

Improving the Prediction of Treatment Response in Depression: *Integration of Clinical, Cognitive, Psychophysiological, Neuroimaging, and Genetic Measures*

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ABSTRACT

Antidepressants are important in the treatment of depression, and selective serotonin reuptake inhibitors are first-line pharmacologic options. However, only 50% to 70% of patients respond to first treatment and <40% remit. Since depression is associated with substantial morbidity, mortality, and family burden, it is unfortunate and demanding on health resources that patients must remain on their prescribed medications for at least 4 weeks without knowing whether the particular antidepressant will be effective. Studies have suggested a number of predictors of treatment response, including clinical, psychophysiological, neuroimaging, and genetics, each with varying degrees of success and nearly all with poor prognostic sensitivity and specificity. Studies are yet to be conducted that use multiple measures from these different domains to determine whether sensitivity and specificity can be improved to predict individual treatment response. It is proposed that a focus on standardized testing methodologies across multiple testing modalities and their integration will be crucial for translation of research findings into clinical practice.

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Needs Assessment

There is no available source that provides coverage of this information in any one publication to date. Moreover, we propose that the complexity of predicting treatment response in depression requires consideration of interactions between multiple datasets collected from clinical, cognitive, psychophysiological, neuroimaging, and genetic measures.

Learning Objectives

At the end of this activity, the participant should be able to:

- Identify two response predictors that have been identified in each of the following domains: clinical, cognitive, psychophysiological, neuroimaging, and genetics.
- List two methodological difficulties associated with research on treatment response in depressions.
- Outline three possible approaches that may improve prediction of response to antidepressants.

Target Audience: Neurologists and psychiatrists

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This activity has been peer-reviewed and approved by James C.-Y. Chou, MD, Associate Professor of Psychiatry at the Mount Sinai School of Medicine. Review date: November 19, 2008. Dr. Chou does not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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INTRODUCTION

Depression is expected to become a leading burden of disease by 2020, due, in part, to its high lifetime prevalence (10% to 25% for women; 5% to 12% for men),¹ as well as its effect on daily function² and its mortality.³ Antidepressants play a particularly important role in the treatment of depression, yet only 50% to 70% of patients respond to first treatment,⁴⁻⁶ and <40% remit.⁷ Moreover, recent meta-analyses⁸ on unpublished trial data suggest that drug-placebo differences in antidepressant efficacy only reach clinical significance for depressed patients at the upper end of the very severely depressed category (>28 on the Hamilton Rating Scale for Depression [HAM-D]). However, it is important to note that far from being a homogeneous disorder, depression comprises multiple subtypes (eg, melancholia, atypical depression, psychotic depression) and significant comorbidity, especially anxiety,⁹⁻¹¹ which may contribute to whether a patient responds to antidepressant treatment.¹²⁻¹⁵ Unfortunately, pharmacologic treatment of depression remains a matter of trial and error,⁴ and this has serious consequences. A prolonged effort to find the right medication for a particular patient results in prolonged suffering, substantial morbidity, and potential mortality, as well as absence from work and other productive activities and increased burden for their family/caregivers. Each treatment trial may require 4–8 weeks to determine if the medication will be effective. To date, while a large number of studies have sought to identify predictors of treatment response, success has generally been limited. These studies have typically focused on a single measure and have generally not examined participant responses across different measures assessing multiple domains of function.

Researchers have long sought to predict response to antidepressant treatment.^{12,16-19} Early reports^{12,19} suggested that a number of clinical (eg, severity and comorbid disorders) and biological variables (eg, dexamethasone nonsuppression) might improve response prediction. More recent studies^{20,21} examining how the brain mediates emotional experience and the impact of antidepressants on these processes suggest that direct measurement of emotional function may further improve prediction of treatment response. Acute administration of citalopram, a commonly prescribed selective serotonin reuptake inhibitor (SSRI), relative to placebo was found to attenuate electrophysiological activa-

tion to psychologically unpleasant stimuli within frontal and occipital cortices of the brain, and potentiate electrophysiological activation to pleasant valence within parietooccipital cortices.²²⁻²⁶ This body of work is particularly important, considering that emotion may be the key vulnerability factor governing risk for depression²⁷ and that SSRIs are the most commonly prescribed antidepressants. Considering that the response to antidepressants is usually not observed until 3–4 weeks following first dosage, these findings, combined with those reported by others (discussed below), underscore the potential value of brain imaging techniques in predicting treatment response to an antidepressant.

Previous studies have employed a variety of measures (including clinical, cognitive, psychophysiological, neuroimaging, and genetic measures) to examine and predict response to antidepressant treatment (discussed below). This review focuses on some of the key findings reported in studies using each of these measures and highlights some of the methodological difficulties. It then integrates these findings in an attempt to account for some of the previously reported inconsistencies and presents a number of strategies for future studies to improve response prediction.

Several points regarding our review should be noted. First, while we focus predominantly on the prediction of response to antidepressant medication, other studies reporting specific predictors to other treatment strategies are discussed where appropriate. Second, for the purposes of this review we use the term “response” in the broadest sense possible. This is consistent with the considerable variability in the characteristics that have been used in previous studies to define this term.²⁸⁻³⁰ Third, we have focused specifically on studies that have reported treatment response in patients with unipolar rather than bipolar depression. Readers may be interested in following up on other reviews that have focused on patients with bipolar depression, specifically the work of Kleindienst and colleagues.³¹ Considering recent discussion on the continuum/spectrum concept of mood disorders,³² such that bipolar II disorder and major depressive disorder (MDD) may lie on a continuum, future consideration of the diagnostic specificity of response prediction may be worthwhile. Finally, the majority of predictors discussed herein relate to those identified in patients with midlife depression. However, we have included some discussion on the predic-

tors of treatment outcome in late-life depression, given the proposal that late-onset (as opposed to early-onset) may be associated with a different etiology^{33,34} and that such patients may be less responsive to treatment.^{19,35}

To our knowledge, no published review has attempted to integrate findings from the fields of clinical psychiatry, neuropsychology, neuroimaging, and pharmacogenetics. Such an approach may help us to better understand the inconsistencies in the literature and improve response prediction in the future.

CLINICAL AND PSYCHOSOCIAL PREDICTORS OF TREATMENT RESPONSE

Clinical and psychosocial predictors are of great interest to clinicians, given the relative simplicity with which these variables are able to be obtained. Key predictors of response to antidepressant treatment in this category include symptom features (“subtypes”); severity; comorbidity; previous course (eg, number of episodes); demographic factors (such as age and age of onset); temperamental factors (including personality traits) and environmental factors (such as social support); interpersonal relationships; and psychological trauma.^{12,18,19,35,36} See also the findings reported by the National Institute of Mental Health Treatment of Depression Collaborative Research Program.³⁷

Symptoms and Severity

From the heterogeneity of depression, symptoms of melancholia (such as psychomotor slowing, weight loss, insomnia) versus their reverse (over-eating, over-sleeping), have characterized primary subtypes. These symptom subtypes may be orthogonal to severity, in predicting response to types of antidepressants. For example, moderate severity without obvious melancholia may respond well to antidepressants modulating only serotonin (5-HT) (of the SSRI class), such as citalopram.³⁸ This level of severity is commonly associated with “atypical” depression (a non-melancholic subtype of MDD). Escitalopram, a newer SSRI, has been found to be successful in treating moderately to severely depressed participants.³⁹⁻⁴² More severe depression levels are commonly associated with melancholic features, and may respond better to antidepressants that modulate 5-HT and norepinephrine (NE), such as serotonin-norepinephrine reuptake inhibitor (SNRI) or tricyclic antidepressants

(TCAs).^{14,15,19,43-45} In addition, anxiety is frequently comorbid with depression and is associated with poor treatment response,^{35,46,47} suggesting it may contribute to greater severity. Consistent with this possibility, venlafaxine, a commonly prescribed SNRI, may be associated with somewhat higher superior remission rates in patients with anxious features (relative to the SSRI fluoxetine and placebo).^{48,49} These findings suggest that a multi-action antidepressant, such as venlafaxine, may also be beneficial as a first-line treatment when anxiety is comorbid with severe depression. Indeed, anxiety may contribute to severity of depression and possibly to the melancholic type. A third type of depression, distinguished by additional psychotic symptoms, shows a poor response to commonly used antidepressants, such as SSRIs. This type may also require a multi-action treatment, in this case, a combination of antidepressants and antipsychotics.^{14,19}

Demographic Factors

Longer duration and more previous episodes of depression are often predictive of poorer response, while the relationship between current age (and age of onset), depression, and recovery remains unclear. An older age of onset, however, is often associated with undiagnosed general medical disorders and such depression may be less responsive to antidepressants.^{19,35,50} In addition, the literature highlights that an older group of patients with late-onset depression, characterized by executive dysfunction and white matter hyperintensities (WMH) (and known as vascular depression,^{33,34,51-56} may be particularly resistant to antidepressant treatment (see related discussion in the cognitive and neuroimaging sections).

Temperament

Research on temperament has focused on personality traits,⁵⁷ especially those measured by self-report. Neuroticism acts as a negativity bias and is strongly implicated in genetic risk for depression (and anxiety).⁵⁸⁻⁶⁰ Response to SSRIs has been found to be mediated via reductions in neuroticism.⁶¹ Depressed patients with maladaptive personality styles also respond less well to antidepressants.⁶²⁻⁶⁴ However, recent research⁶⁵ has suggested that the contribution of comorbid personality disorders may vary according to the type of antidepressant, as do severity and symptom subtype. While comorbid personality disorders may not impact overall treatment outcome, patients with cluster B personality disorders may

respond better to an SSRI (fluoxetine) than a TCA (nortriptyline).⁶⁵ A better response to TCAs (in this case, imipramine) has been associated with less perfectionistic and socially dependent attitudes, and the addition of clinical management and cognitive-behavioral therapy (CBT).²⁸

Social-Environmental Factors

Traumatic stress in early life is a primary environmental factor that enhances risk for depression. It has been shown to alter the neurotransmitter systems involved in depression,⁶⁶ yet there has been no direct research into its role in predicting response to antidepressants. It has been demonstrated that behavioral therapy may be an essential element in the treatment of patients with chronic forms of major depression and history of childhood trauma.⁶⁷ Conversely, positive interpersonal relationships, including an atmosphere of calm and spousal acceptance, has been associated with better response to antidepressants, though research in this area is hampered by methodological problems, such as the confounding of social factors with individual characteristics that influence outcome (eg, personality traits).³⁵ A positive and higher rate of complete response to behavioral (interpersonal) therapy has also been associated with less social dysfunction relative to a placebo control and those with high social dysfunction.^{37,68} Moreover, a superior response to a TCA (imipramine) has also been predicted by poorer work function in depression,³⁷ consistent with findings regarding a more severe illness.

From the range of clinical and psychosocial factors proposed to be related to treatment response, severity may be the most reliable variable for predicting treatment outcome (ie, the less severe the depression, the better the outcome will be).^{69,70} Symptom type and comorbid symptoms (such as anxiety) may be helpful in predicting response to different types of antidepressant. Social-environmental factors may be important in evaluating predictors that distinguish response to drug versus non-drug and combined treatments. However, it is unlikely that clinical and psychosocial predictors will be able to provide reliable indicators of individual response or non-response, without adjunctive objective information from cognitive, biological, and/or genetic measures. Moreover, the self-report nature of symptom and psychosocial ratings may limit their reliability,^{20,71-77} and, thus, capacity for valid prediction of treatment response.

COGNITIVE PREDICTORS OF TREATMENT RESPONSE

A range of cognitive abnormalities, revealed by neuropsychological testing, have been found in depression.⁷⁸⁻⁸⁰ However, only limited attention has been given to predicting treatment response in this disorder on the basis of these measures. Cognition is a substantive predictor of the functional and psychosocial burden of illness in depression⁸⁰ and, thus, a pertinent candidate predictor of treatment response. Cognitive indicators of treatment prediction in depression may be considered in terms of general cognitive measures (including the domains of memory, attention, and information processing speed) and social cognitive measures, of which emotion recognition and negative attributional biases are key components.^{81,82} Cognitive tasks may also help to provide objective and convergent evidence relating to subtype and to assist with identification of more homogeneous samples of depressed patients. Previously proposed predictors of response include psychomotor speed,¹³ executive function^{53,83-85} and measures of perceptual asymmetry from dichotic listening tasks.⁸⁶⁻⁸⁹

Psychomotor Slowing

Taylor and colleagues¹³ found that depressed outpatients with psychomotor slowing, a primary feature of melancholia, predicts non-response to fluoxetine (an SSRI), which suggests that medications other than SSRIs should be prescribed for patients with melancholic features.^{90,91} It was suggested that SSRIs (fluoxetine) may be less effective in melancholic patients due to an underlying dopaminergic dysfunction and that treatments that target dopamine neurotransmission (such as amineptine) may be more appropriate. This proposal is consistent with a functional model of depression, which relates melancholia to disturbances within the NE (and dopamine) rather than the 5-HT systems.⁹² However, melancholic features failed to recommend one versus another second-step treatment⁸⁴ in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,^{94,95} making it unclear whether psychomotor slowing (and melancholic subtype) is a specific predictor of SSRI treatment (non-)response.

Task Complexity

In another study,⁹⁶ responders to SSRIs (specific SSRI not indicated) were characterized by better cognitive functioning on "simple tasks" and by worse functioning on "complex tasks" as com-

pared to non-responders. "Simple tasks" included automatic or recognition tasks, while "complex tasks" included effort demanding and "maintenance plus" functions. The explanation provided by the authors was that depressed patients who perform less well on complex cognitive tasks may be characterized by low serotonergic activity which may manifest as failure to consider enough information before acting (impulsivity). Interestingly this study was able to correctly classify 89% of actual responders (sensitivity), but only 67% of non-responders could be correctly predicted (specificity). Although this study demonstrates that a small number of cognitive tests may be able to reduce the risk of incorrect prediction, it did not control for placebo response or examine responses to non-serotonergic antidepressants. Findings, therefore, remain to be replicated.

Executive Dysfunction

While interesting, this study⁹⁶ on task complexity is somewhat discrepant with the literature documenting a non-response to SSRI medication in those patients with executive dysfunction, insofar as executive dysfunction relates to poor performance in "complex tasks." For example, in an earlier placebo-controlled study,⁸³ the number of categories completed, percent conceptual level responses and number of preservative responses on the Wisconsin Card Sorting Test and more errors on the interference portion of the Stroop test predicted non-response to fluoxetine after controlling for age, past history of depression, education, estimated premorbid IQ, and depression severity. In a more recent study,⁸⁴ future responders were found to outperform future non-responders across all cognitive domains in an assessment that took place prior to treatment with a range of SSRIs, with the largest differences being observed in executive, language, and working memory functions. Furthermore, deficits were reported to be most pronounced in tests demanding greater mental search and manipulation (ie, greater complexity). Importantly, no differences were observed in baseline depression ratings and performance differences were not attributable to premorbid functioning. Studies in older depressed patients also support the proposal that treatment non-response relates to executive dysfunction^{53,85} and that such dysfunction (in older patients) relates to WMH.^{34,37} Executive function impairments may also be a valuable indicator of the need for augmentation treatment (such as modafinil, a wakefulness-promoting agent) in

MDD.⁹⁸ It should be noted, however, that other studies have reported that cognitive measures are unable to predict response to treatment.^{20,77,99}

Perceptual Asymmetry

Dichotic listening tasks have also been used to predict response. In these tasks, word, syllable, or tone stimuli are presented simultaneously to the two ears and the difference in accuracy for reporting right and left ear items provides a measure of perceptual asymmetry, which indicates hemispheric advantage for processing verbal or tonal information. Unmedicated depressed patients who display greater right ear (left hemisphere) advantage for dichotic words and less left ear (right hemisphere) advantage for complex tones show a favorable response to TCAs, fluoxetine, bupropion (an NE and dopamine reuptake inhibitor, and nicotinic antagonist), and cognitive therapy.⁸⁶⁻⁸⁹ Thus, greater left than right asymmetry during dichotic listening is associated with better treatment outcome. These findings are present both before and after successful treatment, suggesting that perceptual asymmetry is a stable trait, rather than a state-dependent feature of depression. These findings are intriguing, given neuropsychological theories of emotion, which highlight the relationship between brain asymmetry patterns (particularly electrophysiological asymmetry) and certain emotional states, such as depression and anxiety.¹⁰⁰ However, uncertainty regarding these findings remains due to a number of confounding variables, including disorder heterogeneity, gender, and methodology of the test used. Furthermore, the sensitivity of perceptual asymmetry as a predictor of treatment response remains unclear, given that bupropion responders⁸⁹ display similar findings reported previously in fluoxetine responders.⁸⁷ Yet, many of the bupropion responders had previously failed to respond to fluoxetine, suggesting a rather substantial overlap between responders and non-responders. Response predictors from dichotic listening tasks also appear to be non-specific to a particular treatment and may reflect placebo response.¹⁰¹

From an integrative point of view, the evidence to date suggest that psychomotor (or response) speed may be of specific benefit in predicting the need for a multi-action antidepressant, consistent with the clinical evidence regarding melancholia. The second key indication is that cognitive impairments related to executive functions may provide a general indicator of the need for augmentation therapy. Third, there is a promising role for assessments of social cognition, such as emotion

identification, in contributing to prediction of antidepressant response.¹⁰² However, there remains a compelling need for more studies of cognition, in regard to antidepressant treatment prediction, to resolve the contradictory findings, and provide replication, placebo controls, and exploratory and confirmatory analyses. Unfortunately, few studies using neuropsychological testing have sought to predict treatment response in non-elderly, depressed individuals. The reason for this may be due, in part, to the traditional approach of assessing specific changes in patients with discrete lesions to determine locus of insult or their functional capacities.¹⁰³ Importantly, depressive symptoms (at least in non-elderly patients) are more likely to be a result of dysfunction in complex neural networks rather than a specific brain lesion, highlighting the importance of integrating neuropsychological testing with measures of brain function (eg, electroencephalogram [EEG], magnetic resonance imaging [MRI]) in order to better understand the underlying impairment in depressed patients and subsequent response to treatment. Future studies might also consider assessment of estimated premorbid intelligence in order to control for cognitive dysfunction that may have preceded depressed mood. Certainly the advances in knowledge of how cognitive measures link to underlying biochemical, neural and genetic foundations highlight the value of pursuing these measures.

PSYCHOPHYSIOLOGICAL PREDICTORS OF TREATMENT RESPONSE

EEG is considered to be a particularly useful technique for predicting treatment response given its sensitivity to acute administration of antidepressants.^{22,104,105} This technique has been widely used in studies examining treatment response and a range of markers, including changes in polysomnography recordings (and sleep EEG, electrooculogram and electromyogram in particular), EEG bandwidths, "cordance", frontal asymmetry and a number of event-related potential (ERP) components, including the loudness dependence of the auditory evoked potential (LDAEP, or N1-P2 intensity dependence), and the P3 ERP component (commonly elicited in the auditory oddball paradigm and reflecting psychological significance of the stimuli) have been identified.

Polysomnography

Consistent with clinical observation of sleep disturbance in depressed patients, polysomnogra-

phy recordings have revealed reduced total sleep time and sleep efficiency; increased time taken to fall asleep; reduced total (and percentage of) slow wave sleep; reduced total non-rapid eye movement sleep (NREM) time; shortened time from sleep to first REM period; increased all-night REM density; increased duration of first REM period; and increased REM percentage of total sleep time in depressed patients reviewed by Argyropoulos and Wilson¹⁰⁶ and Benca and colleagues.¹⁰⁷ Furthermore, sleep EEG is now recommended as a laboratory test to identify depression (and the melancholia subtype, in particular).¹⁰⁸ The best documented effect of antidepressants on sleep parameters is the suppression of tonic REM sleep, as indicated by a delay of REM latency and a reduction of REM time and percentage.¹⁰⁹ A commonly reported predictor of treatment response is initial REM suppression, measured during the first 48 hours,¹¹⁰⁻¹¹² although, it should be noted that some antidepressants (ie, nefazodone, mirtazapine, bupropion, amineptine, iprindole, trimipramine) do not share such a property.^{106,109} Interestingly, it has been hypothesized that REM-suppressing medications may be more appropriate for those patients displaying increases in REM sleep, while those that do not suppress REM sleep may be appropriate for the remainder of patients,¹⁰⁹ highlighting the importance of taking disorder heterogeneity into account when seeking to maximize treatment effectiveness. Other sleep EEG measures, including quantitative measures of eye movement activity during REM sleep; delta sleep ratio (ie, the ratio of the number of delta waves in the first NREM period to those in the second); changes in EEG bandwidths; and sleep arousals; may also assist in the prediction of response to antidepressants,¹¹³⁻¹¹⁶ although replication studies are required.

Electroencephalogram Bandwidths

In addition to sleep EEG parameters, other research¹¹⁷ report that antidepressant responders are characterized by changes in the theta bandwidth, including a pre-treatment decrease and post-treatment increases (2 days and 2 weeks) following treatment with imipramine (aTCA). In another study by the Knott and colleagues,¹¹⁸ increases in pre-treatment theta predicted future response to paroxetine treatment.¹¹⁹ Convergent evidence for these findings come from other researchers^{120,121} who have reported increases in the theta bandwidth within rostral anterior cingulate using low resolution electromagnetic tomography (LORETA) (also

discussed in the neuroimaging section). These latter results are particularly interesting considering that positron emission tomography (PET) and functional MRI (fMRI) studies have also identified this region as a pre-treatment predictor of treatment response.^{20,21} Other research has demonstrated that of the four EEG frequency bands, theta is the only bandwidth to correlate with depression severity, such that increases in theta, particularly in frontal locations, are related to increased depression severity.¹¹⁸ Increases in theta are also positively correlated with motor retardation in depression.^{122,123} However, it is unclear how these positive correlations and response prediction findings for the theta bandwidth are to be interpreted in light of the proposal that increased depression severity also predicts non-response to treatment (as previously discussed). Null and contradictory findings for response prediction by the theta bandwidth have also been reported.¹²⁴⁻¹²⁷

Cordance

Another quantitative EEG (QEEG) measure, "cordance", has generated considerable research interest and is thought to reflect cerebral perfusion (as measured by PET). This measure combines information from absolute and relative power measures¹²⁸⁻¹³⁰ and using this measure, patients, classified as "concordant", prior to treatment, demonstrate a more robust response to fluoxetine (an SSRI) than patients classified as "discordant" in a placebo-controlled trial.¹³¹ "Concordance", particularly in the alpha band, is thought to indicate normally functioning brain tissue, normal perfusion, and/or metabolism, while "discordance", particularly in the beta 1 and/or theta bandwidths, is thought to indicate underlying white matter lesions, low perfusion, and low metabolism.¹²⁸ However, no pre-treatment differences were observed in a more recent study conducted by the same researchers.¹²⁴ Cordance values in the theta frequency band have also been found to positively correlate with cortical perfusion as measured by [$H_2^{15}O$]-PET.¹³⁰ A number of studies^{124,132-134} have now reported that responders to a variety of antidepressants display decreases in prefrontal cordance in the theta bandwidth after 48 hours and 1-week of treatment, while increases in prefrontal cordance is associated with response to placebo after 4 weeks of treatment.¹³⁵ Test sensitivity, specificity, and overall accuracy were reported to range between 69% to 83%, 67% to 75% and 72% to 75%, respectively, and accuracy is greatest at 1 week following commencement of medication. While these findings are intriguing, these studies are characterized by small sample

sizes in each cell (as low as N=6,134), grouping participants on different antidepressants^{124,134,135} and at least two studies^{124,135} seem to be based on the identical dataset of subjects, highlighting the need for independent replication.

Frontal Asymmetry

Another electrophysiological candidate is EEG asymmetry. Research conducted in healthy participants and depressed patients¹³⁶⁻¹³⁹ suggest that negative (withdrawal) affect may be associated with relatively greater activation within the anterior portion of the right hemisphere^{140,141} and that patients who display greater activation of the right hemisphere (reduced EEG alpha) than the left hemisphere during resting state do not respond to fluoxetine.¹⁴¹ Studies remain to be conducted that examine the utility of EEG asymmetry to predict treatment response under resting state and during specific experimental paradigms. For example, it is possible that collection of resting state data is insufficient to challenge the impaired circuitry in depression. In this regard, paradigms that tap into the brain's processing of emotion stimuli may provide more useful information relating to the impairments associated with depression as well as changes associated with antidepressant treatment.

Event-Related Potential Components

Other EEG studies^{120,143-145} have reported that patients displaying strong N1-P2 intensity dependence (ie, greater ERP amplitude associated with LDAEP) respond well to serotonergic antidepressants but not to noradrenergic antidepressants such as reboxetine.^{120,146} Convergent evidence in healthy controls indicates that enhancement of 5-HT with citalopram decreases the slope of this potential (ie, weaker LDAEP, an opposite finding to that reported in unmedicated depression), highlighting the relationship between serotonergic function and the LDAEP.¹⁴⁷ However, strong N1-P2 intensity dependence has also been reported in bupropion (an atypical antidepressant that acts as an NE and dopamine reuptake inhibitor, and nicotinic antagonist), suggesting that such a response may not be as specific to the serotonergic system as previously supposed.^{148,149} Other evidence^{150,151} suggests that smaller P3 amplitude at occipital sites in dichotic listening tasks is related to poor response to fluoxetine and TCAs in middle-aged depressed patients, while longer pre-treatment P300 latency, a measure of prefrontal dysfunction, may be associated with poor or delayed response to a range of antidepressants in depressed elderly patients.¹⁵²

An increasing number of studies have used the EEG to identify treatment response predictors and more recent EEG studies have utilized placebo controls. However, studies have generally reported findings from small samples or have failed to restrict their sample to specific, homogeneous groups of patients that may account, in part, for the considerable overlap between responders and non-responders in these studies. Issues of generalizability, sensitivity, and specificity also remain to be fully examined.

NEUROIMAGING PREDICTORS OF TREATMENT RESPONSE

A number of studies utilizing MRI, PET, single photon emission computed tomography (SPECT), and low-resolution brain electromagnetic tomography ([LORETA] an electrophysiological measure that reveals which brain structures make the major contributions to the brain electrical activity recorded on the scalp) have sought to determine treatment response to antidepressants.¹⁵³⁻¹⁵⁷

Rostral Anterior Cingulate Function

According to one influential model of depression and its treatment based on PET data,^{20,156,158} decreased dorsolateral (DLPFC) and increased ventrolateral (VLPFC) prefrontal cortical activity mediate the depressed state, whilst the reversal of this is necessary for disease remission. In this model, the rostral anterior cingulate cortex (rACC) functions as a bridge linking cortical and subcortical regions for normal integrative functioning of mood and cognitive behavior. The most frequently reported finding^{20,21,120,121,159-164} in the neuroimaging literature which focuses on treatment prediction is that pretreatment activity in rACC, as measured by SPECT, LORETA, PET, and functional MRI (fMRI) techniques, predicts future response to a range of antidepressant treatments, including sleep deprivation, tricyclics, SSRIs, SNRIs, NRIs, and bupropion.^{69,118-120,158-163} These studies have generally reported that treatment responders are characterized by increased pre-treatment activity within this region.^{153,157,160,165} Furthermore, demographic, clinical, and behavioral measures (ie, motor speed, cognitive performance, depression severity, illness chronicity) have been reported not to be able to discriminate between responders and non-responders,²⁰ highlighting the utility of brain imaging techniques in treatment prediction.

It is interesting to note the replicability of the rACC finding across different techniques (including fMRI, PET, SPECT, and LORETA) and research

groups. For instance, two groups of researchers^{120,121} have identified increased pre-treatment activity in the rACC in responders (compared to non-responders) using LORETA. This finding was specific to EEG theta activity, providing convergent evidence for some of the QEEG data previously discussed. The anterior cingulate is known to play a significant role in affect and cognition¹⁶⁶ and comprises the dorsal cognitive division (anterior cingulate cognitive division, ACcd; caudal area 24' and 32' and cingulate motor area) and the rostral-ventral affective division (anterior cingulate affective division, ACad; BAs 25, 32, and 33 and rostral area 24).¹⁶⁷ While the ACcd is often hypoactive in depression, it is the ACad region that is reported to be hyperactive in depressed treatment responders, and it is this latter region that has been targeted in deep brain stimulation studies of treatment-resistant depression.^{168,169} While most studies on response prediction have collected brain imaging data under resting state conditions, studies have begun to scan participants under active task conditions, which may help to better distinguish responders from non-responders by targeting the emotional/cognitive circuitry involved in the depressive state and reduce unexplained variance. For example, in an uncontrolled fMRI study,^{120,163} participants that displayed greater pre-treatment activation within ACC in response to negative versus neutral stimuli were reported to display the most robust response to treatment.^{21,164,170}

Function in Other Regions

Drevets and colleagues¹⁷¹ have proposed that direct inhibition of pathological limbic activity (including amygdala and subgenual ACC) may be required for amelioration of depressive symptoms, while reduction in orbital cortex/VLPFC activity may reflect subsequent relaxation when these regions are no longer required to maintain pathological limbic activity. However, there is less consistent evidence to suggest that other regions may also assist in the prediction of treatment response. For example, an uncontrolled pilot study using fMRI¹⁷² reported that hyperarousal of (left hemisphere) amygdala function in response to picture stimuli (emotional facial expressions) was normalized by treatment with sertraline.^{164,173} Furthermore, a prospective study using fMRI¹⁷⁴ has reported that greater pre-treatment amygdala activation (bilateral) during presentation of sad, happy, angry, and fear faces predicts symptom reduction 8 months later, after controlling for initial depression severity and medication status. Whole-brain analyses also indicated that other

regions were able to predict depression severity after 8 months, including the thalamus, putamen, parahippocampal gyrus, medial frontal gyrus, orbital gyrus, postcentral gyrus, and temporal, occipital, and parietal lobes. This study also reported that reaction times to complete a concurrent behavioral (sex discrimination) task were not predictive of future depression severity, again, highlighting the utility of brain imaging over behavioral responses in predicting treatment response. The finding that greater pre-treatment amygdala activity predicts future antidepressant response is supported by another study,¹⁶⁵ which reported that increased reactivity to negative words in the amygdala predicts response to CBT. It is unclear how to rectify amygdala findings in these studies in light of those reported by others, suggesting that amygdala activity is positively correlated to depression severity^{175, 176} and that depression severity is the most reliable variable for predicting treatment non-response.⁶⁹

While research has begun to focus on distinctive (functional) profiles displayed in response to successful antidepressant treatment with paroxetine versus interpersonal therapy¹⁷⁷; venlafaxine versus interpersonal therapy¹⁷⁸; placebo versus fluoxetine⁷⁷; paroxetine versus CBT¹⁷⁹; and venlafaxine versus CBT,¹⁸⁰ research has seldom sought to determine specific predictors of response to specific antidepressants (see the work of Little and colleagues¹⁸¹ regarding specific pre-treatment markers in responders to bupropion vs venlafaxine). This approach requires larger sample sizes, than are usually included in neuroimaging studies, allowing for an additional factor of response/non-response to be included in analyses in addition to a treatment factor, so that differences between responders and non-responders are able to be explicitly assessed. It is pertinent to distinguish here, the difference between a marker of treatment response (ie, a marker of a current state) and a predictor of treatment response (ie, an indicator of a future state). A predictor of treatment response is ideally identified during pre-treatment recording or during the first week of treatment, to allow for changes to be made to medication if future non-response is predicted. It is important to make this distinction when reviewing the literature and to consider the sensitivity (ie, the ability to predict response versus non-response) and specificity (ie, the ability to distinguish response/non-response to a specific treatment) of such prediction. Although previous studies have displayed some intriguing findings particularly in the rACC, they do not assist clinicians in deciding which particular antidepressant to prescribe to a particular patient. Also, findings

have generally been based on small and heterogeneous patient samples, a lack of a placebo control, and analysis of data using rather simple univariate statistical models. Future studies should consider collection of genetic data in addition to neuroimaging data to explore potential interactions between brain function (and structure) and genetic variability with respects to improving treatment prediction.

It is also possible that amygdala activity may relate to anxiety rather than depression severity. Findings reported from our own laboratory suggest that anxiety (in this case, posttraumatic stress disorder) rather than depression may be responsible for heightened activity that is frequently observed in the amygdala.¹³⁶

Structural Imaging Predictors

Finally, while the majority of predictors discussed in the previous paragraphs relate to those identified using functional imaging techniques in patients with midlife depression, the literature also highlights treatment resistance in an older group of patients with late-onset depression, characterized by WMH.^{33,34,51-56} Research on late-life depression (using a naturalistic rather than controlled design)⁵² has demonstrated that those patients which achieve remission following 2 years of antidepressant treatment display significantly less increases in WMH volume (11.5%) than those that do not (31.6%). This study also demonstrated that greater change in WMH volume was associated with failure to sustain remission after controlling for baseline depression severity, medical illness severity, age, sex, and race. Interestingly, education was also associated with sustaining remission in this study. Patients with moderate to severe deep WMH performed less well on general and delayed recall memory indices, executive functioning, and language testing than those without such lesions and non-depressed elderly subjects with or without WMH,⁹⁷ and poor neuropsychological performance is associated with poor response to antidepressants (see section on cognitive predictors). While structural imaging studies have also reported differences from controls in patients with midlife depression (eg, patients 18–60 years of age¹⁸²), which may be particularly prevalent in non-responders, frontal and basal ganglia abnormalities are prominent in late-onset depression.¹⁸³ It should also be noted that although meta-analysis has documented a reduction of between 8% and 10% in hippocampal volume in patients with depression and a correlation between number of depressed episodes (and the number of days of untreated depression¹⁸⁴) and lower hippocampal volume (particularly right-sided),^{185,186} chronic

treatment may block or even reverse hippocampal atrophy via neurogenesis.^{184,187} Therefore, it is unclear whether hippocampal atrophy is able to predict response to treatment.^{188,189}

GENETIC PREDICTORS OF TREATMENT RESPONSE

Pharmacogenetic and pharmacogenomic information provide ideal candidates for predicting response to antidepressant medication as they are not affected by medication, and do not require the patient to be “washed-out” from prior medication for scientific integrity.¹⁹⁰⁻¹⁹⁴ The search for genetic predictors has largely been focused around a number of key models of depression and its treatment, the primary one being the monoamine hypothesis of depression,^{195,196} which proposes that depletion of the monoamines (ie, NE, 5-HT, and, possibly, dopamine) may underlie the depressed state, and that alteration of monoaminergic transmission is required for successful treatment. The majority of studies that have sought to identify genetic predictors of response have focused on the monoaminergic pathways (discussed below). However, alteration of the monoaminergic system alone may not be sufficient for amelioration of depressive symptoms.¹⁹⁷ Furthermore, it is possible that there is a final common pathway downstream from monoaminergic activation¹⁹⁸ that underlies the efficacy of different classes of antidepressants. Therefore, research on antidepressant treatment response has been guided by other relevant models, including the neurotrophin hypothesis of depression,¹⁹⁹ which is based on observations that stress-induced depression is associated with decreases in hippocampal brain-derived neurotrophic factor (BDNF) levels and that antidepressant treatment increases the expression of BDNF. However, a causal link between administration of antidepressants, cell proliferation (neurogenesis), and antidepressant efficacy remains to be demonstrated.^{200,201} It is also unlikely that impaired hippocampal neurogenesis gives rise to the affective symptoms of depression,²⁰¹ highlighting the importance of not restricting one's focus to specific neurochemical pathway. Another consideration that has guided research on genetic predictors is the knowledge that many depressed patients, particularly those with melancholic features,²⁰² display hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoid resistance, and that normalization of these features is associated with successful treatment.^{193,203,204} Other strategies for selection of candidate genes has been to select

genes on the basis of prior evidence of association with antidepressant outcome and/or major mood disorders²⁰⁵ and identification of other (known) functional variant(s) that may be theoretically relevant to the disorder²⁰⁶⁻²⁰⁸ or involved in the absorption, distribution, metabolism, and elimination of a drug to the target.^{190,192,193} We now highlight some of the polymorphisms that have been identified in the literature as playing a potential role in response or non-response to antidepressant treatment.

Monoaminergic Candidate Genes

Monoaminergic candidate genes include the serotonin transporter (5-HTT) (ie, better response in Caucasian patients with the 5-HTTLPR long allele and in Asian patients with the STin2 12/12 allele); the 5-HT_{2A} receptor (ie, better response in patients with 102T/C C or -1438A/G G alleles); the 5-HT₆ receptor (ie, better response in patients with the C267T CT allele); tryptophan hydroxylase (TPH) (ie, better response in patients with the A218C C allele); and the G-protein $\beta 3$ subunit (ie, better response in patients with the C825TT allele).^{193,194,209} Results of many studies have highlighted the role for a deletion/insertion polymorphism in the promoter region of the 5-HTT gene (SLC6A4) in the vulnerability to depression and in its treatment. Although this gene has no influence on the structure of the 5-HTT, it is thought to affect its expression, such that individuals with the short allele may display decreased gene transcription and lower biological activity in the 5-HTT. SSRIs are considered to be specific and potent inhibitors of 5-HTT. Thus, a genetic variant, such as the short allele, which reduces the expression of this protein, could affect treatment response. Studies have reported that patients identified with the short allele respond poorly to fluvoxamine and paroxetine,²¹⁰⁻²¹⁴ though other studies that tested Asian patients, have reported better response in individuals with the short allele to these same antidepressants.²¹⁴⁻²¹⁷ It is possible, therefore, that poor response to antidepressant medication in patients with the short form of a deletion/insertion polymorphism in SLC6A4 is dependent on the ethnicity of the patient population sampled (in this case, non-Asians).^{190,192,209}

More recent studies in Caucasian samples^{205,218} have not replicated the finding that response is associated with the SLC6A4 (or 5-HTTLPR) gene. For example, findings from data collected in the STAR*D study reported that the only significant and reproducible association with treatment outcome was a variation in the gene encoding the 5-HT_{2A} receptor.²⁰⁵ This study examined a total of 768 single nucleotide polymorphism (SNP) markers from 68

candidate genes from 5-HT (n=20), glutamate (n=16), dopamine (n=3), adrenergic (n=4), and neurotrophic (n=4), and neurotrophic (n=4), along with selected genes in other pathways (n=21) in a total of 1,953 patients with MDD. The SNP rs7997012 residing in the second intron of the gene HTR2A, which encodes the 5-HT_{2A} receptor, was the only gene identified following a rigorous analysis procedure involving a split-sample design comprising a discovery sample and replication sample. Interestingly, this finding was largely confined to white (rather black) participants, such that 79.7% of those homozygous for the A allele were classified as responders, as compared with 63.5% of those homozygous for the G allele. Thus, the AA genotype at rs7997013 confers a 16% to 18% reduction in risk of non-response in this participant sample,²⁰⁵ which represents quite a remarkable impact for a single gene. However, it should be noted that the functional relevance of this allelic variant is unknown. In a more recent study by the STAR*D team,²¹⁸ no association was found between 5-HTTLPR and treatment response even after examining a functional A>G variation in the long allele of SLC6A4 HTTLPR. The LG allele is known to reduce SLC6A4 mRNA expression to levels nearly equivalent to those of the short allele, whereas the LA allele confers higher SLC6A4 expression.^{218,219} These conflicting findings highlight the importance of adequately treating patients in the first instance regardless of the serotonergic allelic variant and indicate that other polymorphisms are involved in an individual patient's response and non-response. Indeed, on review of the literature, it has been concluded that "current information is insufficiently reliable as a basis for implementing genetic testing in the diagnostic work-up of the depressive patient."²⁰⁸ These conflicting findings highlight the importance of future studies examining the extent to which genetics data interact with other variables (eg, combinations of polymorphism²¹⁷ and life stress²¹⁸) when seeking to improve the sensitivity (and specificity) of response prediction. In addition to 5-HT-related genes, preliminary evidence has been reported for NE and dopamine transporters^{221,222} and has also highlighted the role of catechol-O-methyltransferase Val158Met polymorphism^{223,224} in response to mirtazapine (ie, better response in Val/Val and Val/Met alleles) and milnacipran (ie, faster response in Met/Met allele), respectively. Evidence has been reported indicating that the monoamine oxidase A²²⁵ and B²²⁶ genes are associated with short-term antidepressant response to mirtazapine and paroxetine in female but not male depressed patients, highlighting a gender-specific moderator variable.

Brain-Derived Neurotrophic Factor Gene

Response to antidepressant medication has also been shown to be affected by genetic polymorphisms in the BDNF gene, a well-characterized neurotrophin expressed throughout the brain. The effects of a functional coding region SNP at nucleotide change at codon Val66Met (rs6265) of the BDNF precursor protein has generated significant research interest, given the finding that the BDNF methionine (Met) variant is associated with inefficient activity-dependent secretion compared with the valine (Val) variant.²²⁷ A number of studies²²⁸⁻²³¹ have examined the impact of the BDNF Val66Met polymorphism on the success of antidepressant treatment. While one study has reported that mice homozygous for the Val66Met Met allele display decreased biologically relevant BDNF release, increased anxiety-like behavior and reduced response to chronic fluoxetine,²²⁸ other studies²²⁹⁻²³¹ have highlighted the role of the Met allele in improved response to antidepressants in human (Asian) patients. A study conducted in ethnic Chinese patients²²⁹ reported that patients heterozygous for the Val66Met Met allele (Val/Met) display improved response to chronic fluoxetine compared homozygous analogs. Similar findings have since been reported in Japanese patients.²³¹ Finally, another study,²³⁰ conducted in a Korean population, reported that patients carrying the Met allele displayed a higher percentage change in the HAM-D score after chronic citalopram. While it is unclear why patients characterized with an allele associated with inefficient activity-dependent secretion should show improved response to antidepressants, Yoshida and colleagues²³¹ have proposed that this discrepancy may be due to either regionally different effects of the BDNF polymorphism on brain function or a linkage disequilibrium with an as yet unidentified functional polymorphism with a molecular heterotic effect, as discussed by Yoshida and colleagues²³¹ and Comings and MacMurray.²³²

Other Candidate Genes

Other research has reported on a number of genetic polymorphisms relating to the stress hormone system and the HPA axis. In this regard, polymorphisms relating to the corticotropin-releasing hormone (CRH) receptor 1, the glucocorticoid receptor, and the FK506 binding protein 5, a glucocorticoid receptor-regulating cochaperone of heat shock protein 90, upregulated in many cells in response to stress, have been associated with a differential response to treatment.¹⁹³ More recently, research examining three clinically relevant polymorphisms

in the GR gene, including the ER22/23EK, a BclI restriction fragment polymorphism, and N363S, reported that a combination of high levels of adrenocorticotropin after injection of CRH and presence of the BclI polymorphism predicts non-response better than either one of these factors alone,²³³ further highlighting the utility of integrating additional measures with genetic data. Genetic variants affecting the absorption, distribution, metabolism, and elimination of a drug to the target (pharmacokinetic factors) have also been examined and findings suggest that polymorphisms in the liver cytochrome P450 (CYP) isoenzymes (eg, CYP2D6, for which there are 70 known variants) may help predict patients who will not be able to achieve clinically relevant plasma concentrations as well as those who will display adverse interactions due to “ultrarapid” and poor metabolism, respectively. However, no prospective study has yet demonstrated superior clinical outcome or a reduced side-effect profile when drug and dosing choices are guided by CYP2D6 genetic information.¹⁹³ It is interesting to note that recent reports on drug transporter genes, such as the multi-drug resistance 1 (ABCB1, MDR1) gene, which encodes a blood-brain barrier transporter P-glycoprotein, may be associated with SSRI response²³⁴ (ie, the non-synonymous SNP G2677T/A was associated with treatment response to paroxetine, while the wild variants haplotype [3435C–2677G–1236T] were associated with poor response).²³⁵

While there is evidence for poor response to SSRIs in Caucasian patients with 5-HTTLPR short allele, contradictory results have been reported. Other findings either remain to be replicated or examined across different ethnic samples. Few studies have included a placebo control, a methodological consideration especially critical when using clinical response as phenotype.¹⁹⁰ Placebo-response rate may range between 25% and 60%,⁶¹ thus, if no placebo control is included, “active” drug responders may be placebo responders. This problem will consequently raise the number of false positives and lead to incorrect conclusions being made over the predictors associated with a particular medication. In addition to the often vague hypothesis-driven pharmacogenetic approaches to identification of polymorphisms that predict response to treatment, the dramatic increase of publicly available genomic information has allowed research to utilize genomewide approaches to elucidate individual differences in treatment outcome. However, studies remain to be conducted that utilize a pharmacogenomic approach in the prediction of response to antidepressant treatment in unipolar depression.¹⁹³ While this approach raises the number of false posi-

tives, given the high number of multiple comparisons, strategies such as splitting samples and seeking to confirm findings in a discovery versus replication sample will, in part, help to avoid these problems.²⁰⁵ It is pleasing to note the presence in the literature of a number of genetic studies reporting null findings^{206–208} that may help researchers in the future to avoid drawing incorrect conclusions that relate to the “file drawer problem.”^{236,237}

AN INTEGRATIVE NEUROSCIENCE APPROACH TO IMPROVING RESPONSE PREDICTION

As highlighted by the preceding review, a key challenge facing research into objective markers of antidepressant response is how to pool insights from the accumulating findings across individual studies. Yet, the use of different theoretical approaches and experimental protocols makes it difficult to integrate the findings even for those studies focused on a common domain or scale of function, such as cognition. Moreover, studies to date have generally reported findings from these domains in isolation and have seldom sought to identify linkages between predictors across domains to determine if sensitivity and specificity is improved.

Integrative neuroscience is well placed to address this challenge. It provides a framework for integrating theoretical concepts across different areas of research and for linking multiple scales of function, such as cognition, neuroimaging, and genetics, that are normally studied in isolation.^{238–241} Central to integrative neuroscience is the focus on standardization, theoretically and in terms of methodology. Theoretically, the goal is to identify essential commonalities across theoretical models that are based in a particular discipline and terminology and, in terms of methodology, to use standardized experimental protocols that allow data to be linked across samples and types of data. Thus, it becomes possible to compare findings from the testing of individual hypotheses within the same standardized framework.^{238–241} We have previously highlighted that standardization of hardware, software, paradigm details, task instructions, and data analysis is crucial to minimizing measurement error across multiple testing modalities and to integrating data collected for each subject and each site.²³⁸ With such standardization, integrative neuroscience supports a personalized medicine approach²⁴¹ by providing a consistent framework from which cognition-brain-gene indicators of response to treatment in different types of depression may be identified.

This approach to integrative neuroscience addresses some of the reasons as to why integration of data has not, until recently, been undertaken in a systematic way.²⁴² For instance it highlights the importance of theoretical integration, rather than ad-hoc collation of data. While there has been a lack of any explicit theory to guide such research, sufficient details about clinical, temperament, cognitive, brain function and genetics in depression now exist to identify commonalities in theoretical constructs. Second, standardized assessment and the use of neuroinformatics with databasing addresses the aversion to sifting through excessive amounts of data and generation of spurious findings, and to a substantive extent, the cost and demand of multimodal data acquisition. With standardized protocols, it is also possible to apply data-reduction techniques in a systematic way, and test competing hypotheses within the same framework. Taking an integrative neuroscience approach will of course require researchers to gain cross-disciplinary knowledge and expertise not traditionally part of discipline-based training.

Studies using different techniques in different samples have produced a number of inconsistent findings. For example, it is unclear how reports of decreased prefrontal cordance, an electrophysiological measure proposed to reflect cerebral perfusion, in patients that respond to a variety of antidepressants,^{124,132-134} relates to the well-validated model that increased DLPFC and decreased VLPFC activity is required for improvement of depression symptoms.^{20,156,158} One of the difficulties in relating these two separate bodies of research are the differences in study design. While Leuchter and colleagues generally collect data at baseline, 48 hours and 1 week following commencement of antidepressant medication,^{124,132-134} Mayberg and colleagues^{20,158} usually collect data at baseline and 6 weeks, without brain assessment during the first week of treatment. Additional subject factors may also contribute to inconsistent findings. For example, Leuchter and colleagues¹³⁵ have reported that higher levels of perfusion or metabolism during treatment for depression may be associated with placebo response and that the placebo responders (feasibly those with a particular temperament and cognitive profile) are the only group showing prefrontal activity that increases significantly over the baseline value.¹³⁵ However, Mayberg and colleagues⁷⁷ have reported that placebo as well as fluoxetine responders display cortical glucose metabolism increases and limbic-paralimbic metabolism decreases, and that additional subcortical and limbic decreases differentiate fluoxetine from placebo responders. The use of

standardized multi-modal measures in larger samples would be valuable in disentangling the dynamics of treatment and placebo responding over time.

A small number of studies provide concrete examples of how data integration may improve the prediction of antidepressant response in depression.^{120,242,243} These studies highlight complementary approaches to integrating different domains of theory, and the multiple approaches previously used to predict treatment response. These examples are discussed below.

Integrating Temperament, Psychosocial Factors, and Psychophysiology to Predict Response

The study conducted by Simons and colleagues²⁴² emphasized the need to consider different domains of theory in depression and complementary perspectives. In their study, they focused on the domains of cognition (ie, depressogenic attitudes), stress (ie, negative life events) and psychophysiology (ie, sleep electroencephalogram). It was hypothesized that interactions between the three domains would be more informative than interactions within any of these domains in isolation and findings supported this hypothesis. The key finding in this study was that worst treatment outcome was displayed in patients who had experienced a severe negative life event but low depressogenic attitudes and those who had not experienced a severe negative life event but displayed high depressogenic attitudes. These results were interpreted to reflect a realistic response to a negative event that is hard to treat because responses to the event are not exaggerated, and that dysfunctional attitudes are not linked to actual events that are able to be examined and tested, respectively. The authors also reported that REM latency affected the length of time required to achieve remission and that this effect was particularly strong in those patients who had experienced a negative life event. However, this study had a number of limitations, including small sample size (N=53, of which 39 had not experienced a life event) thereby restricting analyses to two-way interactions (ie, three-way interactions were not possible), and only one treatment group (CBT), which did not allow for the specificity of findings to be determined.

Integrating Clinical, Cognitive, and Psychophysiological Domains to Predict Response

In a more recent study, Leuchter and colleagues²⁴³ employed an integrative approach to assist in the prediction of response to placebo ver-

sus fluoxetine and venlafaxine medication using a double-blind design. The authors hypothesized that responses in three domains would assist with identification of likely placebo responders prior to treatment. The domains included neurophysiology (QEEG including power and cordance), neuropsychology (results from a cognitive testing battery), and clinical symptoms (neurovegetative items from the HAM-D). The key finding was that three pretreatment measures, one measure from each domain, including lower pre-treatment frontocentral cordance in the theta frequency band, faster cognitive processing time, and lower reporting of late insomnia, accurately identified 97.6% of eventual placebo responders. While this rate of correct classification is particularly impressive, it should be noted that there were only 10 patients classified as placebo responders, highlighting the need for replication of these findings. Regardless, this study provides an excellent case in point that integration of data from different domains (and measures) may help to improve the prediction of response and non-response. It will be particularly important for future work to examine the ability of these (or like) measures to predict response to active treatment.

Integrating Psychophysiology and Neuroimaging to Predict Treatment Response

In another study, Mulert and colleagues¹²⁰ combine two approaches to predict treatment response in depression including activity in the rACC and LDAEP. As previously discussed, increased pre-treatment activity within the rACC predicts future response to a range of antidepressants,^{20,21,120,121,159,161-164} while greater ERP amplitude associated with the increasing intensity of an auditory stimulus (also known as the LDAEP) predicts patients that respond well to serotonergic antidepressants¹⁴³⁻¹⁴⁵ but not to noradrenergic antidepressants such as reboxetine.¹⁴⁶ The authors sought to replicate earlier findings of rACC (using LORETA) and LDAEP prediction of treatment response to investigate how these approaches are related to serotonergic and noradrenergic antidepressants and to determine whether a combination of both approaches might be useful for clinical decisions. Findings replicated those reported previously, including the finding that rACC predicted response to citalopram and reboxetine combined (although this finding was only significant for the reboxetine group in post-hoc statistical tests), and that LDAEP predicted response to citalopram but not reboxetine at trend levels. Moreover, the rACC finding was specific to the theta frequency range

(delta [1.5–6 Hz], theta [6.5–8 Hz], alpha1 [8.5¹–10 Hz], alpha2 [10.5–12 Hz], beta1 [12.5–18 Hz], beta2 [18.5–21 Hz] and beta3 [21.5–30 Hz] EEG frequencies were examined) as well as the anterior (but not posterior) cingulate cortex.¹⁴⁶ Finally, the authors reported that the different methods may pick up on different neurophysiological aspects and that clinicians could potentially use assessment of rACC function to predict patients at risk of non-response to any standard first-line drug therapy so that alternative treatment options may be selected, while LDAEP assessment in the remaining participants could advise if a particular patient is best treated with a serotonergic or a noradrenergic antidepressant.

Applying an Integrative Theoretical Framework and Standardized Measures to Prediction of Treatment Response in Depression

A theoretical frame of reference used in the present integrative neuroscience approach is the Integrate Model.^{240,244} This model was formulated from a data-driven evidence base. It highlights organizing principles that operate across scales, from the single gene to network and whole-brain level. The core principle is one of the fundamental motivations that drive information processing across timescales; to minimize danger and maximize reward. From this principle, a number of key constructs are outlined, relevant to generating and testing hypotheses concerning integrative predictors of antidepressant response, including:

- Cognition and emotion. Cognition is considered an overarching construct that encompasses all aspects of brain and information processing, including emotion. Within this framework, all domains of cognition (including psychomotor or response speed slowing, executive function and emotion identification) may be studied as candidate treatment predictors in the same depressed patients.
- Cortical and subcortical brain networks. While a neuroanatomical division has typically been used to distinguish different functions, this model also highlights the importance of mode of brain connectivity and activation (as well as anatomy) in subserving distinct functions: a feedforward mode of brain connectivity supporting early automatic processes, and feedback connections supporting subsequent controlled functions.
- Brain-body interactions. In addition to brain connectivity, brain-body interactions are also central

to cognition as well as mood and its regulation (as reflected in measures such as heart rate variability, EEG cordance, and asymmetry).

- Spatial and temporal dimensions of information processing and neural systems. Research has typically focused on either spatial neuroanatomical or temporal aspects of cognition and brain function (for instance, in neuroimaging and in ERPs, respectively). Findings to date suggest that both spatial and temporal dimensions are likely to be important in identifying predictors of treatment response.
- Integration of predisposing factors (such as temperament, genetics, and environmental factors) that influence the spatiotemporal dynamics of brain function, and ongoing neuroplasticity.

The spatiotemporal continuum underlying the Integrate Model is reflected in three key phases of information processing: Emotion, Thinking, and Self-Regulation. These constructs provide a framework for linking measures across scales (eg, the earliest timescale is that of “Emotion,” which has been associated with common patterns of cognition and brain function [ERPs and neuroimaging] linked to specific genetic variants).²⁴⁴ Williams and colleagues²⁴⁵ highlighted the utility of simultaneous recording of autonomic data and neuroimaging (ie, the integration of brain-body measures). Parallel neural networks were found to be preferentially involved in the automatic appraisal of negative emotion (associated with skin conductance responses [SCRs] and with an engagement of rapid direct input to amygdala and medial prefrontal systems) and the contextual evaluation of these stimuli (not associated with SCRs, and involving hippocampal-lateral prefrontal networks operating on the later timescale of controlled cognitive processing). This approach may provide future research one mean to help untangle the mechanisms associated with depression and anxiety, disorders that co-occur in up to 50% of the cases with either disorder²⁴⁶ and impact on treatment response^{35,46,47} and treatment options.⁴⁸

The integration of neuropsychology with functional neuroimaging is also considered to be an approach that will further the understanding of the brain-behavior relationships in psychiatric illness, including depression.⁷⁹ While psychophysiological and neuroimaging studies in depressed participants generally record brain activity under resting state conditions,^{20,121,124,132-134,160} recent research^{21,164,170} has begun to collect data under active task conditions, such as emotion face perception and processing of picture stimuli with emotional content, which may

help to better target impaired emotional/cognitive circuitry associated with depression and to reduce unexplained variance. In addition, the integration of genetic information with functional neuroimaging provides a powerful approach to explore the functional impact of genetic variation in the absence of observable behavior.^{247,248} In a seminal series of studies,²⁴⁹⁻²⁵¹ non-depressed controls with the 5-HTT S allele are reported to display heightened amygdala activity, reduced gray matter volume in the perigenual cingulate and amygdala, and an uncoupling of the feedback circuit in these regions, which may be associated with less effective extinction of negative affect. Moreover, the researchers reported that these brain findings need not be apparent on measures of mood or temperament, concluding that the 5-HTT S allele may represent a susceptibility factor for affective disorders by biasing amygdala activity to hyper-respond during stressful life events or ineffective cortical input.

The proposal that genetic variation may have a functional impact on underlying brain function is a significant one and may account for some of the inconsistent findings reported in studies on depression and its treatment. For example, a number of clinical studies^{229,252,253} have reported non-associations between the BDNF genotype and major depression. Researchers^{57,254,255} have also sought to extend this work further by integration of clinical, cognitive, psychophysiological, neuroimaging, and genetic measures using path modeling to explore the relationship between specific genetic polymorphisms and non-clinical depression and anxiety.²³⁸ This work is based on the proposal that mapping of genotypes onto brain function endophenotypes (ie, internal phenotypes not obvious to the unaided eye, such as EEG or ERPs) may enhance the power of finding genes that contribute to psychiatric disorders such as major depression.^{256,257} Based on the Integrate framework, we have examined how brain endophenotypes may help understand linkages between clinical and cognitive measures and underlying genetic risk.^{57,254,255} The BDNF Val66Met polymorphism has been linked to depression, and provides an example of how it may be involved in neural pathways for both automatic emotional functions and more controlled cognitive functions that in parallel may determine the type of depression manifested, and the associated response to antidepressants. Using a path-modeling approach the Met allele of the BDNF66 polymorphism was found to contribute to prediction of depressed mood and associated cognitive impairment via its impact on early emotion and later working memory-related

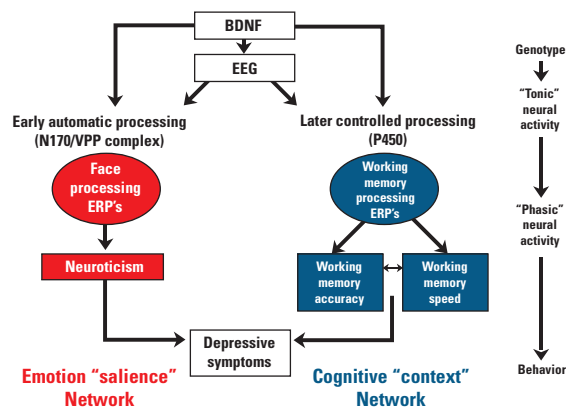
neural activity, assessed by the facial emotion N170 ERP (170 msec post-stimulus) and P450 working memory ERP (Figure). These predictive pathways were further mediated via temperament; namely, neuroticism that confers a negativity bias. This modeling was undertaken in 374 healthy Caucasian subjects assessed for level of depressive symptoms. While this model remains to be tested in patients diagnosed with clinical depression, the path-modeling strategy may provide future studies a more effective means to account for variability in patient response and to predict treatment response.

In a related study, Gatt and colleagues²⁵⁵ used path modeling to examine the role of resting brain EEG in contributing to the link between the BDNF66 Met allele and level of depression in otherwise healthy subjects (n=305). Consistent with the findings for ERP measures, the alterations in EEG activity that predicted higher depression in Met homozygotes reflected complementary alterations in the early automatic timescale of "Emotion" (within 200 msec) and subsequent more controlled cognitive timescale of "Thinking" (200 msec to seconds). That is, higher depression was associated with reduced alpha activity (which cycles approximately every 100 msec) with excessive slower wave theta and delta activity (cycling approximately every 300 msec and 1 second, respectively). Importantly, parallel analyses in matched subsamples confirmed these findings, a strategy seldom adopted, given generally small sample sizes in previous studies. Moreover, no genotype differences were evident for the demographic variables of age, sex, education, and IQ, or for other genetic variants (apolipoprotein E or catechol-O-methyltransferase Val108/158Met) distribution associated with alterations in emotion and thinking.²⁵⁸⁻²⁶⁰ This study provides convergent support for the proposal that the BDNF66 Met allele may contribute to depression severity via an impact on neural pathways modulating cognitive functions in real time. Verification and extension in patient samples is warranted.

Future studies should consider applying an integrative theoretical framework to generating and testing explicitly integrative hypotheses concerning the combination of multi-domain predictors of treatment response in depression. The principles of the Integrate Model provide a framework for linking previous concepts across clinical, psychosocial, cognitive, brain function, and genetic domains. For example, the organizing principle of "minimize danger-maximize" reward is seen to underlie the inherent bias toward negative cues in the environment that occurs automatically, but also weights subse-

quent thinking and feeling. Melancholic type depression may reflect a greater bias toward negative cues (particularly sadness), producing an action tendency of withdrawal, reflected in slowed psychomotor functions (or response speed) and feelings of negative mood. It may concurrently limit the capacity to extract positive cues from the environment, and thus experience pleasure and reward (anhedonia). These alterations are likely reflected in an excessive engagement of the direct, feedforward pathways to amygdala and its medial prefrontal (including ACC) projections, with reduced hippocampal-lateral prefrontal activity and cortical feedback. These alterations involve dysregulation of 5-HT and NE that modulate thinking and feeling. Genetic and psychosocial factors may contribute to the disposition to these alterations. Psychological trauma may be important in triggering an excessive negativity bias. Genetic variants, such as the BDNF66 Met allele, disrupt neuroplasticity, and thus heighten vulnerability to the effectors of such stressors on the brain. On the other hand, atypical depression may be characterized by relatively more anxiety and less overall severity, such that a negativity bias involves fear action tendencies and an excessive engagement of the feedforward amygdala-medial prefrontal/ACC

FIGURE. Path model based on the Integrate framework, that uses standardized assessment and path modeling to test the linkages between genetic variation and clinical, temperamental, and cognitive features of depression via effects on parallel emotion-cognition brain systems



BDNF=brain-derived neurotrophic factor; EEG=electroencephalogram; N170=N170 ERP component; VPP=vertex positive potential; ERPs=event-related potentials.

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system and 5-HT dysregulation in particular, without the subsequent effects on psychomotor poverty and hippocampal-lateral prefrontal systems involved in working memory. Different genetic variants, such as the 5-HTT gene, may contribute to vulnerability for this form of depression.

These proposals may generate hypotheses to test whether better response to SNRIs in melancholic depression is predicted by a combination of BDNF Met allele and exposure to stress, with biases to sadness, slowed psychomotor function and hippocampal as well as amygdala-medial prefrontal disturbances, while better response to SSRIs in atypical depression is predicted by 5-HTT long allele and bias to fear, with preferential increases in amygdala-medial prefrontal/ACC activity involving the early (<200 msec) timescale of processing. On the other hand, non-response to SSRIs may be characterized by both 5-HTT short allele and BDNF Met allele, along with the presence of reduced cortical activation that characterizes melancholia. Testing these hypotheses would draw on the combination of clinical, psychosocial, cognitive (both emotion identification and general cognitive tasks) of psychophysiological, and neuroimaging data (eg, EEG, ERPs, fMRI) data. Concurrent recording of autonomic data may also assist in teasing apart the role of comorbid anxiety in treatment prediction in depression, given that SCRs are associated with automatic elicitation of direct amygdala-medial prefrontal/ACC networks in particular. Similarly, the integration of genetic information with other domains will help to clarify the dispositions that differentiate the pathways involved in treatment response in depressed patients.^{248,249,251,261}

Future studies should also give consideration to utilizing an integrative approach within a placebo-controlled design. Research seeking to identify predictors of antidepressant response has frequently employed open-label designs and excluded placebo-control arms presumably due to ethical (and cost) considerations relating to placing depressed (and suicidal) patients on placebo. Uncontrolled psychopharmacologic trials are useful for generating hypotheses and exploring naturalistic effects. They also allow for an increased number of participants to be recruited, given the reduced cost of conducting such studies compared to those with double-blind and placebo-controlled designs. However, placebo response rates approach 30% to 40%^{6,190} and 50% to 75% of an antidepressant response may reflect the effects of placebo.²⁴³ Thus, if no placebo control is included in a study, "active" drug responders may be placebo responders. This issue will raise the

number of false positives and lead to incorrect conclusions being made over the predictors associated with a particular medication. A number of researchers have now published studies reporting on predictors of placebo response versus medication using double-blind designs, highlighting the importance of a placebo control in order to be able to distinguish between placebo versus active drug response (discussed above).^{77,135,243} On the other hand, employing a double-blind and placebo-controlled design in studies on depression are now of particular concern to human research ethics committees. According to the World Medical Association's Declaration of Helsinki²⁶² "extreme care must be taken in making use of a placebo-controlled trial and in general this methodology should only be used in the absence of existing proven therapy." (See: <http://www.wma.net/e/policy/b3.htm>). Clearly, future studies will need to continue to conduct placebo-controlled studies if specific markers of response and non-response are to be determined and given the implications for patient treatment and impact on health resources strong arguments could certainly be made to human research ethics committees regarding the benefits outweighing the costs of conducting such studies.

Finally, it will be crucial for future studies to give some consideration to the way in which response and non-response are defined. For the purposes of this review, we used the term "response" in the broadest sense possible, consistent with the considerable variability in the characteristics that have been used in previous studies to define this term.²⁸⁻³⁰ For example, descriptions of outcomes have included "response," "partial response," and "full response," and the latter has been used interchangeably with "remission." Response is typically defined as >50% reduction from baseline score using a particular scale, such as the HAM-D or the Montgomery-Åsberg Depression Rating Scale (MADRS), while full response or remission is often defined as a HAM-D score ≤6, and a MADRS score ≤15.²⁸ Assessment of treatment adequacy during antidepressant trials is essential and it is important that records of dose, duration, and compliance are standardized.²⁹ The term "non-response" should be distinguished from intolerance due to side effects, as non-response to an antidepressant usually requires treatment with an antidepressant from a different class, while intolerance requires selection of an alternative antidepressant (possibly from the same class) that is less likely to produce the side effects that were experienced by the patient (eg, changing from a tertiary amine TCA, such as amitriptyline or imipramine, due to anticholinergic side

effects, to a secondary amine TCA, such as desipramine or nortriptyline).²⁶³ The term “non-response” (ie, non-response to a single antidepressant) should also be distinguished from “treatment-resistance” (ie, failure to respond to a second antidepressant of adequate dose and duration).²⁷ It should also be noted that the use of commonly used outcome measures, such as the HAM-D and MADRS, is troubling, given that these were developed long before current classification systems of depression came into use. While the HAM-D has been the gold standard for the assessment of depression and its treatment for >40 years, it has been reported to be psychometrically and conceptually flawed.²⁶⁴ Advances in the knowledge of the biochemical, neural, genetic, and behavioral foundations of depression have led to the proposal that behavioral emotion recognition tasks may be a more sensitive, reliable, and valid outcome measure for treatment studies.¹⁰² Key features of the depressed state that also have good biological validity are mood bias toward negative emotions and anhedonia (impaired reward function).²⁶⁵ It is proposed that future research using an integrative neuroscience approach should apply more objective and valid endpoint measures of treatment outcome (eg, facial expression perception¹⁰² or assessment of psychosocial and functional impairment^{28,30}) in addition to the HAM-D or MADRS, so that comparison with prior research is possible. Such research should also give consideration to “full response,” “remission,” or “wellness” rather than “partial response.”^{28,30} The pros and cons of clinician versus participant measures of response should also be considered.

CONCLUSION

A number of key predictors have been identified and replicated in previous studies, including depression severity; comorbid anxiety (clinical predictors); psychomotor slowing (cognitive predictor); the LDAEP; cordance; perceptual asymmetry (psychophysiological predictors); anterior cingulate metabolism (neuroimaging predictor); and the 5-HTT gene (genetic predictor). However, a number of methodological issues have hindered previous research and this has led to limited sensitivity and specificity of the proposed predictors. These include small sample sizes; heterogeneity and subtypes of depression; recording of brain activity under resting state conditions; reliability of core outcome measures and the way in which treatment outcome is defined; distinction between markers and predictors of treatment response; use of placebo controls to deal with high placebo response rates; medication compliance; and treatment with a sufficient medica-

tion dosage. Studies remain to be conducted that fully integrate the often isolated domains of clinical judgement, neuropsychology, psychophysiology, neuroimaging, and genetics in order to improve the prediction of treatment response in depression. It is proposed that a focus on standardized testing methodologies across multiple testing modalities and their integration will be crucial for translation of research findings into clinical practice. To this end, we are conducting an International Study to Identify Markers that allow the Prediction of Optimized Treatment Response in Depression. (See: <http://www.brainresource.com/> for more information). The scientific feasibility of this study is supported by the adoption of a multidisciplinary approach, including contributions from the disciplines of physiology, psychology, psychiatry, radiology, and physics. The combination of different measures and techniques may provide the power to sensitively identify predictors of individual treatment response. **CNS**

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