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Selective neurocognitive impairments in adolescents with major depressive disorder

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Abstract

This study investigated whether major depression in adolescence is characterized by neurocognitive deficits in attention, affective decision making, and cognitive control of emotion processing. Neuropsychological tests including the Wechsler Abbreviated Scale of Intelligence, the Continuous Performance Test–Identical Pairs, the Attention Network Test, the Iowa Gambling Task, the Emotional Go-NoGo Task, and the Face Go-NoGo Task were administered to adolescents with Major Depressive Disorder (MDD) (n = 31) and psychiatric diagnosis free controls (n = 30). Findings indicated that compared with controls, depressed adolescents exhibited impaired sustained attention; a gender by group interaction on affective decision making such that depressed males tended to make less advantageous choices on the IGT; and an inverse pattern of correlations between depressive symptom counts and reaction time to affective stimuli, characterizing greater affective reactivity in depressed adolescents. Findings demonstrate that adolescents with MDD display selective neurocognitive impairments on tasks capturing 'cool' and 'hot' executive functioning.

Keywords

Major depression; Adolescence; Attention; Executive functioning; Affective decision making; Emotional processing

Introduction

Adolescent major depressive disorder (MDD) is associated with increased risk for severe consequences including poor academic and psychosocial outcomes as well as suicide (Rao et al., 1995; Weissman et al., 1999). In addition, the lifetime prevalence rate of MDD in adolescents has been estimated to range from 15% to 20%, comparable with the lifetime rate of MDD found in adults (Birmaher et al., 1996). Research on neurocognitive function in adolescent depression can help illuminate the pathoetiology of the illness (Gunther,

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Holtkamp, Jolles, Herpertz-Dahlmann, & Konrad, 2004; Kyte, Goodyer, & Sahakian, 2005) as well as identify targeted strategies for treatment.

According to the cortico-limbic neural circuitry model of depression (Mayberg, 1997), on the spectrum of clinical depression, symptoms result from disruptions in a network system involving interactional relationships among the dorsal cortical regions such as the prefrontal cortex that provide top-down regulation to limbic emotional centers such as the amygdala. This neurobiological system integrates the recognition of affective cues, deliberation over emotionally salient decisions, and regulation of attention (Mayberg, 1997; Phillips, Drevets, Rauch, & Lane, 2003). Specifically, the model postulates that impairment within the dorsal structures (including the dorsolateral prefrontal cortex, the dorsal anterior cingulate, inferior parietal cortex, and striatum) results in difficulties with attention and executive functioning in individuals with depression (Mayberg, 1997). This model of neurocognitive dysfunction in depression has been supported by research with adults documenting behavioral deficits on tasks involving planning and working memory, along with compensatory increased activation of pertinent brain structures (e.g., Barch, Sheline, Csernansky, & Snyder, 2003). Furthermore, neurocognitive functions such as attention, decision making, and cognitive control (e.g., inhibition) are also found to be negatively impacted or emotionally biased in adults with depression (Fossati, Amar, Raoux, Ergis, & Allilaire, 1999; Gaultieri, Johnson, & Benedict, 2006; Kaiser et al., 2003; Porter, Gallagher, Thompson, & Young, 2003; Sevigny, Everett, & Grondin, 2003).

Past research has demonstrated that some neurobiological correlates of depression differ across developmental periods of childhood, adolescence, adulthood, and old age (e.g., Halari et al., 2009; Mata & Gotlib, 2011). Further, accumulating evidence supports the perspective that neurocognitive functioning undergo a protracted period of development, with some prefrontal functions not fully reaching maturity until early adulthood (e.g., Gogtay et al., 2004; Somerville & Casey, 2010). Thus, generalizing neurocognitive impairments found in adults with MDD (e.g., Smoski et al., 2008) to adolescent and child samples with depression would be tenuous at best. While some research studies on adolescents with depression have provided preliminary evidence for similar neurocognitive impairments and emotional biases as those that have been documented in the literature with adults (Bradley, Mogg, & Williams, 1995; Gotlib et al., 2004; Murphy et al., 1999), other studies suggest that there is a pattern of neurocognitive impairments in adolescent depression that differs from impairments documented in previous research on adult depression. For example, attention in adolescents with MDD is intact when tasks employ emotionally neutral stimuli, whereas attention is enhanced by emotionally valenced stimuli (Kyte et al., 2005).

To address some of the critical gaps in previous research with adolescents, in the present study, we employed a diverse set of neurocognitive tests, including those that present neutral and those that present affective stimuli in order to disambiguate mixed findings from past research. The inclusion of tasks tapping into conceptually separate brain functions can help us (a) identify patterns of neurocognition that are representative of the selective biases exhibited in clinical depression during adolescence, and (b) offer clues to the emerging interactions across brain systems in typically developing adolescents. We administered tasks to adolescents with and without MDD that broadly correspond to the functionality of dorsal

brain regions including the dorsal lateral prefrontal cortex (DLPFC), ventral brain regions including the ventromedial prefrontal cortex (VMPFC) and the anterior cingulate cortex (ACC), and limbic regions of the brain including the amygdala. Based on findings from previous research in adults and adolescents (Hooper, Luciana, Conklin, & Yarger, 2004; Smoski et al., 2008), we hypothesized that neurocognitive impairments would be more easily detectable in tasks that tap into 'hot' (emotion-valenced) processes as opposed to 'cold' (non-emotional) cognitive processes. Specifically, we predicted that adolescents with MDD would demonstrate impairments on tasks that require cognitive control of emotion processing and affective decision making and, to a lesser extent, on tasks that assess attention.

Methods

Participants

We enrolled sixty-one adolescent participants (14.50–19.90 yrs). Study participants were high school and college students living near the Twin Cities area. Descriptive statistics and significance tests are reported in Table 1. The mean age of the sample was 17.39 (*SD* = 1.58) years, 57.4% were females, 78.7% were Caucasian. Thirty-one adolescents had a current diagnosis of MDD and thirty were free of any psychiatric history. Participants were matched for sex and age. Depressed adolescents were recruited from inpatient and outpatient clinics at the University of Minnesota Medical Center-Fairview Hospital, as well as through community postings (i.e., flyers posted at coffee shops, libraries, etc.). Exclusion criteria for all adolescents consisted of an estimated full scale IQ < 80 (based on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) 4-subtest full scale IQ), significant medical or neurological disorders, and a history of bipolar disorder, autism spectrum disorder, schizophrenia, eating disorder within the past year, and/or substance-related disorder with a history of use in the past 60 days. For the MDD group, MDD was the primary diagnosis and comorbidities that routinely occur in adolescents with moderate to severe depression (e.g., anxiety disorder) were permitted (see Table 2). The most commonly diagnosed comorbid condition was having Generalized Anxiety Disorder (48.4%). One participant diagnosed with MDD was excluded from further study due to an IQ score less than 80. On the day of testing, the depressed group demonstrated variability in self-reported symptom severity, with BDI scores ranging from 1 to 44 (approximately normally distributed). A majority of the depressed participants were taking antidepressants (see Table 3). The comparison group consisted of healthy adolescents recruited from community postings; those who met criteria for any major current or past DSM-IV diagnosis were excluded. Five of the control participants were shared with another concurrent study (Study of Teens At Risk; Kumra & Lim, 2010) and did not complete testing on the emotional processing tasks. The MDD group scored significantly lower than the controls on IQ scores, $t(58) = 2.15$, $p < .05$. Means and standard deviations for IQ scores are 108.63 (13.95) for the MDD group and 115.37 (9.93) for the control group.

Measures

Assessment of depression—The Schedule for Affective Disorders and Schizophrenia for School-aged Children – Present and Lifetime version (K-SADS-PL; Kaufman et al.,

1997), a semi-structured interview, was used to confirm mental health diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV; American Psychiatric Association, 1994). The interview was completed with adolescents and their parents independently by trained clinicians (masters level and above). The diagnosis of current MDD was based on a clinical consensus meeting held by our research group based on information from these informants. The Beck Depression Inventory - II (*BDI-II*; Beck, Steer, & Brown, 1996) was used as an index of adolescents' current self-reported depressive symptom count.

Neurocognitive tasks—The Continuous Performance Task–Identical Pairs version (CPT-IP; Cornblatt, Risch, Faris, Friedman, & Erlenmeyer-Kimling, 1988) measures sustained attention and yields separate scores reflecting increasing memory load on digit span (i.e., 2-digit targets represented by CPT2, 3-digit targets represented by CPT3, and 4-digit targets represented by CPT4). Participants are instructed to respond to any consecutive presentation of identical stimuli by key pressing as quickly as possible. The outcome variable of interest for the present study is *d*'-an index of discrimination sensitivity. This d' index is a well-established metric incorporating both true and false positive responses in its calculation (Coren & Ward, 1989). Accuracy on the CPT-IP is thought to reflect the functioning of the DLPFC and the parietal areas (e.g., Adler et al., 2001).

The Attention Network Test (ANT; Fan, McCandliss, Sommer, Raz, & Posner, 2002) assesses three networks: alerting, orienting, and conflict. The ANT is a widely used task comprised of a combined cued reaction time task and flanker task. Participants are instructed to press either the left or right key to indicate the direction that a central arrow points to. During various presentations, the arrow may appear above or below a center fixation point; in addition, the target stimuli may be presented with or without flankers. Four types of warning cues precede the presentation of the target stimuli: no cue, center cue, double cue, or spatial cue. Flankers may be neutral, congruent, or incongruent (for a more detailed description, see Fan et al., 2002). While the ANT alerting and orienting reaction time scores reflect functioning of the DLPFC and parietal areas, the ANT conflict reaction time score is thought to reflect the functioning of the ACC (Fan et al., 2002).

The Iowa Gambling Task (IGT; Bechara, Damasio, Tranel, & Damasio, 2005) evaluates affective decision-making, which is thought to engage the VMPFC (Bechara, 2004). The task presents participants with four decks of cards and taps into the process of decision making regarding rewards and punishments. Each card selected by the participant comes with a reward; however, some cards will also come with a penalty. Participants are instructed to earn as much money (reward points) as possible. The first two decks (decks 1 and 2) are disadvantageous decks while the latter two decks (decks 3 and 4) are advantageous decks in that playing more from the first two decks would lead to an overall loss. Note that decks 1 and 3 confer frequent small punishments whereas decks 2 and 4 are associated with infrequent yet large punishments. Consistent with the majority of prior research conducted with this task, our focus was on advantageous choices (number of cards selected from decks 3 and 4).

The Emotional Go-NoGo task (Hare, Tottenham, Davidson, Glover, & Casey, 2005) and the Face Go-NoGo task (Ladouceur et al., 2006) assess cognitive control (i.e., engaging the anterior cingulate and the prefrontal cortex) while processing faces with emotional expressions, which are posited to activate limbic structures such as the amygdala and nucleus accumbens (Monk et al., 2008. The Emotional Go-NoGo task evaluated each participant's ability to accurately respond to target (go) emotional facial expressions and abstain from responding to non-target (nogo) expressions (Hare et al., 2008). The stimuli were 12 gray scale images of human faces (six of them female) taken from the NIM set at http://www.macbrain.org, yielding three separate reaction time (RT) scores in response to fearful, happy, and calm faces. The Face Go-NoGo task is performed in the same manner, with alterations in the stimuli presented, which were images of 10 individuals (5 female) in gray scale acquired from the set of Ekman faces. These facial images were cropped on a gray background to exclude hair. It is posited that the exclusion of hair potentially makes facial expressions more salient. For the Face Go-NoGo task, RT measures were obtained for go and nogo trials, reflecting RT to emotional faces (angry, fearful, sad, happy) paired with neutral faces.

Procedures

The study was approved by the Institutional Review Board through the University of Minnesota. In the first visit, clinicians administered the semi-structured interview and the adolescent also completed the *BDI-II* and *WASI*. In a second visit, participants completed the computerized neurocognitive tasks. It took about 1.5 h for each participant to complete the neurocognitive testing with average time spent on each task as follows: CPT (10 min), ANT (20 min), IGT (10 min), Emotional Go-NoGo (25–30 min), and Face Go-NoGo (10 min). A subset of these participants was additionally studied in a neuroimaging study (Cullen et al., 2009, 2010).

Data analyses

A GLM approach was used to analyze some tasks (CPT-IP, ANT, IGT); while like others (Hare et al., 2008), a repeated measures approach was used to analyze the emotional processing tasks which reflect non-independent scales. For MDD participants, bivariate correlations evaluated the associations between depression severity and each of the neuropsychological tasks separately. Initial analyses were conducted without correction of IQ (see Table 4), since both groups had IQ in the above average range, and since we did not have specific hypotheses of how IQ might differentially influence neurocognitive outcomes on tasks measuring different underlying neural substrates. However, given IQ differences (as shown on Table 1), a secondary set of analyses, controlling for full scale IQ, is reported in the text. In order to further explore whether comorbidities and medication use might have impacted neuropsychological functioning of adolescents with major depression, we conducted *t*-tests specifically testing the effect(s) of comorbid GAD and the effect(s) of medication treatment.

Results

Group differences in neurocognitive functioning

Means and standard deviations and significance tests are reported on Table 4. Omnibus analysis yielded a significant effect of group on the CPT-IP. Follow-up analysis that considered individual CPT-IP scales indicate that controls performed better on an index of discrimination sensitivity than depressed adolescents for CPT2 and CPT4. This group difference finding at the omnibus level was attenuated after adjustment for IQ, $F(3,55) = 2.37$, $p = .08$.

Omnibus analysis failed to yield a significant effect of group for the ANT, either with or without IQ correction. Given that brain regions proposed to mediate the different networks of the ANT are of known importance in MDD (Mayberg, 1997), follow up analyses were conducted on the ANT subscales. The Conflict score reaction time was significantly higher in the MDD than in the control group, with higher reaction time indicating worse performance. This Conflict score effect was not significant after adjusting for IQ.

The omnibus analysis for the IGT failed to yield a significant group effect. But because females have typically been found to outperform males on the IGT (e.g., Hooper et al., 2004), we also considered a group by gender interaction with and without controlling for IQ. A significant interaction between group and gender was found only after taking IQ into account, $F(1,55) = 4.40$, $p < .05$. The interaction showed that while depressed girls selected more frequently from the advantageous decks than control girls, depressed boys selected less frequently from the advantageous decks than control boys.

For measures of cognitive control of emotional processing, a GLM repeated measures MANOVA failed to yield significant effect of group on the RT variables for the Emotional Go-NoGo and on both go and no-go trials of the Face Go-NoGo (either without or with IQ correction).

Analyses conducted on the MDD subgroup

The subsample of thirty-one adolescents with MDD reflects heterogeneity in severity, psychiatric comorbidities, and medication use. For adolescents with major depression, associations between depressive symptom severity (measured by the BDI) and the entire neuropsychological test battery were evaluated. None of the indices from the two attention tasks (i.e., CPT, ANT) were significantly correlated with symptom severity. Of the tasks assessing cognitive control of emotion processing, only the Face Go-NoGo was found to be significantly associated with BDI scores. For the MDD participants, five Face Go-NoGo scores were significantly correlated with the BDI scores. For the go trials, significant correlations with BDI were noted, where higher severity was associated with faster reaction times. These correlations included (Face Go-NoGo variables listed are reaction times with target emotion listed first followed by foil emotion): Angry/Neutral ($r = -.487$, $p < .01$), Fear/Neutral ($r = -.470$, $p < .01$), Sad/Neutral ($r = -.426$, $p < .05$), and Happy/Neutral ($r = -.691$, $p < .001$). For the nogo trials, a significant negative correlation with BDI was also detected: Neutral/Angry ($r = -.481$, $p < .01$).

We also considered the potential impact of comorbid conditions and medication utilization associated with MDD. While a wide range of comobid conditions were present, the presence of GAD was represented frequently enough across the sample to allow for exploratory analyses to be conducted. About half of those with MDD also had a diagnosis of GAD (48.4%, see Table 2). When comparing adolescents with MDD with GAD (n = 15) to adolescents with MDD without GAD (n = 16), t-test indicated that the depressed adolescents with comorbid GAD exhibited a faster orienting response on the ANT, $t(29) = -2.81$, $p = .009$. With regard to medication usage, close to half of the participants with MDD were being treated with a selective serotonin reuptake inhibitor (SSRI) medication (45.2%, see Table 3). Analyses failed to reveal any significant differences for the effects of SSRI medication on neurocognitive performance in the available subsamples.

Discussion

This study adds to a small number of studies (e.g., Gunther et al., 2004; Kyte et al., 2005) examining multiple aspects of neuropsychological functioning (i.e., attention, decision making, and affective processing) in adolescents with major depression. Based on previous models of fronto-limbic dysfunction in major depression (Mayberg, 1997; Stein et al., 2007, we hypothesized that adolescents with MDD would exhibit mild to moderate impairments on tasks mediated by fronto-limbic brain circuitry, and that findings would be strongest for tasks that tapped into emotion processing. First, the results revealed a moderate association between depression symptom severity and cognitive control of emotion processing. Second, the current study provided preliminary support for impairments in adolescents with depression on an affective decision making task that is mediated by the ventral paralimbic region. Third, in adolescents with depression, we also found evidence of impairments in ‘cool’ (i.e., non-emotional) domains of executive functions including sustained attention and conflict processing. Overall, results from our research provided partial support for our hypothesis that adolescents with major depression would exhibit stronger impairments in ‘hot’ (i.e., emotional) domains of executive functions. The pattern that we observed is that the deficits in ‘cool’ executive functions seen in adolescent major depression is less dependent on state mood symptoms and thus present more globally, while the ‘hot’ executive function deficits in adolescent MDD seem more associated with current mood state (as indexed by the *Beck Depression Inventory–II*).

Our findings suggest that adolescents currently suffering from more severe depression show greater emotional reactivity to affective cues. This finding is in support of a prior study in which Kyte et al. (2005) found that adolescents with depression exhibited a selective attentive bias towards stimuli conveying negative affect. Similarly, in Ladouceur et al.’s emotional Go/NoGo study (2006), adolescents with MDD reacted more quickly when sad faces were the go signal and embedded in a series of neutral faces that signaled inhibition/nogo. These results demonstrate a bias towards negative stimuli in depressed adolescents, and suggest that positive stimuli may interfere with performance in depressed youth. However, other studies have failed to demonstrate an attentional bias towards negative stimuli in adolescents with MDD (Dalgleish et al., 2003; Neshat-Doost, Taghavi, Moradi, Yule, & Dalgleish, 1997; Taghavi, Neshat-Doost, Moradi, Yule, & Dalgleish, 1999; Wilkinson & Goodyer, 2006). Moreover, results from the current study differ from those of

past studies in that the emotional reactivity found in this sample of adolescents with depression is exhibited towards emotional stimuli of both positive and negative valence while others reported a selective bias towards negative stimuli (e.g., Ladouceur et al., 2006). Faster reaction time during trials associated with an affective go cue is interpreted by our research team to be an indication of depressed adolescents' heightened emotional reactivity and propensity towards emotion dysregulation. From a systems neuroscience perspective, our behavioral data fit well with the conceptualization of deficits in the cortico-limbic neural network in MDD (e.g., Cullen et al., 2009; Mayberg, 1997). In this model, the combination of heightened amygdala mediated emotional response to incoming stimuli and a reduction in frontally mediated cognitive control processes renders heightened emotional reactivity and attenuated regulatory control.

Affective decision making, a form of 'hot' executive functioning (Hongwanishkul, Happaney, Lee, & Zelazo, 2005), was assessed in our study with the IGT. Developmental study of the IGT suggests that its ventromedial prefrontal cortex mediated processing capability is still maturing during adolescence (Hooper et al., 2004). A prior study using the IGT indicated that depressed adults demonstrated better performance than controls by selecting more cards from advantageous decks overall (Smoski et al., 2008). Kyte et al. (2005) used a decision making task that was conceptually similar to the IGT with the exception that both the quality of the selections and the amount of time it took for a participant to arrive at the selection were recorded. They found that adolescents with first-episode MDD exhibited higher rates of impulsivity (i.e., making choices faster) as compared to the control group (Kyte et al., 2005). In addition to a recent study which reported that compared with boys, girls preferred more advantageous decks (Hooper et al., 2004), our results provided initial support for the hypothesis that depressed girls (and not depressed boys) are risk aversive. We found a significant gender by group interaction effect on the number of advantageous choices made on the IGT. Whereas depressed girls selected more frequently than control girls from the advantageous decks, control boys outperformed their depressed counterparts.

Our group-by-gender finding in the reward processing task may provide some clues about sex differences in major depression. Accumulating evidence suggest that beginning in mid-adolescence, girls and women are about twice as likely as boys and men to develop major depression (e.g., Nolen-Hoeksema & Girgus, 1994; Rutter, 1986). Results from this study suggest that the neurobiological underpinnings of reward processing may operate differently between adolescent males and females who are diagnosed with major depression. In the adult depression literature, Knutson, Bhanji, Cooney, Atlas, and Gotlib (2008) found that in contrast to healthy adults who experienced more affective conflict (indexed by anterior cingulate cortex activation) during the anticipation of avoidable losses, adults with MDD exhibited affective conflict during the anticipation of attainable gains. We speculate that during early adolescence, biopsychosocial challenges (e.g., higher levels of relational aggression in adolescent girls; Murray-Close, Han, Cicchetti, Crick, & Rogosch, 2008) may interact with preexisting gender differences in reward processing (Hooper et al., 2004), leading to significant increases of rates of major depression in adolescent girls.

Our results demonstrate mixed outcomes with regard to attentional abilities. Adolescents with MDD had more difficulty with sustained attention than controls on the CPT. Further, although the omnibus test on the ANT networks was not significant, between-subjects contrast tests suggested that depressed adolescents showed impaired executive attention when compared with their healthy counterparts. These findings of attentional differences between depressed and non-depressed adolescents contrast previous research that found no major attentional deficits in depressed adolescents when using emotionally neutral measures of attention. Gunther et al. (2004) had negative results using a battery of five attention tasks- a reaction time task, dual optic and auditory tasks aimed at divided attention, a Go/NoGo task that requires response or inhibition based on a visual cue, and the Sustained Attention task involving 12 dot patterns over 50 series. Kyte et al. (2005) found no statistical differences in attentional switching capabilities between depressed and non-depressed adolescents using the Intra-Dimensional, Extra-Dimensional (ID-ED) Set-Shifting task which is modeled after the Wisconsin Card Sort task. While lack of concentration is a characteristic of depression, studies comparing the attentional abilities of adolescents with and without depression have not consistently documented attentional impairments in adolescent depression when experimental paradigms employed neutral stimuli. One factor that may contribute to equivocal findings across groups is the possibility that across studies, there were different rates of psychiatric comorbidities within the depressed group. In this study, follow-up analyses showed that depressed adolescents with comorbid GAD exhibited a faster orienting response on the ANT than those depressed adolescents without GAD. Results from the current study highlight the importance of evaluating comorbid anxiety disorders when studying neurocognition in MDD. Further, our results are consistent with the view that clinical anxiety is associated with hyperarousal and a readiness to identify potential signs of threat (e.g., Bishop, 2007). Future research would benefit from evaluating the effects of different comorbid anxiety subgroups on neurocognition in adolescent major depression.

Overall, the relatively limited impairments noted in this study as well as previous research may suggest that some neurocognitive deficits and affective biases are not as reliably present in adolescents with depression as in their adult counterparts. Adults with depression have repeatedly demonstrated difficulty on emotionally neutral tasks assessing various aspects of attention and memory (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008; Gaultieri et al., 2006; Porter et al., 2003; Sevigny et al., 2003), whereas current studies only reliably demonstrate impaired recall in depressed adolescents (Gunther et al., 2004; Lauer et al., 1994). For example, adults with depression perform worse than controls at attentional switching on the Wisconsin Card Sort task, while adolescents with depression performed as well as their healthy counterparts on the ID-ED task, a functionally similar task (Fossati et al., 1999). Adolescents with depression also perform well at emotionally neutral inhibitory tasks, whereas depressed adults display deficient functioning on these tasks (Kaiser et al., 2003). Existing research also suggest that adolescents with depression demonstrate emotional bias when attending to or committing stimuli to memory, much like their adult counterparts (Bradley et al., 1995; Gotlib et al., 2004; Murphy et al., 1999). The mixed results of neuropsychological research in adolescents with MDD can be viewed optimistically, especially when considering that attention, decision making, and other

executive functions are skills necessary for utilizing the varieties of therapies and treatments available for treating clinical depression. Although adolescents with depression have comparatively fewer neurocognitive deficits than adults, we should not lull ourselves into believing that neurobiological changes related to depression are not occurring.

Limitations and future directions

Although utilizing neurocognitive assessment instruments can be useful in dissecting constituent processes associated with atypical cognitive processing exhibited in clinical populations, this study has several notable limitations. First, although our study is one of few studies utilizing a diverse set of neurocognitive tasks in assessing adolescents with major depression, it is cross-sectional and cannot address issues pertinent to pathoetiology or broader developmental patterns. Neurocognitive deficits may serve as vulnerability factors increasing adolescents' likelihood of developing a mood disorder; alternatively, a profile of neurocognitive deficits could reflect an accumulation of disease processes, treatment effects, and developmental changes.

Although we administered tasks evaluating discrete systems of 'cool' and 'hot' executive functions, a developmental systems perspective recognizes that cognitive functions are interdependent. Additional research is crucially needed to uncover the degree to which neurocognitive deficits manifested in adolescents with major depression are associated with structural and functional abnormalities of the developing brain. With regard to executive function, it is evident that the next step in research is to pair neuroimaging with neurocogntive testing to elucidate when brain activation begins to reflect changes related to depression. The few functional imaging studies have already demonstrated that changes in brain function and cognition are taking place in adolescence before deterioration of cognitive performance is evident in adulthood (Halari et al., 2009; Killgore, Gruber, & Yurgelun-Todd, 2007; Wilkinson & Goodyer, 2006). Decreased activity in the dorsal compartment during attentional tasks in adolescence contrast with the increased activation in these same regions that have been observed in depressed adults.

In the adult literature, the increase in dorsal compartment activity is interpreted as compensation by dysregulated structures (Mayberg, 1997). It is possible that the decreased signal in adolescent dorsal compartment structures represents the beginning of limbic-cortical dysregulation in depression. Decreased signal may represent a delay in structural maturation in depressed adolescents as compared to their healthy counterparts. In the beginning, these structures may not need to compensate with increased blood flow in order to maintain normal cognitive functioning. Unfortunately, it appears that the brain's ability to compensate is limited over time and into adulthood (Gotlib et al., 2004).

The complex medication regimens that are often used by adolescents with moderate or severe depression are reflected in our clinical sample. These regimens make it difficult to rule out medication effects (including medication interactions) on cognitive functions and to consider either potential ameliorative or adverse effects. Moreover, the same medication may lead to a range of different associated outcomes, as individuals differ in underlying neurophysiology. Future studies of neurocognitive functioning in adolescent depression may

benefit from adopting the following strategies: recruitment of medication naïve participants; randomized placebo-controlled trial evaluating impacts of types of medications; longitudinal neurocognitive investigation incorporating a discontinuation and reinstatement design (for further discussion, see Goodwin & Jamison, 2007). For example, studies specifically designed to evaluate medication effects on neurocognitive functioning in mood disorders might address the role(s) medication withdrawal plays on neurocognitive adaptations.

In order to fully understand the impact of depression on cognition, researchers will need to characterize the abnormalities in functional activation during discrete cognitive tasks. Because complex executive functioning relies on more basic abilities (i.e., attention, memory, motor skills, and inhibition), these basic neural networks will have to be well described and established in typically developing adolescents using methods such as electroencephalography (EEG), event-related potential (ERP), functional magnetic resonance imaging (fMRI), resting-state functional connectivity, and diffusion tensor imaging (DTI). By associating measures of basic cognitive functioning with patterns of neural activation, not only is biological validity for these measures established, but a foundation is laid for studying the cognitive effects of a wide range of psychopathology including MDD. Continued refinement of neurodevelopmental models of interactions between cognition and emotion and adaptations of neuropsychological instruments suitable to be used within neuroimaging protocols will be essential milestones on the road to uncovering the science of the mind and brain affected by adolescent major depression.

Conclusions

The results from this study identified key areas of neurocognitive impairment in depressed adolescents including: (a) compromised sustained attention; (b) less advantageous choices on a gambling task that was indicative of poor affective regulation in depressed males; and (c) that higher levels of depressive symptomatology were related to heightened affective reactivity. On the other hand, several of our measures indicated that adolescents with depression exhibited neuropsychological functioning that is indistinguishable from their non-depressed counterparts. These findings are consistent with the perspective that adolescents with MDD display some impaired cognitive functioning, but is either well compensated for by neural plasticity or less disabled by disease progression and severity as compared to their adult counterparts. Ultimately, this body of research hopes to provide insight into the unique challenges and resiliencies of childhood and adolescence that may benefit young people with depression during their treatment.

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Table 1

Background characteristics of study participants.

	Control Mean (SD)	*n* = 30	MDD Mean (SD)	*n* = 31	Comparison Control vs. MDD
Age	17.46 (1.59)	*n* = 30	17.32 (1.59)	*n* = 31	$t(59) = .33$, $p = .746$
Female Gender, *n* (%)	16 (53.3)	*n* = 30	19 (61.3)	*n* = 31	$\chi^2(1) = .395$, $p = .53$
Ethnicity (Caucasian), *n* (%)	22 (73.3)	*n* = 30	26 (83.9)	*n* = 31	χ^2 (1) = 1.01, *p* =
BDI	3.0 (3.0)	*n* = 19	20.72 (11.97)	*n* = 29	$t(33.15) = -7.62$, $p < .001$
IQ Full-4	115.37 (9.93)	*n* = 30	108.63 (13.95)	*n* = 30	$t(58) = 2.15$, $p<.05$

BDI, Beck Depression Inventory; IQ, intelligence quotient; MDD, Major Depressive Disorder.

Table 2

List of comorbid diagnoses for MDD group.

Current Comorbidity (Secondary Diagnoses)	***n* (%)**
No Comorbidity	3 (9.7%)
Attention Deficit Hyperactivity Disorder	4 (12.9%)
Conduct Disorder (Childhood Onset)	2 (6.5%)
Oppositional Defiant Disorder	4 (12.9%)
Any externalizing disorder	7 (22.6%)
Dysthymia	5 (16.1%)
Generalized Anxiety Disorder	15 (48.4%)
Panic Disorder	2 (6.5%)
Obsessive-Compulsive Disorder	2 (6.5%)
Posttraumatic Stress Disorder	7 (22.6%)
Social Phobia	6 (19.4%)
Any anxiety disorder	23 (74.2%)

Table 3

Summary of medications taken by study participants in depressed group.

Medication Class:	***n* (%)**
Not Medicated	11 (35.5%)
Selective Serotonin Reuptake Inhibitor (SSRI)	14 (45.2%)
Atypical Antidepressant	2 (6.5%)
Tricyclic Antidepressant (TCA)	1 (3.2%)
Mood Stabilizer	2 (6.5%)
Atypical Antipsychotic	1 (3.2%)
Benzodiazepine	1 (3.2%)
Stimulant	2 (6.5%)
Norepinephrine Reuptake Inhibitor (NRI)	1 (3.2%)
Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)	2 (6.5%)

Table 4

Summary of Neurocognitive Testing.

	Control (*n* = 30) Mean (SD)	MDD (*n* = 31) Mean (SD)	Comparison Control vs. MDD
Attention			GLM MANOVA
CPT-Identical Pairs[a]	*n* = 30	*n* = 31	$F(3,57) = 3.52$, $p < .05$
CPT2	3.82 (.40)	3.39 (.71)	$F(1,59) = 8.38$, $p < .01$
CPT3	2.82 (.92)	2.43 (.90)	$F(1,59) = 2.80$, $p = .10$
CPT4	1.68 (.90)	1.20 (.86)	$F(1,59) = 4.55$, $p < .05$
			GLM MANOVA
ANT	*n* = 29	*n* = 31	$F(3,56) = 1.23$, $p = .31$
Alerting (RT)	43.29 (19.28)	42.99 (34.55)	$F(1,,58) = 0.01$, $p = .97$
Orienting (RT)	49.78 (20.16)	55.83 (29.62)	$F(1,58) = 0.84$, $p = .36$
Conflict (RT)	92.60 (22.81)	118.62 (69.65)	$F(1,,58) = 3.68$, $p = .06$
Affective Decision Making			
			GLM ANOVA
IGT	*n* = 30	*n* = 30	$F(1,57) = 3.07$, $p = .09$[b]
Advantageous Choices	Male (*n* = 14): 59.5 (12.98)	Male (*n* = 11): 51.73 (13.37)	
	Female (*n* = 16): 49.94 (8.68)	Female (*n* = 19): 52.26 (10.86)	
Cognitive Control of Emotion Processing			
			GLM Repeated Measures MANOVA
Emotion Go/NoGo	*n* = 25	*n* = 31	$F(2,104) = 0.43$, $p = .65$
Fear (RT)	485.94 (67.82)	523.07 (82.79)	
Happy (RT)	461.08 (65.96)	493.51 (74.30)	
Calm (RT)	483.02 (87.29)	510.03 (73.67)	
			GLM Repeated Measures MANOVA
Face Go/NoGo			
Go Trials	*n* = 25	*n* = 31	$F(3,162) = 0.13$, $p = .94$
Angry/Neutral (RT)	336.51 (43.46)	343.81 (58.76)	
Fear/Neutral (RT)	328.55 (46.81)	347.90 (54.03)	
Sad/Neutral (RT)	362.36 (52.59)	378.34 (48.45)	
Happy/Neutral (RT)	303.71 (40.68)	322.07 (55.0)	
NoGo Trials	*n* = 25	*n* = 31	$F(3,50) = 1.36$, $p = .27$
Neutral/Angry (RT)	345.32 (50.67)	383.66 (67.19)	
Neutral/Fear (RT)	339.22 (55.28)	346.05 (57.14)	
Neutral/Sad (RT)	368.61 (61.91)	383.75 (75.64)	
Neutral/Happy (RT)	324.58 (90.03)	347.52 (55.07)	

Mean unadjusted scores of adolescents with Major Depressive Disorder and psychiatric-diagnosis free adolescents.

ANT, Attention Network Test; CPT, Continuous Performance Test; IGT, Iowa Gambling Task; MDD, Major Depressive Disorder; RT, reaction time.

[a]CPT 2, 3, and 4 reflect increasing demands on digit span for recognition of identical number pairs.

[b] Significant at $p < .05$ after adjustment for IQ Full-4 scores.