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Editorial

Introduction to Special Issue on the Neurobiology of Depression

As cogently described in the articles in this special issue, major depression is a highly prevalent and frequently debilitating psychiatric disorder. For example, data from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) (Jonas et al., 2003) and National Epidemiological Survey on Alcohol and Related Conditions (NESARC, 2001–2002) (Moreno et al., 2012) both found that approximately 10% of the population had a life time history of major depression, with even higher rates reported in the National Comorbidity Survey (Kessler and Walters, 1998). Major depression can strike throughout the lifetime, starting as early as preschool in a minority of cases (Gaffrey et al., 2011; Luby et al., 2002, 2003), but sometimes not emerging until late in life (Buchtemann et al., 2012). Some individuals will experience only a single episode of depression, but unfortunately many people experience recurrent episodes that interfere with life function and place a tremendous burden on families and the public health system (Kessler, 2012). Although there are a range of treatments that can be effective for individuals with major depression, including pharmacotherapy, psychotherapy, electroconvulsive therapy and transcranial magnetic stimulation, there is still much work to be done in terms of developing approaches that will work for those with treatment-resistant depression and which prevent recurrence and relapse even among those who seemingly respond to first line treatments.

As the articles in this special issue clearly illustrate, the pathophysiological mechanisms giving rise to major depression are complex and need to be understood at multiple levels of analysis. Although a similar statement can be made about any major neuropsychiatric disorder, the work on major depression perhaps best illustrates the complex interplay between the environment, genetics, neurobiology and psychological mechanisms that synergistically interact to give rise to this debilitating disorder. For many years, work on each of these types of mechanisms proceeded somewhat independently, with studies focusing primarily on one level of analysis (e.g., genetics, brain function, stress, cognitive distortion) as a means of making tractable progress on understanding the etiology of major depression. However, as advances in the basic sciences have helped us to understand how different levels of analysis interact, work on major depression has increasingly focused on bridging levels of analysis to understand both risk and protective factors for this form of psychopathology. This is nicely illustrated in a number of the articles in this special issue, including work focused on understanding how genetics influence the neurobiology of reward and stress responsivity (Bogdan et al., in press), how brain function and structure can be used to predict response to both pharmacological and psychological treatments (Fu et al., in press), how life stress and adversity influence hippocampal function and structure (Frodl and O'Keane, in press), how normative brain development may influence the mechanisms giving rise to major depression (Gaffrey et al., in press; Morgan et al., in press), and how abnormalities in neural circuits contribute to the symptoms of major depression (Hamilton et al., in press).

The critical interactions between different types of mechanisms are outlined in Fig. 1, which attempts to illustrate the bidirectional influences among these different levels of analysis, with all of the arrows quite deliberately leading in both directions. Perhaps better than any other disorder, the research on major depression has taught us that one can only understand the neurobiology of this disease by understanding how environmental influences shape neurobiological mechanisms at the level of neural circuits, brain structure and neurotransmitter function, and even at the level of genetics when one takes into account how environment and behavior may influence gene expression (Lenroot and Giedd, 2011; Meaney and Szyf, 2005; Murgatroyd and Spengler, 2011). Importantly however, work in the field is also demonstrating influences in the opposite direction, as research is beginning to show that genetic and neurobiological function can influence environmental and behavioral selection in ways that lead to dynamic changes in the functional trajectory of an organism in both health and disease (Grimm and Steinle, 2011). To make matters more complicated, all of these mechanisms and their interplay need to be understood in the context of normative developmental changes that occur across the lifetime of the individual. Taking into account the developmental trajectory of both environmental and neurobiological mechanisms will help us understand how the manifestations or lasting impacts of abnormalities in such mechanisms differ as a function of development (Gaffrey et al., in press), as well as how normative developmental changes may influence the timing of both risk and protective factors associated with depression (Morgan et al., in press).

The discussion above was framed somewhat abstractly, focusing in general on factors or principals that may govern the synergistic interplay among etiological mechanisms in depression. However, the articles in this special issue go beyond this abstract level to highlight some of the specific mechanisms and domains that have identified as contributing to the development and maintenance of major depression. Although these articles do not review all of the research in the field, they do highlight the emerging importance of the interplay between stress, HPA axis function and reward processing in the evolution of depression, at multiple levels of analysis. The article by Frodl and colleagues reviews the work on early stressful events and how they influence HPA axis function and hippocampal structure in humans, as potential contributors to risk for depression (Frodl and O'Keane, in press). This human work is beginning to mirror the elegant animal work that has illustrated the ways in which early environmental experiences influence brain development and lifelong responses to stress (Sapolsky, 2003, 2004; Meaney and Szyf, 2005). Consistent with such findings, the article by Bogdan and colleagues extends our understanding of the role of stress and depression by examining genetic influences on stress responsivity. Bogdan and colleagues also argue for the role of alterations in reward responsivity in the emergence of depression, outlining the current state of knowledge about genetic

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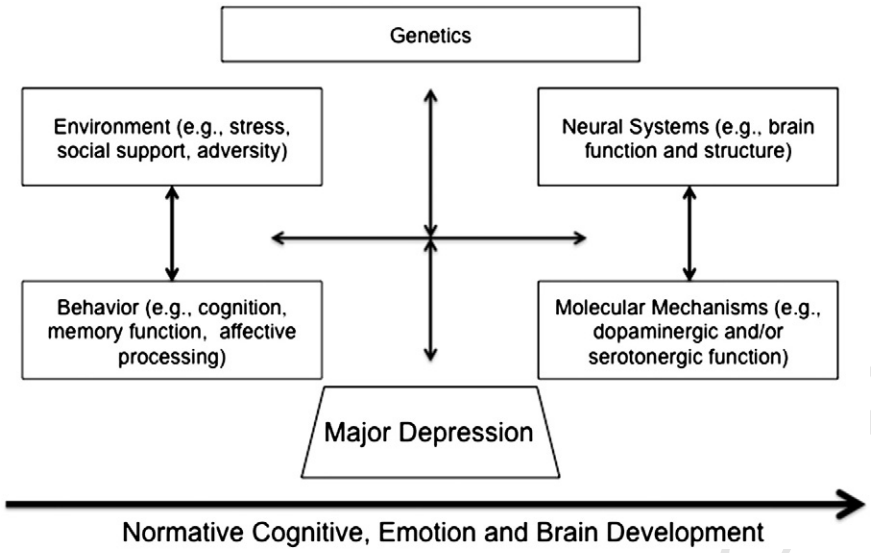

Fig. 1. Synergistic interplay among mechanisms contributing to the development and maintenance of major depression.

mechanisms that modulate reward function (Bogdan et al., in press). Importantly, Bogdan and colleagues illustrate potential connections between stress sensitivity and reward function in the development of depression, describing work that has shown that stress can lead to reductions in reward responsivity, as a potential mechanism for understanding the contributions of stress to anhedonia in depression. The types of genetic mechanisms identified by Bogdan include variations in genes that code for different functional aspects of neurotransmitter systems such as dopamine and serotonin, including changes in availability, receptor sensitivity/density, enzymatic breakdown and transport. This fits nicely with the work summarized by Savitz and Drevets, which reviews the receptor imaging literature supporting alterations in both serotonergic and dopaminergic mechanisms, including 5-HT1a, 5-HT1b and D1 receptor function among others.

Morgan and colleagues extend our understanding of the role of reward processing in depression, by describing ways in which normative developmental changes in the neural mechanisms supporting reward processing during puberty may influence risk for depression (Morgan et al., in press). In this work, Morgan and colleagues emphasize how a shift in the balance of the neural systems that support reward processing may contribute to depression, with changes in the relative activation of both striatal and ventral medial PFC regions predicting risk for depression differentially as a function of gender and pubertal status. Gaffrey and colleagues further emphasize the need to understand the potential neurobiological, environmental and psychological mechanisms contributing to depression in a developmental context, with two goals (Gaffrey et al., in press). One goal is to understand how mutually interactive influences of environment, behavior and neurobiology evolve to shape normative development, as well as abnormal development, using the Interactive Specialization model as a guiding theoretical framework. The second goal is to understand how the occurrence of depression at different timepoints in development may influence neural and behavioral systems in diverging ways. For example, emotion regulation systems are relatively underdeveloped in early childhood, and thus may or not be as influenced by depression related process as compared to later in development. Alternatively, depression occurring early in childhood may be associated with a greater disruption in normative developmental trajectories of brain function and structure, given that these systems are still undergoing maturation.

Hamilton and colleagues broaden the discussion of the neural mechanisms contributing to depression to the neural circuit level, reviewing the literature on alterations in functional connectivity in the default mode network, the salience network, and the executive network (Hamilton et al., in press). As described in their article, the default mode network is thought to be involved in self-referential processing, the executive network is thought to be involved in cognitive rand emotional regulation, and the salience network is thought to be involved in attending to survival-relevant or "salient" stimuli in the environment. Their work highlights the influence of the connectivity and balance of activation in the default and executive networks as being relevant for understanding rumination in depression, with relatively greater default mode activity predicting higher levels of rumination. This emphasis on a circuit level understanding again supports the theme of needing to examine interactions between systems in trying to understand the pathophysiology of major depression, as it is highly unlikely that dysfunction in a single brain region, or even a single circuit, will be enough to account all of the phenomenology associated with this illness. Lastly, Fu and colleagues overview the literature on neural predictors of depression, showing that there is growing evidence neural predictors of treatment response (Fu et al., in press). As one example, these authors overview evidence for a relationship between the degree of anterior cingulate activation (a region in the salience network) prior to treatment and the magnitude of treatment response. Although it is not yet clear that such markers can be used in a "personalized medicine" approach, they do offer promise for a more tailored approach to treatment selection.

In addition to providing an excellent overview of the current status of a number of domains of etiological research relevant to major depression, the articles in this special issue also point to important pathways for future research. First, the emphasis on interacting systems brings into relief the need to better understand the causal directions relating one mechanism to another, with a likely answer that some of the relationships are dynamically interacting and mutually causative. Second, in order to address such questions, it is imperative to initiate longitudinal prospective studies that work with children and/or adolescents prior to the onset of major depression, selecting participants based on one or more different types of risk factors (e.g., genetic, environmental, behavioral/cognitive). Such studies can help us identify and understand the relative timing and influences of these different mechanisms, and how they may manifest differentially across the course of development. There is already promising work in this area, such as the high risk research on adolescent female offspring of mothers with depression conducted by Gotlib, Joormann and colleagues (Chen et al., 2012; Gotlib et al., 2010; Joormann et al., 2007, 2012; Waugh et al., 2012). However, even more research of this type is needed, particularly studies of even younger children that will help us understand how early neurobiological risk factors can

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manifest and interact with environmental factors, and to identify optimal times for intervention. Third, such studies should, where possible, attempt to assess multiple levels of analysis, including environmental, person-centered behavior, and neurobiology in order to deepen our understanding of the interactions among these levels of analysis and mechanisms. Fourth, it will also be important to understand how heterogeneity in symptom presentation is (or is not) related to heterogeneity in etiological mechanisms, and to determine whether unique patterns of risk or protective factors modify symptom presentation. Fifth, it will also be important to gain a better understanding of the specificity of any such etiological mechanisms to major depression, versus "internalizing" disorders more generally. There is certainly evidence in the literature that the contribution of at least some of the factors discussed in the following articles may not be unique to major depression (Anderson and Hope, 2008; Hettema, 2008). As such, examining similarities and differences across current diagnostic categories may help us refine and improve our current nosology in ways that are highly consistent with the Research Diagnostic Criteria Initiative (Cuthbert and Insel, 2010; Insel et al., 2010).

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