The Effects of Chronic Stress on Executive Function, Coping, and Prefrontal Function in Children of Depressed Parents

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INTRODUCTION

Previous research has suggested that chronic stress impacts the prefrontal cortex and its associated functions, including executive functioning and the ability to regulate emotions and cope with stress. These processes have particular relevance for a high-risk population characterized by exposure to chronic stress: children of depressed parents. The literature examining these processes is currently somewhat limited and has appeared in diffuse areas of research. A goal of the current studies is to integrate this research by examining the effects of chronic stress on the executive functioning, coping, processing speed, and symptoms of psychopathology in an at-risk group of children (children of mothers with current or past depression) as well as a comparison sample of children of parents without a history of depression.

This paper includes an overview of the relevant literatures to understanding how stress impairs an individual's ability to cope effectively with stress and why these processes are especially pertinent to children of depressed parents. This introduction includes a review of literature on children of depressed parents and their risk for psychopathology, the effects of chronic stress on coping and emotion regulation, the role of the prefrontal cortex in executive function and coping, and the effects of chronic stress on the prefrontal cortex and its functioning. This paper also presents two studies examining these processes in a sample of children of depressed and non-depressed parents. In the first study, executive functioning, processing speed, coping, and affective, anxiety, and oppositional defiant symptoms were examined in children and adolescents of mothers with a history of depression within the lifetime of the child and children and adolescents of mothers without a history of depression within the child's lifetime. In the second study, brain activation in the region responsible for executive function and coping, the

prefrontal cortex, in response to an executive functioning task was examined in a sub-sample of adolescents from Study I. Together, these studies provide novel information on the effects of chronic stress on executive functioning, processing speed, coping, the prefrontal cortex, and symptoms of psychopathology in an at-risk group, children of depressed parents.

What is "Stress"?

Stress is a common characteristic of modern life, including adverse events and experiences in interpersonal, financial, or work-related domains, and the day-to-day hassles of living in a fast-paced environment. Contemporary stressors faced by humans in industrialized nations, in contrast to earlier points in human history or other species, are more chronic and psychological or social in nature rather than the acute, direct threats to survival experienced by earlier societies or other species (Sapolsky, 2004). Chronic stress puts individuals at increased risk for adverse physical and mental health problems, including heart disease, chronic fatigue, reproductive problems, and psychopathology (Miller, Chen, & Zhou, 2007). But why are some individuals vulnerable to the effects of stress while others are resilient?

Individual differences in vulnerability and resilience may be due in part to the effects of chronic stress. Specifically, chronic stress affects individuals through two processes: first by directly contributing to higher rates of symptoms of psychopathology as well as physical illness and disease and second, by impeding adaptive coping with stress (Compas, 2006). The same processes that have historically provided for adaptive responses to stressors [e.g., activation of the sympathetic-adrenal-medullary (SAM) system to allow for a fight or flight response; activation of the hypothalamic-pituitary-adrenal (HPA) system to regulate physiological processes] can become problematic when they are chronically activated. While these stress response systems are adaptive for short term, acute stressors (e.g., fleeing a predator), chronic

activation of these systems leads to allostatic load, defined as "the wear and tear that results from chronic overactivity or underactivity of allostatic systems" (McEwen, 1998, p. 171). Areas of the brain responsible for coping and emotion regulation, including the prefrontal cortex, are among the most vulnerable to the deleterious effects of allostatic load (e.g., Admon et al., 2009; Cerqueira et al., 2005; McEwen, 2003; Taylor et al., 2006). While previous research has provided evidence for the direct and indirect effects of stress on mental and physical health in both animals and humans, research addressing the biological, cognitive, and psychological mechanisms by which chronic stress impedes adaptive coping has been reported in related but relatively disconnected literatures.

Children of Depressed Parents: A Prototype of Exposure to Chronic Stress

One population characterized by exposure to chronic stress is children of depressed parents. Empirical evidence shows that having a depressed parent can put children and adolescents at an increased risk for internalizing and externalizing symptoms of psychopathology (England & Sim, 2009). An integrative, developmental model of transmission of risk presented by Goodman and Gotlib (1999) includes (a) the heritability of depression; (b) innate dysfunctional neuroregulatory mechanisms; (c) exposure to negative maternal cognitions, behaviors, and affect; and (d) the stressful context of the children's lives. Depression in a parent creates chronic stress for children and adolescents through exposure to parental negative cognitions, impaired parent-child communication, stressful parent-child interactions, and elevated levels of stressors associated with depression in their environment.

Parental depression may lead to psychopathology in children through three interrelated processes, including modeling of the parents' negative cognitions, dysfunctional child-parent relationships, and exposure to stressful family environments (Garber & Martin, 2002). Through

social learning, children and adolescents also may acquire these negative cognitions, behaviors, and affects. For example, infants of depressed mothers appear to "match" their mother's negative state (Field et al., 1990; Field, Healy, & LeBlanc, 1989).

Family communication and parent-child interactions are affected by a parent's depression (e.g., Brennan, Brocque, & Hammen, 2003; Jacob & Johnson, 1997; Lovejoy et al., 2000). These processes may be especially important for children in that parenting and family dynamics are fundamental to healthy psychological development in children and adolescents. For example, positive parent-child relationships contribute to positive development for children in at-risk families (Rutter, 1990) and are a cornerstone of good parenting (Gest et al, 1993; Glantz, 1992). For example, Brennan et al. (2003) examined the parent-child relationship as a resource and as a protective factor for resilient outcomes in families of parental depression. They found resilient outcomes in youth as a function of the interaction of maternal depression and low levels of parental psychological control, high levels of maternal warmth, and low levels of maternal over-involvement (Brennan et al., 2003).

Other pathways by which parental depression may affect children and adolescents are stressful parent-child and family interactions (Brennan et al., 2003; Howard & Medway, 2004; Jacob & Johnson, 1997; Sheeber et al., 1998) and negative parenting behaviors. For example, families of depressed mothers are characterized by less positivity and congeniality than normal, control families when interacting with each other (Jacob & Johnson, 1997). Parenting behaviors are a mediating factor between children and adolescent emotional and behavioral problems and their parent's depression (Jaser et al., 2005, 2007, 2008).

Parents with depression are more likely to exhibit both withdrawn and intrusive behaviors than parents who have not experienced depression (Jaser et al., 2008). Withdrawn behaviors

include avoiding interaction with the child, ignoring the child's needs, and social and emotional withdrawal, whereas intrusiveness includes irritability and over-involvement in the child's life. The vacillation between these types of behavior in an unpredictable pattern is hypothesized to exacerbate the effects of either of these behaviors alone (Jaser et al., 2005; Langrock et al., 2002). These behaviors contribute to the child's stressful family environment (Adrian & Hammen, 1993; Lovejoy et al., 2000). Seifer et al. (2001) demonstrated that parents exhibit these negative parenting behaviors even outside of a depressive episode, suggesting chronicity of children's exposure to these stressors. Finally, children are not only exposed to the parental depression, but also to the stressors that are associated with depression, such as marital conflict (Goodman & Gotlib, 1999). Offspring of depressed parents are exposed to elevated levels of stressful events and situations, as well as elevated interpersonal conflict (Adrian & Hammen, 1993). Furthermore, children of depressed parents are more vulnerable to developing depressive symptoms in response to general stressful life events that occur outside of the family (Bouma et al., 2008).

In summary, having a parent with depression puts children and adolescents at risk for psychopathology through both biological (inheriting an increased vulnerability to depression) and environmental (e.g., living in a chronically stressful environment associated with a parent's depression) risks. The underlying mechanisms of these environmental risks have only begun to be understood but likely include the effects of stress on coping, executive function, and the brain region responsible for these processes, the prefrontal cortex.

Effects of Stress on Coping

One possible mechanism by which the chronic stress associated with a parent's depression may affect children is through the impairment of children's ability to cope with stress.

Individuals respond to stress with complex cognitive, behavioral, emotional, and biological processes with the goal of adaptation (e.g., Compas, 2006; Compas et al., 2001; McEwen, 1998). These responses can be categorized into two fundamental processes: automatic responses and controlled coping responses. Automatic responses are hypothesized to be driven by amygdala activation and the perception of threat and include intrusive thoughts, impulsive action, emotional arousal, escape behaviors, and physiological arousal (e.g., Pine, 2007). In contrast, coping refers to "conscious volitional efforts to regulate emotion, cognition, behavior, physiology, and/or the environment in response to stressful events or circumstances" (Compas et al., 2001, pg. 89). Coping skills change with development and the skills available to an individual are constrained by their biological, cognitive, social, and emotional development.

Coping behaviors can be further categorized into primary control engagement coping, secondary control engagement coping, and disengagement (Connor-Smith et al., 2000). Primary control coping refers to acting directly on the stressor or one's emotional response to a stressor and includes behaviors such as problem-solving, emotional expression, and emotion modulation. Secondary control coping refers to efforts to adapt to the stressful situation or to one's emotional response to the stressor. Secondary control coping behaviors include acceptance, distraction, cognitive reappraisal, and positive (but realistic) thinking. Disengagement coping refers to efforts to withdraw from the stressor and one from one's emotional responses to the stressor, and includes behaviors such as avoidance, denial, and wishful (i.e., unrealistic) thinking (Compas et al., 2001; Connor-Smith et al., 2000; Wadsworth et al., 2004). Primary and secondary control coping have been demonstrated to be associated with better psychological adjustment across a variety of samples, including children of depressed parents (e.g., Jaser et al., 2005, 2006), children with cancer (e.g., Campbell et al., 2009), Native American youth (Wadsworth et al.,

2004), children with chronic pain (e.g., Compas et al., 2006), and children faced with family economic hardship (e.g., Reising et al., 2011; Wadsworth & Compas, 2002).

Across various populations of children and adolescents exposed to stress, their responses to such stressors have been demonstrated to be important for understanding the development of psychopathology (Compas et al., 2001). Not only do parent-child stressors create additional stress for children and adolescents, but these situations can actually impede effective coping (e.g., Jaser et al., 2005; Langrock et al., 2002; Wadsworth & Compas, 2002). In various populations, studies have demonstrated that as stress increases, children and adolescents employ less primary control coping (e.g., problem-solving), less secondary control coping (e.g., cognitive reappraisal), and more disengagement coping, which can lead to an increase in symptoms of psychopathology. Exposure to chronic stress undermines coping effectiveness, which in turn leaves children more vulnerable to the effects of stress (e.g., Wadsworth & Compas, 2002). For example, studies examining parental depression related stress exposure, coping, stress reactivity, and symptoms of psychopathology in children of adolescents of depressed parents and found that higher rates of parental depression related stressors (i.e., parental withdrawn behaviors, parental intrusive behaviors, and marital conflict) were related to less use of primary and secondary control coping and greater disengagement and stress reactivity. Langrock et al. (2002) examined these processes in children and adolescents (ages 7-17), as reported by their parents, and found primary and secondary control coping was inversely related to parental withdrawn behaviors and parental intrusiveness. A similar study examining these processes in offspring of depressed parents found a similar pattern using adolescents' self-reports, as parental withdrawal was related to less primary control coping and less secondary control (Jaser et al., 2005). Further, some of these findings held up when examined across

informants. For example, parental intrusiveness as reported by the adolescents was related to children's use of less primary and secondary coping as reported by the parents.

Similarly, a study of adolescents experiencing various levels of economic strain demonstrated that children who reported higher stress levels related to economic strain and family conflict also used less primary and secondary control coping and had greater stress reactivity (Wadsworth & Compas, 2002). For example, both primary and secondary control coping were inversely related to economic strain and family conflict. Thus, chronic stress creates a dual process of stress, by which (1) chronic stress directly contributes to higher rates of symptoms of psychopathology and (2) chronic stress impedes adaptive coping with stress. However, the biological, cognitive, and psychological effects of stress on the ability to cope are not well understood.

Role of the Prefrontal Cortex in Executive Function and Coping

Prefrontal Functions

The prefrontal cortex is important for top-down processing and higher order cognition processes in humans and has been indicated in studies of executive function and coping. While other areas of the brain are responsible for bottom-up processing involved in simple, automatic behaviors, the prefrontal cortex is implicated in higher order processes that are often necessary for the regulation of more automatic processes.

Several characteristics of the PFC are outlined in a model by Miller and Cohen (2001). These characteristics include: (1) the maintenance of activity despite distraction until a behavioral goal is attained (e.g., Fuster, 1973, 1995; Fuster & Alexander, 1971; Goldman-Rakic 1987; Miller, Erickson, & Desimone, 1996), (2) flexibility for integration of novel information into representations of goals, stimuli, and activities (e.g., Fuster 1985, 1995), (3) involvement in

attentional processes and control of behavior (e.g., Ferrier 1976), (4) high capacity for multimodality and integration (e.g., Grafman, 1994; Shallice, 1982; Wise, Murray, & Gerfen, 1996), (5) plasticity (e.g., Asaad, Rainer, & Miller, 1998; Bichot, Schall, & Thompson, 1996; Schultz & Dickinson, 2000), and the (6) ability to self-organize (e.g., Egelman, Person, & Montague, 1998). The PFC's flexibility, accommodation, organization, and control facilitate the higher order functions in the PFC (Miller & Cohen, 2001).

The Role of the PFC in Executive Functions

Executive functions refer to a set of higher order cognitive processes that are responsible for controlling and regulating behaviors and emotions through functions such as planning, cognitive flexibility, abstract thinking, rule acquisition, selective attention, initiation, and inhibition (Miller & Cohen, 2001). Processing speed is a cognitive function underlying such cognitive complex processes that increases through development and has been demonstrated to be related to increases in executive functions (e.g., Kail, 2007).

Two salient examples of executive functions are working memory and attentional control. Working memory refers to the ability to actively maintain and manipulate information and is fundamental to tasks such as imagining how an object might look from different perspectives, solving a math problem mentally, or strategizing in games involving planning such as checkers (e.g., Baddeley, 1992; Wager & Smith, 2003). Neuroimaging studies have focused on one aspect of executive functions, working memory, which involves activation of regions of the prefrontal cortex. Wager and Smith (2003) conducted a meta-analysis of 60 neuroimaging studies utilizing both PET and fMRI examining working memory in healthy adults. Results of this meta-analysis provide evidence for left lateralization of verbal memory (e.g., memory pertaining to words, letters, numbers, or anything encoded or rehearsed linguistically) and object memory (e.g.,

nonspatial information, object identity, form) while spatial memory, or memory of spatial positioning of stimuli or objects of interest, demonstrated right lateralization in the prefrontal cortex (e.g., Reuter-Lorenz et al., 2000; Smith & Jonides, 1999). When executive demand was involved (such as the manipulation of an object or any of its properties), these studies provided evidence for lateralization in the frontal cortex. More specifically, Wager and Smith (2003) found that Brodmann Areas (BAs) 10 & 47 (ventral frontal cortex) respond more to tasks requiring manipulation, BA 32 responds more to tasks requiring selective attention, and BA 7 (in the posterior parietal cortex) showed involvement in all types of executive functions.

Owen, McMillan, Laird, and Bullmore (2005) synthesized the findings of 24 functional neuroimaging studies using the N-back working memory paradigm, one of the most often employed paradigms for the assessment of working memory in an imaging context. Evidence of robust activation was found in the lateral premotor cortex, dorsal cingulate cortex, medial premotor cortex, dorsolateral and ventrolateral prefrontal cortices, frontal poles, and medial and lateral posterior parietal cortices (Owen et al., 2005). Studies examining activation during the N-back within samples of children and adolescents has similarly identified prefrontal-parietal networks (Nelson et al., 2000; Thomas et al., 1999). The attentional filtering and control functions of the prefrontal cortex are hypothesized to underlie individual differences in several executive functions including working memory as well as emotion regulation (Braver, Cole, & Yarkoni, 2010). This hypothesis has been supported by several ERP and fMRI studies in humans (e.g., Edin, Klingberg, Johansson, McNab & Klingberg, 2009; Vogel, McCollough, & Machizawa, 2005).

The executive control of attention is another example of executive function that is regulated by the PFC. For example, Rossi, Pessoa, Desimone, and Ungerleider (2009) examined

attentional processes in both animals and humans. First, they examined top-down attentional control in two macaques with lesion unilaterally to the right PFC (specifically BAs 8, 9, 46, 45, and 12). These animals demonstrated impairment on a target-distracter repetition task that required top-down attentional control. Second, Rossi et al. (2009) examined these abilities in 20 healthy human participants in a similar task with alternative attentional demands based on color cues while completing fMRI scans. Conditions requiring top-down attentional control demonstrated activation in the left medial frontal gyrus as well as left inferior frontal gyrus (Rossi et al., 2009).

Other human imaging studies have demonstrated the functions of the PFC, and specifically the dorsolateral PFC (DLPFC) through deficits in executive functions in populations with direct injury to these areas, such as traumatic brain injury patients and patients with prefrontal lesions (e.g., Anderson, Jacobs, & Harvey, 2005; Anderson, Anderson, & Anderson, 2006; Perlstein et al., 2004). The DLPFC has also been implicated as a region responsible for executive function in fMRI tasks requiring executive functions such as attention and working memory across a variety of populations including patients with ADHD, multiple sclerosis, human immunodeficiency virus, as well as healthy controls (Anderson, Anderson, & Anderson, 2006).

Further evidence for the role of the PFC comes from studies of cognition and brain development. For example, in a developmental study of executive function, Crone et al. (2006) found that the youngest cohort (ages 8-12 years old) both performed worse on working memory manipulation tasks but showed little to no recruitment of the DLPFC and other cortical regions associated with working memory as compared to adolescents (ages 13 –17) and adults (ages 18 – 25).

Other studies have suggested that injury to the prefrontal regions associated with executive function results in compensatory activation. That is, an individual will recruit more activation to these regions to obtain the same performance as an individual without such injury. For example, patients with MS both recruit more activity within the PFC regions directly associated with working memory but adjacent, nontraditional neural circuitry for these processes as well (Sweet et al., 2006; Wishart et al., 2004).

The Role of the PFC in Coping and Emotion Regulation

Adverse effects of stress on the PFC and on executive functions have implications for impairment in the ability to regulate emotions and cope with stress. Adaptive coping skills rely on fundamental executive function abilities such as working memory and attentional control. One such example is cognitive reappraisal, a cognitive coping strategy that involves thinking about a stressor and changing one's cognitions about that stressor to make it less aversive. For example, the thought, "My mom is depressed today; it's all my fault," could be reappraised to become, "Mom is depressed today, but I know it's not my fault; it's something she struggles with and it will get better." Cognitive reappraisal relies on working memory, as reappraising a problem situation involves thinking about the problem and acting on or changing one's perspective (e.g., Campbell et al., 2009; Compas, 2006; Compas et al., 2009; Ochsner & Gross, 2005). Thus, an individual with impaired executive function may be less able to use such adaptive approaches to stress. Executive functions provide an important foundation for the regulation of emotions and coping with stress (Ochsner et al., 2002; Compas, 2006). For example, cognitive reappraisal relies on working memory and attentional control (Campbell et al., 2009). Thus, an individual with impaired executive functions will be less able to use such adaptive approaches to stress. Campbell et al. (2009) demonstrated that less adaptive coping

(less use of primary and secondary control, more use of disengagement) was related to problems in executive functions and accounted for the relation between executive functions and emotional and behavioral problems in a sample of child and adolescent cancer patients.

Studies have also demonstrated the parallels between reports of coping and demonstrated executive functioning skills, such as inhibitory control and working memory. For example, both primary and secondary control are associated with neuropsychological measures of inhibitory control while the use of disengagement coping is associated with poorer performance on inhibitory control tasks (Copeland & Compas, 2012). Similarly, Campbell et al. (2009) demonstrated that less adaptive coping (less use of primary and secondary control, more use of disengagement) is associated with poorer performance on neuropsychological measures of executive function, especially working memory, and deficits in executive function and coping were both associated with greater emotional and behavioral problems in childhood cancer survivors.

Neuroimaging studies have further indicated the role of the PFC in coping and emotion regulation. For example, Ochsner and Gross (2005) provided evidence for the role of PFC across a variety of emotion regulation or coping strategies including cognitive control strategies and cognitively changing the meaning of emotionally evocative stimuli. The role of the PFC in emotion regulation was also indicated in studies of controlled generation and controlled regulation of responses to emotionally salient stimuli (e.g., Knutson et al., 2001; Ochsner et al., 2002; Ochsner et al., 2004; Phan et al., 2005; Porro et al., 2002). Focusing on one's beliefs about a stressful stimulus rather than just the direct perception of a negative stimulus was associated with activation of the anterior cingulate cortex (ACC) and medial PFC as involved in top-down processes of controlled emotion generation (Ochsner & Gross, 2005). In contrast,

controlled regulation or "reappraisal," defined as "reinterpreting the meaning of a stimulus to change one's emotional response to it" (Gross, 1998), was associated with activation of the dorsal ACC and PFC systems. Goldin et al. (2008) utilized negative film images while participants were instructed to use reappraisal (think about the stimuli in a different, less stressful way). Participants in this study exhibited less negative emotional experience, and less activity in regions associated with emotional experience as a function of increased activation of the PFC, as compared to participants instructed to use suppression (try not to think about the stimuli) in response to the negative film images (Goldin et al., 2008).

A similar study used neutral and negative pictures and either asked the participants to simply look at the pictures and to view the image, understand its content, and allow themselves to feel/experience any emotional response it might elicit or to reappraise the emotional value of those images so that the emotional impact was less negative (Wager et al. 2008). Right VLPFC activity was correlated with reduced negative emotional experience during cognitive reappraisal of aversive images task. Further, pathway-mapping analysis on subcortical regions to find mediators of VLPFC and reappraisal success (measured by reduced reported emotional response to the stimuli) identified two separable pathways that together explained approximately half of the variance in self-reported emotion in response to aversive images in cognitive reappraisal task. While the path through the nucleus accumbens was related to greater reappraisal success, the path through the ventral amygdala was associated with reduced reappraisal success. These findings suggest that the VLPFC is involved in both generation and regulation of emotion through different subcortical pathways and plays a general role in the reappraisal process (Wager et al., 2008).

Effects of Stress on the Prefrontal Cortex and Executive Function

Although stress affects multiple areas of the brain, the prefrontal cortex is one of the brain regions most vulnerable to the effects of stress. The effects of chronic stress on the prefrontal cortex have been most extensively studied through animal models. These studies have methodological advantages over human studies and provide valuable information about the effects of stress on the prefrontal cortex that cannot be gained from human studies. Studies utilizing animals have demonstrated the adverse effects of allostatic load on the prefrontal cortex and other brain regions responsible for higher-order cognitive processes and executive functions. Allostatic load has been shown to result in volumetric, structural, and functional changes in the prefrontal cortex. For example, Dias-Ferreira et al. (2009) found overall volume reduction in the MPFC of rats exposed to chronic stress. Structural changes resulting from stress exposure include dendritic density reduction (e.g., Perez-Cruz et al., 2007; Radley et al., 2006), dendritic length reduction (e.g., Cerquiera et al., 2005), and retraction of dendritic arbors (e.g., Liston et al., 2006). Functional changes in the prefrontal cortex include disruption of cellular processes such as the suppression of neurogenesis and cytogenesis (e.g., Czèh et al., 2007) as well as impaired executive function when animals were tested on animal-appropriate executive function tasks such as a perceptual set-shifting task involving the animal's ability to find hidden food cued by changing signals (e.g., Liston et al., 2006).

Prefrontal functions, such as executive functioning, have also been demonstrated to be adversely affected by chronic stress exposure. For example, animal studies have shown that rats exposed to chronic stress demonstrate impairments in attentional set-shifting (Liston et al, 2006), working memory (Cerqueira et al., 2007b), and behavioral flexibility (Cerqueira et al., 2007a). In one such study, Fox, Barense, and Baxter (2003) examined whether stress-induced dendritic changes in the orbitofrontal cortex (OFC) and the medial prefrontal cortex (mPFC) would predict

deficits in functions dependent on these brain regions. Rats completed a perceptual attentional set-shifting task which tested their ability to correctly find buried food based on changing odors, digging media, and predictors of food presence. In rats exposed to 21 days of restraint stress, dendritic arborization reduction in the mPFC predicted attentional set-shifting performance deficits as compared with non-stressed control rats. Interestingly, this study found that reversal learning was not adversely affected by stress and in fact, an *increase* in apical dendritic arborization was observed in the OFC following stress exposure (Fox, Barense, & Baxter, 2003).

Cerqueira et al. (2007b) examined both working memory and behavioral flexibility in relation to synaptic plasticity in the hippocampus-PFC connection. This study utilized a spatial reference memory task that required rats to learn the position of a hidden platform across four different trials (different starting points in a water maze each day). After four days, the rats were tested for three days to ensure they had learned the location of the platform before the reversal-learning test on day eight. The reversal-learning task involved the platform being placed on the opposite quadrant of the maze. Using electrophysiological and morphological assessment, this study found that chronic stress reduced LTP induction in the hippocampus-PFC connection, induced selective PFC atrophy, and disrupted both working memory and behavioral flexibility (Cerqueira et al., 2007b).

Building on animal studies, human imaging studies have found similar interesting findings for the effects of stress on the prefrontal cortex and its functions. The majority of these studies have examined acute stressors within the laboratory. Overall, consistent patterns have been found for the effects of acute stressors on PFC activation and an inverse association between cortisol (a marker of activation of the HPA axis) and prefrontal activation (e.g., Pruessner et al., 2008; Root et al., 2009). For example, Qin et al. (2009) exposed two groups of

participants to four short movie clips while they completed fMRI. The stress induction group viewed four movie clips with aversive content (e.g., male to male and male to female violence) while participants in the control group viewed four movie clips from another movie similar in language and equalized in luminance but containing only non-emotionally arousing scenes. In both conditions, participants were asked to watch attentively and imagine themselves in the scenes as an eyewitness. Between the second and third movie clips, participants completed the N-Back Task, a measure of working memory. Participants also provided emotion ratings at baseline and three time points during the scan and salivary cortisol samples were obtained (two at baseline, before the N-Back, after the last movie clip, and 20 minutes following the scan). Heart rate frequency (HR) and variability (HRV) were also measured throughout the scan. An interaction effect of group and time was found for cortisol levels, such that cortisol levels were higher in the stressed group at the time points preceding the N-back and surrounding the stressful images. Significant group differences were also found for HR and HRV, with increased HR and decreased HRV in the stress group. Qin et al. (2009) did not find a group effect on changes in working memory performance as the task increased in difficulty.

In analyses of working memory along with biological indicators of stress, however, the authors found that cortisol levels immediately before the N-back task and HR during the task were significantly positively correlated with processing speed (as measured by reaction time change), suggesting that individuals with greater stress responses were slower in responding as the task increased in difficulty. Thus, it appears that while stress did not impair performance universally, participants demonstrating the greatest response to the stressful images (as indicated by cortisol and HR) were significantly slower in their performance (Qin et al., 2009).

Porcelli et al. (2008) examined the role of stress induced by a physically painful stimulus on executive functioning in two studies. Both experiments utilized the cold-pressor task methodology, which involves hand immersion in cold-water chilled to 4°C; hand immersion in room-temperature water and no-hand immersion served as comparison conditions. A working memory task was also completed while participants' hands were intermittently immersed in water (Porcelli et al., 2008). The WM task consisted of sequentially presentation of letters (1 at a time in the low WM demand condition; up to 6 in the high WM demand condition), followed by questions about whether letters had been presented or not. This study yielded non-significant findings for associations between factors of stress, working memory demand, and processing speed (Porcelli et al., 2008). A trend for an interaction between stress and WM load was found in predicting accuracy on the WM task, however. Gender effects were observed in regards to the physiological data in that men had higher cortisol levels than women and no interaction effects were found with stress or stress and gender. This study demonstrates that while stress induction affected stress responses more significantly in males (who had greater cortisol responses), these differences did not translate to significant differences in reaction time and only demonstrated a trend for differences in accuracy.

Other imaging studies have examined both acute and chronic stressors by examining prefrontal response to acute laboratory stressors in chronically stressed populations (Admon et al., 2009; Taylor et al., 2006). One such study utilized an adult population who had been exposed to chronically stressful familial environments as children, referred to as "high risk" families (Taylor et al., 2006). Taylor et al. (2006) investigated neural response to emotional stimuli in adults who grew up in "risky" families, defined as families marked by harsh, conflict-ridden, or chaotic parenting and chronic or recurrent familial stress, as determined by responses

to the risky families questionnaire (Felitti et al., 1998). On the risky families questionnaire, participants rate various aspects of their childhood family environment on items including whether an individual felt loved or cared for, was comforted, insulted, put down, sworn at, or made to feel threatened, and whether the individual was abused verbally or physically. This questionnaire has been validated against coded clinical interviews in previous research (Taylor et al., 2004). Though this questionnaire is not without problems (i.e., a retrospective measure of stress exposure over a substantial course of time), it demonstrates an approach to examining populations characterized not only by stress, but chronic stress, which is implicated in the processes of allostatic load. Thirty healthy (non-psychiatric) participants were recruited for this study and scores on the risky families questionnaire were treated as a continuous variable of chronic stress exposure.

Participants also completed neuroimaging tasks involving exposure to negative faces, which are designed to activate the amygdala (Taylor et al., 2006). Participants completed three types of tasks: (1) observe only, which required the participants to simply attend to the faces; (2) emotion-labeling, which required the participants to choose the emotion being expressed by the face (e.g., anger, fear); and (3) gender-labeling, a comparison condition with similar processing demands without an emotional processing aspect. No physiological indicators (outside the functional imaging outcome variables) or subjective ratings of the stressfulness of the task were included in this methodology, making it difficult to know if the presentation of negative faces successfully induced stress in this study.

Results of the Taylor et al. (2006) study indicated that there were no significant behavioral group differences for reaction time or accuracy between the participants in the low and high-risk family groups. Functionally, the groups demonstrated differences in brain

activation for both the observe-only and labeling conditions. Differences in prefrontal activity, however, were only observed in the labeling condition and only in connectivity analyses with the amygdala. While the amygdala was less activated in the observe-only condition for the group scoring higher on the risky family assessment, no such differences were observed in the labeling condition.

In analyses of connectivity, however, Taylor et al. (2006) found that individuals scoring lower on the risky family assessment demonstrated greater right VLPFC activity was significantly correlated with reduced amygdala activity while individuals scoring higher on family risk demonstrated an opposite pattern. Individuals from higher risk family backgrounds demonstrated higher activations of the right VLPFC was significantly correlated with greater amygdala activation. These findings suggest that exposure to chronic stress, such as that resulting from a high risk family environment in childhood, is associated with impairment in the ability of the PFC (specifically the right VLPFC) to downregulate emotional regions of the brain, such as the amygdala.

Admon et al. (2009) examined responses to stressful stimuli in chronically stressed populations utilized a unique population of 50 healthy new recruits to the Israeli Defense Forces. This study examined the emotional experience and neural responses of these recruits before entering their mandatory military service as well as after their subsequent exposure to stressful events during deployment. Participants had been exposed or experienced one or more stressful experiences that were accompanied by negative emotions (i.e., a potentially traumatic event) between the two time points. Though the authors discuss the population of recruits as having experienced at least one acute, traumatic stressor, the nature of military service also makes this population interesting from a chronic stress perspective as well. The authors also discuss their

rationale for predefined limbic regions of interest as indicated by this population's exposure to "an augmented load of life stress" more generally during this time. Imaging tasks involved the presentation of photographs of either military medical or civilian content but did not require any processing or evaluation of the images. Twelve young healthy civilians also completed these imaging tasks (Admon et al., 2009). Functional analyses between the baseline and post-stress time points revealed an increase in activation in several brain regions, including the VMPFC. Again, these changes were not observed in the control group. Interestingly, while the increased activation in some regions (e.g., amygdala, hippocampus) was derived from the response to pictures of medical content, the increased activation in the VMPFC was not content specific, no specific interaction.

Functional connectivity analyses revealed that while the amygdala was positively coupled with the MPFC at baseline, the hippocampus did not demonstrate functional coupling with the MPFC until the post-stress time point (Admon et al., 2009). Furthermore, increased stress symptoms over time were related to a weaker functional coupling change between the hippocampus and VMPFC, while changes in stress symptoms did not affect functional coupling between the MPFC and the amygdala. Higher activation in the amygdala at baseline also predicted weaker coupling between the hippocampus and the VMPFC as well. Findings from this study suggest that while MPFC activation did not change over time or in response to changes in stress symptoms, the activation of the PFC in response to a lab stressor might be affected by chronic stress through differences in baseline emotional reactivity to a stressful task and/or changes in functional coupling as a result of stressful experiences, specifically between the VMPFC and the hippocampus.

Perhaps the strongest evidence for the effects of chronic stress on the prefrontal cortex and executive functioning are imaging studies examining the effects of chronic stress on executive functioning performance and the associated prefrontal functioning. For example, Kishiyama et al. (2008) examined the effects of chronic stress associated with low socioeconomic status on measures of attention and other executive functions in children. Participants included both an at-risk sample of children (n = 13) in low socioeconomic status families, and a sample of children (n = 13) at lower risk as a consequence of being from high socioeconomic status families. The authors note that children from low SES backgrounds (in comparison with children from higher SES backgrounds) are at greater risk for physical and mental health problems both in childhood and into adulthood, citing greater levels of stress as one of the greatest contributors to these differences. Performance across several neuropsychological measures of prefrontal function differed between the high SES and low SES group, with the high SES outperforming the low SES group, consistent with previous research (Kishiyama et al., 2008). The high SES group performed one standard deviation above the mean and significantly better than the low SES group on digit span (Wechsler, 1994), a measure of working memory. The high SES group also scored significantly better on Part B of the Trail Making Test (TMT; Lezak, 1995), a measure of cognitive flexibility, as well as on an index of processing speed, calculated by differences between part A and part B scores on the TMT. The groups also differed on verbal fluency tests (Baron, 2004), with the high SES group outperforming the low SES group. The groups did not differ in their performance on the Stroop Color Word Test (Golden, 1978), however. These results suggest that exposure to stress associated with low SES is related to poorer performance on executive function tasks, as early as childhood.

Kishiyama et al. (2008) also utilized electroencephalography (EEG) to examine the effects of chronic stress associated with low socioeconomic status on prefrontal-dependent electrophysiological measures of attention in children. Children were instructed to press a button in response to low-probability targets embedded in streams of task-irrelevant stimuli as a measure of attentional control (Kishiyama et al., 2008). Stimuli included high-probability standard stimuli, low-probability targets, and novel stimuli. Standard and target stimuli were black triangles against white background, with target triangles tilted more clockwise than the standard, upright triangles. Novel stimuli consisted of pleasant (as opposed to neutral or unpleasant, as used in previously mentioned studies) affective IAPS pictures, such as happy characters at Disneyland. These images were chosen for their high valence ratings of pleasantness and moderate ratings of arousal. Participants completed this task while EEG signals were continuously recorded through electrodes arranged according to the 10-20 system and average ERPs were computed from 100 milliseconds prior to stimulus onset to 1000 milliseconds post-stimulus presentation. Results from the EEG phase of the Kishiyama et al. (2008) study indicated that while the groups did not differ on performance in the target detection tasks in either response time or accuracy, they did differ in prefrontal function. Group comparisons revealed greater P1 and standard N1 ERP component amplitudes during presentation of the standard stimuli in the HSES group as well as higher novelty N2 amplitudes during presentation of the novel stimuli. That is, comparisons of the at risk low SES group and the lower risk high SES group of children on a task of attention demonstrated similar performance but less activation in the PFC and temporal-parietal cortex in the low SES group. The authors noted similar patterns of decreased activation as measured by P1 and N1 ERP responses have been observed in patients with PFC lesions (Barcelo et al., 2000; Knight, 1997;

Yago et al., 2004). The authors discussed several factors that may be associated with low SES and social inequality that could contribute to this PFC damage including lack of access to cognitively stimulating materials and higher levels of stress (Kishiyama et al., 2008).

Liston, McEwen, and Casey (2009) examined the effects of chronic stress on prefrontal function by recruiting participants currently experiencing chronic stress and administering tasks requiring attentional control while stress was ongoing in their lives and again after the stressor had passed. Specifically, 20 healthy young adult medical students were tested after 4 weeks of preparing for a major academic examination as well as twenty healthy adult controls who were not exposed to the psychological stressor (the exam). The experimental and control groups were matched for age, gender, occupation, and sleep habits. Participants in the Liston et al. (2009) completed the perceived stress scale (PSS), a 10-item well-validated questionnaire measuring chronic stress on a scale of 1-40 (Cohen, Kamarck, & Mermelstein, 1983) and completed an attentional-shift paradigm while completing fMRI. The attentional-shift task involved the viewing of two moving, circular square-wave objects and participants were instructed to respond based on the color ("C") or the motion ("M") of the objects. While the participants had several trials in a row of the same cue (i.e., either "C" or "M"), the task would switch dimensions, creating "shift" trials. The task also included "reversals" during which the participant was required to respond with an opposite response than the stimulus to which they were responding (e.g., if the "M" of the object was moving up, the participant would have to respond by pressing an "up" key). These "reversals" required the subject to override previously learned responses.

Results demonstrated that chronic stress selectively impaired attentional shifting, but also that these effects were reversible (Liston et al., 2009). More specifically, behavioral results demonstrated that performance on shift trials was significantly slower than on repeat trials for

both groups, but that the attention-shift cost (the difference between mean shift RT and mean repeat RT) was significantly greater in the chronically stressed group. The chronically stressed group also reported significantly higher PSS scores; however, PSS scores predicted impairments in attentional shifts in both groups. Results indicated a unique impairment in shifting, evidenced both by equivalent RTs for the repeat trials as well as the reversal trials. Interestingly, however, after one month of reduced stress (post-exam), the chronically stressed group no longer showed significant differences from the control group on the PSS or on the attentional-shift paradigm, suggesting that the effects of stress on attentional shift (and perhaps other executive functions) are more state-dependent than trait- dependent.

Results also demonstrated that chronic stress disrupted prefrontal functional connectivity. Functional neuroimaging data confirmed previous animal research that attentional shift tasks engage a network involving the DLPFC, a homolog of the rodent MPFC (Brown & Bowman, 2002; Birrell & Brown, 2000; Liston, et al., 2006; McAlonan & Brown, 2003). Functional connectivity analyses demonstrated decreased functional coupling between DLPFC and other areas of the aforementioned network, including the premotor and posterior parietal cortex (e.g., L DLPFC decoupling with L premotor). This decoupling was associated with greater impairments in attentional shifting. Further, the authors found that chronically stressed participants showed a relative decoupling of the left DLPFC with areas of the right DLPFC, left premotor, bilateral ventral PFC, and left posterior parietal cortex, but increased coupling with temporal lobe areas (e.g., visual processing). Right DLPFC coupling demonstrated less connectivity to the left DLPFC, right ventral PFC, the striatum, right premotor cortex, cingulate cortex, left fusiform cortex, and left cerebellum, but no areas with greater connectivity. These disruptions in

connectivity support the hypothesis that this network is affected by chronic stress and may be responsible for impairment in attentional shifting.

Interestingly, however, after one month of reduced stress (post-exam), functional analyses, similar to self-reports of stress and attentional shift performance, indicated that the effects of stress on the DLPFC and its connectivity to the other areas of the parietal network involved in attentional shifting were reversed in all areas, with the exception of the ventral PFC (BA 13, 47); the ventral PFC remained decoupled compared to the control group (Liston et al., 2009). The findings from this study indicate that chronic stress does have effects on the PFC, specifically through the decoupling of the DLPFC with other areas imperative to attentional shift. Importantly, the majority of these effects were reversible after a period of relieved stress, suggesting that the effects of stress on attentional shift (and perhaps other executive functions) are more state-dependent than trait- dependent. The irreversibility of the decoupling between the DLPFC and the ventral PFC, however, suggests an important specificity in how various areas within the PFC are affected by chronic stress.

The Kishiyama et al. (2008) and Liston et al. (2009) studies reported similar findings: that chronic stress was related to less prefrontal activation in response to an executive function task and that this lower activation was associated with poorer performance on executive function tasks. An important difference between these two studies, however was that the children of low SES families were faced with more pervasive, enduring stressors while the stressor examined in the study of students had an objective endpoint (i.e., when the exam was over). Importantly, the study of students found reversibility of the prefrontal and executive performance effects once the exam was over (Liston et al., 2009).

These studies are just a few examples to demonstrate that the PFC plays a role in executive functioning; thus deleterious effects of allostatic load to these regions may exacerbate the consequences of stress by impeding the ability to cognitively cope with stress. These processes may be especially pertinent to populations such as children of depressed parents, who are exposed to more chronic stress and are more vulnerable to developing psychopathology.

While there is relatively little research directly examining executive function, processing speed, and prefrontal function in children of depressed parents, there is evidence for such deficits in both (1) children diagnosed with depression or other psychiatric disorders and (2) adults with depression. In addition to increased stress exposure, this research suggests that children of depressed parents may be at increased risk for executive function and processing speed deficits. For example, Calhoun and Mayes (2005) demonstrated that children with various clinical disorders, including ADHD and depression, exhibited deficits in processing speed while children with other clinical disorders, such as anxiety and oppositional disorders, did not demonstrate processing speed deficits. These findings suggest specificity in the pathway of risk for such cognitive deficits. Additionally, processing speed has been demonstrated to mediate executive function difficulties in various child and adolescent populations (e.g., Kail, 2007; Mulder, Pitchford, & Marlow, 2011). There is also evidence that adults with major depressive disorder have impaired executive function and processing speed (e.g., George et al., 1997; Matsuo, Kato, & Kato, 2002; Rogers et al., 2004; Tsourtos, Thompson, & Stough, 2002). Chronic stress may contribute to two processes by which (1) chronic stress directly contributes to higher rates of psychopathological symptoms as well as physical health difficulties and (2) chronic stress impedes the cognitive skills necessary for adaptive coping with stress (Compas, 2006).

Current Studies: Rationale and Hypotheses

Children and adolescents exposed to chronic stress, such as the stress associated with parental depression, have been found to have impairment in their ability to coping with such stress. Additionally, chronic activation of the stress response system of the HPA leads to allostatic load, including damage to the prefrontal regions of the brain responsible for higher order executive functions that are foundational to the implementation of adaptive coping strategies. The goals of this current research are to examine these previously separate lines of research through two studies. Study I examines the effects of chronic stress on executive function, coping, and psychopathology in children and adolescents (which I refer to as "children" for brevity) of mothers with and without depression histories in the lifetime of their children. Study II examines the effects of stress on the prefrontal cortex in a sub-sample from Study I. These studies seek to integrate and unify these previously independent lines of research to the examination of chronic stress, executive functioning, coping, and the role of the PFC in children of depressed parents and healthy children of parents without a history of depression.

STUDY I

The goals of Study I were to explore to associations between exposure to stress, executive functioning, coping, and affective, anxiety, and oppositional defiant symptoms in children of mothers with histories of depression (both current and past) in the lifetime of their children (which, for the sake of brevity, I will refer to as "children of depressed mothers" and children of mothers with no history of depression ("controls")). These constructs were examined through the use of questionnaire data, interviews, and children's neuropsychological assessment. The following specific hypotheses were tested:

Hypothesis 1. Children of depressed mothers will demonstrate higher levels of chronic stress exposure, lower scores of tests of executive functions (e.g., working memory), less

processing speed, less use of adaptive (e.g., secondary control) coping, and greater affective, anxiety, and oppositional defiant symptoms.

Hypothesis 2. Across groups, exposure to chronic stress will be related to poorer performance on tests of executive functions and processing speed, less use of adaptive coping, and greater affective, anxiety, and oppositional defiant symptoms.

Hypothesis 3. Exposure to chronic stress will partially account for differences in executive function and processing speed performance, use of adaptive coping, and affective, anxiety, and oppositional defiant symptoms between children of depressed mothers and children of mothers without a history of depression.

METHOD

Participants

Participants included 35 children of mothers with a history of major depressive disorder within the child's lifetime or meeting criteria for a current episode of major depression and 30 children of mothers without a history of depression from the areas in and surrounding Nashville, Tennessee. Children enrolled in the study ranged from 9 to 15-years-old and included 28 girls (mean age = 12.52, SD = 2.12) and 37 boys (mean age = 13.38, SD = 1.62). Seventy percent of children were Euro-American, 20% African-American, 3.1% Asian American, 7.7% Hispanic American, and 3.1% mixed ethnicity.

Parents enrolled in the study included 35 mothers with a positive history of current or past major depressive disorder (MDD) within the lifetime of their child (mean age of 43.80 years, SD = 13.53) and 30 mothers without a history of MDD (mean age = 42.33, SD= 5.44). Mothers with and without a history of depression did not differ significantly on age, race, income, or marital status. Seventy-two percent of parents were Euro-American, 20% African-

American, 4.6% Hispanic-American, 3.1% Asian-American, 1.5% Native American, and 1.5% mixed ethnicity. Annual family income ranged from $19,000 to 200,000, with a mean annual income $68,625 (SD= $38,891). Sixty-two percent of parents were married, 18.5% were divorced, 7.7% separated, 7.7% had never married, and 4.6% were widowed. Mothers with a history of MDD had completed more education than mothers without a history of depression in the lifetime of their child. Mothers with a history of MDD were approximately six times as likely as control mothers to have completed education beyond high school (χ= 6.12, $p < .05$). Data on father education was not available, however, so the implication of maternal education for overall SES and economic strain should be interpreted with caution, especially given that the groups did not differ on family income.

Participants were recruited through study advertisements on Vanderbilt's Study Finder website as well as email advertisements sent to staff and faculty of Vanderbilt University and Meharry Medical College. Separate advertisements were used to recruit mothers with a history of depression and healthy mothers.

In order to enroll a sample of families with chronic stress associated with parental depression, we screened for parents with histories of MDD who do not meet criteria for certain other psychiatric disorders, including bipolar disorder- type I, schizophrenia or other psychotic disorders, and current alcohol or substance abuse. These exclusionary criteria were successfully used in a previous depression prevention intervention study (Compas et al., 2009). We also screened out children with neurodevelopmental disorders, such as autism spectrum disorders or intellectual deficits, that could affect their performance on the cognitive tasks involved in this study.

Procedures

All families were recruited to participate in a study aimed at understanding parent-child emotions, communication, and problem-solving. Study sessions were conducted at Vanderbilt University in Nashville, Tennessee. All procedures in the study were approved by the Institutional Review Board at Vanderbilt University.

Upon expressing interest in the study, mothers completed an initial telephone interview to begin to determine eligibility. If determined eligible from the phone interview, the family was scheduled for a one-time study appointment. These appointments included structured clinical interviews with the mothers, questionnaires completed by mothers and children, and neurocognitive testing completed by the child. Structured clinical interviews were conducted in the Department of Psychology and Human Development at Vanderbilt University by doctoral students in clinical psychology who had completed extensive training for these interviews.

Measures

Questionnaire, interview, and neurocognitive testing data were collected to assess chronic stress exposure, executive functioning, coping, and internalizing and externalizing symptoms.

Demographics. Mothers completed a basic demographic questionnaire in order to socioeconomic status, parental marital status, parent and child race, ethnicity, and age.

Parental Depression. Parental depression was assessed through both semi-structured clinical interview and questionnaire.

Structured Clinical Interview for DSM-IV Diagnoses. Parents were administered the major depressive disorder modulate of the Structured Clinical Interview for DSM-IV Diagnoses (SCID, First, Spitzer, Gibbon, & Williams, 2001). The SCID is a semi-structured diagnostic interview used to assess current and previous episodes of psychopathology according to DSM-IV criteria (American Psychiatric Association, 1994). This interview was used to identify the

number and duration of episodes of major depression experienced by a parent within the lifetime of the child. The SCID also confirmed parent's diagnosis of MDD and provided indices of parental depression including current levels of symptoms, current and past diagnostic status (in episode, past episodes, no history), and an estimate of total number and duration of episodes within the child's lifetime.

Beck Depression Inventory-II. Mothers also completed the Beck Depression Inventory-II (BDI-II, Beck, Steer, & Brown, 1996) to assess levels of depression symptoms over the past month. The BDI-II is a standardized and widely used self-report checklist of depressive symptoms with adequate internal consistency, reliability and validity (Beck et al., 1996). Internal consistency in this sample was $\alpha = .90$. The BDI-II was used to measure current depressive status.

Children's Chronic Stress. Chronic stress exposure was assessed across the domains of family stress, social stress, economic disadvantage, and stressful life events. In order to obtain an overall index of exposure to chronic stress, each construct was transformed into a z-score and an overall "stress exposure" composite was created and used in all the analyses.

Responses to Stress Questionnaire. Stressor items from the *family stress,* and *social stress* versions of the Responses to Stress Questionnaire (RSQ; Connor-Smith et al., 2000; Wadsworth & Compas, 2002) were completed by parents and children reporting on the frequency and intensity with which children and adolescents have been exposed to stressors in the past 6 months. Family stressors included items such as "having a hard time talking to your parents," "arguing or fighting with your sibling(s)," and "your parents hassling or nagging you." Social stressors included items such as "having someone stop being your friend," "being left out or rejected," and "being teased or hassled by other kids." Participants rated these stressors,

according to how stressful they have been for the participant in the past 6 months, as "not at all," "a little," "somewhat," or "very." The RSQ has well-established reliability and validity in studies with diverse samples (Connor-Smith et al., 2000; Wadsworth et al., 2004). Using these different versions of the questionnaire provided information on children's and adolescents' stress exposure across common sources of stress for children and adolescents in the family and social environments.

Economic Disadvantage. As described previously, mothers also provided information on the family's economic status. Maternal education and family income were used as two markers of economic disadvantage, which has been demonstrated to be a source of stress for children and adolescents (e.g., Wadsworth & Achenbach, 2005; Reising et al., 2012).

Adolescent Perceived Events Scale (APES). The Adolescent Perceived Events Scale (APES; Compas, Davis, Forsythe, & Wagner, 1987) is a self-report of major (e.g., death of a relative, parents' divorce) and daily life events (e.g., taking care of younger siblings, doing homework). The APES assesses events that have occurred in the past 3 months and instructs the participant to indicate which of the listed events have occurred, complete a 9 point Likert scale of experienced events' desirability (-4 = extremely bad, 0 = neither good nor bad, +4 = extremely).

Children's Executive Function.

Wechsler Abbreviated Scales of Intelligence. Children and adolescents completed the Matrix Reasoning and Vocabulary subtests of the Wechsler Abbreviated Scales of Intelligence (WASI; Axelrod, 2002) in order to obtain a two-scale derived intelligence index. This IQ score is not included in the indices of executive function, but was used to control for overall intelligence.

Wechsler Intelligence Scales for Children- Fourth Edition. Children and adolescents completed the Digit Span subtest of the Wechsler Intelligence Scale for Children- Fourth Edition (WISC-IV; Wechsler, 2003) as an index of working memory.

Delis-Kaplan Executive Functioning System. Children and adolescents also completed the Trail-Making and Color-Word Interference subtests of the Delis-Kaplan Executive Functioning System (DKEFS; Delis, Kaplan, & Kramer, 2001), which provide additional assessment of executive functions such as working memory and inhibition, respectively.

Children's Processing Speed.

Wechsler Intelligence Scales for Children- Fourth Edition. Children and adolescents completed the Coding subtest of the Wechsler Intelligence Scale for Children- Fourth Edition (WISC-IV; Wechsler, 2003) as an index of processing speed. Though processing speed is involved in many of the executive function tasks listed above, the Coding subtest is the most direct measure of processing speed.

Children's Coping.

Responses to Stress Questionnaire. The family stress version of the Responses to Stress Questionnaire (RSQ; Connor-Smith et al., 2000; Wadsworth & Compas, 2002) will be completed by parents and children reporting on the frequency and intensity with which children and adolescents were exposed to stressors in the past 6 months as well as how they responded to such stressors. The RSQ has well-established reliability and validity in studies with diverse samples (Connor-Smith et al., 2000; Wadsworth et al., 2004). Confirmatory factor analyses have identified 5 categories of voluntary and involuntary responses to stress (Connor-Smith et al., 2000). These factors include primary control engagement coping (e.g., problem-solving, emotional expression), secondary control engagement coping (e.g., cognitive reappraisal,

positive thinking), disengagement (e.g., avoidance, denial), involuntary engagement (e.g., physiological arousal, rumination), and involuntary disengagement (e.g., emotional numbing, cognitive interference). For this study, the secondary control coping index from both parent and children's self-reports will be used as measures of children's coping. Internal consistency for secondary coping was adequate across reporter and stressor type (all α's > .75). Parent and child reports will be combined by creating z-scores and taking the average of the two scores to create a composite score of secondary control coping.

Children's Internalizing and Externalizing Symptoms.

Child Behavior Checklist and Youth Self-Report Questionnaire. Children's symptoms were assessed using the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) and the Youth Self-Report (YSR; Achenbach & Rescorla, 2001). The CBCL includes a 118-item checklist of problem behaviors that parents rate as not true (0), somewhat or sometimes true (1), or very true or often true (2) of their child in the past 6 months. Adolescents completed the YSR, the self-report version of the CBCL for adolescents ages 11 to 18-years-old. Reliability and validity of the CBCL and YSR are well established (Achenbach & Rescorla). Internal consistency for the scales used in this study ranged from α = .67 to .76 for the CBCL and α = .47 to .62 for the YSR. Nine and 10 year-old children completed the YSR to allow for complete data on all measures. The internal consistency for the YSR scales ranged from α= *.40-.63*.

Normalized *T* scores were calculated for adolescent symptoms for descriptive purposes for comparison to the normative sample for the CBCL and YSR. Raw scores were used in analyses because of a loss of some variance with *T* scores (i.e., in some instances more than one raw score corresponds to the same *T* score). Parents' and children's reports of affective (r = .45, p < .01), and oppositional defiant symptoms (r = .48, p < .01) were significantly correlated.

Therefore, parent and child reports were combined to form composite measures of affective and oppositional defiant symptoms that were used in all analyses. Parent and child report of anxiety symptoms were not significantly correlated (r= .21, ns), but for the sake of utilizing a multi-method approach, we created a composite from parent and child report for these symptoms as well.

Data Analytic Plan

Hypothesis 1. Group differences between the children of depressed mothers and children of non-depressed mothers were examined using a series of one sample *t*-tests.

Hypothesis 2. Relations between stress exposure, maternal depressive symptoms, executive function, processing speed, coping with family stress, coping with peer stress, and affective, anxiety, and oppositional defiant symptoms were examined with a series of Pearson correlations.

Hypothesis 3. In order to determine whether stress exposure accounted for the association between group status and executive function, processing speed, coping, and affective, anxiety, or oppositional defiant symptoms, a series of linear multiple regressions were utilized. These regressions were run predicting affective, anxiety, and oppositional defiant symptoms separately and included group status at Step 1, stress exposure at Step 2, either executive function or processing speed at Step 3, and coping at Step 4.

RESULTS

Descriptive Statistics

Descriptive information regard participants' demographic characteristics, scores on standardized clinical measures, and children's scores across standardized neurocognitive measures are presented in Tables 1 and 2. As noted previously, children of parents with and

without a history of depression did not differ significantly on child age, maternal age, gender, race, or family income, but did differ on maternal education. Mothers in the depression group had significantly higher education than mothers in the control group. Data on fathers' education was not available, however, so the implication of maternal education for overall SES and economic strain should be interpreted with caution, especially given that the groups did not differ on family income.

As expected, mothers in the history of depression group demonstrated higher levels of current symptoms of depression on both a self-report questionnaire (BDI; t= -3.54, p< .01) and interview (SCID; t= -5.17, p< .01). Mothers in the depression group had a mean of 2.09 (SD= 2.50) episodes of depression within their child's lifetime.

Hypothesis 1

Means and standard deviations for children's neurocognitive measures, coping, and symptoms are displayed in Table 2. As hypothesized, the groups differed on stress exposure, cognitive function, symptoms, and coping, though these results were limited to a subset of measures more than anticipated. Overall, children of mothers with a history of depression experienced more chronic stress (not including their mothers' depression) than children in the control group (t= -2.12, p< .05), performed worse on a measure of processing speed (WISC-IV Coding test; t= 2.86, p< .01), reported less secondary control coping only in response to familial stress (t= 2.02, p< .05), and had greater affective symptoms (t= -2.63, p= .011) and anxious symptoms (t=-2.78, p< .01) based on parent-report (but not based on children's self-reports).

Hypothesis 2

Correlations among the constructs of interest (i.e., stress exposure, processing speed, executive function, coping, and affective, anxiety, and oppositional symptoms, and maternal

depressive history within the child's lifetime) for the whole sample are presented in Table 3. As hypothesized, children's exposure to stress was positively related to children's affective (r= .30, p< .05) and oppositional defiant symptoms (r= .39, p< .01), but not to anxiety symptoms. Current and past maternal depression in the child's lifetime was also related to affective symptoms (r= .26, p< .05), but not anxiety or oppositional symptoms. Exposure to stress was also inversely related to lower levels of children's use of secondary control coping in response to family stress (r= -.26, p< .05) but not to secondary control coping in response to peer stress. Current and past maternal depression was also related to lower levels of children's use of secondary control coping in response to family stress (r= -.33, p< .01) but not peer stress. Secondary control coping in response to family stress and peer stress were significantly related to each other, however (r= .67, p< .01). Secondary control coping in response to both family and peer stress was inversely related to affective symptoms (r= -.56 and r= -.37, respectively, both p< .01) and oppositional defiant symptoms (r= -.51 and -.33 respectively, both p< .01). However, only coping with family stress was related to anxiety symptoms (r= -.47, p< .01). Children's executive function and processing speed performance were related to each other (r= .53, p< .01) and processing speed was also related to current and past maternal depression symptoms (r= -.28, p< .05). Unexpectedly, executive function and processing speed were not related to any of the other constructs.

In order to examine group differences in the relations among the constructs of interest, correlations among stress exposure, processing speed, executive function, coping, and affective, anxiety, and oppositional symptoms, and maternal depressive history within the child's lifetime are presented separately by group status (i.e., for mothers with and without a history of depression) in Table 4. For the maternal depression group but not the comparison group,

children's coping with family stress was significantly related to anxiety symptoms (r= -.56, p< .01), and coping with peer stress was related to oppositional defiant symptoms (r= -.37, p< .05), and affective symptoms were related to anxiety symptoms (r= .51, p< .01). In order to determine whether the correlations among these constructs were significantly different between children of mothers with and without a history of depression, Fisher's z tests were run and yielded non-significant *z*'s (Fishers *z*'s = 1.45, 1.09, and .51, respectively), indicating that despite the correlation among these constructs being significant for one group and not for the other, the correlations were not significantly different from each other. Several significant correlations were found for children of non-depressed mothers were not significant for the depression group. For example, stress exposure was related to affective symptoms (r= .41, p< .05) and oppositional defiant symptoms (r= .55, p< .01). Fisher's *z* tests indicated that these correlations were not significantly different from each other, however (Fisher's *z*'s= 1.01, 1.63 respectively). Past and current maternal depressive symptoms were related to affective symptoms (r= .42, p< .05) in children of mothers without a history of depression but again, the correlations for the groups did not differ significantly (Fisher's z= 1.56). Similarly, coping with peer stress was related to affective symptoms (r= -.51, p< .01) in children of non-depressed mothers only but this correlation did not differ significantly from the depression group (Fisher's z=1.05). One significant between-group difference did emerge, however. Past and current maternal depressive symptoms were related to processing speed (r= .38, p< .05) for children of mothes without a history of depression, but not the depression group (r= -.31, ns; Fisher's z= 2.76).

The children of depressed and non-depressed parents demonstrated similar relations among processing speed and executive function (r = .45 and .62, respectively, both p< .01), coping with family stress and coping with peer stress (r= .63 and .71, respectively, both p< .01),

coping with family stress and affective symptoms (r= -.45 and -.74, respectively, both p< .01), and affective and oppositional defiant symptoms (r= .42, p< .05, and r=.57, p< .01).

Hypothesis 3

In order to examine whether exposure to stress accounted for the relations among executive function, processing speed, coping, and affective, anxiety, and oppositional defiant symptoms, linear multiple regression analyses were performed with maternal depressive history group status (children of mothers with and without a history of depression), executive function, and coping predicting affective, anxiety, and oppositional defiant symptoms. Regression analyses were also performed examining the role of processing speed along with maternal group status and coping in predicting affective, anxiety, and oppositional defiant symptoms. To avoid problems due to multicollinearity, which can occur when two predictor variables are highly correlated and compete for the same variance in predicting the dependent variable (Mason & Perreault, 1991), regression equations with processing speed and executive function (r= .53, p< .001) were run separately. These regression analyses are presented in Tables 5-10.

A linear regression predicting affective symptoms is presented in Table 5. Group status was a significant predictor (β= .29, t= 2.36, p< .05) when entered by itself, but shared the variance with stress exposure in Step 2 and 3 and neither were significant (p's .06 and .07). Executive function was not a significant predictor. In Step 4, only coping (β= -.51, t= -4.6, p< .01) remained a significant predictor of affective symptoms. A linear regression predicting anxiety symptoms (Table 6) revealed that maternal group status, stress exposure, and executive function were not significant predictors of anxiety symptoms. In Step 4, coping emerged as the only significant predictor of anxiety symptoms (β= -.46, t= -3.85, p< .01). Linear regressions predicting oppositional defiant symptoms (Table 7) demonstrated that while group status was not

a significant predictor at Step 1 or 2, stress exposure was a significant predictor at Step 2 (β= .39, *t*= 3.19, *p*< .01) and Step 3 (β= .38, *t*= 3.14, *p*< .01). Executive function was not a significant predictor. At Step 4, both stress exposure (β= .29, *t*= 2.60, *p*= .012) and coping (β= -.46, *t*= -4.16, *p*< .01) were significant predictors of oppositional defiant symptoms.

Linear regressions with maternal group status, stress exposure, processing speed, and coping are exhibited in Table 8. Group status was a significant predictor (β= .30, *t*= 2.53, *p*= .014) when entered into the equation by itself, but shared variance with stress exposure (group status, β= .24, *t*= 1.99, *p*= .051; stress exposure, β= .24, *t*= 1.95, *p*= .055) in Step 2 and each variable approached significance. Once processing speed was entered at Step 3, however, only stress exposure approached significance (β= .24, *t*= 1.94, *p*= .057). Finally, only coping was a significant predictor of affective symptoms when all predictors were entered into Step 4 (β=-.49, *t*= -4.49, *p*< .01). Linear regression (Table 9) revealed that group status, stress exposure, and processing speed were not significant predictors of anxiety symptoms but coping was significant when all predictors were entered at Step 4 (β= -.43, *t*= -3.64, *p*< .01). Linear regressions predicting oppositional defiant symptoms are presented in Table 10. Maternal group status was not a significant predictor at Step 1 or 2, but stress exposure was significant at Steps 2 (β= .38, *t*= 3.15, *p*< .01) and 3 (β= .38, *t*=3.17, *p*< .01). Processing speed was not a significant predictor. In Step 4, both stress exposure (β= .29, *t*= 2.62, *p*= .011) and coping (β=-.44, *t*= -3.98, *p*< .01) were significant predictors of oppositional defiant symptoms.

Similar regression analyses were also conducted substituting the continuous variable of current and past maternal depression within the child's lifetime, which included scores on current depressive symptoms on the BDI, number of current symptoms of depression on the SCID, number of episodes in the child's lifetime, and duration of depressive episodes in the

child's lifetime. These results of these regression analyses were generally similar to those in which maternal depression status was included as a dichotomous variable based on history of depression but notable differences emerged for the regression with current and past maternal depression, stress exposure, processing speed, and coping predicting oppositional defiant symptoms. Stress exposure remained a significant predictor at Step 2 (β=.40, t= 3.26, p< .01) but shared the variance with processing speed at Step 3 (stress exposure, β=.39, t=3.31, p< .01; processing speed, β=-.25, t= -2.06, p< .05). When all predictors were entered at Step 4, stress exposure (β=.31, t= 2.85, p< .01), processing speed (β= -.24, t= -2.18, p< .05), and coping (β=-.46, t= -4.08, p< .01) were all significant predictors of oppositional defiant symptoms.

STUDY II

The goals of Study II were to explore the association of prefrontal response to an executive function task with exposure to stress, executive functioning, processing speed, coping, and affective, anxiety, and oppositional defiant symptoms in a sub-sample from Study I. These constructs were examined through the use of data from Study I as well as additional questionnaires and interviews, and fMRI completed during a working memory task. The following specific hypotheses were tested:

Hypothesis 1. Children of depressed mothers, as compared with children of mothers with no history of depression, will demonstrate different activation of the prefrontal cortex, specifically in those regions previously demonstrated to be responsible for working memory (i.e., the DLPFC and ACC) in response to a working memory task. Previous studies with depressed adults have found less activation in these regions in response to executive function tasks (e.g., George et al., 1997; Matsuo, Kato, & Kato (2002)) while studies with depressed adults and other at-risk populations have demonstrated greater, compensatory activation of

these regions in response to executive function tasks (e.g., Sweet et al., 2006; Wishart et al., 2004). Therefore, the direction of these relations is difficult to predict and therefore the approach of this part of the study is largely exploratory.

Hypothesis 2. For children of mothers with and without a history of depression, activation in the prefrontal cortex in response to an executive function task will be related to stress exposure, performance on executive function tasks, secondary control coping (including more use of cognitive reappraisal), and affective, anxiety, and oppositional defiant symptoms.

Hypothesis 3. For children of mothers with and without a history of depression, activation in the prefrontal cortex in response to a working memory task will account for the associations between group status, stress exposure, and coping.

METHOD

Participants

Participants included 8 male (mean age = 14.18, SD = .81) and 8 female (mean age = 14.00, SD = 1.00) children of mothers with and without histories of depression in the lifetime of their child. For this study, an age range to 12 to 15-years-old to control for the rapid changes in brain development during puberty. There were four male and four female participants in each group (i.e., children of mothers with and without a history of MDD). The groups did not differ significantly on age, pubertal status, race, or family income but did differ on maternal age and education. Fifty-six percent of children were Euro-American, 37.5% African-American, and 6.3% Asian American.

Participants were recruited from Study I if the family met the following criteria: (1) the family had indicated interest in participating in other related studies during Study I, (2) the child

was between the ages of 12-15 years-old, and (3) the child was determined eligible following a screening to insure their safety to complete MRI (e.g., children with braces or implanted metal, children with histories of claustrophobia were ineligible). Efforts were taken to recruit age and gender matched participants for each group as well.

Procedures

Scanning eligibility forms were completed with mothers over the phone to determine whether it is safe for the child to be placed into an MRI machine, and if eligible and interested, appointments will be made for scanning protocols to be run. At the scanning session, mothers and children signed consent forms, mothers completed an official MRI screening form, and both the child and their mother completed an additional set of questionnaires. Children were then taken to a mock scanner room, which included a structure resembling an MRI, and were encouraged to climb into the scanner to become familiar with the enclosed space. Children were also shown the headset and the response pad that would be attached to each child's dominant hand during the scan. Once children were comfortable with the scanning environment, children were taught how each task would appear during the scan and were allowed to practice the executive function task (described further below). Once children completed the mock scanning and training session, any remaining questions were addressed before taking the child back to the scanning room.

Neuroimaging Scanning

All imaging was conducted on a 3Tesla MR scanner (Philips Medical Systems, The Netherlands) dedicated for research. The general imaging protocol involved acquiring data for anatomic, functional, functional connectivity and diffusion-tensor analysis. These provided measures of brain tissue volume, function, and microstructure in an exam of 60-70 minutes.

Following a certified technician's review of the MRI safety screening form, children were placed in the scanner by the technician and trained study personnel. In addition to the response pad, a pulse oximeter was attached to participants' non-dominant index finger to record heart rate, and a respiration belt was placed over participants' diaphragm to record respiration rate. Protocols were run via computer in an adjacent room, and task stimuli appeared via rear projector on a screen mounted in the MRI. Participants were able to respond to questions using buttons on the response pad, and they were able to communicate reciprocally with study personnel throughout the scan through headphones and a microphone.

Measures

In addition to data collected during Study I, questionnaire, interview, and neuroimaging data were collected to assess chronic stress exposure, affective, anxiety, and oppositional defiant symptoms, and brain activation in response to a stressful task.

Puberty. In order to account for potential confounds of age/developmental level, a more narrow age range of participants were selected for the imaging study. All participants completed a Tanner Staging Form (Tanner, 1962). Following permission from parents, drawings depicting gender-specific Tanner Stages of development were provided to participants, who selected the drawings most closely resembling their own pubertal status across two domains.

Chronic Stress. Participants completed additional measures of stress exposure to create a more comprehensive index of stress exposure specific to parental depression as well as chronic stress from more general sources in the past 12 months.

Responses to Stress Questionnaire. In addition to the *family stress* and *social stress* versions of the Responses to Stress Questionnaire, stressor items from the *parental depression* version of the Responses to Stress Questionnaire (RSQ; Connor-Smith et al., 2000; Jaser et al.,

2005; Wadsworth & Compas, 2002) were completed by parents and children reporting on the frequency and intensity with which children and adolescents have been exposed to stressors in the past 6 months. The parental depression version of the RSQ has stressor items such as "my mom does not want to spend as much time with me as I would like," "my mom is too upset, tense, grouchy, angry, and easily frustrated," and "my mom does not listen to me, or pay attention to events in my life." These stressors are rated, based on the past 6 months, on a 0 ("never") to 3 ("almost every day") scale. The RSQ has well-established reliability and validity in studies with diverse samples (e.g., Connor-Smith et al., 2000; Wadsworth et al., 2004). Using these different versions of the questionnaire will provide information on children's and adolescents' stress exposure across parental depression-specific as well as common sources of stress for children and adolescents in the family and social environments.

Perceived Stress Scale. In order to obtain a measure of chronic stress in the last month at the time of study completion, all participants will complete the Perceived Stress Scale during their evaluation, a well validated 10-item questionnaire that gauges chronic stress on a 40-point scale (PSS; Cohen, Kamarck, & Mermelstein, 1983; Cohen & Williamson, 1988). Items include statements such as "In the last month, how often have you felt nervous and 'stressed,'?" "In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?" Participants rate each item on a scale of 0 (never) to 4 (very often). This measure has been used with great success as a predictor of stress response, executive function, and neural responses to neurocognitive tasks (Liston et al., 2009). Furthermore, this measure was used in an integral study to this proposal in which chronic stress predicted impairments in cognitive function and PFC functional connectivity (Liston et al., 2009).

Children's Trauma History.

North Shore – Long Island Jewish Health System (NSLIJHS) Trauma History Checklist and Interview (NSLIJHS). In order to determine whether participants had experienced any traumatic events in their lifetime, two clinical measures of trauma were utilized. Children completed the NSLIJHS Trauma History Checklist (© 2006 by North Shore-Long Island Jewish Health System, Inc., Great Neck, New York), by interview, covering a variety of potentially traumatic events, including natural disasters, witnessing violence, and abuse. Participants simply responded with a "yes" or "no" regarding whether they had experienced these specific events. Interviews were completed by trained clinical graduate students in consultation with a licensed clinical psychologist.

UCLA PTSD Index for DSM-IV- Parent Version. Similarly, mothers completed the UCLA PTSD Index for DSM-IV (© Pynoos et al., 1998), a clinical tool assessing the same traumatic events through parent-report questionnaire. Psychometric properties are under investigation for the UCLA PTSD Reaction Index (Rodriguez, Steinberg & Pynoos, 1999). Mothers provided "yes" or "no" responses as to whether their participating child had experienced specific traumatic events. When participants reported any personal experience with physical or sexual abuse or witnessing any such abuse, the trained graduate student contacted a licensed clinical psychologist, discussed the issue with the family, and reported to the Department of Children's Services as appropriate and required by Tennessee law.

Children's Executive Function.

Behavior Rating Inventory of Executive Function. In addition to standardized testing of executive functioning abilities from Study I (i.e., Digit Span from the WISC-IV, Trail-Making and Color-Word Interference subtests from the DKEFS), mothers completed the Behavior Rating Inventory of Executive Function (BRIEF, Gioia, Isquith, Guy, & Kenworthy, 2000; Gioia,

Isquith, Retzlaff, & Espy, 2002) to assess day-to-day attentional and executive function. The BRIEF assesses behaviors such as a child's ability to inhibit, emotional control, working memory, organization, self-monitoring and specific items include "forgets what he/she was doing," "does not think before doing," "has trouble with chores or tasks that have more than one step," and "has good ideas but does not get the job done (lacks follow-through)." The BRIEF yields a Global Executive Composite (GEC) score as well as more specific indices of executive functioning and has demonstrated good reliability and validity. The GEC was used as a global index of executive functioning impairments.

Neural Responses to a Working Memory Task.

N-Back Task. Participants completed the N-back task, which is designed to assess working memory. A letter version of the visual N-back task (Barch, Sheline, Csernansky, & Snyder, 2003) has been developed, and involves sequences of uppercase consonants. In the 0-back condition, participants were instructed to respond to a single target (i.e., V). In the 1-back condition, participants were instructed to respond only when the consonant was identical to the one preceding it (e.g., M, M). In the 2-back condition, participants responded only when the consonant was identical to the one presented two trials prior (e.g., M, T, M), and in the 3-back condition, participants responded when the consonant was identical to the one presented three trials prior (e.g., M, T, F, M). Each condition was presented three times in order of increasing difficulty, for a total of 12 blocks. Each block contained 15 consonants, and 3 of these consonants required a response. This task has been used effectively with children in this age group with no adverse effects (Robinson, Livesay, et al., 2010). N-back task performance data were extracted using ePrime software (Psychology Software Tools Inc., Pittsburgh, PA). Accuracy, reaction time, number of omissions, and number of false positive responses were

calculated for each participant at each level of N-back difficulty. Overall accuracy and reaction time total scores across N-back difficulty level were also calculated.

Image Acquisition

Imaging consisted of a 3-plane localizer (5 slices per plane, 22s scan time) from which 33 oblique axial slices (parallel to the AC-PC plane) were prescribed. High resolution 3D anatomical images were acquired using an inversion-prepared spoiling gradient recalled echo sequence (IR-SPGR), with an inversion time T1 of 400ms, a TR of 15ms, minimum TE (3ms), a matrix size 256x256 for a FOV of 256x256x270mm^3 with near isotropic resolution, for use in volumetric analysis. All functional images were acquired with a gradient echo EPI pulse sequence, with TE 30ms (optimized for T2* at 3T), flip angle of 70°, TR 2000ms, 33 slices 3.5mm thick and .35mm skip, and a matrix size of 80x80 (reconstructed to 128x128) sampled at +/-62.5kHz. During the N-back task, each condition contained 15 consonants and a pause between each condition, for a total of 192 dynamic scans per run. The first 6 image volumes of the functional image dataset were discarded to allow magnetization to reach equilibrium.

Data Analysis

Statistical Power

Due to the small sample size (n = 8 per group), the power to detect statistical significance at $p < .05$ is limited to only very large effects. For example, for independent samples *t*-tests, a sample size of 8 per group would require a *t*-statistic of greater than 2.145 to reach significance at $p < .05$. This corresponds to an effect size (Cohen's *d*) of $d = 1.94$. Cohen (1988) provides guidelines for determining the magnitude of an effect size of a group comparison (Cohen's *d*), which state that effect sizes of $d = 0.2$-0.5 indicate a small effect, effect sizes of $d = 0.5$-0.8 indicate a medium effect, and effect sizes of $d = 0.8$ or larger indicate a large effect. Therefore,

in addition to discussing findings in terms of statistical significance, group differences reaching Cohen's threshold for medium and large effects will also be identified. Further, many analyses will also be examined a whole group level, using stress exposure as a continuous variable (as opposed to group status) to predict individual differences.

fMRI Data Preparation. All functional data were analyzed using BrainVoyager QX software (Brain Innovation B. V., Maastricht). For each participant, functional images from the participants' N-back run were corrected for 3D motion and slice-time delays, and linear trends were removed and temporally filtered. Motion correction results were assessed to ensure that all data fell within movement criteria (>3mm displacement, 3° rotation). Individualized design matrices were generated for these participants for use in group analysis.

The functional data for each participant was aligned to the participant's high-resolution 3D anatomic dataset. Each participant's activation map was normalized to a common reference space (Talairach), using registration techniques. Following Talairach transformation, within-group GLM analyses were conducted by designing a multi-study design matrix. This analysis calculated all significantly activated voxels, both positively and negatively, during all levels of the N-back. Individual contrasts were then set and activation at any given contrast could be examined individually. Analyses of covariance were conducted to determine whether patterns of activation differed as a whole between groups, or between different levels of the N-back. For the current analyses, a cluster threshold of 8 functional voxels was established for examining the main effect of N-back level, and a cluster threshold of 4 functional voxels was established for examining specific N-back level contrasts between groups. Each of these cluster thresholds maintained a significance criterion of $p < .01$. Significantly activated clusters that met this criterion were considered further. Region-of-interest (ROI) analyses were conducted using

Talairach Daemon software (Lancaster et al., 2000) to determine the brain region in which significantly activated clusters occurred and the corresponding center-of-gravity coordinates in Talairach space for each relevant cluster. Composite *F*-statistics were calculated to measure the degree of activation in each cluster for examination of main effects of group and N-back level.

Data Analytic Plan

Study hypotheses were analyzed as follows:

Hypothesis 1. Between-group GLM and Analysis of Covariance was conducted to detect BOLD signal differences between the children of depressed mothers and children of non-depressed mothers in response the N-back task during the fMRI. Specifically, activation in response to the 3-back (the most difficult N-back condition) vs. the 0-back (most simple, baseline condition) was examined. Clusters within *a priori* regions of interest (ROIs), PFC and ACC regions, were considered.

Hypothesis 2. In order to examine associations between activation in *a priori* ROIs indicated by whole group and between-group GLM and Analysis of Covariance and other constructs of interest, a series of Pearson correlations was used. Correlations were examined between BOLD signal differences for the 3-back vs. 0-back contrast in the ROIs, stress exposure, executive function performance, processing speed, BRIEF scores, N-back performance, coping, and symptoms were examined.

Hypothesis 3. Linear regressions were utilized to examine whether activation within *a priori* ROIs indicated by whole group and between-group GLM and Analysis of Covariance accounted for the association between group status, stress exposure and use of secondary control coping. Group status was entered at Step 1, followed by stress exposure at Step 2.

Each ROI was added at Step 3. Separate regressions were examined for each ROI due to the high correlation of activation among these related regions within the brain.

RESULTS

Descriptive Statistics

Descriptive information on the Study II participants is presented in Table 11. Children of mothers with a history of depression and children of mothers without a history of depression were matched for age and gender as closely as possible. Thus, the groups did not differ significantly on any demographic variables, with the exception of maternal age and education. The mean age of mothers with no history of depression in their child's lifetime was 45.75 (*SD*= 6.49) whereas the mean age of mothers with depression during their child's lifetime was younger (*M* = 39.59, *SD*= 4.29), *t*= 2.24, *p*< .05. Seven of the mothers with a history of MDD had a level of education beyond a high school degree, whereas only one mother without a history of MDD had an education beyond high school. Data on father education was not available, however, so the implication of maternal education for overall SES and economic strain should be interpreted with caution, especially given that the groups did not differ on family income.

Group comparisons on the updated stress exposure composite, scores on the BRIEF, and N-back performance are presented in Table 12. The groups did not differ significantly on stress exposure or N-back performance (accuracy or reaction time). However, parental report of children behaviors resulting from executive function deficits on the BRIEF demonstrated group differences across the Initiate (*t*= -3. 41, *p*< .01), Working Memory (*t*= -2.67, *p*= .018), Plan/organize (*t*= -3.51, *p*< .01), and Monitor scales (*t*= -2.62, *p*< .05), as well as the Meta-Cognition Index (*t*= -3.39, *p*< .01), and the overall Global Executive Composite (*t*= -3.15, *p*<

.01). Children of mothers with depression demonstrated more problems than the control group in executive function across these indices.

Examination of Cohen's *d* as a measure of effect sizes demonstrated that many of the non-significant findings were likely due to our small sample size. Medium size effects were found for group differences in full scale IQ (*Cohen's d*= .77), the Emotional Control (*Cohen's d*= .75), Behavioral Regulation (*Cohen's d*= .79*),* and Organization of Materials (*Cohen's d*= .74) scales of the BRIEF, omission errors on the one-back condition (*Cohen's d*= .53), correct "hits" (*Cohen's d* = .72) and omissions (*Cohen's d*= .72) on the two-back condition, correct "hits" (*Cohen's d*= .79) and omission errors (*Cohen's d*= .79) on the three-back condition of the N-back, as well as overall errors on the N-back (*Cohen's d*= .69). Medium effects were also found for group differences on CBCL Anxiety Problems (*Cohen's d*= .54), the CBCL/YSR Anxiety composite (*Cohen's d*=.51), and the Oppositional Defiant composite (*Cohen's d*=.57). Additionally, large effects were found for group differences on executive function (*Cohen's d*= .98), the Inhibit scale of the BRIEF (*Cohen's d*= .95), the Affective Symptoms composite (*Cohen's d*= .96) and CBCL Oppositional Defiant symptoms (*Cohen's d*= .93). These effect sizes suggest a trend for children of depressed mothers (as compared to children of non-depressed mothers) having higher overall IQ, lower executive function scores, greater executive function-related problems (as indicated by the BRIEF), worse performance on the N-back task, and more affective, anxiety, and oppositional defiant symptoms. These trends, however, should be considered with caution due to the small sample size.

Functional Brain Activation in Response to the N-back Task

In analyses of responses to the n-back task for the whole sample, as expected, participants made more errors and demonstrated slower reaction times as the N-back increased in difficulty

from 0-back ("find the letter 'V'") to the 3-back ("find the same letter repeated with two different letters in between"). Brain regions activated by the N-back task across the two groups are presented in Table 13. As hypothesized, clusters within the PFC and ACC displayed greater activation in response to the most challenging condition of the N-back (3-back) as compared with the easiest level (0-back), as well as other regions related to more basic processes involved in the task such as visual processing. Significant effects were found for two *a priori* regions of interest: the right DLPFC (BA9; Talairach coordinates: 33, 18, 33; F= 6.40, p< .001) and the left dorsal ACC (DACC[1], BA32; Talairach coordinates: -19, 22, 35; F= 2.69, p< .001).

Hypothesis 1

Group differences in brain activation in response to the N-back task (3 vs. 0 contrast) are also presented in Table 13. Significant differences were found on three *a priori* regions of interest in the between-group comparisons: right anterior PFC (BA10; Talairach coordinates: 16, 49, 11; F = 2.96, p< .001) and two clusters within the left dorsal ACC (BA32; DACC[2]- Talairach coordinates: -21, 11, 29; F= 2.90, p< .001) and DACC[3]- Talairach coordinates: -22, 36, 17, F= 2.60, p< .001). The children of depressed mothers demonstrated less activation than controls in the anterior PFC and the DACC[2] cluster but greater activation in the DACC[3] cluster in response to the N-back task.

Hypothesis 2

Correlations between the regions of interest indicated by both the whole group and between group effects of the N-back task and the other constructs of interest (stress exposure, maternal depression, executive function, processing speed, coping, and affective, anxiety, and oppositional defiant symptoms) are presented in Table 14. In analyses of responses from the whole sample, activation of the APFC in response to the N-back task was positively related to

stress exposure (r= .60, p< .05*)* but was inversely related to secondary control coping in response to family stress (r= -.88, p< .01). Secondary control coping in response to family stress was also inversely related to DLPFC activation (r= -.66, p< .01) and DACC[1] activation (r= -.59, p< .01). Another DACC region (DACC[2]) was also inversely related to processing speed (r= -.55, p< .05).

Hypothesis 3

Multiple linear regressions were conducted to examine whether activation in *a priori* regions of interest would account for the associations between group status, stress exposure, and coping. These regressions are displayed in Tables 15-19. Group status was entered at Step 1 and stress exposure was added at Step 2. Stress exposure (β= -.52, t= -2.22, p< .05) but not group status was a significant predictor of children's coping. At Step 3, each of the significant *a priori* regions of interest was added to the regression equations. DLPFC (β= -.52, t= -2.29, p< .05), DACC[1] (β= -.49, t= -2.32, p< .05), and APFC (β= -.89, t= -5.06, p< .01) activation were all significant predictors of children's secondary control coping in response to family stress. Once each of these regions was entered into the regression, stress exposure was no longer a significant predictor.

DISCUSSION

Children of depressed parents are exposed to greater chronic stress than children of parents without a history of depression (e.g., Garber & Martin, 2002). Previous research has suggested that chronic stress may impair an individual's ability to cope effectively with stress (e.g., Wadsworth & Compas, 2002). Research has also demonstrated that adaptive coping skills (e.g., cognitive reappraisal) are related to an individual's executive function abilities (e.g., Campbell et al., 2009), and that the regions of the brain responsible for these cognitive functions,

such as the prefrontal cortex and anterior cingulate cortex, are some of the most vulnerable to the effects of chronic stress exposure (e.g., McEwen, 2003). Taken together, these lines of research suggest that children of depressed parents may be at increased risk for psychological problems by way of an impaired ability to effectively deal with stress. The pathways underlying impaired coping may include biological damage to the prefrontal cortex and associated deficits in executive function abilities, which are foundational to cognitive coping skills, such as cognitive reappraisal. In this paper, these processes were examined across two studies. In Study I, children's stress exposure, executive function, processing speed, and affective, anxiety, and oppositional defiant symptoms were examined in children of mothers with a history of depression in the child's lifetime and children of mothers with no history of depression in the child's lifetime. As hypothesized, children of depressed mothers had experienced greater chronic stress than children in the control group.

In Hypothesis 1, group differences across stress exposure, executive function, processing speed, coping, and affective, anxiety, and oppositional defiant symptoms were explored. Unexpectedly, children in the two groups did not significantly differ on any measures of executive function but the children of depressed mothers did demonstrate slower processing speed. Similarly, executive function was not related to stress exposure or any other constructs, but processing speed was related to maternal depressive symptoms. Campbell et al. (2009) found a relation between executive functions and coping as well as executive functions and symptoms, but these findings were only found in a group of childhood acute lymphocytic leukemia (ALL) survivors and not in their control group. However, the childhood ALL survivors from Campbell et al (2009) are a much different population than children of depressed mothers in that they were exposed to not only environmental stress but also to endogenous

damage to the brain regions responsible for executive function due to intrathecal chemotherapy treatments which directly target fast growing cells in the brain (e.g., Campbell et al., 2007). The measurement of chronic stress exposure as a "dosage" effect is more challenging to accurately quantify and may have affected Study I's ability to find associations between stress exposure, executive function, and the other constructs of interest. Andreotti et al. (2012) also found associations between executive functions, coping, and symptoms in a group of college students. Both of these studies, however, utilized both direct testing of executive function and parent or self-report of behavioral manifestations of executive function problems with the BRIEF. While we utilized this questionnaire for Study II, this behavioral data was not available for our Study I sample. The Andreotti et al. (2012) participants also demonstrated mean levels of working memory that were three-fourths of a standard deviation higher than average, with a standard deviation of a three-fourths of a standard deviation. It is possible that the associations between executive functions, coping, and symptoms may differ at different levels of cognitive functioning.

It is interesting that processing speed was different between the children of depressed parents and the children in the control group and that processing speed was related to maternal depression. Processing speed deficits have been demonstrated in children with various clinical disorders (Calhoun & Mayes, 2005) as well as adults with depression (e.g., George et al., 1997; Matsuo, Kato, & Kato, 2002; Rogers et al., 2004; Tsourtos, Thompson, & Stough, 2002). Because the development of processing speed has been demonstrated to mediate the development of executive function (e.g., Kail, 2007; Mulder, Pitchford, & Marlow, 2011) and because these two constructs are so highly correlated ($r = .53$, $p < .01$ in Study I), it is possible that the effects of chronic stress on the developing prefrontal cortex appear first in processing

speed deficits and later translate into more executive function problems later in development. It is also possible that since children with depression in the Calhoun and Mayes (2005) study only demonstrated deficits in processing speed, and not in other executive functions, that there is specificity for this type of deficit and risk for this deficit in families with depression. Both of these possibilities warrant future, specific investigation. Consistent with previous research, children of depressed mothers had greater affective symptoms and experience greater family stress than children of mothers without depression (e.g., Goodman & Gotlib, 1999). Consistent with previous research, coping was a robust predictor of affective, anxiety, and oppositional symptoms (e.g., Jaser et al., 2005, 2006; Wadsworth & Compas, 2002).

In Hypothesis 2, associations among the constructs of interest were examined for the whole group as well as individually for each group. Consistent with previous research, greater stress exposure was related to less use of adaptive coping symptoms and greater symptoms (e.g., Compas, 2006; Connor-Smith et al., 2000). These findings were not consistent across all measures, however; greater stress exposure was only related to less use of secondary control coping in response to family stress, but not in response to peer stress. More stress exposure was only related to greater affective and oppositional defiant symptoms, but not anxiety symptoms. Similarly, past and current maternal depression was related to less use of adaptive coping (again, only in response to family stress) and greater symptoms in the children, but only for affective symptoms. Also consistent with previous research, less use of adaptive coping in response to family or peer stress was related to greater affective symptoms and coping in response to peer stress was related to anxiety symptoms (e.g., Jaser et al., 2005, 2006). Unexpectedly, executive function was not related to other constructs and processing speed was only related to past and current maternal depression. It is possible that other measures of executive function might

demonstrate more effects or that these effects would only be demonstrated in populations with more impairment with these cognitive skills.

In Hypothesis 3, regressions examined whether stress exposure, processing speed, and/or coping would account for the associations between group status and affective, anxiety, and oppositional symptoms. Group status only predicted affective symptoms until coping was entered into the equation. Stress exposure only predicted affective symptoms until coping was included in the equation but remained an independent significant predictor (along with coping) in predicting oppositional defiant symptoms. Processing speed only emerged a significant predictor of oppositional defiant symptoms when maternal depression was considered as a continuous variable rather than a dichotomous (group status) variable, suggesting that the effects of children's exposure to their mothers' depressive symptoms on processing speed may be more related to overall exposure to symptoms and maternal behaviors than whether or not their mother met criteria for a DSM-IV Major Depressive Episode. It is notable that in this regression, processing speed, along with stress exposure and coping, remained a significant predictor of oppositional defiant symptoms when all predictors were entered into the regression.

The neural underpinnings of the processes examined in Study I were investigated in a sub-sample of adolescents in Study II. With a smaller sample (n=16), Study II had less power to detect between group differences and relations among the constructs of interest. In Study II, group differences between the children of depressed mothers and the children of mothers without a history of depression were examined. Group differences in some of the behavioral manifestations of executive function deficits (as measured by the BRIEF), and symptoms were indicated. It is possible that while direct examination of executive functioning abilities did not yield significant between group differences or associations with stress exposure, coping, or

symptoms that the behavioral manifestations of such problems is a more advantageous approach to understanding the impact of executive function deficits on other processes contributing to children's risk for psychopathology. Furthermore, in considering Cohen's *d* as a measure of effect size, other group differences in executive function performance across neurocognitive testing and the N-back task as well as additional indices on the BRIEF, were indicated. Additional indicators of differences in symptoms across groups also suggest that with a larger sample size, more significant results would have been demonstrated. However, these trends should be considered with caution; it is possible that the trends are due to the specific sample of 16 adolescents in this study and would not generalize to a greater sample.

The brain regions activated during the N-back task, a measure of working memory, were examined at both whole group and between group levels. Consistent with previous research (e.g., Robinson et al., 2010) and as hypothesized, activation was found in the DLPFC and ACC. Specifically, a general linear model examining the effect of the N-back task across the groups, measured by examining the contrast of the most challenging condition (3-back) and the baseline condition (0-back), activated two *a priori* regions of interest: the DLPFC (BA9) and the DACC (BA32). For Hypothesis 1 of Study II, a general linear model examining the effects of the task between groups revealed two other significant regions of interest within the DACC (BA32) as well as activation in the APFC (BA10). The DLPFC and ACC have been indicated not only generally in executive function and working memory specifically, but also specifically in response to the N-back task itself. The anterior prefrontal cortex has been described as "one of the least well understood regions of the human brain," (Ramnani & Owen, 2004, pg. 184) but has been demonstrated to be involved in memory retrieval and executive function in some studies (e.g., Pisapia & Braver, 2008; Koechlin et al., 1999).

Interestingly, there was specificity within *a priori* regions for group differences. While the children of depressed mothers demonstrated less activation in one region within the DACC and the APFC, they also demonstrated greater activation in another region of the DACC. Because the groups did not differ significantly on performance on the N-back task, it is possible that these differences in activation might be linked to differences in performance on a task with greater difficulty and more variance in scores. On the most difficult condition, the 3-back, controls made only a mean of 3 ½ errors out of 48 trials and the children of depressed mothers made only a mean of 6 errors out of 48 trials.

For Hypothesis 2 of Study II, associations between activation in the whole group and between-group ROIs in response to the N-back task and stress exposure, executive function performance, processing speed, BRIEF scores, N-back performance, coping, and symptoms. Activation of the APFC, DLPFC, and one of DACC regions were all inversely related to adaptive coping in response to family stress. Another DACC region was inversely related to processing speed. There was also a trend for a positive association between stress exposure and DLPFC activation, though this should be interpreted with caution due to the small sample size. Thus, activation in regions within the prefrontal cortex and anterior cingulate cortex in response to a working memory task demonstrated associations with parent and child report of children's use of secondary control coping, a type of coping previously demonstrated to be related to executive function, and working memory specifically as well (e.g., Andreotti et al., 2012; Campbell et al., 2009).

Finally, in Hypothesis 3 for Study II, multiple linear regressions examining the effect of group status, stress exposure, and activation within the significant ROIs on children's coping were examined. Results indicated that while stress exposure was related to children's coping,

activation in the DLPFC, one of the ACC regions, and the APFC each accounted for this relation. These findings provide further evidence that chronic stress exposure may impede adaptive coping through its impacts on the areas of the brain necessary for higher order cognitions, such as working memory.

These findings, along with previous research demonstrating the associations between executive function abilities and associated brain regions and coping suggests that a potential pathway for stress putting children and adolescents at increased risk for psychopathology may be through effects on the brain regions necessary for the higher order cognitive abilities necessary for adaptive coping skills, including working memory and cognitive reappraisal. The small sample size in Study II made it difficult to examine all of these related processes together; therefore, future studies should build upon these hypotheses by examining chronic stress exposure, executive function, processing speed, coping, and symptoms of psychopathology in at-risk populations such as children of depressed parents.

The current studies indicate several future directions for continued research on the effects of stress on coping in populations exposed to chronic stress, such as children of depressed mothers. Primarily, these complicated processes and methods will require larger sample sizes to fully understand the associations between these constructs, especially group differences in neural responses to executive function tasks. Additionally, future studies examining these processes with an executive function task that has a higher ceiling and greater variance in participants' performance would help elucidate the association between activation and accuracy on such tasks. Future studies could also examine the specificity within constructs on their associations. For example, this study focused on creating a composite variable of chronic stress, including a variety of types of stressors to obtain an overall index children's stress exposure.

It is possible that different sources of chronic stress have different effects on executive functioning, processing speed, coping, and psychopathology. Similarly, children of mothers with depression were chosen as a prototype of an at-risk population exposed to chronic stress, but there are other populations exposed to chronic stress which might present different associations between these constructs. The group differences in processing speed and the association of processing speed with the DACC activation in response to the N-back task also present a future direction for research. For example, diffusion tensor imaging analyses might be a better method for examining the effects of chronic stress on processing speed and any associations with coping deficits as well.

Overall, this study provides additional evidence that chronic stress may put children and adolescents at risk for psychopathology through impediment of adaptive coping. The effects of chronic stress on the brain regions responsible for higher order cognition, executive function, and cognitive coping skills (e.g., cognitive reappraisal), such as the DLPFC, APFC, and DACC, represents a potential neural pathway by which stress impairs coping and puts children and adolescents at risk. These processes merit future investigation for further understanding of the pathways by which stress impairs coping and the implications for intervention with at-risk populations, such as children of depressed parents.

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Table 1

Group Comparisons on Demographic Information

	Controls (*n = 30)*	At-Risk Group (*n = 35)*	t/χ^2	*p*
Demographics				
Child Age	12.97 (2.03) [a]	13.04 (1.78)	-.14	ns
Child Gender	50% Female	37.1% Female	1.09	ns
Child Race	60% Caucasian	80% Caucasian	3.27	ns
Mother Age	42.33 (5.44)	43.80 (13.53)	-.56	ns
Mother Race	70% Caucasian	76.5% Caucasian	.34	ns
Mother Marital Status	66.7% Married	57.1% Married	.61	ns
Mother Education	26.7% post- HS[b]	57.1% post- HS[b]	6.11	< .01
Family Income	$73,517.24 (sd=$43,685.26)	$64,571.43 (sd=$34,549.44)	.92	ns
Clinical Descriptives- Mothers				
BDI	5.54 (5.79)	12.48 (9.76)	-3.54	< .01
SCID Current Symptoms	1.20 (1.81)	5.11 (3.80)	-5.17	< .01
Total Number of MDEs[c]	0	2.09 (2.50)	-4.59	< .01

Note.
[a]Values in parentheses indicate standard deviation.
[b]Post-HS indicates that mothers completed education beyond a high school degree.
[c]MDD Episodes indicates the number of maternal depressive episodes lasting two weeks or more within the lifetime of the child, as estimated by mothers during a structured interview

Table 2

Group Comparisons on Neurocognitive Measures, Coping, and Affective, Anxiety, and Oppositional Defiant Symptoms

	Controls (*n = 30)*	At-Risk Group (*n = 35)*	t/χ^2	*P*
Stress Exposure Composite	-.145 (.57)	.13 (.48)	-2.12	< .05
Children's Neurocognitive Scores[a]				
WASI Full Scale IQ (2 Subtests)	107.23 (11.30)[b]	106.60 (13.08)	.21	Ns
WISC-IV Coding	10.60 (3.04)	8.57 (2.68)	2.86	< .01
WISC-IV Digit Span	10.93 (2.77)	10.31 (2.90)	.88	Ns
DKEFS Trail-Making 4	10.67 (2.80)	9.94 (3.34)	.94	Ns
DKEFS Color-Word 3	10.40 (3.25)	10.57 (2.30)	-.25	Ns
DKEFS Color-Word 4	10.10 (3.04)	10.29 (2.35)	-.27	Ns
Executive Function Composite	.13 (.77)	-.09 (.59)	1.30	Ns
Internalizing and Externalizing Symptoms (Children)[c]				
CBCL Affective Symptoms	52.60 (4.53)	57.63 (7.52)	-3.32	< .01
YSR Affective Symptoms	53.67 (3.65)	55.74 (6.25)	-1.66	Ns
Affective Symptoms Composite	-.28 (.57)	.24 (.98)	-2.63	.011
CBCL Anxiety Problems	53.37 (5.35)	57.71 (7.22)	-2.78	< .01
YSR Anxiety Problems	53.10 (4.37)	52.83 (4.02)	.26	Ns
Anxiety Problems Composite	-.14 (.65)	.12 (.86)	.19	Ns
CBCL Oppositional Defiant	53.63 (5.29)	56.20 (6.23)	-1.77	Ns
YSR Oppositional Defiant	54.20 (5.40)	53.66 (4.75)	.43	Ns
Oppositional Defiant Composite	-.13 (.88)	.11 (.83)	-1.14	Ns
Child Secondary Control Coping				
Family Stress RSQ Composite	.22 (.77)	-.19 (.87)	2.02	< .05
Peer Stress RSQ Composite	.11 (.82)	-.10 (.72)	1.08	ns

Note.
Stress exposure composite includes measures of family stress, peer stress, stressful life events, and economic disadvantage. Exposure to parental depressive episodes or symptoms is *not* included in this composite.
[a]All neurocognitive measures provided are scaled scores (mean= 10, SD=3) with the exception of the Full-Scale IQ standard score (mean= 100, SD= 15)
[b]Values in parentheses indicate standard deviation.
[c]All Clinical Scores provided represent both parent-report (CBCL) and child-report (YSR). These scores are *T* scores (mean=50, SD=10)

Table 3

Correlations Among Children's Stress Exposure, Processing Speed, Executive Function, Coping, Symptoms, and Past and Current Maternal Depression

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
1. Stress Exposure	1	-.10	-.07	-.26*	-.16	.30*	.19	.39**	.18
2. Processing Speed	--	1	.53**	.15	-.07	-.20	-.23	-.21	-.28*
3. Executive Function	--	--	1	-.05	-.18	-.11	-.17	-.13	-.02
4. Secondary Control Coping-Family Stress	--	--	--	1	.67**	-.56**	-.47**	-.51**	-.33**
5. Secondary Control Coping-Peer Stress	--	--	--	--	1	-.37**	-.19	-.33**	-.09
6. Affective Symptoms	--	--	--	--	--	1	.48**	.47**	.26*
7. Anxiety Symptoms	--	--	--	--	--	--	1	.34**	.15
8. Oppositional Defiant Symptoms	--	--	--	--	--	--	--	1	.08
9. Past and Current Maternal Depression	--	--	--	--	--	--	--	--	1

Note. All constructs represent composite variables (see Methods)

*p< .05

**p< .01

Table 4

Correlations Among Children's Stress Exposure, Processing Speed, Executive Function, Coping, Symptoms, and Past and Current Maternal Depression, by group

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
1. Stress Exposure	1	.22	-.09	-.25	-.12	.17	.15	.19	-.03
2. Processing Speed	-.21	1	.45**	.24	.12	-.21	-.29	-.17	-.31
3. Executive Function Composite	-.02	.62**	1	-.02	-.07	-.09	-.07	-.04	-.08
4. Secondary Control Coping-Family Stress	-.17	-.13	-.14	1	.63**	-.45**	-.56**	-.55**	-.25
5. Secondary Control Coping-Peer Stress	-.14	-.34	-.30	.71**	1	-.28	-.24	-.37*	.05
6. Affective Symptoms	.41*	.06	-.12	-.74**	-.51**	1	.51**	.42*	.03
7. Anxiety Symptoms	.16	-.07	-.27	-.25	-.10	.32	1	.32	.04
8. Oppositional Defiant Symptoms	.55**	-.18	-.19	-.43*	-.25	.57**	.33	1	-.10
9. Past and Current Maternal Depression	.17	.38*	.19	-.32	-.16	.42*	.10	.22	1

Note. Values in top-half diagonal (in grey) represent correlations among constructs for the children of mothers with a history of depression while values in bottom-half diagonal (in white) represent correlations among constructs for control group.

*p< .05

*p< .01

Table 5. *Linear regression with maternal depression history group status, stress exposure, executive function, and coping predicting children's affective symptoms.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	.29	2.36	.02
Step 2			
Group Status	.23	1.88	.06
Stress Exposure	.24	1.90	.06
Step 3			
Group Status	.23	1.10	.28
Stress Exposure	.23	1.24	.22
Executive Function	-.08	-.66	.51
Step 4			
Group Status	.13	1.18	.24
Stress Exposure	.13	1.14	.26
Executive Function	-.12	-1.12	.27
Coping	-.51	-4.60	< .01

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, and family stressors. Executive function: includes the Digit Span subtest of the WISC-IV and the Trail-Making and Color-Word Interference subtests of the DKEFS. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 6. *Linear regression with maternal depression history group status, stress exposure, executive function, and coping predicting children's anxiety symptoms.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	.18	1.40	.17
Step 2			
Group Status	.14	1.06	.29
Stress Exposure	.16	1.27	.21
Step 3			
Group Status	.13	.99	.33
Stress Exposure	.16	1.22	.23
Executive Function	-.15	-1.15	.25
Step 4			
Group Status	.04	.33	.75
Stress Exposure	.06	.52	.61
Executive Function	-.18	-1.60	.11
Coping	-.46	-3.85	< .01

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, and family stressors. Executive function: includes the Digit Span subtest of the WISC-IV and the Trail-Making and Color-Word Interference subtests of the DKEFS. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 7. *Linear regression with maternal depression history group status, stress exposure, executive function, and coping predicting children's oppositional defiant symptoms.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	.15	1.22	.23
Step 2			
Group Status	.06	.50	.62
Stress Exposure	.39	3.19	< .01
Step 3			
Group Status	.06	.45	.66
Stress Exposure	.38	3.14	< .01
Executive Function	-.10	-.86	.39
Step 4			
Group Status	-.04	-.31	.76
Stress Exposure	.29	2.60	.012
Executive Function	-.14	-1.32	.19
Coping	-.46	-4.16	< .01

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, and family stressors. Executive function: includes the Digit Span subtest of the WISC-IV and the Trail-Making and Color-Word Interference subtests of the DKEFS. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 8. *Linear regression with maternal depression history group status, stress exposure, processing speed, and coping predicting children's affective symptoms.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	.30	2.53	.01
Step 2			
Group Status	.24	1.99	.051
Stress Exposure	.24	2.00	.055
Step 3			
Group Status	.21	1.61	.11
Stress Exposure	.24	1.94	.057
Processing Speed	-.11	-.84	.40
Step 4			
Group Status	.12	1.09	.28
Stress Exposure	.14	1.24	.22
Processing Speed	-.07	-.66	.51
Coping	-.49	-4.49	< .01

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, and family stressors. Processing Speed: measured by the Coding subtest of the WISC-IV. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 9. *Linear regression with maternal depression history group status, stress exposure, processing speed, and coping predicting children's anxiety symptoms.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	.16	1.32	.19
Step 2			
Group Status	.12	.96	.34
Stress Exposure	.16	1.24	.22
Step 3			
Group Status	.06	.42	.68
Stress Exposure	.16	1.24	.22
Processing Speed	-.20	-1.53	.13
Step 4			
Group Status	-.02	-.14	.89
Stress Exposure	.07	.57	.57
Processing Speed	-.17	-1.43	.16
Coping	-.43	-3.64	< .01

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, and family stressors. Processing Speed: measured by the Coding subtest of the WISC-IV. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 10. *Linear regression with maternal depression history group status, stress exposure, processing speed, and coping predicting children's oppositional defiant symptoms.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	.14	1.14	.26
Step 2			
Group Status	.04	.36	.72
Stress Exposure	.38	3.15	< .01
Step 3			
Group Status	-.02	-.13	.90
Stress Exposure	.38	3.17	< .01
Processing Speed	-.18	-1.46	.15
Step 4			
Group Status	-.09	-.78	.44
Stress Exposure	.29	2.62	.011
Executive function	-.15	-1.36	.18
Coping	-.44	-3.98	< .01

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, and family stressors. Processing Speed: measured by the Coding subtest of the WISC-IV. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 11

Group Comparisons on Demographic Information

	Controls (*n = 8)*	MDD group (*n = 8)*	t/χ^{2a}	*p*
Demographics	M (SD)	M (SD)		
Child Age	14.19 (.84)[a]	13.98 (.97)	.45	ns
Child Gender	50% Female	50% Female	0.00	ns
Child Race	50% Caucasian	62.5% Caucasian	.25	ns
Mother Age	45.75 (6.49)	38.68 (3.70)	2.54	< .05
Mother Race	50% Caucasian	62.5% Caucasian	.25	ns
Mother Marital Status	62.5% Married	37.5% Married	1.00	ns
Mother Education	12.5% Post-HS[b]	87.5% Post-HS[b]	9.00	< .01
Family Income	$70,000 ($22,834.81)	$60,125 ($31,593.12)	.72	ns

[a]Chi-square analyses could not be traditionally used because of the small sample size so these were computed only for a 2x2 table.
[b]Post-HS indicates that mothers completed education beyond a high school degree.

Table 12

Group Comparisons on Stress Exposure, Neurocognitive Scores from Study I, BRIEF Scores, N-back Performance, Symptoms from Study I and Coping from Study I

	Controls (*n = 8)*	MDD group (*n = 8)*	t/χ^2	*P*	*Cohen's d*
	M (SD)	M (SD)			
Stress Exposure Composite	-.19 (.51)	-.03 (.30)	-.74	ns	.28
Children's Neurocognitive Scores					
WASI Full Scale IQ (2 Subtests)	103.25 (14.64)	113.13 (10.86)	-1.53	ns	.77
Executive Function Composite	.35 (.44)	-.24 (.73)	1.94	ns	.98
Processing Speed (Coding subtest)	9.88 (4.32)	10 (1.85)	-.08	ns	.04
BRIEF[a,b] Scores					
Inhibit Scale	49.13 (7.97)	59 (12.28)	-1.91	ns	.95
Shift Scale	51.88 (10.18)	57.38 (12.33)	-.97	ns	.49
Emotional Control Scale	48.88 (9.46)	56.63 (11.06)	-1.51	ns	.75
Behavioral Regulation Index	50.00 (8.96)	58.38 (11.92)	-1.59	ns	.79
Initiate Scale	48.50 (10.13)	63.25 (6.41)	-3.48	< .01	1.74
Working Memory Scale	49.63 (9.81)	64.25 (9.87)	-2.97	.01	1.49
Plan/Organize Scale	47.75 (8.76)	64.13 (7.57)	-4.00	< .01	2.00
Organization of Materials Scale	54.00 (11.94)	62.50 (10.97)	-1.48	ns	.74
Monitor Scale	46.75 (9.00)	58.13 (6.10)	-2.96	.01	1.48
Meta Cognition Index	49.13 (10.18)	64.63 (4.63)	-3.92	< .01	1.96
Global Executive Composite	49.38 (10.17)	63.50 (6.97)	-3.24	< .01	1.62
N-Back Performance					
0-Back Hits	9 (0)	9 (0)	.00	ns	--
0-Back False Positives	.25 (.46)	.25 (.46)	.00	ns	--

0-Back Omissions	0 (0)	0 (0)	.00	ns	--
0-Back Response Time	524.97 (123.89)	548.40 (58.82)	-.48	ns	.24
1-Back Hits	9 (0)	8.88 (.35)	1.00	ns	.48
1-Back False Positives	.38 (.74)	.38 (.52)	.00	ns	0
1-Back Omissions	0 (0)	.13 (.35)	-1.00	ns	.53
1-Back Response Time	556.44 (137.95)	601.83 (84.27)	-.79	ns	.40
2-Back Hits	8.75 (.46)	8 (1.41)	1.43	ns	.72
2-Back False Positives	.75 (.71)	.50 (.76)	.68	ns	.34
2-Back Omissions	.25 (.46)	1 (1.41)	-1.43	ns	.72
2-Back Response Time	685.62 (89.78)	670.62 (101.66)	.31	ns	.16
3-Back Hits	6.75 (.71)	5.25 (2.60)	1.57	ns	.79
3-Back False Positives	1.25 (1.04)	1.25 (1.04)	.00	ns	0
3-Back Omissions	2.25 (.71)	3.75 (2.60)	-1.57	ns	.79
3-Back Response Time	869.23 (147.04)	820.53 (183.24)	.59	ns	.29
Total Number of Errors	5.13 (2.36)	7.25 (3.65)	-1.38	ns	.69
Overall Average Reaction Time	659.07 (104.65)	660.34 (78.54)	-.03	ns	.01
Internalizing and Externalizing Symptoms (Children)[c]					
Affective Symptoms Composite	-.57 (.44)	.20 (1.05)	-1.89	ns	.96
Anxiety Problems Composite	-.10 (.64)	.23 (.66)	-1.02	ns	.51
Oppositional Defiant Composite	-.30 (.67)	.21 (1.07)	-1.15	ns	.57
Child Secondary Control Coping					
Family Stress RSQ Composite	.48 (.42)	.20 (.97)	.76	ns	.37

Note. Stress exposure composite includes measures of family stress, peer stress, stressful life events, and economic disadvantage. Exposure to parental depressive episodes or symptoms is *not* included in this composite.

[a]BRIEF= Behavior Ratings Inventory of Executive Function

[b]Higher scores reflect more problems with executive function

[c]All Clinical Scores provided represent both parent-report (CBCL) and child-report (YSR). These scores are *T* scores (mean=50, SD=10)

Table 13.

Significant BOLD fMRI Responses During the N-back Task

				Talairach Coordinates					
	Region	Hemisphere	BA	x	y	z	*F*	*p*	# Voxels
Whole Group	DLPFC	R	9	33	18	33	6.40	< .001	26685
	DACC[1]	L	32	-19	22	35	2.69	< .001	35837
Between Groups	APFC	R	10	16	49	11	2.96	< .001	130
	DACC[2]	L	32	-21	11	29	2.90	< .001	905
	DACC[3]	L	32	-22	36	17	2.60	< .001	109

Note. BA = Brodmann Area; DLPFC = Dorsolateral Prefrontal Cortex; DACC = Dorsal Anterior Cingulate Cortex; APFC= anterior prefrontal cortex; R = Right hemisphere; L = Left hemisphere.

Table 14. Correlations Among Brain Activation in Response to the N-Back Task, Children's Stress Exposure, Executive Function, Processing Speed, BRIEF Scores, N-Back Performance, Coping, and Symptoms

	DLPFC (BA9)	DACC (BA32)[1]	APFC (BA10)	DACC (BA32)[2]	DACC (BA32)[3]
Stress Exposure	.43[+]	.28	.60*	.31	-.01
Executive Function Composite	-.31	-.29	.04	-.10	-.18
Processing Speed	-.25	-.08	.08	-.55*	-.20
BRIEF GEC[a]	.06	-.13	.18	.37	-.40
N-back Errors	-.06	-.19	-.26	-.12	-.16
N-back RT	.05	.03	-.09	.20	-.24
Secondary Coping- Family Stress	-.66**	-.59*	-.88**	-.23	-.22
Affective Symptoms (Composite)	-.36	-.40	-.29	-.09	-.16
Anxiety Symptoms (Composite)	-.08	-.10	-.05	-.03	-.01
Oppositional Defiant Symptoms (Composite)	-.16	-.21	.03	.06	-.22

Note. DLPFC= dorsolateral prefrontal cortex; DACC= dorsal anterior cingulate cortex; APFC= anterior prefrontal cortex

[a]BRIEF GEC= Global Executive Composite from the Behavioral Rating Inventory of Executive Function

*p< .05

**p< .01

[+]p= .10

Table 15. *Linear regression with maternal depression history group status, stress exposure, and DLPFC activation predicting children's coping.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	-.20	-.76	.46
Step 2			
Group Status	-.10	-.41	.69
Stress Exposure	-.52	-2.22	.045
Step 3			
Group Status	-.01	-.06	.96
Stress Exposure	-.32	-1.44	.18
DLPFC Activation	-.52	-2.30	.04

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, family stressors, intrusive and neglectful parenting, items from the PSS, exposure to traumatic events. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 16. *Linear regression with maternal depression history group status, stress exposure, and DACC[1] activation predicting children's coping.*

Model	Beta (β)	t-value	p-value
Step 1 Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	-.20	-.76	.46
Step 2 Group Status Stress Exposure	-.10 -.52	-.41 -2.22	.69 .045
Step 3 Group Status Stress Exposure DCC[1] Activation	-.13 -.38 -.49	-.66 -1.79 -2.32	.53 .10 .04

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, family stressors, intrusive and neglectful parenting, items from the PSS, exposure to traumatic events. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 17. *Linear regression with maternal depression history group status, stress exposure, and APFC activation predicting children's coping.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	-.20	-.76	.46
Step 2			
Group Status	-.10	-.41	.69
Stress Exposure	-.52	-2.22	.045
Step 3			
Group Status	.08	.53	.61
Stress Exposure	-.02	-.14	.90
APFC Activation	-.89	-5.06	< .01

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, family stressors, intrusive and neglectful parenting, items from the PSS, exposure to traumatic events. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 18. *Linear regression with maternal depression history group status, stress exposure, and DACC^2 activation predicting children's coping.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	-.20	-.76	.46
Step 2			
Group Status	-.10	-.41	.69
Stress Exposure	-.52	-2.22	.045
Step 3			
Group Status	-.09	-.33	.74
Stress Exposure	-.51	-2.01	.07
DACC^2 Activation	-.05	-.18	.86

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, family stressors, intrusive and neglectful parenting, items from the PSS, exposure to traumatic events. Coping: secondary control coping as reported on the family stress version of the RSQ.

Table 19. *Linear regression with maternal depression history group status, stress exposure, and DACC[3] activation predicting children's coping.*

Model	Beta (β)	t-value	p-value
Step 1			
Group Status (children of mothers with a history of depression vs. children of mothers with no history of depression)	-.20	-.76	.46
Step 2			
Group Status	-.10	-.41	.69
Stress Exposure	-.52	-2.22	.045
Step 3			
Group Status	-.14	-.60	.56
Stress Exposure	-.52	-2.21	.048
DACC[3] Activation	-.25	-1.07	.31

Note: Stress Exposure: includes stressful life events from the APES, economic disadvantage, social stressors, family stressors, intrusive and neglectful parenting, items from the PSS, exposure to traumatic events. Coping: secondary control coping as reported on the family stress version of the RSQ.