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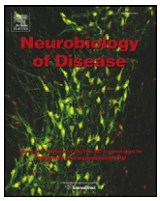

Review

Towards the study of functional brain development in depression: An Interactive Specialization approach

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ABSTRACT

Depression is a significant and impairing mood disorder with onset possible as early as age 3 and into adulthood. Given this varying pattern of age of onset, identifying the relationship between brain development and depression across the lifespan has proven elusive. This review identifies some of the factors that may have limited the advancement of our knowledge in this area and discusses how synthesizing established models of depression and normative brain development may help to overcome them. More specifically, it is suggested that current neurobiological models of depression fail to account for the developmental variance associated with early neural network development and the potential influence of experience on this process. The utility of applying an established framework of normative brain development to this topic is described and its potential utility for conceptualizing the influence of depression on brain function across the life span is addressed. Future directions including longitudinal neuroimaging studies of early onset depression and groups at risk for this disorder are proposed.

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Introduction

Depression has been increasingly recognized as a significant and impairing mood disorder with widespread public health implications. Current estimates suggest that up to 16% of the general population will experience at least one major depressive episode in their lifetime and that approximately 80–90% will go on to have additional occurrences (Kessler et al., 2005; Mueller et al., 1999; Solomon et al., 1995). Interestingly, the probability of experiencing future episodes of depression may be age dependent, with an earlier onset (e.g., in childhood) associated with greater risk for- and increased frequency of recurrence (Birmaher et al., 2002; Lewinsohn et al., 1999). Additionally, studies have generally suggested a more complex clinical picture in pediatric depression as well, with increased comorbidity and functional impairment. Given that an earlier onset of depression may signal a more chronic and impairing form of this disorder (Birmaher and Axelson, 2006; Birmaher et al., 2002; Harrington et al., 1996; Perlis et al., 2004), it is remarkable how little is known about its neurodevelopmental course. The growing consensus that childhood may represent a developmental period when the brain is potentially more amenable to prevention and treatment efforts further underscores the need for such information (Fox et al., 2010).

Skepticism about the application of traditional definitions of major depressive disorder (MDD) in early childhood and the pragmatic challenges of using neuroimaging techniques in children has undoubtedly slowed research into depression related effects on brain development. However, we also suggest that the varying timing of depression onset has not allowed for a straightforward interpretation of MDD within a traditional developmental disorder framework. Specifically, many of the more "traditional" developmental disorders such as autism or attention deficit/hyperactivity disorder are considered disorders of childhood and require symptom manifestation prior to a specific age (for example 3 years of age in autism; APA, 2000). Though depression can also be identified in childhood, depression frequently emerges post-puberty and, as such, tends to be viewed as a disorder of adulthood that can be and often is diagnosed at earlier ages. This age related distinction (i.e., disorders of childhood or adulthood), while not arbitrary, presents a very real quandary for addressing the developmental neurobiology of a given "adult" disorder. Of primary importance for the current discussion is the common inference that a fixed or static neurobiological model of depression can be directly applied at any age, leading one to overlook the dynamic and highly plastic nature of the brain development process. The assumed direct applicability of adult neurobiological models to pediatric depression is often notable in studies and reviews focused on this condition. For example, studies and reviews addressing brain related findings in pediatric depression commonly frame their discussion using current neurobiological models derived from the adult literature (e.g., restricting or largely focusing their literature review or analyses on brain regions included in these models). While highly informative and thought provoking, these previous works have not discussed, nor fully considered, how current theories of normative brain development processes should be incorporated and considered in neurobiological models of depression. This is not to say that specific periods of brain development (e.g., changes in brain structure or function during adolescence) and general concepts (e.g., neuroplasticity) have not been considered in previous reviews of pediatric depression, as they have (e.g., Davey et al., 2008; Forbes and Dahl, 2012). However, these discussions have generally stopped short of using well-developed theoretical frameworks to inform the *process* of brain development across the *lifespan* in this disorder. Rather, they have largely been constrained to identifying patterns of group differences at a given point in development (e.g., childhood) and evaluating the identified differences as consistent or not consistent with different developmental time periods (e.g., adulthood). To be fair, the currently available literature informing brain function and structure in pediatric mood disorders does not allow for much more.

Recent neurobiological reviews of pediatric depression suggest that the field is now at a tipping point for identifying advantageous paths forward in this developing area of study (Hulvershorn et al., 2011; Monk, 2008). As such, the goal of the current review is to suggest one such path forward. Specifically, we suggest that synthesizing established models of depression and normative functional brain development would help provide an important theoretical step forward for identifying how the potential effects of this disorder on brain function emerge across the lifespan. In order to illustrate this approach and how it fits within the broader field of depression research, we discuss the use of a developmental psychopathology perspective (Cicchetti, 1984) as an overarching framework to study depression and the more recent inclusion of general system neuroscience principles into this perspective (Cicchetti and Tucker, 1994). Following this, we propose that incorporating a well-developed theory of normative brain development (Johnson, 2001) into this discussion may provide unique insights through empirically testable predictions about the relationship between depression and the *process* of functional brain development. As an illustrative example of this, we selectively review research examining emotion regulation and its associated neurobiology in healthy and depressed children, adolescents, and adults. Given recent in-depth reviews discussing reward processing and other etiologically relevant endophenotypes in depressed adolescents and adults (including two within this special issue), we take a broader approach to this topic by focusing on the process of brain development and how it can inform a lifespan approach to depression. That is, this review does not aim to provide an in-depth discussion of any one developmental period but rather will apply this "process model" of normative brain development to a domain of specific interest in depression to provide an example of how it might be applied. Therefore, in this review we will restrict our discussion to the regulation of negative affect over the course of normative development and in depression. We conclude the review by suggesting future directions that may help address some of the outstanding gaps in our knowledge about depression and its interaction with normative brain development processes.

It is our hope that the following discussion will help contribute to the creation of a unifying framework for brain research in depression, allowing for the potential identification of developmentally specific as well as age independent or common underlying neurobiological effects of this disorder across the life span. What is presented here is far from a complete account of what is known about the relationship between depression and brain development; rather it is intended to propose a direction and agenda for future research on this topic.

Developmental psychopathology as an overarching framework for the study of brain development in depression

While rapid advances in technology have offered new and exciting opportunities to examine depression in unprecedented ways, their continued use in the absence of a developmentally informed conceptual framework is unlikely to move our understanding of psychopathological brain processes beyond the "*what*" and "*where*" of differences to the more central questions of "*when*" and "*how*" did they arise (Cicchetti, 1984). The adaption of such a conceptual framework is uniquely important for the study of developmental phenomena, which by their very nature are perhaps best captured by an examination of process rather than outcome. We believe that such a framework should have several features in order to be useful for this purpose. Succinctly, such a framework must sufficiently capture the complex nature of factors affecting mood disorder onset and course as well as define development as an ongoing process. Further, the given framework must be broad enough to consider the interplay between multiple relevant factors (e.g., psychological, biological,