NeuroImage: Clinical 4 (2014) 209–231

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Review

Functional brain imaging studies of youth depression: A systematic review☆

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ARTICLE INFO

Article history:
Received 12 June 2013
Received in revised form 13 November 2013
Accepted 18 November 2013
Available online 11 December 2013

Keywords:
Major depressive disorder (MDD)
Youth
Functional magnetic resonance imaging (fMRI)

ABSTRACT

Background: There is growing interest in understanding the neurobiology of major depressive disorder (MDD) in youth, particularly in the context of neuroimaging studies. This systematic review provides a timely comprehensive account of the available functional magnetic resonance imaging (fMRI) literature in youth MDD.
Methods: A literature search was conducted using PubMED, PsycINFO and Science Direct databases, to identify fMRI studies in younger and older youth with MDD, spanning 13–18 and 19–25 years of age, respectively.
Results: Twenty-eight studies focusing on 5 functional imaging domains were identified, namely emotion processing, cognitive control, affective cognition, reward processing and resting-state functional connectivity. Elevated activity in "extended medial network" regions including the anterior cingulate, ventromedial and orbitofrontal cortices, as well as the amygdala was most consistently implicated across these five domains. For the most part, findings in younger adolescents did not differ from those in older youth; however a general comparison of findings in both groups compared to adults indicated differences in the domains of cognitive control and affective cognition.
Conclusions: Youth MDD is characterized by abnormal activations in ventromedial frontal regions, the anterior cingulate and amygdala, which are broadly consistent with the implicated role of medial network regions in the pathophysiology of depression. Future longitudinal studies examining the effects of neurodevelopmental changes and pubertal maturation on brain systems implicated in youth MDD will provide a more comprehensive neurobiological model of youth depression.

Contents

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http://dx.doi.org/10.1016/j.nicl.2013.11.009

1. Introduction

Major depressive disorder (MDD) is the single greatest cause of disability and morbidity in adolescence and young adulthood (Jamison et al., 2006), and is associated with social and academic impairment, and recurrent illness through adulthood (Birmaher et al., 2007; Jamison et al., 2006). By the time a young person reaches 25 years of age the prevalence of MDD is as high as 24% (Lewinsohn et al., 1998), with the peak age of onset occurring between 15 and 29 years of age (Blazer et al., 1994). Depression is also a significant contributor to mortality in this age group: it is the illness most often associated with suicide, which is the third leading cause of death for youth aged 15–24 (CDC, 2007). The fact that most first episodes of depression emerge during early adolescence (starting at puberty) through to early adulthood underscores the importance of research focusing on this age cohort. Research in youth MDD not only will allow us to better understand the etiology of depression at its onset, but will also help work towards better clinical interventions to prevent recurrent, chronic episodes.

Influential models of adolescent brain development have emphasized the importance of social (increased reward-seeking behavior and peer affiliation), neural (protracted cortical maturation of prefrontal brain areas), and hormonal (onset of puberty and subsequent rise in sex hormones) changes in contributing to the onset of adolescent depression (Casey et al., 2008, 2011; Ernst et al., 2006; Forbes and Dahl, 2005). These models propose that increased reward-seeking and risk-taking behaviors that are characteristic of adolescence may be underpinned by a temporal mismatch between the development of brain networks that support emotion generation and reward-processing (e.g., striatum, amygdala), and those implicated in the cognitive regulation of emotion (e.g., prefrontal cortex). Prefrontal cortical regions supporting cognitive–affective processes such as the cognitive regulation of emotion follow a protracted course of maturation compared to subcortical regions supporting reward and emotion, with development continuing into young adulthood (Gogtay et al., 2004; Rubia, 2012). This temporal imbalance of subcortical and cortical maturation, in conjunction with genetic and other environmental risk factors (e.g., stress) is suggested to render adolescents more vulnerable to depression. An alternative model, proposed by Davey et al. (2008) argues that the development of the prefrontal cortex itself may contribute to adolescent-onset MDD. Specifically, it is proposed that adolescent development of the prefrontal cortex promotes decision-making with respect to complex, and often distal, social rewards. It is hypothesized that when such rewards are not achieved, this suppresses the reward system, resulting in depressive symptoms (Davey et al., 2008).

In parallel with a growing focus on the clinical management of depression in youth (McGorry, 2007), there is an emerging research focus on the neurobiological correlates of the disorder during this age period. One such area that has shown recent promise is the application of neuroimaging to examine the neural underpinnings of youth MDD. Studies employing such techniques, in particular functional magnetic resonance imaging (fMRI), are relevant for the investigation of neural mechanisms that may contribute to the emergence of depression in youth, and for the identification of potential biomarkers that may be associated with early stages of the illness. While existing neuroimaging studies in youth MDD have been informed by structural and functional imaging studies in adult patients, there are several compelling reasons why a greater focus on younger samples is both necessary and important for expanding current neurobiological models of the disorder. For example, studies of youth populations are less confounded by factors that are associated with the natural trajectory of the illness (e.g., functional impairments) and medications. Further, as mentioned, adolescence is characterized by rapid cortical maturation (increased synaptic pruning, myelination and neuronal plasticity) of neural areas implicated in emotional perception and regulation and reward processing (Gogtay et al., 2004; Rubia, 2012; Sowell et al., 2004) that, when altered during development, may give rise to depressive pathophysiology that has distinct underlying mechanisms from those in adult-onset MDD. In addition, pubertal processes have been linked to adolescent depression, particularly for girls, where there is evidence that *early* pubertal maturation is associated with increased risk for the development of depression (Angold and Costello, 2006; Ge et al., 2001).

In light of the above discussion, recent neuroimaging studies of youth MDD employing task-based and resting-state fMRI have begun to reveal abnormalities in neural networks implicated in emotion generative (i.e., bottom-up) processes, as well as cognitive regulatory (i.e., top-down) processes. However, to date, most studies of youth MDD have examined restricted age ranges that typically end at age 18 despite the fact that neuroimaging studies of adolescent brain development have shown that maturation of prefrontal cortical brain regions continues well into early adulthood (Gogtay et al., 2004; Sowell et al., 2004). A greater focus on studies of youth depression encompassing mid-adolescence through to young adulthood (i.e., up to 25 years of age) is also necessary given that the peak age of onset of the disorder coincides with this age period. The US Food and Drug Administration's (FDA) black-box warning about the potential use of antidepressants to precipitate suicidal behaviors also extends to this older age, suggesting that the neurobiological factors that underlie the effects distinguish youth from adults (US FDA, 2007). Finally, studies examining this age cohort are clinically relevant in the context of some clinical youth mental health services, which extend their treatment programs to 25-year olds (McGorry, 1998, 2007). Thus a systematic review is warranted that captures studies of youth MDD, spanning 13–25 years of age. To date, only one review of the adolescent MDD literature has been published (Hulvershorn et al., 2011). This review provided a broad overview of studies across various imaging modalities including diffusion tensor imaging (DTI), structural and functional MRI and magnetic resonance spectroscopy (MRS). In summary, it emphasized cortico-limbic alterations as being central to emotional dysregulation in adolescent MDD. However while their review focused on studies of childhood and adolescent depression, it did not explicitly focus on studies of youth MDD up to 25 years of age, or make comparisons between younger and older youth with MDD.

Therefore the aims of this article are to provide an updated, systematic review of fMRI studies in adolescent and youth MDD populations, and to directly compare findings between younger and older youth with MDD. For the reasons previously stated, we selected studies that included patients ranging from early adolescence to early adulthood (13–25 years old). We focused our review on fMRI studies, and as such, aimed to build on the Hulvershorn et al. (2011) review by providing a more detailed description of fMRI studies and their implications. We also included task-based functional connectivity studies in youth MDD, whereas the Hulvershorn et al. (2011) review focused only on studies employing resting-state functional connectivity. Furthermore, to provide a more comprehensive account of the literature we extended our search to encompass neuroimaging studies of adult MDD, in order to identify studies that included young samples (mean age $\leq$ 25 years old). To this end we identified additional four studies. One of the studies identified focused on first-episode MDD patients with a mean age slightly higher than our cut-off of 25 (Guo et al., 2011; see Table 1). This study was included in the review.

2. Method

2.1. Literature search

A computerized search using the databases PubMED, PsycINFO and Science Direct, covering the period from January 2001 to September 2012, was conducted using the following key search terms (* = truncated): "adolescen* AND depress* AND brain imaging", and advanced searches: "youth* NEAR/5 depression AND (brain OR imaging)". January 2001 was chosen as the start date because the first neuroimaging study in adolescent MDD was published in 2001. Additional