

Using Neuroimaging to Predict Treatment Response in Mood and Anxiety Disorders

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Background. Functional neuroimaging has begun to show promise as a clinical tool in the prediction of treatment response in mood and anxiety disorders. Given the variance in patient responses to psychiatric treatments, the use of such predictive tools could be tremendously valuable, especially in situations where treatments carry substantial risks or costs.

Methods. A literature search was conducted in December 2004 to identify published neuroimaging treatment prediction papers. “Neuroimaging,” “treatment,” and “depression or anxiety” were used as keywords. Studies of treatment prediction were complemented by studies of treatment effects to provide context.

Results. Fifteen original published papers were identified as investigations of treatment prediction in mood and anxiety disorders. These studies have predominantly been conducted in patients with major depression (MDD) and obsessive-compulsive disorder (OCD). We review this literature and provide a discussion of design considerations in psychiatric neuroimaging studies of treatment response prediction.

Conclusions. The neuroimaging literature pertaining to treatment response prediction is largely limited to studies of MDD and OCD. While these initial reports are preliminary, the findings reviewed suggest that treatment outcome may be predicted by patterns of pre-treatment brain activity in psychiatric patients. However, the actual clinical utility of such tests remains to be shown.

Keywords Neuroimaging, Treatment, Anxiety, Depression

INTRODUCTION

For more than a decade, structural and functional neuroimaging methods have provided powerful tools for advancing pathophysiological models of psychiatric disorders. As investigators make progress in delineating the underlying neural phenotypes of various psychiatric illnesses, an important goal for continued work in this field is to determine whether measures of brain activity might assist in predicting subsequent response to treatment. The ultimate goal, in this regard, is to provide information that will guide clinical decision-making and result in improved patient care. However, to date, relatively few neuroimaging studies have focused on issues relating to treatment response. This area of research has held a fairly narrow scope, largely limited to studies of major depression (MDD) and

obsessive-compulsive disorder (OCD). In the current article, neuroimaging treatment studies in patients with mood and anxiety disorders will be reviewed with particular emphasis on the studies that have identified brain activity patterns that may serve as potential predictors of treatment response. In addition, study design considerations for psychiatric neuroimaging studies of treatment response will be addressed.

STUDY DESIGN CONSIDERATIONS FOR IDENTIFYING NEUROIMAGING PREDICTORS OF TREATMENT RESPONSE

General Considerations in Subject Selection

The central objective of neuroimaging predictor studies is to identify common patterns of pre-treatment brain activity in patients who respond to a specific treatment. In the best of circumstances, inferences from such data could be generalized

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from the study group to a population of patients. Subject exclusion criteria for the typical neuroimaging treatment predictors study are often more liberal than those employed in neuroimaging studies designed to identify structural or functional abnormalities underlying the pathophysiology common to individuals in a specific diagnostic category. Considerations regarding diagnostic subtypes, symptom severity and comorbid illness are critical in avoiding type II error in studies of pathophysiology, whereas these sources of variance can enhance the clinical utility of neuroimaging treatment predictor findings. For example the differentiation of clinical subgroups showing good response from those showing poor response, can identify and account for the meaningful variance in the broader population of subjects within a specific diagnostic category. Given this emphasis on heterogeneity within neuroimaging treatment predictor study groups, we do nonetheless stress the necessity of proper clinical characterization of subjects at the time of enrollment. Indeed, the accurate categorization of subjects by diagnoses, subtypes, and symptom severity remains critical to interpretations of their contributions to variance in treatment response.

In addition to diagnostic heterogeneity, the presence of concurrent pharmacotherapy, psychotherapy or other therapeutic interventions should also be considered during subject selection. Such treatments in addition to the treatment of interest/study are likely to have an additive biological effect. Again, this type of diversity among study subjects may prove favorable in generalizing inferences of treatment response to real clinical populations. However, to afford the optimal interpretation of study results, such patients should be on a stable regimen of the other treatment(s).

General Considerations in Clinical Trial Designs

As with any clinical research trial that involves patients and a treatment intervention, decisions regarding placebo control, blinding, treatment response measures and adequate trial length, should be considered in trial design. Given the inherent costs associated with neuroimaging and the potential for placebos to substantially degrade signal to noise in psychiatric trials, the majority of published neuroimaging treatment predictor studies have been open trials, as randomized placebo controlled trials have been often considered impractical. Neuroimaging treatment predictor hypotheses have been typically constructed to test between-group differences in baseline brain activity related to subsequent treatment response. The measures of treatment response in published treatment predictor studies of MDD have included; the Beck Depression Inventory (BDI) (1), the Hamilton Depression Rating Scale (HAM-D) (2), Clinical Global Assessment Scale (GAS) (3) and Clinical Global Impression Scale (CGIS) (4). Similarly, standardized rating scales such as the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (5), and Hamilton Anxiety Rating Scale (HAM-A) (6) have been used in treatment predictor studies of OCD. Non-standard assessments of treatment response have also been employed, such as chart reviews (e.g., assessing

hospital re-admission, and physician notes). Like measures of treatment response, trial lengths have significantly varied across the published neuroimaging treatment predictor studies. Neuroimaging medication trials reporting significant results have been as short as six weeks (7,8) and as long as twelve (9) to sixteen weeks (10). Trial lengths have also varied across patients within individual studies (10). Studies designed to employ uniform trial length across subjects tend to yield results that are more readily interpreted. Yet with all clinical trials, subjects can and do drop-out prior to completing the intended length of treatment. Data management strategies for such subjects should be considered. As the salient neuroimaging data is collected at the beginning of treatment predictor studies (prior to the treatment trial), variable trial lengths across the subjects in any particular study could still contribute informative data. To the extent that dropping out of treatment represents one type of poor outcome, response prediction studies should seek to capture this aspect of treatment response. However, the issue of how to operationally accommodate drop-outs is unclear; simply carrying forward the last data point may have the unintended consequence of representing such subjects as fair or even good responders. Therefore, reasonable strategies include: 1) excluding drop-outs from further analysis; 2) performing separate analyses to predict drop-outs as a categorical type of outcome; 3) employing last time point carried forward; 4) assigning all drop-outs a predetermined response value (e.g., 0% change); or 5) in categorical analyses simply considering drop-outs among the group of non-responders.

Neuroimaging Treatment Predictor Study Paradigms

Neuroimaging paradigms can be categorized based upon the type of state manipulations employed by investigators. The most common paradigm used in treatment predictor studies is the neutral state paradigm where subjects are studied during a nominal "resting" state, or while performing a non-specific continuous performance task. Thus, hypotheses regarding differences in treatment response associated with regional brain activity are tested, without particular attention to momentary state variables. This approach has been used in most typical neuroimaging treatment predictor studies by measuring resting or neutral state cerebral metabolism during brain images acquired by fluoro-deoxyglucose positron emission tomography (FDG-PET). FDG-PET is particularly sensitive for detecting regional differences in cerebral glucose metabolism (11). Several other scanning modalities could be employed (e.g., structural, receptor-ligand, spectroscopy), however the scope of this review is limited to the functional approaches that directly assess indices of regional brain activity (e.g., metabolism or blood flow).

While neuroimaging treatment predictor studies may eventually serve as a tool for clinical decision-making, their value for illuminating pathophysiology or mechanism of disease is

quite limited. Symptom provocation is a type of neuroimaging paradigm that has been used in treatment prediction that also confers the potential to address hypotheses related to pathophysiology. In a symptom provocation paradigm subjects are scanned during a symptomatic state as well as during neutral or control conditions. Analyses of these data test hypotheses regarding anticipated treatment related changes in functional anatomy during the symptomatic state (see,12). Still another neuroimaging paradigm that may inform questions related to pathophysiology is a pre-treatment/post-treatment study. As the name implies, in pre-treatment/post-treatment studies, a baseline acquisition of neuroimaging data is followed by a treatment intervention and one or more follow-up imaging acquisitions. Comparisons of pre-treatment with post-treatment scans are performed to identify changes in regional brain activity that are associated with the therapeutic mechanisms related to the intervention.

The various paradigm types are mentioned to provide a comprehensive overview. Again, the focus of this review is on neuroimaging treatment predictor studies that may ultimately serve as clinical tools. In this regard, the best replicated findings to date, with respect to treatment effects and predictors of treatment response in the mood and anxiety disorders have been garnered using FDG-PET acquired in the context of a neutral state (7,13–19).

General Analytic Approaches to Neuroimaging Data

Two general approaches to image analysis have been commonly used in treatment predictor studies: 1) region-of-interest (ROI)-based, and 2) voxel-wise. The ROI-based approach requires testing hypotheses regarding pre-specified anatomically defined ROIs, typically via co-registration of PET data with high-resolution magnetic resonance images (MRIs). The ROI approach conveys the advantage of precision in anatomical definition. However the ROI approach is particularly vulnerable to Type II errors, since treatment effects in regions other than those driven by a priori hypothesis may be neglected, and treatment effects within sub-territories of a given ROI may be overlooked due to dilution that occurs from averaging across the entire ROI. The voxel-wise approach typically employs statistical parametric mapping (SPM) methods. This method requires the transformation of each subject's brain data into a common anatomical space via rescaling and/or warping. This brain space is then searched voxel-by-voxel. Given that voxel-wise (voxel-by-voxel) SPM searches for associated treatment effects can be performed on either the whole brain or a priori search territories of interest, this method is inherently no less hypothesis-driven than ROI-based methods. In contrast to ROI-only approaches, SPM based approaches have the advantage of being data driven, and facilitate the ability to search salient sub-territories for relevant treatment responses. However, SPM based approaches are subject to errors related to imprecision in the procedure whereby

the brain data from various subjects are transformed into a common space.

Beyond the standard analytic approaches, “connectivity” approaches represent advances in neuroimaging data analysis that convey the ability to investigate the interaction of regional brain activity within large-scale neural networks (see, 20, 21–23). More specifically, in contrast to ROI approaches that solely rely on a model of causal relation between a priori ROIs and covariance data (treatment response), connectivity approaches have the potential to consider inter-related brain activity via several different functional anatomic models for the same covariance data. Given that connectivity approaches are still in development and not in universal use, their utility in treatment predictor studies has yet to be established. Once refined and validated, connectivity approaches may serve as valuable analytic tools to test pathophysiological models of anxiety and depression in neuroimaging treatment predictor studies.

Approaches to Identify Treatment Responders

Neuroimaging treatment response predictor studies have typically employed two different approaches to identifying treatment responders. Investigators often make their decisions on one of these two approaches in tandem with the image analysis considerations discussed in the previous section. The categorical approach of treatment responder identification categorizes subjects as either responders or non-responders based on distinct post-treatment end-points (often via a threshold set on a standard rating scale). Group image analyses are typically performed to identify differences in baseline brain activity indices between the clinically defined responder and non-responder groups. By its nature the strict binary categorization (e.g., responders or non-responders) of outcome can possibly neglect subtle predictors of response. Another limitation of the categorical approach is the requirement for a sufficient sample size (adequate numbers of both responders and non-responders) to enable meaningful interpretation of the data. The other approach, the continuous variable approach, obviates the need for an operationalized definition of “responder.” The continuous variable method employs covariate analyses of continuously changing clinical variables with neuroimaging data. This approach has been used in the majority of recent neuroimaging treatment predictors studies (9,18,19,24,25). Of note, the continuous variable method tends to involve use of the general linear model, or simple Pearson product moment tests of correlation. In this context, tests of covariance can be performed to account for the contribution of nuisance variables (sources of variance that may confound main effects). One limitation of using the general linear model or Pearson correlations is that they do not accommodate the possibility of a non-linear relationship between brain imaging indices and clinical outcomes. To obviate this limitation, use of non-parametric tests of correlation may also be considered.

TREATMENT PREDICTOR STUDIES IN AFFECTIVE DISORDERS

Neuroimaging Support for a Pathophysiological Model of MDD

The prevailing pathophysiological model for MDD is based on dysfunction within cortical-limbic networks. The model is supported by an impressive convergence of data from several lines of research including human neuroimaging, lesion, deep-brain stimulation, post-mortem, and animal studies. While there is considerable variability in the MDD neuroimaging literature with respect to regions of interest, laterality, and direction of change in brain activity, the most consistent findings (7,8,26–33) support the model of primary cortical-limbic dysfunction. The model describes the depressed state as characterized by relative decreases in frontal activity within the territories of the dorsolateral and ventral prefrontal cortices. Concurrent increases in amygdalar, orbitofrontal and mediodorsal thalamic activity have also been associated with the depressed state. Aberrant interactions among functionally and anatomically differentiated circuits (e.g., limbic-thalamic-cortical and limbic-cortical-striatal-pallidal-thalamic circuits) have been proposed to mediate the depressed state (34–37). Structural neuroimaging provides further support for this model of MDD, as focal white matter lesions as well as decreased volumes of the frontal cortex hippocampus, amygdala and basal ganglia in depressed patients have been reported (33,38–41). In functional neuroimaging studies, aberrant neutral-state activity in the amygdala, basal ganglia, prefrontal and cingulate cortices have been common findings in patients with affective disorders (37,42,43). Interestingly some of the same regions implicated in neutral state studies of MDD patients have also been identified during functional imaging studies that used emotion-induction paradigms (e.g., sad or depressed mood) in healthy control subjects (44–49). Imaging studies of treatment in MDD patients have demonstrated attenuation of abnormalities in the amygdala, cingulate and prefrontal areas following treatment (7,29,30,43,50–53). Taken together, the findings from neuroimaging studies of brain structure, neutral state activity, symptom provocation and treatment all merge to support the pathophysiological model of cortical-limbic network dysfunction in MDD.

Neuroimaging Treatment Response Predictor Studies in MDD

The findings from neuroimaging treatment response predictor studies in MDD have been consistent with the working pathophysiological model for MDD. Several pharmacologic treatment studies have demonstrated differences in neutral state prefrontal and anterior cingulate activity to be associated with clinical response. One early treatment predictor study of

MDD compared pre-treatment neutral state FDG-PET scans in 11 unipolar depressed outpatients with neutral state scans of 33 matched healthy control subjects (10). Six of the patients randomized to venlafaxine or bupropion in a double-blind protocol were categorically identified as responders (defined by “marked to moderate response” assessed by CGIS). Compared to scans of healthy controls, voxel-wise analyses of responder pre-treatment scans demonstrated responders to have lower activity in bilateral temporal regions and broad regions of the prefrontal cortex including the left middle frontal gyrus, both pregenual and subgenual anterior cingulate cortex as well as the orbitofrontal cortex. This pattern of lower pretreatment activity was unique to the responders as it was absent in similar analyses conducted in the non-responders (where the cerebellum was the only region to exhibit lower pre-treatment activity). A finding of lower pre-treatment anterior cingulate activity was also reported as predictive of efficacious treatment response by Brody and colleagues (24). After treatment with paroxetine (40 mg/day) 9 of 16 depressed outpatients were categorized as responders (>50% improvement in HAM-D and CGIS much or very much improved). Both SPM and MRI-based ROI analyses were performed on neutral state pre-treatment and post-treatment FDG-PET data. Lower pre-treatment left ventral anterior cingulate activity was correlated with greater improvement of HAM-D scores via SPM analyses. In addition, ROI analyses demonstrated responders to have greater change (reduction) in ventral lateral prefrontal and orbitofrontal activity from pre-treatment to post-treatment scans.

In contrast to lower pre-treatment anterior cingulate activity as reported by Little et al. (10), and Brody et al. (24), a principal finding of higher pre-treatment anterior cingulate activity being predictive of pharmacologic response in MDD inpatients was reported by Mayberg et al. (7). In that study, responders (8 of 18 inpatients) were assessed by chart review after six weeks of treatment. Antidepressant therapy varied across subjects (e.g., bupropion, serotonin or tricyclic agents). Both SPM and MRI-based ROI analyses of neutral state FDG-PET scans demonstrated greater pre-treatment rostral (pregenual) anterior cingulate activity as predictive of treatment response in responders compared to healthy control subjects. The directional differences (higher vs. lower pre-treatment activity) in the common regional finding of the anterior cingulate cortex across these treatment response predictor studies have been attributed to methodological differences including sample types (inpatient vs. outpatients), medications and rating instruments used.

Sleep deprivation has been known to provide transient relief from depressive symptoms in 30–60% of treatments (54,55). Two neuroimaging response predictor studies by Wu and colleagues have implicated the anterior cingulate cortex with reduction in depressive symptoms after sleep deprivation. In the first study, 15 unmedicated depressed patients and 15 control patients were studied with FDG-PET

scans during a continuous performance task before and after a 30 – 35 hour period of sleep deprivation. Categorical, ROI analyses of baseline scans demonstrated higher pre-treatment amygdalar and anterior cingulate cortex activity in the responders ($n = 4$; $>40\%$ improvement in HAM-D) when compared to either normal controls or non-responders (56). In the subsequent study by Wu and colleagues (55), 21 additional depressed patients and 11 additional healthy controls underwent FDG-PET scans before and after sleep deprivation, during an experimental protocol identical to the first study. The two data sets were merged to yield a total of 12 sleep deprivation responders. Between-group comparisons of the merged data set were conducted with voxel-wise SPM analyses. When compared to baseline scans of healthy controls and non-responders, responders exhibited higher pre-treatment activity in medial prefrontal, pregenual anterior cingulate and subcallosal (subgenual) cortices. The anterior cingulate findings are consistent with those reported by Mayberg and colleagues (7).

The predictive value of pre-treatment anterior cingulate activity has been extended to the surgical intervention of severe treatment-refractory MDD. Dougherty and colleagues conducted pre-surgical resting PET-FDG scans in patients with treatment-refractory MDD before anterior cingulotomy (19). On follow-up (12 month average) the surgical intervention was associated with statistically significant changes in BDI scores for the group, however only 4 of the 13 patients exhibited a robust post-operative response ($>50\%$ improvement in BDI). SPM based continuous variable regression analyses were performed to test the relationship between pre-treatment neuroimaging data and improvement in BDI scores. Greater pre-treatment activity in the left subgenual anterior cingulate cortex and left thalamus was correlated with enhanced postoperative outcome. The subgenual anterior cingulate finding is consistent with the findings of Mayberg et al. (7) and Wu et al. (55), however the locus identified in the surgical study was more ventral than the loci reported to predict response to medication or sleep deprivation. While differences in localization may be attributed to the surgical subjects' resistance to standard treatments and other methodological differences, the pre-treatment subgenual cingulate predictor in this neurosurgical study is consistent with the cortical-limbic network model for MDD proposed by Mayberg (57) and others (35,37). The predictive thalamic locus observed in this neurosurgical study is also consistent with the cortical-limbic network model, as thalamic involvement in MDD has been reviewed elsewhere (35,37,42,57), and changes in thalamic metabolism have been reported in the pharmacologic treatment of MDD (8,27,58). Despite strong concordance with other studies and the prevailing model of MDD, the findings of this initial MDD neurosurgical treatment response predictor study should be considered as strictly preliminary, particularly given the limited number and heterogeneity of patients studied.

Neuroimaging Treatment Predictor Studies in Bipolar Disorder

While there are only a few published neuroimaging treatment predictor studies in unipolar depression, there are even fewer such reports in bipolar disorder. One study by Ketter and colleagues (59) evaluated neutral state pre-/post-treatment FDG-PET scans in a mixed group of patients (bipolar I, bipolar II, and unipolar depression) who underwent placebo-controlled trials of carbamazepine, nimodipine or separate trials of both agents. Seven of 26 patients were categorized as carbamazepine responders based on much or very improved CGIS ratings. Compared to non-responders, carbamazepine responders were shown to have greater pre-treatment activity in the left insular cortex in between-group voxel-wise SPM analyses. In contrast, relatively lower pre-treatment insular cortical activity was associated with superior nimodipine response. Interestingly, while a heterogeneous group of affective disordered patients was studied, only bipolar patients (not unipolar depressed patients) demonstrated the positive insular correlation to carbamazepine response, suggesting disorder specific neural correlates of treatment response in this instance.

TREATMENT RESPONSE PREDICTOR STUDIES IN OCD

Neuroimaging Support for a Pathophysiological Model of OCD

One pathophysiological model of OCD describes dysfunction in cortico-striato-thalamo-cortical (CSTC) circuitry (60,61). In this model, OCD symptoms are hypothesized to be mediated by dysfunctional interactions among components within the CSTC circuit (e.g., caudate nuclei, thalamus, orbitofrontal and cingulate cortices). The findings from several different neuroimaging modalities support the model. For example, compared to healthy controls, OCD patients have consistently demonstrated abnormal baseline orbitofrontal, anterior cingulate and caudate metabolism during PET and SPECT scans (62–65). Several morphometric-MRI studies have identified volumetric abnormalities in OCD patients involving the striatum, orbitofrontal cortex and amygdala (66–70). Evidence from magnetic resonance spectroscopy also points to relative deficiencies of striatal and thalamic N-acetyl aspartate (a marker for neuronal health) in patients with OCD (71–73). Moreover, functional imaging studies employing symptom provocation and cognitive activation protocols have provided further support for the CSTC model by revealing dynamic activation or deficits in the striatum (particularly the caudate nuclei), thalamus, anterior cingulate and orbitofrontal cortices (74–78).

Neuroimaging Treatment Response Predictor Studies in OCD

Consistent with the proposed CSTC model, several prospective neuroimaging studies of OCD patients have reported significant inverse correlations between pre-treatment orbitofrontal activity and subsequent response to serotonergic reuptake inhibitors (12–14,16,17). Saxena and colleagues (17) conducted FDG-PET scans in 20 OCD outpatients before and after 8–12 weeks of paroxetine treatment (40 mg/day) with the primary objective of identifying pharmacologic treatment associated changes in regional brain activity. Eleven of the patients met criteria for response (>25% Y-BOCS improvement). Group (responders vs. non-responders) by condition (post-treatment vs. pre-treatment) ROI analyses demonstrated responders to have significantly lower activity, on post-treatment scans in the right anterolateral orbitofrontal cortex and the right caudate nucleus. While the authors were cautious to report their findings related to treatment prediction as “secondary, exploratory analyses,” their data set represents one of the largest published in OCD neuroimaging. Consistent with their a priori hypotheses, lower pre-treatment activity in both the right and left orbitofrontal cortices was correlated with greater improvement in Y-BOCS scores.

More recently, Rauch et al., (12) employed OCD symptom provocation in parallel with a treatment predictors paradigm. In this study, symptom provocation techniques (75) were employed pre-/post-fluvoxamine treatment (300 mg/day) during oxygen-15 (O-15) PET scans of four men and five women with contamination-related OCD. Using Y-BOCS as a continuous variable in voxel-wise SPM regression analyses, the finding of lower orbitofrontal activity as a treatment predictor was confirmed and extended as this inverse correlation was observed in both neutral and provoked pre-treatment states. This study additionally revealed bilateral pre-treatment activity in the posterior cingulate cortex (PCC) to be positively correlated with pharmacologic treatment response.

In addition to pharmacotherapy, cognitive-behavioral therapy (CBT) has been demonstrated as effective in the treatment of OCD (79), in fact expert consensus has suggested CBT be used as first-line treatment in most cases (80). Brody, Baxter and colleagues have conducted several imaging studies to identify the neural predictors for CBT in OCD patients (13,15,16). Their most recent study (16) compared outcome measures and pretreatment FDG-PET scans in a cohort of OCD patients who received CBT (10 weeks, $n = 18$) to a cohort of patients treated with fluoxetine (60 mg/day, 10 weeks, $n = 9$). Following treatment, mean symptom improvement as measured on Y-BOCS, HAM-A and Ham-D was similar for both groups, however the correlation of pre-treatment PET data with symptom improvement demonstrated an inverse relationship between groups. A priori ROIs (including caudate nuclei, orbitofrontal and anterior cingulate cortices) were evaluated with a multiple regression approach that demonstrated higher pre-treatment activity in the left orbitofrontal cortex to be

correlated with improvement in Y-BOCS scores for patients treated with CBT. A subsequent rank-order Kendall's tau correlation confirmed the association of higher pre-treatment left orbital frontal activity with Y-BOCS improvement in the CBT group and revealed lower pre-treatment left orbital frontal activity associated with Y-BOCS improvement in the paroxetine group. In addition to replicating the previous findings of lower orbitofrontal pre-treatment activity predicting pharmacologic response in OCD, the work of Brody et al. (16) reveals an inverse relationship of higher pre-treatment orbitofrontal activity predicting response to CBT.

Lastly, as in the treatment of MDD, surgical interventions have been used in severe, otherwise treatment refractory cases of OCD. Interestingly, in a neuroimaging response predictor study of anterior cingulotomy for OCD, the predictive brain regions were similar to those identified in pharmacologic trials. Rauch and colleagues (18) acquired pre-surgical FDG-PET scans in a cohort of 11 treatment-refractory OCD patients before anterior cingulotomy. More than one third of the cases received significant reduction in their symptoms (>25% improvement in Y-BOCS) 6 months after anterior cingulotomy. Voxel-wise SPM regression analyses using % change in Y-BOCS as a continuous variable, determined outcome to be positively correlated with pre-operative activity in the right PCC. The stereotaxic coordinates of the surgical PCC predictor locus were similar to those observed for pharmacologic treatment (12). Similar to the surgical findings in MDD, here again, we wish to emphasize that the surgical findings in OCD should be treated as preliminary.

Neuroimaging Treatment Response Prediction; Differentiating MDD and OCD Phenotypes

This review has focused on neuroimaging studies that have identified unique patterns of pre-treatment brain activity thought to be predictive of treatment response in specific diagnostic groups (e.g., MDD, OCD). A recent study by Saxena et al. (25) sought to confirm differentiation in predictive pre-treatment brain activity patterns between different diagnostic groups (MDD and OCD) for the same medication. Both MRI-based ROI and SPM approaches were used to evaluate pre-/post-paroxetine treatment brain scans in 27 patients with OCD, 27 patients with MDD and 17 patients with comorbid OCD + MDD. Pre-treatment activity in the right caudate nucleus was uniquely correlated with symptom improvement in OCD responders. In contrast to the findings in the OCD cohort, symptom improvement in the MDD cohort was correlated with higher pre-treatment activity in the midline prefrontal cortex, extending to the rostral (pregenual) anterior cingulate and lower pre-treatment activity in the right amygdala and thalamus. The correlation of the right caudate as predictive of treatment response in OCD was novel, however consistent with the CSTC model, as the caudate nuclei have been demonstrated as having increased resting baseline activity in OCD patients compared to controls and MDD patients (62,63). Moreover, the

right caudate in particular, has been demonstrated to be active during symptom provocation in OCD patients (74–76). The anterior cingulate finding in the MDD cohort was consistent with that reported by Mayberg et al. (7). Taken together, the disorder-specific predictive data of Saxena et al. (25) provide further evidence that MDD and OCD have different underlying pathophysiology despite patients from the two different diagnostic categories sharing therapeutic benefits from the same pharmacologic agent.

SUMMARY AND FUTURE DIRECTIONS IN TREATMENT RESPONSE PREDICTOR STUDIES

The use of neuroimaging in the prediction of treatment outcome is an exciting and evolving science. The results from several of the studies in this review suggest that treatment efficacy may be predicted by patterns of pre-treatment brain activity. We wish to emphasize that our current state of knowledge regarding the predictive value of the neuroimaging studies is however limited. As there are relatively few published studies, most with small sample sizes, the findings reviewed here should be considered as preliminary.

Some authors have speculated that this sort of data may provide insight into the underlying pathophysiology of the particular disorders being studied. For example we discussed Mayberg's association of treatment response to elevated pre-treatment pregenual anterior cingulate activity (7). We further discussed how such findings, when considered in the context of converging lines of other evidence, might support the prevailing cortical-limbic network model for MDD (81). While the empirically derived associations between pre-treatment brain imaging data and subsequent treatment response may be of clinical value, it remains unclear as to what these associations actually represent. One possibility is that these patterns of brain activity serve to differentiate subtypes/phenotypes within a diagnostic group that are more or less responsive to a specific treatment. Yet another explanation could be that the neuroimaging results represent otherwise "healthy" regions serving in the capacity of compensatory or surrogate role to support treatment efficacy. We hold optimism that the use of connectivity analyses in future studies could further elucidate the differential contribution of individual brain regions within patterns of gross network activity.

Proceeding under the assumption that neuroimaging studies can indeed identify patterns of brain activity that are predictive of subsequent treatment response, to date, few disorders and few treatments have been studied. Thus far, neuroimaging treatment response predictor studies have been generally limited to the investigation of two diagnostic groups, MDD, the most prevalent psychiatric disorder (82) and OCD, a disorder with high rates of relapse (79). Future neuroimaging treatment predictor studies would have great utility in diagnostic groups where numerous treatment options exist and the costs (or risks) of sub-optimal treatments are high. For instance, in the case of

post-traumatic stress disorder, there is a broad array of pharmacologic options, each of limited efficacy, and little basis for choosing among the various treatment options for a given patient. Hence, it would be of great value if a neuroimaging test could provide predictive information that would guide treatment selection from among the available options in a given case. Beyond the exploration of neuroimaging treatment predictor studies in various diagnostic groups, other clinical considerations are likely to influence this line of research. For example, neuroimaging predictor response studies could also be of substantial utility in cases when a particular treatment has relatively high associated risks and/or costs (e.g., psychiatric neurosurgery, ECT). However, given the high cost of neuroimaging studies, it may be unrealistic to use neuroimaging predictor response studies for less expensive, low risk treatments such as medications. In addition, it is possible that clinical predictors of response may ultimately be a more cost effective manner of choosing appropriate treatments.

In addition to potentially serving as a stand-alone or supplementary clinical test, new neuroimaging paradigms are likely to evolve to address further questions about how the brain responds to psychiatric treatments. The current review has summarized studies that followed 'classic' experimental paradigms of comparing treatment outcome measures with pre-treatment neuroimaging data subsequent to brief 6–12 week treatment trials. Furmark and colleagues (83) recently conducted a pre-/post-treatment O-15 PET study in patients with social phobia that correlated acute treatment related changes in regional brain activity to long-term (one year) clinical outcome. A wide range of outcome predictor paradigms could emerge in the spirit of Furmark and colleagues' novel approach. If characteristic post-treatment changes in brain activity can be systematically correlated to symptom remission after acute treatments, future neuroimaging studies could possibly address the prediction of symptom remission or relapse on or off treatment. Still other paradigms that could provide significant clinical value would be neuroimaging studies designed to investigate acute brain changes related to treatment outcome after a very brief treatment exposure (e.g., test dose of medication, initial session of ECT, or CBT).

While replication has been imperfect among the initial studies of MDD and OCD comprising the neuroimaging treatment response predictor literature, disorder specific trends of pre-treatment brain activity associated with treatment response have emerged. Future studies will be necessary to determine if these findings can be reproduced and generalized. Moreover, given the great costs associated with neuroimaging, clinical neuroimaging tests will have to demonstrate some superiority over other standard clinical tests and assessments if neuroimaging is to achieve genuine clinical utility in the treatment of psychiatric illnesses. Lastly, further studies are needed to determine whether the use of neuroimaging in the identification of predictors of other aspects of outcome (e.g., adverse effects, sustained remission, subsequent relapse, etc.) may have broader clinical utility.

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