Depression

IAN H. GOTLIB and DANIELLA J. FURMAN

Abstract

Major depressive disorder (MDD) is a costly, prevalent, and recurrent psychiatric disorder that can involve significant impairment across multiple domains of functioning. In this essay, we provide an overview of the theory and research associating aberrant information processing and neural structure and function with the etiology and maintenance of MDD. We begin by highlighting the foundational work that characterizes depressed persons' cognitive and neural responses to valenced stimuli. We then examine recent efforts to clarify the nature of the temporal relation between depression and these cognitive and neural anomalies, focusing on research designed to identify abnormalities that are present before the onset on MDD and to examine the consequences of manipulating cognitive and neural anomalies. Finally, we describe several areas and questions to be examined in future research that we believe will lead both to a more comprehensive psychobiological understanding of MDD and to improvements in the assessment, diagnosis, and treatment of this disorder. In particular, we focus on the need for innovation in diagnosis, better characterization of symptom heterogeneity in MDD, on extending neural research in MDD to the study of abnormalities in larger-scale brain networks, and on elucidating the mechanisms that underlie the successful effects of training programs designed to reduce cognitive biases in depression.

INTRODUCTION

Major depressive disorder (MDD) is among the most prevalent of all psychiatric disorders and is associated with enormous personal and societal costs (Gotlib & Hammen, 2009). Almost 20% of the American population, or more than 30 million adults, will experience an episode of major depression during their lifetime (Kessler *et al.*, 2014). In addition to the two cardinal symptoms of sadness and decreased interest or pleasure in usually enjoyable activities, MDD is associated with psychomotor agitation or retardation, marked weight loss, insomnia or hypersomnia, decreased appetite, fatigue, extreme feelings of guilt or worthlessness, concentration difficulties, and suicidal ideation. To meet Diagnostic and Statistical Manual of Mental Disorders criteria for MDD, a subset of these symptoms, including at least one of the two cardinal symptoms, must be present concurrently for at least

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a 2-week period. MDD is a highly recurrent disorder: 75% of depressed patients experience more than one depressive episode in their lifetime, often relapsing within 2 years of recovering from an episode. Further, epidemiological studies have found depression to be associated with other mental and physical difficulties, most often with anxiety disorders, but also with smoking and cardiac problems. Given its prevalence, recurrence, comorbidity, and costs, it is not surprising that the World Health Organization (2004) projects that MDD will be the single most burdensome disease in the world in the twenty-first century.

Over the past two decades, investigators have made considerable progress elucidating psychological and biological aspects of MDD. In particular, there are now large bodies of research examining anomalies in cognitive functioning and in the processing of positively and negatively valenced information in depression and, more recently, aberrations in neural function and structure. In this essay, we describe our current understanding of the psychobiological functioning of depressed individuals, focusing in particular on abnormalities in information processing and in brain function and structure. We begin by presenting foundational research in these areas, discussing findings from studies that have helped to form our current conceptualization of MDD. We then describe cutting-edge developments in the study of depression—recent investigations and research directions that have begun to sharpen, if not refocus, our picture of cognitive and neural aspects of MDD. Finally, we discuss key issues for future research in the study of MDD, highlighting what we consider to be the most pressing needs and questions that investigators must address and directions that researchers should take in moving the field forward.

FOUNDATIONAL RESEARCH

In this section, we present a brief overview of theory and research that has helped to shape our understanding of cognitive and neural aspects of MDD. Foundational work in both of these areas has focused in large part on elucidating depressed persons' responses to valenced stimuli in an effort to understand processes that serve to maintain or exacerbate this disorder.

Cognitive Aspects of Depression

Cognitive theories of depression originated over 50 years ago and provided the impetus for a large body of research [see Foland-Ross and Gotlib (2012) and Gotlib and Joormann (2010) for reviews]. Beck (1967) posited that depressed individuals (and, importantly, persons who are vulnerable to developing depression) have memory representations, or schemas, that

lead them to view their environment in systematically negative ways. Beck postulated further that when these biases in cognitive processing interact with a stressful life event, these individuals initiate a cycle of negative automatic thoughts about the self, the world, and the future (the "cognitive triad") and, consequently, experience high levels of negative affect. Early studies of cognitive functioning in MDD tested Beck's theory by comparing the responses of depressed and nondepressed persons to self-report measures of dysfunctional attitudes and automatic thoughts. While these studies were important in documenting depression-related aberrations in self-perceived cognitive functioning, it was clear that Beck's formulation involved the operation of cognitive processes at an "automatic" level that was not necessarily accessible through self-report methodologies. Thus, more recent studies have utilized more sophisticated experimental tasks designed to examine schematic functioning. These tasks have now been used to assess biases in attention to, interpretation of, and memory for negatively and positively valenced stimuli in MDD, and provide the basis for innovative treatments for this disorder.

The first studies in this area assessed reaction times of depressed and nondepressed individuals to name the ink colors in which positive, neutral, and negative words were printed in an emotional version of the classic Stroop task, and found that the attention of depressed persons is "captured" by negatively valenced stimuli. Results of subsequent studies assessing not only attentional processing but also other aspects and stages of information processing, such as interpretation and memory, have helped to refine this formulation. For example, using a variety of experimental tasks, researchers have found that depressed persons interpret ambiguous information more negatively than do nondepressed individuals and exhibit preferential recall of negative versus positive material. On the basis of these and other findings, theorists have now extended cognitive formulations of depression to include a consideration of the role of inhibitory functioning. Researchers have posited that the attention of depressed individuals is relatively easily and quickly captured by negative stimuli, leading this information to be more likely than positive material to enter working memory (WM). Given the limited capacity of the WM system, it is important for adaptive functioning that the contents of WM be updated efficiently and continually by discarding information that is no longer relevant. Importantly, researchers have now documented that once negative information is in WM, depressed individuals are impaired in their ability to inhibit processing of, or remove, this material, a difficulty that may underlie the better memory of depressed individuals for negative than for positive stimuli, the sustained negative affect, and the high levels of rumination, or repetitive negative thinking, that characterize MDD (Whitmer & Gotlib, 2013).

Neurobiological Aspects of Depression

Since the discovery that pharmacological interventions targeting the serotonin, norepinephrine, and dopamine neurotransmitter systems reduced symptoms of depression, considerable research has been conducted characterizing depression-associated abnormalities in neurotransmitter production and binding, receptor density and function, and reuptake mechanisms [see Thase (2009), for a review]. Investigators have also attempted to induce depressive symptoms in humans and animals by selectively depleting brain dopamine or serotonin, usually by administering a cocktail of amino acids that lacks the components critical for producing these neurotransmitters, and have found that reductions in serotonin levels, for example, cause cognitive dysfunction in non-disordered individuals similar to that found in depressed persons, including increased attention toward negative stimuli.

With advances in brain imaging technology, researchers have been able to examine depression-related changes in regions of the brain implicated in mood and cognitive processes (and that are sensitive to permutations in neurotransmitter activity). In addition to volumetric and metabolic abnormalities, investigators have identified anomalous neural responding in depressed individuals in brain areas associated with the generation [e.g., amygdala, subgenual anterior cingulate cortex (sACC), and insula] and regulation [e.g., dorsolateral prefrontal cortex (DLPFC)] of emotion, the anticipation of rewarding outcomes and motivation of behavior (e.g., ventral striatum), and memory formation (e.g., hippocampus).

The *amygdala* has been implicated in the integration of information from the senses and viscera, particularly in the service of detecting and mobilizing responses to signs of threat in the environment. Depressed individuals exhibit both decreased volume of, and increased glucose metabolism in, the amygdala; further, hyper-metabolism of the amygdala in MDD is associated with increases in plasma cortisol, a critical stress-related glucocorticoid hormone. Researchers using functional magnetic resonance imaging (fMRI) have documented increased amygdala responses in MDD across a wide range of negative emotional conditions, including anticipating, viewing, and remembering negative words and pictures. Abnormal amygdala responsivity has also been found to correlate with severity of depressive symptoms and level of ruminative responding, suggesting that the amygdala may contribute to the cognitive biases in MDD described above.

Investigators have associated the *sACC* and the *insula* with the induction of negative emotions, including sadness. In addition to reports of both decreased volume and anomalous blood flow and metabolism in the sACC in depression, researchers have documented increased reactivity of both the sACC and the insula to negative emotional stimuli in depressed individuals,

and have found decreases in sACC activity following recovery from MDD [see Hamilton *et al*. (2012), for a review]. The *DLPFC*, in contrast, is involved in WM and executive control processes, and has also been implicated in the regulation of emotion. DLPFC metabolism has been found to be lower in depressed individuals than in healthy controls, and researchers have documented decreased DLPFC responses as depressed persons process negative stimuli or attempt to regulate their emotions.

The striatum has been implicated in generating responses to cues predicting future rewards and to the receipt of unexpected rewards, and more generally, it has been associated with responses to positive stimuli and positive mood. Thus, it is not surprising that investigators have reported reduced striatal response in MDD in a range of positive emotional contexts, including receipt of monetary rewards and positive feedback, suggesting that anomalies in this structure contribute to decreased pleasure, or anticipation of pleasure, in depressed individuals.

Finally, the *hippocampus* is critical in the formation of new memories about experienced events and in the regulation of the stress response. Meta-analyses have documented reduced hippocampal volume and lower levels of hippocampal activation during performance of memory tasks in MDD, suggest that abnormalities in this structure contribute to both the cognitive and affective difficulties experienced by depressed individuals.

CUTTING-EDGE RESEARCH

This foundational research is important in documenting consistent associations between MDD and both aberrant cognitive functioning and anomalous neural function and structure. We know much less, however, about the temporal or causal relation of these patterns of cognitive and neural function and neural structure to MDD; that is, we do not yet understand whether these characteristics are symptoms of the depressed state, consequences of having been depressed, or vulnerability factors that increase the likelihood that individuals will develop an episode of MDD. In this section we focus on research designed to elucidate the functional nature of the relation between depression and both cognitive and neural anomalies, including studies examining whether cognitive and neural abnormalities are present before the onset of a depressive episode, and investigations in which researchers have manipulated cognitive or neural functioning and examined the effects on depressive symptoms.

Cognitive Functioning

A growing literature is demonstrating that depression-related biases in cognition are not necessarily correlates or consequences of the experience of

depression, but instead, could reflect a pattern of dysfunction that precedes the initial onset of this disorder. Indeed, like depressed adults, young individuals who are not themselves depressed but are at high risk for developing depression by virtue of having a depressed parent have been found to exhibit negative biases in the identification and interpretation of emotional material [see Foland-Ross and Gotlib (2012), for a review]. Moreover, similar to depressed adults, never-disordered girls at familial risk for depression selectively attend to negative facial expressions on the visual-probe task, an experimental paradigm that enables the quantification of attentional biases toward or away from emotional stimuli. It is possible, therefore, that negative cognitive biases play a role in placing children at increased risk for developing MDD. Indeed, we recently found that high-risk girls (daughters of depressed mothers) who exhibited a greater attentional bias to sad faces on the visual-probe task, and who made either less positive or more negative interpretations on an ambiguous word completion task, were more likely to experience a subsequent depressive episode than were high-risk girls who exhibited weaker negative cognitive biases. Thus, biases in attention and interpretation may represent important targets for early intervention in MDD. In fact, investigators have begun to report promising initial findings in using two forms of cognitive bias training (CBM)—attentional bias training (ABT), which teaches depressed individuals to attend more to positive and less to negative material, and interpretation bias training (IBT)—both of which attempt to attenuate cognitive biases in order to reduce depressive symptoms. Initial studies have documented improvement in depressive symptoms using these techniques, although more research is needed to draw strong conclusions about the effectiveness of these approaches.

Neurobiological Functioning

Investigators have recently begun to examine the nature of the relation between anomalous structure and function of particular brain regions and manifestations of depression by examining whether neural abnormalities precede the onset of depressive symptoms as risk factors for the development of MDD. Researchers have now identified abnormalities in the structure and function of several key brain regions in individuals who are at elevated risk for the development of depression [see Foland-Ross, Hardin, and Gotlib (2013), for a review]. Importantly, these studies have revealed that anomalies in high-risk individuals often mirror those that have been documented in currently depressed individuals. For example, investigators have found decreased volume of the hippocampus and the DLPFC in never-depressed individuals at familial risk for MDD, as well as decreased activation of the striatum to monetary reward. Similarly,

researchers have documented abnormal activation of the amygdala during sad mood induction and reductions in amygdala volume in individuals at genetic risk for depression. Thus, aberrations in neural regions implicated in attention to emotional information, in generating and regulating emotional and stress responses, and in forming emotional memories may render high-risk individuals less able to disengage from, or regulate the emotional consequences of, negative or stressful life events.

A second method by which researchers are beginning to exam the nature of the relation between symptoms and neural function is by examining whether directly altering anomalous neural activation in depressed individuals affects clinical aspects of the disorder. In a ground-breaking study, Mayberg *et al*. (2005) demonstrated that by applying electrical current directly to white matter tracts adjacent to the sACC using a method called deep-brain stimulation (DBS), they were able to immediately reduce depressive symptoms in individuals with treatment-resistant depression. Investigators have now begun to explore the feasibility of altering neural function in circumscribed brain regions through less invasive means. Real-time neurofeedback training (NFT) procedures, for example, are designed to teach individuals to exert volitional control over brain states by presenting them with continuously updated graphical representations of brain activity during fMRI scanning or electroencephalography (EEG), and asking them to learn to modulate these representations. Researchers in this area have examined the ability of individuals to learn to control key areas involved in emotional experience, such as the amygdala, insula, and sACC (e.g., Hamilton, Glover, Hsu, Johnson, & Gotlib, 2011). Linden *et al*. (2012) found improvement in depressive symptoms immediately following NFT designed to increase activation in brain regions associated with the elicitation of positive emotions. These preliminary results suggest that anomalous activity in critical brain regions may not simply convey risk for the development of the disorder or represent a neuropathological consequence or marker of the disorder, but may also reflect the ongoing maintenance of particular symptoms. Thus, NFT that targets regions of known dysfunction in MDD may ultimately enable researchers to identify which of the neural features of depression are causally linked to the maintenance of specific behavioral and emotional components of this disorder.

KEY ISSUES FOR FUTURE RESEARCH

Given our current understanding of cognitive and neural aspects of MDD, it is clear that there are a number of key issues that must be addressed in future research. Most important are issues concerning improvements in the diagnosis of MDD, the considerable heterogeneity of the disorder, the extension of

research in MDD to the study of abnormalities in large-scale neural networks, and the integration of cognitive and neural research in the service of elucidating the mechanisms that might underlie successful CBM. We briefly describe each of these issues in the following sections.

Diagnosis

The primary method of diagnosing MDD is the clinical interview, which relies in large part on an individual's ability to accurately self-report a considerable range of emotions, cognitions, and somatic experiences. Indeed, the information provided by an individual to a physician or researcher is the only means for determining whether he or she is currently depressed and whether a given treatment regimen has been effective. Unfortunately, these reports may be unreliable, unstable, and subject to the memory biases that characterize depressed individuals. In working toward innovation in the diagnosis of MDD, researchers have begun to use automated multivariate approaches, such as machine learning, to classify depressed and nondepressed individuals on the basis of neural activation to sad faces, neural structure, and even vocal prosody and facial expression. Some work suggests, in addition, that these methods can predict remission following cognitive-behavioral therapy. Thus, the move away from self-report as the diagnostic gold standard may dramatically alter the way in which individuals are diagnosed, treated, and assessed for treatment response.

Heterogeneity

To meet criteria for a diagnosis of MDD according to DSM-IV, individuals must have one or both of the cardinal symptoms of MDD, depressed mood and anhedonia, but may present with up to 17 additional possible symptoms across seven broad categories of functioning, including changes in weight, appetite, sleep, and psychomotor function, fatigue, worthlessness, guilt, cognitive impairment, and suicidal thoughts or self-harm. Given the heterogeneity of possible symptom profiles in individuals who meet criteria for MDD, some emphasis has been placed on delineating reliable and clinically relevant subtypes of the disorder that might facilitate more effective and individually tailored interventions, by examining which symptoms and other manifestations of disorder tend to cluster together. For example, the DSM-IV defines the melancholic subtype of depression as an episode characterized by severe anhedonia, profound feelings of guilt (often over trivial events), and marked psychomotor abnormalities. These symptoms have also been associated empirically with overreliance on external cues during cued-response tasks and abnormal neural correlates of action monitoring.

Nonetheless, despite efforts to define reliable symptom clusters and to identify the neurobiological and cognitive correlates of various symptoms, we do not yet fully understand why specific symptoms cluster together. Thus, the development of a comprehensive and neurobiologically informed understanding of why and how symptoms and other behavioral and neural correlates co-occur in depressed individuals is an important future step that would help clinicians and researchers to better characterize the etiology of subtypes of MDD and treat specific profiles of the disorder. Further, given that genetic and other risk factors for MDD have been associated with anomalies in cognitive, affective, and neurobiological functioning, multivariate approaches to characterizing subtypes of MDD could be extended to inform our understanding of, and our ability to tailor interventions for, distinct forms of psychobiological risk for the development of the disorder.

Network-Level Neural Analysis

Although identifying abnormalities in the structure and activation of particular brain regions has been important in advancing our understanding of neural aspects of MDD, we still lack a cogent, comprehensive, and therapeutically useful model of brain function and dysfunction in this disorder. In this context, it is critical to note that massive interconnectivity among populations of neurons in the brain means that neural events seldom occur in isolation; consequently, it is important that we attempt to understand depression from a larger, neural-network, perspective. Only recently, however, have neuroimaging analysis techniques, as well as our understanding of the architecture of the brain, advanced sufficiently to make network-level explorations and conceptualizations of MDD feasible.

By far, the majority of neuroimaging studies of MDD use protocols that involve the presentation to participants of affective or cognitive tasks. While the results of these studies can inform network-level formulations of depression, researchers using fMRI and positron emission tomography (PET) have increasingly been investigating neural functioning in MDD over relatively long durations in the scanner in the absence of externally presented tasks or stimuli. This "resting state" approach has led to the identification of abnormalities in the "default mode network" (DMN), a cluster of medial brain regions that appears to mediate internally generated thought processes and is typically inhibited in tasks that require subjects to attend to cognitively engaging, external stimuli. In depressed individuals, this network shows greater interconnectivity with the sACC (Greicius *et al*., 2007), a region that, as we noted earlier, is associated with the generation of sadness. Further, depressed individuals do not deactivate this network in the same way that nondepressed persons do during the active processing of

external stimuli (Sheline *et al*., 2009), suggesting that MDD is characterized by difficulty inhibiting the processing of negative, internally generated, thought content. Indeed, given these and other findings [see Hamilton, Chen, and Gotlib (2013), for review], it is not surprising that DMN dynamics have been associated, in depressed individuals, with the tendency to engage in rumination (Hamilton *et al*., 2011). Examinations of large-scale neural networks in MDD have now extended beyond the DMN. For example, a growing body of work is implicating anomalous function and structure in the *salience network* in MDD, a group of regions that includes the insula and amygdala, that undergirds responding to biological relevant stimuli, and that may subserve heightened attention toward negative stimuli (Hamilton *et al*., 2012).

In addition, most investigators to date have relied on simple correlative methods, or "functional connectivity," to assess intrinsic network-level function in depression. Importantly, there is growing interest in examining issues involving the temporal and directional relations among areas. For example, multivariate Granger causality analysis is a technique that has been applied to neuroimaging data to estimate temporal influence, or "effective connectivity," of one brain region with respect to another region. In the first work using this analytic method to examine neural connectivity in MDD, Hamilton *et al*. (2011) found that, to a significantly greater extent in depressed than in nondepressed participants, activations in emotion generative areas are not only mutually excitatory, but further, are associated with subsequent decreases in brain regions associated with emotion regulation, such as the DLPFC.

Researchers have also recently begun to use graph theory to examine large-scale brain network organization. This method provides a means for quantifying the overall organization of brain connectivity, allowing the brain to be depicted as a series of "nodes," representing particular regions, and "edges," representing correlations in structural volume or activity between nodes. A handful of studies have now used graph analyses to examine network connectivity in depressed individuals, and have identified abnormalities in both path length, that is, how many steps it takes to get from a node to any other node in the network, and number of hubs and connections, features that may relate to the efficiency of information processing within and between neural networks. Therefore, research that continues to integrate this method with other connectivity- and activation-based analytic techniques has the potential to greatly increase our understanding of the nature of neural function and dysfunction in MDD, as well as the way in neural anomalies may underlie deficits, biases, and difficulties in cognition and information processing in this disorder.

Mechanisms Underlying the Effects of Cognitive Bias Modification

Despite the promise of CBM procedures in reducing depressive symptoms, the mechanisms that might contribute to this improvement are not yet clear. While it is possible that ABT and IBT simply "train away biases" and thereby improve symptoms of MDD, it is likely that the mechanisms underlying the effects of these training procedures are more complex. Investigators have already begun to examine the neural foundations of traditional cognitive-behavior therapy for depression (DeRubeis, Siegle, & Hollon, 2008), but it will be important to extend this research to elucidate the mechanisms by which CBM achieves its beneficial effects. MacLeod and Mathews (2012) recently distinguished between "near" and "far" transfer of training effects of CBM. They noted that while training typically transfers to the same task with different stimuli (near transfer), changes in functioning on tasks that are less closely related to the training task (far transfer) are particularly informative for our understanding of mechanisms. Initial work indicates that the effects of ABT can transfer to alter interpretive biases, and that similarly, the effects of IBT may influence biases in both attention and memory. These findings suggest not only that the distinctions made by researchers among biases in attention, interpretation, and memory need to be reconsidered, but further, that at least some aspects of these biases share common mechanisms of action.

We posit that there are three mechanisms in particular that underlie the positive effects of CBM in depression: decreased attentional capture of negative stimuli (bottom-up processing); increased inhibition of negative material (top-down processing); and, as a consequence of these changes, decreased negative self-referential thinking (rumination). Importantly, as we noted earlier in this essay, all three of these constructs have been found to distinguish depressed from nondepressed individuals. Moreover, investigators are beginning to examine neural underpinnings of each these mechanisms (Cooney, Joormann, Eugene, Dennis, & Gotlib, 2010; Dichter, Felder, & Smoski, 2009; Foland-Ross *et al*., 2013). It will be important to continue this line of investigation, integrating assessments of cognitive and neural functioning in depressed individuals in order to gain a more comprehensive understanding of, and to continue to develop and refine, innovative treatments for this debilitating disorder.

REFERENCES

Beck, A. T. (1967). *Depression: clinical, experimental, and theoretical aspects*. New York, NY: Harper & Row.

Cooney, R. E., Joormann, J., Eugene, F., Dennis, E. L., & Gotlib, I. H. (2010). Neural correlates of rumination in depression. *Cognitive, Affective, and Behavioral Neuroscience*, *10*, 470–478. doi:10.3758/CABN.10.4.470

DeRubeis, R. J., Siegle, G. J., & Hollon, S. D. (2008). Cognitive therapy versus medication for depression: Treatment outcomes and neural mechanisms. *Nature Reviews Neuroscience*, *9*(10), 788–796.

Dichter, G. S., Felder, J. N., & Smoski, M. J. (2009). Affective context interferes with cognitive control in unipolar depression: An fMRI investigation. *Journal of Affective Disorders*, *114*, 131–142.

Foland-Ross, L. C., & Gotlib, I. H. (2012). Cognitive and neural aspects of information processing in major depressive disorder: An integrative perspective. *Frontiers in Emotion Science*, November, 3 Article 489, 1–17.

Foland-Ross, L. C., Hamilton, J. P., Joormann, J., Berman, M. G., Jonides, J., & Gotlib, I. H. (2013). The neural basis of difficulties disengaging from negative irrelevant material in Major Depression. *Psycholological Science*, *24*, 334–344.

Foland-Ross, L. C., Hardin, M. G., & Gotlib, I. H. (2013). Neurobiological markers of familial risk for depression. In P. Cowen, T. Sharp & J. Lau (Eds.), *Behavioral neurobiology of depression and its treatment: Current topics in behavioral neurosciences* (Vol. 14, pp. 181–206). New York, NY: Springer.

Gotlib, I. H., & Hammen, C. L. (Eds.) (2009). *Handbook of depression* (2nd ed.). New York, NY: The Guilford Press.

Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: Current status and future directions. *Annual Review of Clinical Psychology*, *6*, 285–312.

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., … Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry*, *62*(5), 429–437.

Hamilton, J. P., Chen, G., Thomason, M. E., Schwartz, M. E., & Gotlib, I. H. (2011). Investigating neural primacy in Major Depressive Disorder: Multivariate granger causality analysis of resting-state fMRI time-series data. *Molecular Psychiatry*, *16*, 763–772.

Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in Major Depressive Disorder: Implications for adaptive and maladaptive rumination. *Biological Psychiatry*, *70*, 327–333.

Hamilton, J. P., Glover, G. H., Hsu, J.-J., Johnson, R. F., & Gotlib, I. H. (2011). Modulation of subgenual anterior cingulate cortex activity with real-time neurofeedback. *Human Brain Mapping*, *32*, 22–31.

Hamilton, J. P., Etkin, A., Furman, D. J., Lemus, M. G., Johnson, R. F., & Gotlib, I. H. (2012). Functional neuroimaging of Major Depressive Disorder: A meta-analysis and new integration of baseline activation and neural response data. *American Journal of Psychiatry*, *169*, 693–703.

Hamilton, J. P., Chen, M. C., & Gotlib, I. H. (2013). Neural systems approaches to understanding Major Depressive Disorder: An intrinsic functional organization perspective. *Neurobiology of Disease*, *52*, 4–11.

Kessler, R. C., de Jonge, P., Shahly, V., van Loo, H. M., Wang, P. S., & Wilcox, M. A. (2014). The epidemiology of depression. In I. H. Gotlib & C. L. Hammen (Eds.), *Handbook of Depression* (3rd ed., pp. 7–24). New York, NY: The Guilford Press.

Linden, D. E. J., Habes, I., Johnston, S. J., Linden, S., Tatineni, R., Subramanian, L., … , Goebel, R.. (2012). Real-time self-regulation of emotion networks in patients with depression. *PLoS One*, *7*(6), e38115.

MacLeod, C., & Mathews, A. (2012). Cognitive bias modification approaches to anxiety. *Annual Review of Clinical Psychology*, *8*, 189–217.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., … , Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron 45*(5), 651–660.

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., … , Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences*, *106*(6), 1942–1947.

Thase, M. E. (2009). Neurobiological aspects of depression. In I. H. Gotlib & C. L. Hammen (Eds.), *Handbook of depression* (2nd ed., pp. 187–217). New York, NY: Guilford Press.

Whitmer, A. J., & Gotlib, I. H. (2013). An attentional scope model of rumination. *Psychological Bulletin*, *139*(5), 1036–1061.

World Health Organization (2004). *The global burden of disease: 2004 update*. Geneva, Switzerland: WHO.

IAN H. GOTLIB SHORT BIOGRAPHY

Ian H. Gotlib is the David Starr Jordan Professor of Psychology and Director of the Stanford Mood and Anxiety Disorders Laboratory at Stanford University. From 2005 to 2010, Dr. Gotlib served as Senior Associate Dean for the Social Sciences, and he has been Chair of the Department of Psychology at Stanford since 2012. In his research, Dr. Gotlib is broadly examining psychological and biological factors that place individuals at increased risk for depression, as well as processes that are involved in recovery from this disorder. Dr. Gotlib conducts research examining cognitive, social, endocrinological, and neural factors and genetics in depressed individuals, as well as predictors of depression in children at familial risk for developing this disorder. He also examines the impact of innovative procedures to reduce young children's risk for depression. Dr. Gotlib's research is supported largely by grants from the National Institute of Mental Health. He has also been funded by the National Health Research Development Program, the Medical Research Council of Canada, and the Hope for Depression Research Foundation. He has received the Distinguished Investigator Award from the National Alliance for Research in Schizophrenia and Affective Disorders, the Joseph Zubin Award for lifetime research contributions to the understanding of psychopathology, the APA Award for Distinguished Scientific Contribution, and the APS Distinguished Scientist Award. Dr. Gotlib has published over 500 scientific articles and has written or edited several books in the areas of depression and stress, including the *Handbook*

of Depression with Constance Hammen. He is a Fellow of the American Psychological Association, the Association for Psychological Science, and the American Psychopathological Association, and is Past President of the Society for Research in Psychopathology.

DANIELLA J. FURMAN SHORT BIOGRAPHY

Daniella J. Furman is completing her PhD in Psychology at Stanford University, where she works with Dr. Ian Gotlib to characterize anomalies in brain structure, function, and connectivity associated with Major Depressive Disorder and risk for the development of this disorder. Daniella was named the 2012–2013 Gerald J. Lieberman Fellow in the Social Sciences; she has also received the Smadar Levin Award from the Society for Research in Psychopathology, the American Psychological Association Dissertation Research Award, and a National Science Foundation Graduate Research Fellowship.

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Clarifying the Nature and Structure of Personality Disorder *(Psychology)*, Takakuni Suzuki and Douglas B. Samuel
Taking Personality to the Next Level: What Does It Mean to Know a Person? *(Psychology)*, Simine Vazire and Robert Wilson
A Gene-Environment Approach to Understanding Youth Antisocial Behavior *(Psychology)*, Rebecca Waller *et al*.
Crime and the Life Course *(Sociology)*, Mark Warr and Carmen Gutierrez
Rumination *(Psychology)*, Edward R. Watkins
Emotion Regulation *(Psychology)*, Paree Zarolia *et al*.