25]

From remission to treatment selection

Efforts to define the neurobiology of MDD share the aim of improving treatment approaches to the illness. An alternative approach to identifying optimal treatment approaches in MDD is to work backwards from treatment response outcomes to the pretreatment imaging states. This approach is relatively nondirected about the underlying biology of the syndrome, but aims to identify imaging signatures that are associated with differential outcomes to treatments with differing mechanisms of action. In contrast to the symptom-construct reductionist approach (ie, focusing on a core depressive symptom as the target of biological research), the primary goal of this treatment-based approach is to directly impact clinical care by finding biomarkers that indicate optimal treatment selection. Such treatment-based approaches may eventually provide information on the pathophysiology of disease, but their real value is in improving patient outcomes. In this manuscript, we will review the literature on such treatment-based research for guiding treatment selection and identify future directions and caveats to consider.

Predictors, moderators, and biomarkers

In medicine, the fundamental goals of the clinical encounter with an ill patient are to provide a diagnosis and a prognosis and to select a treatment for the illness. There is inconsistency in the literature regarding the use of terms associated with prediction of outcomes. For the purpose of this article, we differentiate between predictors and moderators. Prognosis stems from predictor (or "prognostic") variables, ie, those baseline characteristics that have a main effect on outcome regardless of the treatment administered. For example, across all treatments, a chronic episode of depression predicts a poorer outcome compared with a nonchronic episode.[26] In contrast, treatment selection depends on moderators, which are pretreatment variables that are associated with differential outcomes between two or more treatments.[27] These moderators are of the greatest clinical value as they identify subgroups of patients within heterogeneous conditions who are most likely to benefit from a specific form of treatment. Another commonly used term, "mediator," refers to a biological or psychological feature thought to contribute to the mechanism of improvement, identified by observing both a change in the feature during treatment and an association of that change with treatment outcome.

"Biomarker" is another term with a variety of uses depending on the specific meaning. Diagnostic biomarkers are measures that can be used to distinguish states of illness and health. These biomarkers do not necessarily inform treatment, but are to be used in making a diagnosis or to determine the subtype in a syndrome. In contrast, a treatment-selection biomarker (TSB) is a biological moderator that can be measured prior to initiating treatment to guide selection of the optimal treatment for particular patients.[28] The TSB does not necessarily con-

tribute to making a diagnosis, but is used to maximize treatment outcomes. Other types of biomarkers may be identified in which the degree of change in a biological factor occurring soon after initiating treatment could be used to predict likely treatment outcomes. Such biomarkers do not help select initial treatment, but have clinical value through identifying the utility of continuing an intervention early in the treatment course, thus obviating the need to wait for the full, longer treatment period to determine outcome.[29]

Neuroimaging biomarkers in major depressive disorder

There are many forms of neuroimaging that have the potential to be used as biomarkers in MDD. Positron emission tomography (PET) can be used to: (i) characterize resting-state metabolic signatures; or (ii) to measure the density of neurotransmitter receptors or transporters for which a radioligand exists. Magnetic resonance imaging (MRI) can be used to measure: (i) brain structure volume (structural MRI); (ii) white matter integrity and density [diffusion tensor imaging (DTI)]; or (iii) functional metabolic activity patterns (fMRI), either in the resting state or in response to a certain challenge or task. fMRI patterns reflect states of brain metabolic activity. Greater metabolic activity in a brain region is accompanied by increases in blood flow, which is detected as alterations within the magnetic field of the MRI scanner. Furthermore, fMRI may be used to examine activity in single brain regions or in coordinated temporal patterns of activity across multiple regions (functional connectivity MRI [fcMRI]).[30]

This article emphasizes neuroimaging treatment-related biomarkers for MDD, although there is certainly a need for diagnostic biomarkers in MDD, particularly to improve the accuracy of diagnosis in primary care settings. Comprehensive reviews and meta-analyses of neuroimaging predictors of treatment outcomes have recently been published.[31,32] These reviews have reported a broad array of potential predictors, identifying a great deal of inconsistency in the results. These inconsistent results are not surprising given that the studies vary substantially on many factors, including patient sample characteristics, treatment types and duration, outcomes definitions, imaging modality, patient activity in the scanner (resting state versus task engagement), and image analysis approaches.

Here, we focus on select biomarkers that appear to be emerging across studies of MDD and that have theoretical support based on other imaging work. We emphasize imaging studies conducted on patients prior to a prospective treatment trial rather than cross-sectional case-control studies of historical response/nonresponse, which are subject to a variety of selection biases. We place less weight on studies that investigate pre- to post-treatment changes in brain activity. Although these studies may refer to observed changes in regional activity as "predicting" treatment outcome, they are actually correlates of outcome, because the activity changes can be observed only after the outcome is known, true prediction is not possible from these analyses. These studies are of value in contributing to understanding mediators of change, but mediators do not necessarily serve as moderators of outcome.[27] Finally, this review does not include studies in which patients were on medication at the time of their baseline predictor scan due to the effects of medication on neuroimaging measures.

The clinical practice of psychiatry would be substantially enhanced if a reliable TSB could be identified that could guide selection of the initial treatment (ie, a moderator of outcome). First-line treatments for MDD consist of either antidepressant medication or an evidence-based psychotherapy (though in some cases they are applied conjointly).[33] These two types of treatments have fundamentally different mechanisms of action, which opens up the possibility that, in patients with MDD, specific brain states may be more or less likely to respond to one of these approaches. If these brain states can be reliably identified, then a TSB could be developed that indicates whether psychotherapy or medication represents the best treatment for particular patients, based on their brain state at the time of treatment initiation.

A second type of treatment biomarker would be one that does not indicate which treatment would likely work for a given patient, but rather identifies which patients are unlikely to benefit from standard MDD treatments (ie, a predictor or prognostic variable). This type of biomarker would indicate that the usual treatment approaches should be skipped and that interventions reserved for highly treatment-resistant patients, such as stimulation treatments (eg, repetitive transcranial magnetic stimulation [rTMS], deep brain stimulation, or electroconvulsive therapy [ECT]) or unconventional

medications, should be used earlier in the treatment algorithm. In current clinical practice, applying the standard treatment algorithms of psychotherapy and multiple medication trials requires months before treatment resistance can be determined, making this type of nonresponder biomarker arguably of the greatest clinical importance. Integrating biomarker predictors of nonresponse with the known clinical predictors of poor treatment outcome (eg, a chronic depressive episode or severe medical comorbidity) would save time and money, reduce patient suffering, and reduce the possibilities of despair and suicide.

Single versus multiple treatment modalities

The majority of MDD studies reporting neuroimaging moderators of treatment outcomes have used a single psychotherapeutic or pharmacologic intervention. These studies examine differences in the pretreatment imaging signal between patients who responded to a specific intervention versus those who did not. Without a comparison group, these studies cannot conclusively separate nonspecific predictors of outcome versus a treatment-specific moderator. Reviews of studies that examined regional pretreatment 2-[18F]-fluoro-2-deoxy-D-glucose PET (FDG-PET) metabolism as a predictor of outcome in studies of single treatments found inconsistent results, with the strongest finding being that higher levels of pregenual ACC metabolic activity predicted response to antidepressants and sleep deprivation.[31,32,34] Although single-treatment modality imaging studies do not help answer the clinical question of what is the optimal type of intervention for an individual, they may provide supporting data toward understanding treatment response patterns for a specific modality.

More clinically informative are studies that compare two differing treatment options. A small number of imaging studies have examined predictors between two classes of antidepressant medication, but the results, to date, have been difficult to interpret and apply clinically.[35-37] As all antidepressants modulate monoamine systems, studies looking to identify imaging predictors specific to individual classes of medications will be very challenging, given the early stage of imaging TSB research. More promising approaches compare interventions with highly divergent mechanisms, such as psychotherapy versus medication.[9,28,38-41]

Anterior insula metabolism as a treatment selection biomarker (moderator)

The insula is classically divided into three subcomponents that are associated with specific functions.[42] The posterior regions of the insula predominantly process pain and viscerosensory sensation. The ventroanterior portion is involved in chemosensory (gustatory, olfactory) processing. In terms of the biology of MDD, the most important component is the dorsoanterior insula, which, in addition to its aforementioned role in the SN, also functions in processing risk, reward, consciousness, and performance monitoring.[43,44]

The insula's function as a convergence zone of multimodal sensory processing and subjective state awareness positions it as a crucial hub for affective processing.[42] Given the well-established biasing toward negatively valenced stimuli present in depressed patients,[45] the frontoinsular cortex is positioned to potentially play a key role in perpetuating the depressed state. Imaging studies of MDD patients have found inconsistent results regarding the level of metabolic activity in the insula relative to healthy controls, both in the resting state and during emotion processing tasks.[46,47] This inconsistency likely represents the heterogeneity between studies of the types of MDD patients enrolled. However, it is precisely this variability that opens the possibility of finding brain activity biomarkers that differentially predict treatment outcomes to distinct forms of treatment.

The potential value of insula metabolism as a predictive TSB is supported by findings from several research groups.[48] Recently, the first comparative neuroimaging TSB that predicted differential outcomes to 12 weeks of randomly assigned treatment with either a structured psychotherapy (cognitive behavior therapy [CBT]) or antidepressant medication (escitalopram) was published.[28] Eighty adults with *DSM-IV-TR*-defined MDD, aged 18 to 60, underwent pretreatment resting state FDG-PET scanning prior to their randomization to treatment. A total of 63 patients completed the 12 weeks of treatment and had a usable baseline PET scan for analysis. A total of 38 patients with clear outcomes (ie, meeting criteria for either remission, defined as a Hamilton Depression Rating Scale 17-item [HDRS] score of ≤7 at both weeks 10 and 12, or nonresponse, defined as a week 12 HDRS score of ≤30% decrease from baseline) were analyzed. To maximize signal detection, the 25 patients with unclear outcomes (ie, had a

response >30% decrease from baseline, but short of full remission) were not used in defining the TSB.

In this analysis, a brain region was considered a potential TSB if it differentiated both the remitter-nonresponder differences (by treatment) and the escitalopram-CBT differences (by outcome, *Figure 1A*). Six brain regions met the TSB definition: right anterior insula (rAI), right inferior temporal cortex, right motor cortex, left premotor cortex, left amygdala, and left precuneus. Using the combination of these six regions as a predictor did not exceed the predictive utility of the rAI alone. Moreover, across all 63 completing patients, pretreatment metabolic activity in the rAI correlated with percentage reduction in HDRS scores for both CBT (positive correlation) and escitalopram (negative correlation, *Figure 1B*).

This study also included a second 12-week treatment phase for nonremitting patients. In this phase, patients who did not remit with their initial treatment with either CBT or escitalopram received the combination of these two treatments by continuing their initial treatment and adding the other treatment. A total of 30 patients entered this second phase, 27 of whom completed. The findings from the initial 12-week treatment phase were supported by findings from Phase 2. In this phase patients whose second (added) treatment matched the one indicated by the Phase 1 pre-treatment rAI TSB were more likely to remit than those whose second treatment did not match the TSB (53% vs 25%, respectively; risk ratio, 2.11, 95% confidence interval [CI], 0.59-7.52).[49]

In one of the few other imaging studies comparing treatment with psychotherapy (interpersonal therapy) or a selective serotonin reuptake inhibitor (SSRI; paroxetine), changes in insula activity emerged as the most statistically significant effect of treatment.[38] In both groups, anterior insula metabolism increased after treatment; however, this study did not evaluate baseline metabolic activity as a predictor of outcome. Right ventrolateral PFC activity significantly decreased, but only in the paroxetine-treated patients.[38]

Support for the relevance of AI metabolism in somatic treatment outcome studies emerges from other studies. Greater insula reactivity to emotional stimuli at baseline predicted improvement to 4 weeks of treatment with venlafaxine or mirtazapine.[50] AI metabolic activity was reduced after 6 weeks of effective paroxetine treatment.[9,51,52] Poor response to rTMS was associated with reduced pretreatment metabolic activity in bilateral insula and ACC compared with healthy controls, providing partial support for the conceptualization that lower insula metabolism may serve as a biomarker for a form of MDD predictive of poor response to somatic treatments.[53] In another rTMS study, response to low-frequency rTMS was correlated with reduced right AI and posterior insula cerebral blood flow after treatment.[54]

A meta-analysis of functional neuroimaging studies concluded that greater baseline insula (and extending into the right inferior frontal gyrus) and striatum activity is predictive of poorer treatment outcomes across treatments.[32] More recently, greater anterior insula response to emotional stimuli predicted poor response to treatment with combination fluoxetine-olanzapine,[55] and greater resting state metabolic activity in the anterior insula predicted poor response to vagus nerve stimulation.[56] These findings are not necessarily in conflict with the results reviewed above. In the study by McGrath and colleagues described above, although good responses to CBT were predicted in the great majority of patients with low rAI activity, the converse did not hold as strongly *(Figure 1)*.[28] That is, although higher rAI metabolism predicted better response to escitalopram than to CBT, many patients with elevated AI metabolism did not respond to the medication. A reasonable conclusion from these results is that elevated levels of insula activity are a marker for needing a more intensive intervention than psychotherapy, but that optimal treatment selection for these patients may require additional biomarkers beyond the insula state.

Low insula resting state activity (and perhaps lower reactivity in challenge tasks) may be a particularly strong indicator that the patient may be a good candidate for psychotherapy. We posit that downregulation of insular activity in the setting of MDD represents intact emotion regulation circuitry, such that the processing of negative emotional states is susceptible to inhibitory controlling forces. With competent psychotherapeutic guidance, this intact regulatory network may be harnessed to permit even greater control, allowing the patient to process and learn from positive experiences, thereby leading to a resolution of the depressive episode. Support for this identification of a psychotherapy-specific form of MDD is found in the long-term follow-up studies of patients treated with psychotherapy or medication. Patients who benefit from psychotherapy showed sustained protection against relapses compared with patients who benefit from medication, but discontinue it after recovery.[57]

Hippocampal volume as a prognostic biomarker

Volumetric reductions in the hippocampus, basal ganglia, SCC, and orbitofrontal cortex are well-replicated findings in MDD patients versus healthy controls, and are particularly prominent among patients with more severe or chronic forms of depression.[10] A recent neuroimaging meta-analysis identified reduced volume of the right hippocampus and reduced gray matter volume in the left DLPFC as structural imaging predictors of nonresponse to antidepressant medication.[32] In a study of 46 MDD patients, volume reductions in the body/tail, but not the head, of the hippocampus predicted poorer remission rates after 8 weeks of antidepressant medication.[58] In the largest study to date, smaller left hippocampal volumes predicted poorer response among 167 depressed inpatients treated with medication; this effect was primarily driven by patients with recurrent MDD.[59] Smaller hippocampal volume is also associated with poorer treatment outcomes continuing through 2 or 3 years of follow-up.[60,61] Small studies suggest that treatment with antidepressant medication[62] or ECT[63] is associated with increases in hippocampal volume. However, improvements in hippocampal volume have not reliably been associated with treatment response, resulting in uncertainty in determining whether reductions in hippocampal volume are a "state" or "trait" marker of MDD. Remarkably, no studies have evaluated the predictive value of hippocampal volume on outcome from MDD with CBT treatment, though a recent study found that CBT increased hippocampal volume among patients with post-traumatic stress disorder.[64] Thus, of the structural imaging predictors, reduced hippocampal volume may serve as a nonspecific predictor of a poor treatment outcome, but the data, to date, do not demonstrate its value as a TSB.

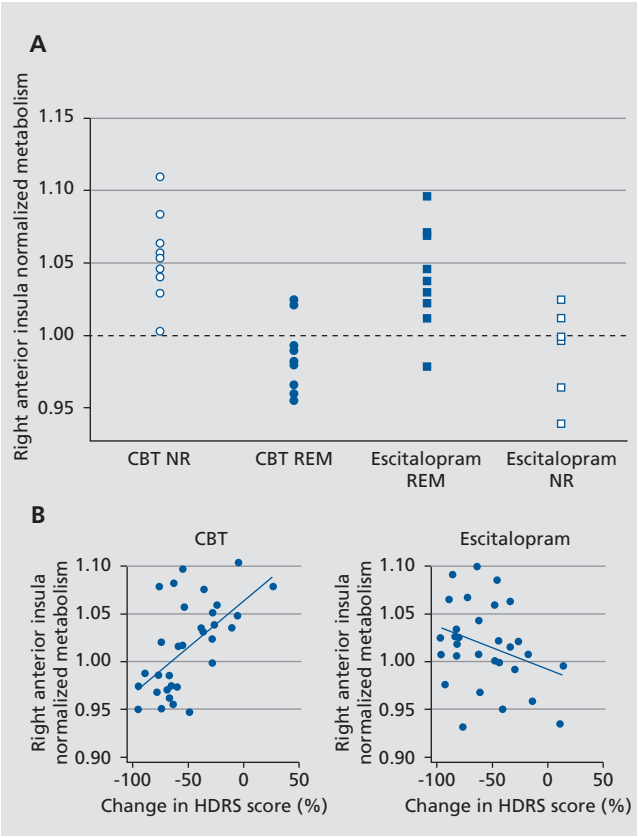

Figure 1. (A) Scatterplot of pretreatment 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (PET) metabolic activity in the anterior insular cortex of individual patients remitting (REM) and not responding (NR) to treatment with either escitalopram or cognitive behavioral therapy (CBT). Normalized metabolic activity in the anterior insula subdivided patients into hypermetabolic and hypometabolic subgroups. **(B)** Insula activity correlated with changes in the Hamilton Depression Rating Scale (HDRS) score in the full cohort of subjects treated with either CBT or escitalopram oxalate.

From reference 28: McGrath CL, Kelley ME, Holtzheimer PE, et al. Toward a neuroimaging treatment selection biomarker for major de-pressive disorder. *JAMA Psychiatry*. 2013;70:821-829.Copyright © American Medical Association 2013

Subcallosal cingulate cortex metabolism as a prognostic biomarker

The above study of 46 patients with MDD by McGrath and colleagues included a second phase that provided information for a nonresponse TSB *(Figure 2)*.[65] A total of 9 patients completed the combination treatment of phase 2 with a week 24 HDRS score ≤30% (compared with, their phase 1 baseline score). The patients who failed to respond to both psychotherapy (CBT) and escitalopram (P+SSRI nonresponders) demonstrated a clear pattern of hyperactivity in the SCC at baseline compared with the 36 patients who had achieved remission either by the end of phase 1 or phase 2. These patients also demonstrated hyperactivity in the superior temporal sulcus.[65] The importance of the elevated SCC metabolism in predicting poorer treatment outcomes has also been reported in several other studies of medications and CBT.[41,66,67] Furthermore, hyperactivity in this region is present among patients with multiple

treatment failures, including nonresponse to ECT.[68] Patients with refractory MDD also demonstrate increased connectivity between the SCC and the DMN.[69] The need for alternative interventions for patients demonstrating elevated pretreatment SCC activity is supported by studies demonstrating greater reduction in depressive symptoms among patients treated with anterior cingulotomy[70] and those receiving deep brain stimulation to this region.[68] Furthermore, clinical efficacy of TMS applied to separate regions of the DLPFC was predicted by the degree to which the DLPFC site and the SCC were anticorrelated.[71]

Integration of findings

Taken together, the results reviewed here provide support for the concept that pretreatment brain states, as identified by neuroimaging, may be used in the prediction of treatment outcomes for MDD. Although confirmatory studies are certainly required, evidence is converging that there is a brain state specifically predictive for response to psychotherapy, in particular CBT.

Psychotherapy-responsive depression may represent a brain state that is able to effectively adapt to negative emotional states (eg, induce downregulation of the

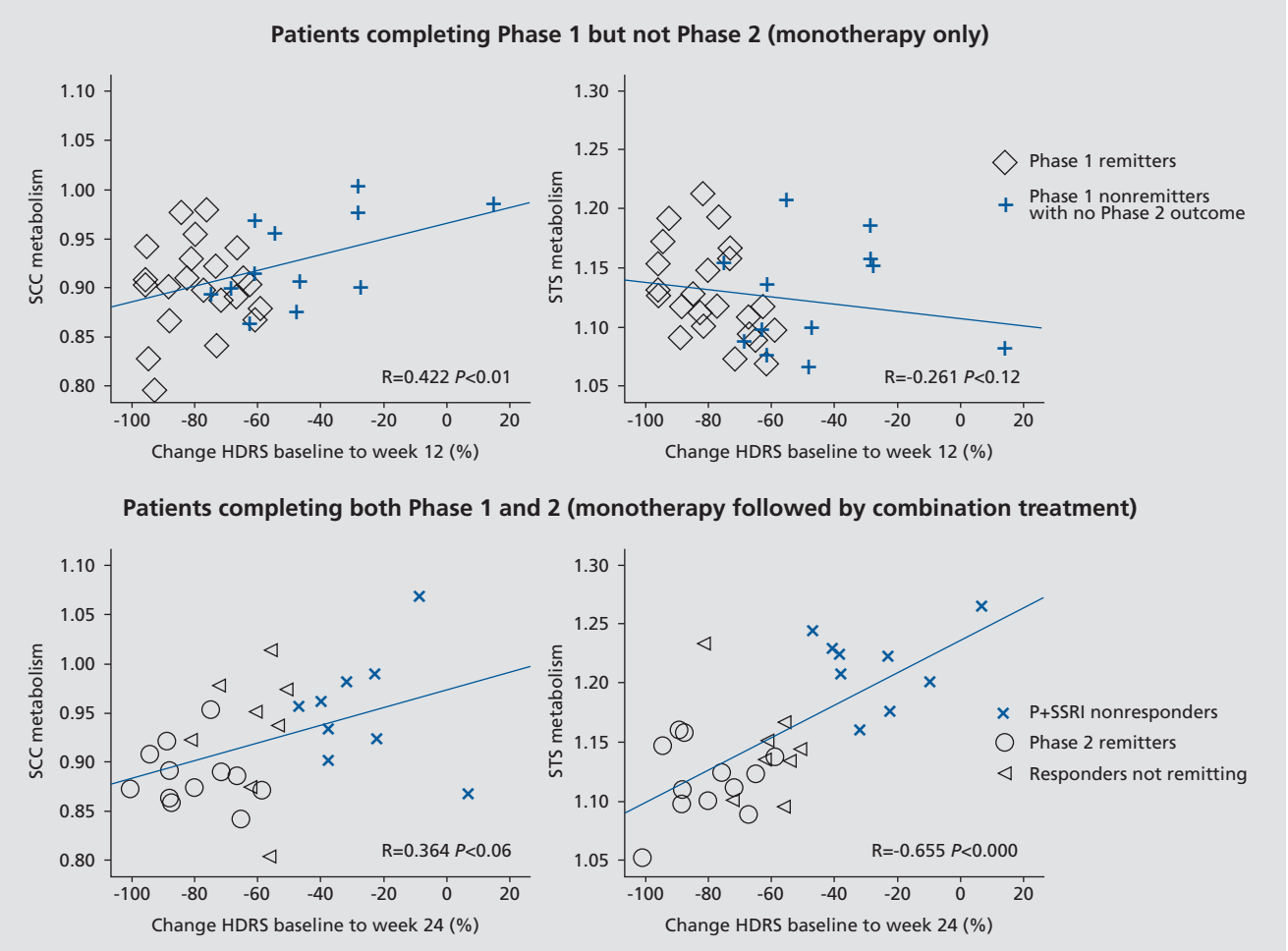

Figure 2. (A) Percent change in the Hamilton Depression Rating Scale (HDRS) after 12 weeks of treatment with either escitalopram or cognitive behavioral therapy (CBT) correlated with pretreatment metabolic activity in the subcallosal cingulate cortex (SCC) and superior temporal sulcus (STS). **(B)** Percentage change in HDRS correlated with pretreatment SCC and STS metabolic activity among patients completing 12 weeks of monotherapy followed by 12 weeks of combination escitalopram plus CBT.

From reference 65: McGrath CL, Kelley ME, Dunlop BW, Holtzheimer PE, Craighead WE, Mayberg HS. Pretreatment brain states identify likely nonresponse to standard treatments for depression. *Biol Psychiatry*. 2014;76:527-535.Copyright © Elsevier 2014

anterior insula, amygdala, and SCC), and therefore, is capable of integrating externally presented information, such as psychotherapeutic interventions. This psychotherapy-responsive form of depression possesses the ability to utilize countervailing influences to reduce negative affective states and may require intact hippocampal functioning. In contrast, forms of MDD that do not improve with psychotherapy may reflect brain states that fail to adapt in the setting of negative emotion and cannot effectively incorporate psychotherapy to alter the mood state. These psychotherapy-nonresponsive depressions likely represent several forms of dysregulated neurocircuitry, which will require some form of somatic intervention to induce sustained improvements in the affective state. High metabolic activity in the anterior insula may represent a TSB for treatment with medication, but there are likely other biological characteristics that will need to be identified to specifically determine whether a standard antidepressant or some other form of intervention (eg, a stimulation treatment) will be required for remission. Particularly in highly dysregulated cases, represented by patients with the greatest levels of SCC activation, medication may be least likely to be effective and alternative somatic treatments should be pursued. These hypotheses will require careful prospective testing before they are applied in routine clinical settings.

Considerations for future studies

Continued progress in the identification of neuroimaging TSBs requires careful consideration of patient selection and study design. Ideally, such studies will compare two active modalities, either with or without a placebo arm. Imaging from placebo-treated patients can provide information about the mediators of change with treatment and aspects of treatment outcomes shared across treatment types. However, placebo treatment is not an option in the clinical care of patients with MDD; thus, placebo arms are not a necessary component for studies in which the aim is to identify markers to help choose between active treatment options.

Defining treatment outcomes is an important aspect of analyses. Categorical outcomes (as opposed to group-level continuous outcomes, such as overall mean change or percent improvement) are the most appropriate outcome metric for TSB studies because the individual is the unit of analysis, although more sophisticated techniques using random regression models to determine a trajectory of change for each individual patient may allow for more sensitive analyses.[16] For categorical outcomes, remission should be the standard for successful treatment, not response as typically defined (ie, ≥50% reduction from baseline score). Response as an outcome is vulnerable to regression to the mean effects and is a less meaningful clinical outcome, in that response short of remission is associated with ongoing role dysfunction and increased risk of depressive episode recurrence. Conversely, previous studies used to identify patients with unequivocal nonresponse have used a definition of ≤30% improvement from baseline.[28,72] This standard diminishes regression to the mean effects, and patients who remain close to the illness severity required for study inclusion can be confidently believed to remain significantly ill.

An important aspect of using imaging to identify TSBs is that the results should hold true regardless of previous treatment history or stage of depression that characterizes participants. That is, a patient with advanced illness that is resistant to multiple medication and psychotherapy interventions should show an activity pattern consistent with a poor response to standard treatments. Of course, there are ethical concerns preventing the enrolment of patients in a study using a treatment to which they have already demonstrated a poor response, but the concept that remote prior treatment should not alter the TSB remains applicable.

An individual's TSB should be considered a state, as opposed to a trait, marker because the TSB may change over time depending on the patient's illness progression. A significant proportion of MDD patients who initially show good response to medication over time develop the need for increasingly complex medication regimens and may ultimately lose response to medication altogether. In such patients, the TSB is expected to change from indicating medication-responsiveness to a poor-outcome predictor.

Controlling for some illness-related factors may have a significant adverse effect on neuroimaging studies designed for treatment prediction. For example, controlling for baseline severity in assessing predictors of outcome may eliminate the very imaging difference that could identify treatment outcome differences. The goal of a predictive biomarker is to identify optimal treatments for patients presenting for clinical care, which will require studies to have reasonable generaliz-

ability. This need must be balanced against the fact that TSB development is in the early stages of research, so signal detection may require some measures to limit heterogeneity, such as exclusion of patients with significant medical or nondepressive psychiatric comorbidities. Given that active treatment may alter the imaging results, all participants in TSB research should have an ample washout period from any previous treatments prior to obtaining the baseline imaging. Antidepressant medication, regardless of response, may alter connectivity in insular, prefrontal, and subcortical regions.

The financial strains facing health care delivery across the globe, along with limited access to quality imaging systems, make it possible that even if a TSB with reliable accuracy is developed, adoption of neuroimaging to select treatments for patients with MDD may be limited. Thus, there is a need to explore and test simpler, nonimaging methods as part of neuroimaging studies to see if a nonimaging "bedside" surrogate test could be derived from the neuroimaging findings. Electroencephalography (EEG) is a tool with the potential to map on to imaging-based predictors of treatment outcome, and some preliminary investigations have used EEG in the service of response prediction.[29,73-76] However, to pursue only research using nonimaging markers would be a mistake because imaging methods provide the most direct assessment of the organ that is the source of the illness. Given the relatively recent application of neuroimaging techniques to treatment outcome prediction in MDD, the progress to date is quite encouraging and portends significant advances in the near future. ❑

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Biomarcadores en base a neuroimágenes para la selección del tratamiento del trastorno depresivo mayor

Está en pleno desarrollo el empleo de técnicas de neuroimágenes para identificar las probabilidades del resultado del tratamiento en pacientes con trastorno depresivo mayor. Hay trabajos recientes que sugieren que la actividad metabólica en estado de reposo en la corteza fronto-insular pretratamiento puede distinguir entre pacientes con probabilidad de responder a psicoterapia o a medicación, y puede funcionar como un biomarcador para la selección del tratamiento. A la inversa, la alta actividad metabólica en la corteza cingulada anterior subgenual puede predecir un pobre resultado tanto para los fármacos como para la psicoterapia, lo que sugiere que los tratamientos no habituales se podrían emplear más precozmente. Aunque estos hallazgos requieren ser replicados antes de incorporarse en la clínica, ellos aportan un soporte preliminar para el concepto que se refiere a que los estados cerebrales pueden ser medidos y empleados en la selección de un tratamiento específico que tenga la mayor probabilidad de beneficiar a un paciente individual.

Biomarqueurs de neuro-imagerie pour la sélection du traitement lors de trouble dépressif majeur

L'utilisation des techniques de neuro-imagerie pour identifier les résultats thérapeutiques chez des patients atteints de trouble dépressif majeur, se développe rapidement. D'après des travaux récents, l'activité métabolique de repos avant traitement dans le cortex fronto-insulaire pourrait différencier les patients susceptibles de répondre à une psychothérapie ou un médicament et pourrait représenter un biomarqueur du choix thérapeutique. Au contraire, une activité métabolique élevée dans le cortex cingulaire antérieur ventral pourrait prédire de mauvais résultats, à la fois pour un traitement psychothérapeutique ou médicamenteux, indiquant de prévoir plus tôt dans le traitement la mise en place de mesures thérapeutiques non usuelles. Ces résultats demandent à être répétés et validés avant d'être adoptés en clinique, mais ils suggèrent le concept que des états cérébraux sont mesurables et peuvent être appliqués à la sélection d'un traitement spécifique plus à même de bénéficier à un patient donné.

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