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Neural predictors of depression symptom course

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Depression is a debilitating illness causing significant societal and personal suffering. Improvements in depression identification and treatment are essential to reduce its toll. Recent developments in rodent models of depression and neuroimaging of humans suffering from the illness provide avenues through which gains can be made toward reducing its burden. In this review, new findings, integrating across rodent models and human imaging are highlighted that have yielded new insights toward a basic understanding of the illness and provide possibilities for improved identification and treatment — hopefully reducing the duration of depression episodes across the population.

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Introduction

Major Depressive Disorder is a debilitating illness that in the United States is estimated to affect 13–14 million adults each year. The lifetime prevalence rate (16–20%) is even higher, with an estimated 32–35 million US residents expected to develop the disorder at some point during their lifetime [1•,2]. The world health organization has similarly recognized the burden of depression in predicting that it will perhaps be the most costly disease worldwide this century [3]. To wit, depression has high rates of comorbidity with other mental illness such that nearly three-quarters of people who meet the criteria for depression during their lifetime will also suffer from another psychiatric disorder. More specifically, approximately three-fifths will be co-morbid for an anxiety disorder, one-quarter for substance-use disorders and one-third for impulse-control disorders [4]. Lastly, depression is not solely associated with disorders classically considered to reside 'above the neck'. Individuals suffering from depressive disorders are known to respond more poorly to treatment for cancer [5••], have worse prognosis when diagnosed with heart disease [6], and typically have increased circulating markers of inflammation which are associated with a variety of medical ailments [7]. In sum, the effects of depression are vast and demand a wide lens to grasp the full impact it can have. As such, a greater understanding of both the pre-treatment predictors of depression symptom course as well as the neurobiological changes effected by successful treatment — both in animal models as well as in humans — are highly relevant to better understanding the disorder and to potentially improving treatment. The growing scientific and social awareness devoted to depression is underscored by a recent special issue in Nature highlighting the illness [8••,9–11].

Despite a large and ever growing literature on the neural predictor of depression course, this article highlights two recent areas of particular growth. The first pertains to developments in animal models of depression whereby changes in hippocampal size and arborization are being used to uncover potentially novel avenues for depression treatment. The second area will focus on human imaging methods and will focus on both the pre-treatment prediction outcome as well as neurobiological changes that appear to follow the course of depression severity. This article will end with brief considerations going forward.

Animal models of depression course

While an imperfect model to encapsulate the complexity and full diversity of symptoms experienced in human depression [12•,13], animal models of depression are hugely important to gain mechanistic understandings of the course of the disorder. For that reason, recent developments in animal models of depression course are briefly reviewed here. Over the years, several rodent models have been developed to model depression, but the social defeat stress model appears to have particularly good face and construct validity [13,14]. In this model, a young mouse is placed in a cage with a larger adult male mouse and is subjected to brief periods of aggression by the larger mouse. After a series of bouts of these experiences the younger mouse exhibits a variety of symptoms which appear to model human depression including reduced locomotion (psychomotor retardation), decreased socialization, as well as suppressed interest in previously pleasurable activities (anhedonia) [15]. Importantly, chronic, but not acute treatment with Selective Serotonin Reuptake Inhibitors (SSRIs) normalizes many of the behavioral symptoms in this animal model — a temporal period that mimics the course of antidepressant treatment — when successful [16]. This particular facet of the social defeat

stress model is relevant as several other rodent models of depression respond to acute and not chronic SSRI treatment [17]. Neural changes resulting from the social defeat stress model include decreased arborization in the hippocampus — an area known to be important in both memory formation as well as in the stress response [18,19•] — changes in brain derived neurotrophic factor (BDNF; decreases in the hippocampus and increases in the mesolimbic dopamine circuit), decreased CREB (cyclic-AMP-response-element-binding-protein) activity in the hippocampus, increased Hypothalamic Pituitary Adrenal-Axis (HPA) activity [16,17], and changes in interactions between striatal, amygdalar and medial frontal regions [20,21]. Changes in hippocampal structure in rodent models of depression are paralleled by consistent findings in human depressed patients of decreased hippocampal size and gray matter density [22]. Further, the number of depressive episodes in humans is negatively correlated with hippocampal size further implicating the hippocampus in depression course [23]. Many of the cellular changes in the hippocampus are normalized with treatment in these rodent models.

At a molecular level, the neurogenic theory of depression has gained substantial traction and posits that antidepressant treatments work by facilitating neurogenesis in the dentate gyrus of the hippocampus [24••]. In fact, some researchers argue that increased hippocampal neurogenesis is required for successful antidepressant treatment [25]. Evidence in support of this view is that studies in which hippocampal neurogenesis is rendered impossible, traditional SSRI antidepressants are ineffective in normalizing behavioral deficits caused by rodent models of depression [26,27]. Behaviors that increase hippocampal neurogenesis including enriched environment and exercise both have antidepressant effects in rodents and humans alike [28]. Furthermore, the recently discovered fast-acting effects of ketamine on depressive symptomatology in humans (which occurs on the order of hours as compared to weeks with traditional antidepressants), may effect symptomatic change by encouraging synaptic remodeling and alterations in AMPA and NMDA receptor density specifically in the hippocampus [29••]. The potential use of ketamine to treat depression is perhaps one of the most exciting recent developments for a novel and fast-acting pharmacological treatment of depression.

Human imaging of depression course

While rodent studies provide the ability to examine changes in brain function from a mechanistic perspective modeling specific symptoms, human studies using neuroimaging provide the opportunity to study the full spectrum of the disorder. In particular, deficits in the ability to adaptively regulate positive and negative emotion are thought to be core to depression and its course. Whether the treatments are pharmacological or psychological [30,31], changes in interactions between limbic and prefrontal structures have been hypothesized to underlie symptom amelioration and improvements in emotion regulation. Broadly speaking, two parallel lines of evidence from functional neuroimaging support the claim that abnormalities in fronto-limbic interactions underlie symptoms of depression and its course: first, resting state imaging studies using either PET or fMRI based functional connectivity, and second, task-based studies attempting to isolate processes hypothesized to be specific to depression.

Human imaging resting-state studies

Perhaps the best-known result in human imaging of major depression is that of aberrant activity at rest in the subgenual cingulate cortex (i.e. region BA25) [32]. Across several studies, mostly using regional Cerebral Blood Flow (rCBF) based Positron Emission Tomography (PET), Helen Mayberg and colleagues have repeatedly found BA25 to be hyperactive in patients with depression [32]. rCBF in this region appears to normalize with successful pharmacological and psychotherapeutic treatment. Given these data, Mayberg and colleagues used deep brain stimulation (DBS) of the white matter pathways passing through area 25 in an attempt to ameliorate depression in highly severe and treatment-resistant patients. They reported that DBS to area 25 ameliorated depression severity in several patients who had not responded to any other form of treatment including multiple bouts of electroconvulsive shock therapy. Post-DBS treatment PET imaging also has found reductions in resting rCBF in area 25. While DBS will never be a front-line treatment of major depression, these data are encouraging for those patients suffering from the most severe and intractable forms of the illness and they also represent one of the few examples of neuroscience data being translated from 'bench-to-bedside' — whereby imaging data have informed novel approaches to treatment.

More recently, Mayberg and colleagues used resting rCBF PET to test if it could be used as a biomarker to predict which depressed patients would respond better to either medication (escitalopram) or psychotherapy (cognitive behavioral therapy) [33•]. Following patients for twelve weeks and performing voxelwise discriminant analyses, they found that the right insula was the area that contained the most robust discriminant properties. Right inferior insula hypometabolism (relative to the mean metabolism across the entire brain) was associated with remission to cognitive behavior therapy and poor response to escitalopram, while insula hypermetabolism was associated with remission to escitalopram and poor response to cognitive behavior therapy. Although it is important to temper interpretations regarding the specific role of the insula in predicting depression treatment response so as not to fall prey to reverse inference, it is possible that the insula's role in processing visceral and emotional experiences, and it's dense interconnections with frontal, limbic and hypothalamic structures make it well-positioned predict depression course.

In addition to resting state PET imaging, resting state functional connectivity (RSFC) using fMRI has grown in popularity to examine intrinsic brain activity and interactions between medial prefrontal (extending into the orbitofrontal cortex) and subcortical regions. This network, typically found to be deactivated during engagement in tasks and activated when no external task is present has been called the default mode network (DMN) [34]. While perhaps less theoretically constrained than task-based studies, one clear benefit of RSFC studies is the ease of repeatability and replication across samples and sites. It has been suggested that resting state connectivity abnormalities may reflect dysregulated self-representation in depression [35–37]. And in fact, studies have in general found that patients with depression evince decreased corticolimbic connectivity between the anterior cingulate cortex, thalamus and striatum [38]. Further, successful treatment has been associated with increased fronto-limbic connectivity (For an excellent meta-analysis see: [39••]), perhaps reflecting improvements in affective regulation [40–42]. In line with this suggestion, two recent studies found that before repeated transcranial magnetic stimulation (rTMS) treatment, higher resting dorsomedial PFC-subgenual cingulate connectivity was associated with better treatment outcome [43,44].

The recent application of graph theory as a method to analyze and visualize resting state fMRI data to better understand human neural 'connectomics' [45] has also provided another avenue to better understand abnormalities in neural structure and function in depression [46]. Healthy individuals typically display higher local clustering with relatively short path lengths [47]. While the few studies using graph theory to date to examine connectomic differences in depression have been mixed in their findings [46], they perhaps highlight the oft-cited difficulty in studying the endophenotypes of psychiatric disorders as they are amalgamations of a host of distinct symptoms, only some of which overlap. Nonetheless, the potential of using graph theory to better characterize abnormalities in neural structure and function in depression is an exciting and growing area.

Task-based studies

While a full review of the task-based studies is beyond the scope of this article, we highlight a couple of recent imaging studies using tasks putatively central to depression. Several recent meta-analyses have been published [22,48–51]. Similar to the resting studies, a majority of studies have found abnormalities in fronto-limbic circuitry. Often, but not always, it appears that this circuitry appears to normalize with treatment.

In response to negative words, studies have shown that *lower* pretreatment activity in the subgenual cingulate cortex (around BA25) predicts cognitive therapy treatment response [52•,53,54]. Interestingly, these studies have typically shown that while BA25 activity is prognostic of treatment response to cognitive therapy, activity in this region does not appear to change with treatment, perhaps suggesting that pretreatment BA25 activity is trait-like and impedes the use of emotion regulation training that is core to cognitive therapy.

The course of depression can last for months and years with significant week-to-week fluctuations in symptomatology [55,56], however, the majority of imaging research follows patients for eight or perhaps twelve weeks. The rationale behind such brief follow-up periods is often two-fold: the first is that most antidepressant outcome treatment studies have followed patients for this similar time frame, and it is the time window in which an improvement in symptoms is most likely to be seen ([57] though not always). Nonetheless, studies following patients for longer temporal windows are critical to better understand the course of the disorder and who may not only respond to initial treatments, but also who may be at risk for relapse over these extended periods. As such, we published a study in which depressed patients were scanned using task-based functional MRI at three time points over six months [58••]: Once before treatment, once at eight weeks after being randomized to receive a SSRI or SNRI and once again a six months after the initial pre-treatment scan. Participants performed a cognitive emotion regulation task during functional imaging in which they were instructed to reappraise their negative emotional response to aversive images. While three imaging timepoints were acquired, depression severity was assessed approximately every other week. To utilize the multiple scans and depression assessments, individualized within-subjects growth models were performed which yielded separate beta-estimates corresponding to rate of change of depression severity and rate of change of fMRI BOLD activity when regulating negative affect. Then, a between subjects regression was performed using these within subjects beta-estimates and it was found that those depressed individuals who showed the steepest decrease in depression severity over the 6-month period were the same individuals who showed the most rapid increases in activity in Brodmann area 10 and the right dorsolateral prefrontal cortex activity. Importantly, this relationship was more robust than using only the baseline and end-point data. Overall these findings suggest that changes in prefrontal cortex engagement when regulating negative affect predict changes in depression severity over 6 months and that following patients for six months is important to understanding the course of depression.

Future directions

As noted above, perhaps one of the most replicated findings in the neurobiology of depression is the presence of hippocampal abnormalities with the hypothesis that hippocampal neurogenesis is required for successful treatment. Direct evidence for increases in neurogenesis or hippocampal size directly correlating with depressive

symptoms in humans has yet to be demonstrated. However, with advancing methods in MR spectroscopy and structural imaging there may be opportunities to extend findings from the animal models and test the neurogenic theory of depression in human participants. Examining changes in the jacobian determinant ([59] a voxelwise measure of amount of warping required to fit the template brain) is an indirect measure of region size but may yield important insights into structural changes over depression course. Recent developments in MR spectroscopy may permit the imaging of hippocampal progenitor cells which eventually can become adult neurons integrated into the hippocampal (or cortical) circuitry [60,61••].

Other features of depression known to impact course, severity and prognosis will continue to be important to take into consideration. Among others, these include age of onset of initial depressive episode, number of previous depressive episodes [62], duration of depressive illness [63,64], existence of early childhood trauma [65], and features of emotional dynamics [66–69], etc. While some studies have indeed controlled for (or specifically examined) such features, it is possible that such individual differences will account for variability (and lack of replication) across studies and help the field better understand the course of the illness.

Lastly, psychotherapy outcome data suggest that changes in symptom severity in fact does not change linearly across sessions but occurs in spurts— sudden gains appear to occur [70,71] flanked by weeks with little symptom change. Presently unknown is what in fact changes in the brain that subserves such rapid and seemingly idiosyncratic changes in symptoms. This would require more frequent scanning — perhaps prohibitive up to now. Nonetheless, such data would be quite useful in forwarding our knowledge of the mechanisms of symptom amelioration.

In sum, the advent of functional neuroimaging has provided a rich toolset for psychologists and neuroscientists to better understand the basic science of depression, its course and begin to examine novel avenues for treatment. Much has yet to be done to fulfill the hope that use of more proximal biomarkers will improve and quicken treatment outcome but initial forays have yielded some promising directions going forward.

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