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Stress, coping, executive function, and brain activation in adolescent offspring of depressed and nondepressed mothers

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Abstract
This study examined the associations among chronic stress, activation in the prefrontal cortex (PFC), executive function, and coping with stress in at-risk and a comparison sample of adolescents. Adolescents (N = 16; age 12–15) of mothers with (n = 8) and without (n = 8) a history of depression completed questionnaires, neurocognitive testing, and functional neuroimaging in response to a working memory task (N-back). Children of depressed mothers demonstrated less activation in the anterior PFC (APFC) and both greater and less activation than controls in distinct areas within the dorsal anterior cingulate cortex (dACC) in response to the N-back task. Across both groups, activation of the dorsolateral PFC (DLPFC; Brodmann area [BA9]) and APFC (BA10) was positively correlated with greater exposure to stress and negatively correlated with secondary control coping. Similarly, activation of the dACC (BA32) was negatively correlated with secondary control coping. Regression analyses revealed that DLPFC, dACC, and APFC activation were significant predictors of adolescents’ reports of their use of secondary control coping and accounted for the effects of stress exposure on adolescents’ coping. This study provides evidence that chronic stress may impact coping through its effects on the brain regions responsible for executive functions foundational to adaptive coping skills.

The concepts of stress, coping, and emotion regulation are central in models of risk and resilience for psychopathology in children and adolescents. Exposure to chronic stress puts individuals at increased risk for symptoms of psychopathology, including anxiety and depression, and the effects of stress may be particularly pronounced during adolescence (e.g., Vrshek-Schallhorn et al., 2015). In contrast, across various populations of children and adolescents exposed to stress, coping and emotion regulation skills have been demonstrated to be an important source of resilience to the adverse effects of stress and the development of psychopathology (e.g., Compas, Jaser, et al., 2014; Eisenberg, Spinrad, & Eggum, 2010). It is noteworthy that some of the wide-ranging...
adverse effects of chronic stress may occur through disruption in functioning in the prefrontal cortex (PFC), impacting important aspects of executive function (e.g., Radley, Morilak, Viguia, & Campeau, 2015). These effects may also include impairments in the ability to regulate emotions and cope with stress, as the brain regions responsible for coping and emotion regulation, especially regions of the PFC, are among the most vulnerable to the deleterious effects of chronic stress (e.g., Admon et al., 2009; Arnsten, 2015; Rahdar & Galván, 2014; Shansky, Hamo, Hof, McEwen, & Morrison, 2009). Thus, the effects of chronic stress may be twofold: chronic stress may directly contribute to higher rates of symptoms of psychopathology and chronic stress may impede adaptive coping with stress. However, the biological, cognitive, and psychological effects of chronic stress on the ability to cope are not well understood.

Coping refers to “conscious volitional efforts to regulate emotion, cognition, behavior, physiology, and/or the environment in response to stressful events or circumstances” (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001, p 89). The closely related construct of emotion regulation includes processes or strategies that allow individuals to change the duration or magnitude of an emotional response (Gross, 2013), including emotions that are experienced in response to stressful events or chronic adversity (e.g., Aldao, Nolen-Hoeksema, & Schweizer, 2010; Joormann & Vanderlind, 2014). Within a control-based model, coping behaviors can be categorized into three distinct sets of responses: primary control coping (e.g., problem solving, emotion modulation), secondary control coping (e.g., cognitive reappraisal, acceptance), and disengagement coping (e.g., avoidance, denial) (e.g., Connor-Smith, Compas, Wadsworth, Thomsen, & Saltzman, 2000; Weisz, McCabe, & Dennig, 1994). Strategies included in secondary control coping include acceptance, distraction, cognitive reappraisal, and positive thinking and are also widely studied as examples of emotion regulation skills. These skills are best suited for stressful situations or events that are not under an individual’s control. Secondary control coping is associated with better psychological adjustment (i.e., lower levels of internalizing and externalizing symptoms) across samples of children and adolescents facing uncontrollable chronic stress, such as economic hardship (e.g., Wadsworth & Compas, 2002; Wadsworth et al., 2008) or chronic illness (e.g., Compas, Desjardins, et al., 2014; Compas et al., 2006).

These processes have particular relevance for adolescents who are at risk due to high levels of chronic stress associated with parental depression. Parental depression puts children and adolescents at an increased risk for both internalizing and externalizing symptoms and disorders through several processes, including exposure to stressful family environments (e.g., Goodman, 2007, National Research Council/Institute of Medicine [NRC/IOM], 2009). Parent–child interactions in families of parents with a history of depression are characterized by parental withdrawal, parental intrusiveness, and marital conflict and are sources of chronic stress (Lovejoy, Gracyzyk, O’Hare, & Neuman, 2000). Secondary control coping is especially important for children and adolescents faced with the uncontrollable stress of living with a depressed parent. Secondary control coping is related to lower levels of anxiety and depression in this population (e.g., Dunbar et al., 2013; Jaser et al., 2005; Langrock, Compas, Keller, Merchant, & Copeland, 2002), and interventions teaching these coping skills to children of depressed parents have demonstrated effectiveness in reducing these symptoms.
(Compas et al., 2010, 2011). Further, greater use of secondary control coping is related to a biological marker of stress (i.e., lower diurnal levels of cortisol) in daughters of mothers with history of depression (Foland-Ross, Kircanski, & Gotlib, 2014).

An important next step in research on coping is to identify factors that may be related to individual differences in the use of secondary control coping strategies. Several processes that affect coping are relevant to adolescents of depressed parents. Executive function refers to a set of higher-order cognitive processes that are responsible for controlling and regulating behaviors and emotions and includes working memory/updating, attention/inhibitory control, and cognitive flexibility (e.g., Diamond, 2013; Miyake & Friedman, 2012). Chronic stress is one factor that may impact coping in children and adolescents through impairment of executive function. For example, Quinn and Joormann (2015) found that stress-induced change in executive control in older adolescents predicted an increase in depression symptoms several months later. One executive function skill particularly relevant to the ability to cope with stress is working memory, which involves the ability to actively maintain and manipulate information over a brief period of time. Working memory is related to activation in regions of the PFC (e.g., Baddeley, 2012; Wager & Smith, 2003). Owen, McMillan, Laird, and Bullmore (2005) reviewed the findings of 24 functional neuroimaging studies using the N-back working memory paradigm with adults and found evidence of robust activation in several brain regions, including the dorsal anterior cingulate cortex (dACC) and the dorsolateral PFC (DLPFC). Studies examining activation during the N-back within samples of children and adolescents have similarly identified prefrontal-parietal network activation in response to this working memory paradigm (e.g., Nelson et al., 2000; Robinson et al., 2010, 2014). Further, both children and adolescents of depressed parents and those with depressive disorders show abnormalities in brain structure and function in brain regions that are involved in executive function, including areas of the ACC and the PFC (e.g., Foland-Ross, Gilbert, Joormann, & Gotlib, 2015; Miller, Hamilton, Sacchet, & Gotlib, 2015).

Adverse effects of stress on prefrontal regions and executive function, including working memory, have implications for how children and adolescents are able to regulate emotions and cope with stress. For example, cognitive reappraisal is a secondary control coping skill that involves thinking about a stressor differently or changing one’s perspective on a stressor and therefore utilizes working memory (e.g., Andreotti et al., 2013; Campbell et al., 2009; Ochsner & Gross, 2005; Robinson et al., 2015). Individuals with impaired executive function may also demonstrate impairment in the ability to use adaptive approaches to cope with stress. Campbell et al. (2009) found that poor executive function skills were related to less use of secondary control coping, and less use of secondary control coping accounted for the relation between executive function and emotional and behavioral problems in a sample of children and adolescents with cancer. In a study of pediatric brain tumor patients, Robinson et al. (2015) found that increases in brain activation in prefrontal regions in response to a working memory task were associated with greater use of secondary control coping strategies and better psychosocial functioning. Further, coping accounted for a significant portion of the association between brain activation and behavioral and emotional problems (Robinson et al., 2015). Given the high levels of chronic stress associated with parental depression, children of parents with a history of depression provide an important
opportunity to examine the associations among chronic stress, executive function, and coping.

The current study provides one of the first examinations of the associations among chronic stress, prefrontal activation, executive function, and secondary control coping in children of mothers with and without a history of depression. First, we hypothesized that adolescents of depressed mothers, as compared with adolescents of mothers with no history of depression, would demonstrate different patterns of activation in the PFC, specifically in those regions previously demonstrated to be activated in response to working memory tasks (e.g., DLPFC, ACC). There is limited evidence regarding functional neural differences in these regions in adolescents of depressed parents specifically, and the evidence in research on both children and adults with depression has been mixed. That is, some studies have demonstrated hyperactivation of prefrontal regions in individuals with a history of depression while other studies have demonstrated hypoactivation of prefrontal regions in individuals with a history of depression. Further, some studies demonstrate hypoactivation of some regions and hyperactivation of other regions within the PFC and associated neural networks within the same study (e.g., Hamilton et al., 2012; Miller et al., 2015). Therefore, while we predicted differences between groups, analyses regarding group differences in prefrontal activation were exploratory in nature in regard to whether adolescents of depressed mothers would display hyperactivation versus hypoactivation as compared to controls. Second, we hypothesized for both adolescents of mothers with and without a history of depression, activation in the PFC in response to a working memory task would be related to stress exposure, executive function, and secondary control coping. We hypothesized that greater stress exposure would be related to poorer performance on executive function tasks and less use of secondary control coping. As noted above, given inconsistency in the field, analyses examining the relationship between stress exposure and activation in the PFC were exploratory in terms of hyperactivation versus hypoactivation. Third, we hypothesized that group status (adolescents of depressed mothers versus nondepressed mothers) and greater stress exposure would predict lower levels of secondary control coping, but that activation in the PFC in response to a working memory task would partially account for the associations between group status, stress exposure, and coping.

Method

Participants

The current study included 16 adolescents (age 12–15; M = 14.09, SD = 0.88; 50% female) and their mothers (M age = 42.67, SD = 6.19). Families were recruited from a larger study examining how mothers with and without histories of depression and their children (age 9–15) communicate and cope with stress (N = 65 families). The current study focused on a smaller age range to control for possible changes in brain development associated with puberty and to have a more developmentally homogenous sample. Families were eligible for the current study if the child was 12–15 years old at the time of enrollment and if the child was determined eligible following a screening to insure their safety to complete magnetic resonance imaging (MRI) (e.g., children with braces or implanted metal, children with histories of claustrophobia were ineligible).
potential participants were excluded because they had orthodontic devices or braces and one participant was unable to complete the scan due to significant claustrophobia during mock neuroimaging practice. Participant tolerated the protocol without incident and no participants had to be excluded due to excess movement (>3 mm) during the scan.

Efforts were taken to recruit age- and gender-matched participants for each group (adolescents of mothers with and without histories of depression). Recruitment started with adolescents of mothers with a history of depression and followed with age- and gender-matched adolescents of mothers without a history of depression.

**Procedure**

Participants completed the current study in two sessions: (1) an initial behavioral research session and (2) a subsequent neuroimaging session. The initial study session included structured clinical interviews with the mothers, questionnaires completed by mothers and adolescents, and evaluation of executive function skills with the adolescent. At the second session, adolescents and their mothers completed an additional set of questionnaires. Adolescents then completed a “mock” neuroimaging session to become familiar with the enclosed scanning space and the scanning procedures. Adolescents were guided through a practice N-back task prior to the neuroimaging session in order to become familiar with the task instructions. Adolescents then completed structural and functional MRI scans. Study sessions were conducted at a university research laboratory and imaging center. All procedures were approved by the university institutional review board, and all participants provided informed consent.

**Neuroimaging**

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 and functional analysis and providing measures of brain structure and function in an exam of 60–70 min. Following a certified technician’s review of the MRI safety screening form, adolescents were placed in the scanner by the technician and trained study personnel. 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 a response pad, and they were able to communicate reciprocally with study personnel throughout the scan through head-phones and a microphone.

**Measures**

*Demographic information.* Mothers completed a basic demographic questionnaire assessing socioeconomic status, marital status, and mother and child race, ethnicity, and age.

*Maternal depression history and current depressive symptoms.* Maternal depression was assessed through semi-structured clinical interview. Mothers were administered the major depressive disorder module of the Structured Clinical Interview for DSM-IV
Diagnoses (First, Spitzer, Gibbon, & Williams, 2001) to establish mothers’ depression history status. Mothers also completed the Beck Depression Inventory-II (BDI-II; Beck, Steer, Ball, & Ranieri, 1996) as a measure of current depressive symptoms ($\alpha = .97$).

**Exposure to chronic stress.** In order to best capture adolescents’ exposure to stress, chronic stress was sampled across different sources of stress, including stressors associated with parental depression, family conflict, peer stress, economic disadvantage, stressful major life events, daily hassles, and the experience of chronic stress. Stressor items from the parental depression, family stress, and social stress versions of the Responses to Stress Questionnaire (RSQ; Connor-Smith et al., 2000; Wadsworth & Compas, 2002) were completed by mothers and adolescents. Items are rated on a 1–4 scale, the frequency and intensity with which children and adolescents have been exposed to specific stressors in the past 6 months, including uncertainty about how parent(s) will react when the child asks for something, conflict with siblings and/or parents, and being teased and/or hassled by other kids (mean $\alpha$ across reporters and versions = .74).

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., Reising et al., 2013; Wadsworth & Achenbach, 2005). In addition, mothers and adolescents completed the Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983) during their evaluation, a well-validated 10-item questionnaire that gauges chronic stress on a 40-point scale (child self-report $\alpha = .80$, parent report $\alpha = .69$). Lastly, adolescents completed the Adolescent Perceived Events Scale (Compas, Davis, Forsythe, & Wagner, 1987), 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) that have occurred in the past 3 months. In order to obtain an overall index of the child’s exposure to chronic stress, each score was transformed into a $z$-score and the mean of the $z$-scores was used a composite index of chronic stress.

**Executive function.** Adolescents completed the Digit Span subtest of the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler, 2003), an index of working memory. Adolescents also completed the Trail-Making and Color-Word Interference tests of the Delis–Kaplan Executive Functioning System (DKEFS; Delis, Kaplan, & Kramer, 2001), which provide an index of working memory and inhibition, respectively. The scores on the WISC-IV and DKEFS tests were transformed into $z$-scores and the average was used as an executive function composite in analyses.

**Child coping.** The family stress version of the RSQ (Connor-Smith et al., 2000; Wadsworth & Compas, 2002) was completed by mothers and adolescents. The RSQ includes 57 items that assess how the child copes with family-related stressors in the past 6 months. The RSQ has well-established reliability and validity in studies with diverse samples (e.g., Connor-Smith et al., 2000; Wadsworth, Rieckmann, Benson, & Compas, 2004). A five-factor model of responses to stress has been established and supported by confirmatory factor analyses across diverse samples of children and adolescents (e.g., Benson et al., 2011; Compas et al., 2006; Connor-Smith et al., 2000; Wadsworth et al., 2004; Yao et al., 2010). The five factors include three coping factors
and two stress reactivity factors. For the current study, the secondary control coping factor was examined. A composite index of secondary control coping using mother report on the adolescent and adolescent self-report was created by converting both reports to z-scores; the mean of the z-scores was used in analyses as a composite of adolescent secondary control coping. Internal consistency for secondary coping was adequate across reporters and stressors (all α’s >.75).

Functional MRI (fMRI) task. During fMRI, adolescents completed a letter version of the N-back task (Barch, Sheline, Csernansky, & Snyder, 2003), which is designed to assess verbal working memory. 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 letter was identical to the one preceding it (e.g., M, M). In the 2-back condition, participants responded only when the letter was identical to the one presented two trials prior (e.g., M, T, M), and in the 3-back condition, participants responded when the letter 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 (approximately 31 s per block). Each block contained 15 letters presented for 2 s each, and three of these letters required a response. The entire task was 6 min 24 s in length; however, the first six images acquired were not active parts of the task, so the 186 images acquired during the active part of the N-back task were 6 min and 12 s in duration. This task has been used effectively in this age group with no adverse effects (e.g., Robinson et al., 2014). 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, 22 s scan time) from which 33 oblique axial slices (parallel to the anterior commissure-posterior commissure (AC-PC) plane) were prescribed. High-resolution three-dimensional (3D) anatomical images were acquired using an inversion-prepared spoiled gradient recalled echo sequence (IR-3D-TFE), with an inversion time T1 of 400 ms, a repetition time (TR) of 15 ms, minimum echo time (TE; 3 ms), a matrix size 256 × 256 for a field of view (FOV) of 256 × 255 × 270 mm with near isotropic resolution. From this anatomical image, 33 axial slices were obtained, at an oblique angle, in AC-PC orientation, for use in functional data analysis. All functional images were acquired with a gradient echo planar imaging pulse sequence, with TE 30 ms (optimized for T2* at 3 T), flip angle of 70°, TR 2000 ms, 33 slices 3.5 mm thick, and .35 mm gap thickness, yielding a FOV of 240 × 240 (anterior–posterior, right–left) and a matrix size of 80 × 80 (reconstructed to 128 × 128) sampled at ±62.5 kHz. The first six image volumes of the functional image data set were discarded to allow magnetization to reach equilibrium.

Data analyses

Statistical power. Due to the relatively small sample size (N = 16; n = 8 per group), the power to detect statistical significance at p < .05 is limited to only large effects. Therefore, in addition to discussing findings in terms of statistical significance, group
differences reaching Cohen’s threshold for medium \((d = .5–.8)\) and large effects \((d = .8\) or larger) were also identified (Cohen, 1992). Further, a subset of analyses was conducted using the whole sample, using stress exposure as a continuous variable (as opposed to group status as a dichotomous variable) to examine individual differences in coping.

**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. Additionally, high-pass filtering and smoothing were done using a frequency space filter with a cutoff of two cycles. Motion correction results were assessed to ensure that all data fell within movement criteria (<3 mm displacement, 3° rotation). As previously stated, no participants had to be excluded due to excess motion. Individualized design matrices were generated for these participants for group analysis.

The functional data for each participant was aligned to the participant’s high-resolution 3D anatomic data set. N-Back data were modeled using a block design and task time-course reference files were included in individual subject level analyses convolved with a double-gamma hemodynamic response function. Each participant’s activation map was normalized to a common reference space (Talairach), using registration techniques. This process effectively resampled functional data to a voxel size of \(3 \times 3 \times 3\) mm. However, for the sake of continuity with anatomi cal images, volume will be discussed henceforth in anatomical voxel size \((1 \times 1 \times 1)\) mm. Following Talairach transformation, within-group general linear modeling (GLM) analyses were conducted by designing a multi-study design matrix (see details below). Cluster level thresholds were applied to correct for multiple comparisons via 1000 iterations of a Monte Carlo simulation. For the current analyses, this process yielded a cluster threshold of 8 functional voxels (216 anatomical voxels) for examining the main effect of N-back level, and a cluster threshold of 4 functional voxels (108 anatomical voxels) for examining specific N-back level contrasts between groups. Each of these cluster thresholds maintained a significance criterion of \(p < .001\), deemed likely to adequately reduce the likelihood of Type 1 error in subsequent analyses. 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. Details regarding the identified ROIs are provided in the "Results" section. 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 analyses.** Analyses 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 (ANCOVA) were conducted to determine whether patterns of activation differed as a whole between groups, or between different levels of the N-back. Between-group GLM
and ANCOVA were conducted to detect blood-oxygen-level dependent (BOLD) signal differences between the adolescents of depressed mothers and adolescents of nondepressed mothers in response to the N-back task during the fMRI. Specifically, activation in response to the 3-back versus the 0-back was examined. Clusters within a priori ROIs in the PFC and dACC were considered. In order to examine associations between activation in a priori ROIs indicated by whole group and between-group GLM and ANCOVA and other constructs of interest, a series of Pearson correlations was used. Correlations were examined between BOLD signal differences for the 3-back versus 0-back contrast in the ROIs, stress exposure, executive function performance, N-back performance, and secondary control coping. Linear regressions were utilized to examine whether activation within a priori ROIs indicated by whole group and between-group GLM and ANCOVA accounted for the association between group status, stress exposure, and use of secondary control coping. Group status was entered (Step 1), followed by stress exposure (Step 2). Lastly, each ROI was added (Step 3). Separate regressions were examined for each ROI due to the high correlation of activation among these related regions within the brain.

Results

Demographic information for mothers and children are presented in Table 1. Adolescents of mothers with a history of depression and adolescents of mothers without a history of depression were matched for age and gender as closely as possible. Adolescents of mothers with and without depression histories did not differ significantly on age, pubertal status, race, or family income, but did differ on maternal age and education. Mothers with a history of depression were younger (mean age = 38.68 versus 45.75, $p < .05$) and had more education (87.5% had completed education beyond high school versus 12.5%, $p < .01$) than mothers without a history of depression. Data on father education was not available; therefore, only maternal education was used to estimate socioeconomic status and economic strain. Fifty-six percent of children enrolled in the current study were Euro-American, 37.5% African American, and 6.3% Asian American.

N-back task performance and brain activation

N-back performance and brain activation was examined across the groups as well as between groups. Several ROIs were indicated in these analyses. Because multiple clusters within the dACC were identified in the whole group and between-group

| Table 1. Group comparisons on demographic information. |
|---------------------------------|---------------|-----|-----|
|                                | Controls ($n = 8$) | MDD group ($n = 8$) | $t/\chi$ | $p$ |
| Demographics                   | M (SD)         | M (SD)         |       |     |
| Child age                      | 14.19 (.84)    | 13.89 (.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$^a$ | 87.5% Post-HS$^a$ | 9.00  | < .01 |
| Family income                  | $70,000 ($22,834.81) | $60,125 ($31,593.12) | .72   | ns  |

$^a$Post-HS indicates that mothers completed education beyond a high school degree. HS: high school.
analyses, we have referred to these clusters with superscripts for clarification. As expected, for the full sample, as the N-back increased in difficulty from 0-back to the 3-back, adolescents made more errors (mean errors = 0.25 versus 4.25, respectively) and demonstrated slower reaction times (mean reaction times = 536.69 ms versus 844.44 ms, respectively). Brain regions activated by the N-back task across both groups are presented in Table 2. As hypothesized, clusters within the PFC and dACC as well as other regions related to more basic processes involved in the task such as visual processing displayed greater activation in response to the most challenging condition of the N-back (3-back) as compared with the easiest condition (0-back). Both adolescents of mothers with and without a history of depression demonstrated differences in response to the 0-back and 3-back conditions in two a priori ROIs: the right DLPFC (Brodmann area [BA9]; Talairach coordinates: 33, 18, 33; \( F = 6.40, p < .001 \)) and the left dACC (dACC\(^1\), BA32; Talairach coordinates: −19, 22, 35; \( F = 2.69, p < .001 \)). While this study was underpowered to detect performance differences between groups, a medium effect size (\( d = 0.69 \)) indicated that adolescents of mothers with a history of depression made more errors (\( M = 7.25, SD = 3.65 \)) than adolescents of mothers without a history of depression (\( M = 5.13, SD = 2.36 \)).

Group differences in brain activation in response to the N-back task (3-back versus 0-back contrast) are presented in Table 2. As hypothesized, significant differences were found in three a priori ROIs in the between-group comparisons: right anterior PFC (APFC, BA10; Talairach coordinates: 16, 49, 11; \( F = 2.96, p < .001 \)) and two clusters within the left dACC (BA32; dACC\(^2\)-Talairach coordinates: −21, 11, 29; \( F = 2.90, p < .001 \), and dACC\(^3\)-Talairach coordinates: −22, 36, 17, \( F = 2.60, p < .001 \)). Adolescents of depressed mothers demonstrated less activation than adolescents of mothers without a history of depression in the APFC and the dACC\(^2\) cluster but greater activation in the dACC\(^3\) cluster in response to the N-back task.

**Stress, executive function, and coping**

Group comparisons on chronic stress exposure, executive function performance, N-back performance, secondary control coping, and mothers’ depressive symptoms are presented in Table 3. The only significant group difference was for mothers’ current depressive symptoms, with the mothers with a history of depression reporting significantly higher levels of current depressive symptoms compared to mothers with no depression history.

<table>
<thead>
<tr>
<th>Region</th>
<th>Hemisphere</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>( F )</th>
<th>( p )</th>
<th># Voxels</th>
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<td>dACC(^1)</td>
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<td>35</td>
<td>2.69</td>
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<tr>
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<td>49</td>
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<tr>
<td></td>
<td>dACC(^2)</td>
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<td>17</td>
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</tbody>
</table>

BA = Brodmann area; DLPFC = dorsolateral prefrontal cortex; dACC = dorsal anterior cingulate cortex; APFC = anterior prefrontal cortex; R = right hemisphere; L = left hemisphere. Clusters are described in terms of anatomical voxel sizes (1 × 1 × 1 mm).
Correlations between the ROIs indicated by both the whole group and between-group effects of the N-back task and stress exposure, executive function, and secondary control coping are presented in Table 4. Activation of the DLPFC (BA9) \((r = -.66, p < .01)\), dACC (dACC\(^1\), BA32) \((r = -.59, p < .01)\), and APFC (BA10) \((r = -.88, p < .01)\) was negatively correlated with secondary control coping. Activation in two other regions of the dACC (dACC\(^2\) and dACC\(^3\); BA32) was not significantly correlated with secondary control coping. Activation of the APFC was significantly positively correlated with stress exposure \((r = .60, p < .05)\). Similarly, a positive association between stress exposure and DLPFC activation also approached significance \((r = .43, p = .10)\), though this should be interpreted with caution due to the small sample size. Stress exposure was not significantly correlated with any other ROIs. Executive function was also not significantly correlated with any of the ROIs.

### Table 3. Group comparisons on stress exposure, executive function composite scores, N-back performance, secondary control coping, and mother current depressive symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 8)</th>
<th>MDD group (n = 8)</th>
<th>(t)/(\chi^2)</th>
<th>(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress exposure composite</td>
<td>(-.19 (.51))</td>
<td>(-.03 (.30))</td>
<td>(-.74) ns</td>
<td>.28</td>
</tr>
<tr>
<td>Executive function composite</td>
<td>(.35 (.44))</td>
<td>(-.24 (.73))</td>
<td>(1.94) ns</td>
<td>.90</td>
</tr>
<tr>
<td>N-back task performance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-Back omissions 0 (0)</td>
<td>0 (0)</td>
<td>(.00) ns</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>0-Back response time (RT)</td>
<td>524.97 (123.89)</td>
<td>548.40 (58.82)</td>
<td>(-.48) ns</td>
<td>.24</td>
</tr>
<tr>
<td>1-Back hits 9 (0)</td>
<td>8.88 (.35)</td>
<td>1.00 ns</td>
<td>.48</td>
<td></td>
</tr>
<tr>
<td>1-Back false positives</td>
<td>(.38 (.74))</td>
<td>(.38 (.52))</td>
<td>(.00) ns</td>
<td>0</td>
</tr>
<tr>
<td>1-Back omissions 0 (0)</td>
<td>(.13 (.35))</td>
<td>(-1.00) ns</td>
<td>.53</td>
<td></td>
</tr>
<tr>
<td>1-Back response time</td>
<td>556.44 (137.95)</td>
<td>601.83 (84.27)</td>
<td>(-.79) ns</td>
<td>.40</td>
</tr>
<tr>
<td>2-Back hits 8.75 (.46)</td>
<td>8 (1.41)</td>
<td>1.43 ns</td>
<td>.72</td>
<td></td>
</tr>
<tr>
<td>2-Back false positives</td>
<td>(.75 (.71))</td>
<td>(.50 (.76))</td>
<td>(.68) ns</td>
<td>.34</td>
</tr>
<tr>
<td>2-Back omissions</td>
<td>(.25 (.46))</td>
<td>(1) (1.41)</td>
<td>(-1.43) ns</td>
<td>.72</td>
</tr>
<tr>
<td>2-Back response time</td>
<td>685.62 (89.78)</td>
<td>670.62 (101.66)</td>
<td>(.31) ns</td>
<td>.16</td>
</tr>
<tr>
<td>3-Back hits 6.75 (.71)</td>
<td>5.25 (2.60)</td>
<td>1.57 ns</td>
<td>.79</td>
<td></td>
</tr>
<tr>
<td>3-Back false positives</td>
<td>1.25 (1.04)</td>
<td>1.25 (1.04)</td>
<td>(.00) ns</td>
<td>0</td>
</tr>
<tr>
<td>3-Back omissions</td>
<td>2.25 (.71)</td>
<td>3.75 (2.60)</td>
<td>(-1.57) ns</td>
<td>.79</td>
</tr>
<tr>
<td>3-Back response time</td>
<td>869.23 (147.04)</td>
<td>820.53 (183.24)</td>
<td>(.59) ns</td>
<td>.29</td>
</tr>
<tr>
<td>Total number of errors</td>
<td>5.13 (2.36)</td>
<td>7.25 (3.65)</td>
<td>(-1.38) ns</td>
<td>.69</td>
</tr>
<tr>
<td>Overall average RT</td>
<td>659.07 (104.65)</td>
<td>660.34 (78.54)</td>
<td>(-.03) ns</td>
<td>.01</td>
</tr>
<tr>
<td>Child secondary control coping (RSQ composite)</td>
<td>(.48 (.42))</td>
<td>(.20 (.97))</td>
<td>(.76) ns</td>
<td>.37</td>
</tr>
<tr>
<td>Mothers’ depressive symptoms (BDI-II)</td>
<td>3.98 (4.43)</td>
<td>18.03 (14.54)</td>
<td>(-2.62) p &lt; .05</td>
<td>(-1.31)</td>
</tr>
</tbody>
</table>

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

### Associations among brain activation with stress, executive function, and coping

Correlations between the ROIs indicated by both the whole group and between-group effects of the N-back task and stress exposure, executive function, and secondary control coping are presented in Table 4. Activation of the DLPFC (BA9) \((r = -.66, p < .01)\), dACC (dACC\(^1\), BA32) \((r = -.59, p < .01)\), and APFC (BA10) \((r = -.88, p < .01)\) was negatively correlated with secondary control coping. Activation in two other regions of the dACC (dACC\(^2\) and dACC\(^3\); BA32) was not significantly correlated with secondary control coping. Activation of the APFC was significantly positively correlated with stress exposure \((r = .60, p < .05)\). Similarly, a positive association between stress exposure and DLPFC activation also approached significance \((r = .43, p = .10)\), though this should be interpreted with caution due to the small sample size. Stress exposure was not significantly correlated with any other ROIs. Executive function was also not significantly correlated with any of the ROIs.

### Table 4. Correlations among brain activation in response to the N-back task, children’s stress exposure, N-back performance, and secondary control coping.

<table>
<thead>
<tr>
<th></th>
<th>DLPFC (BA9)</th>
<th>dACC (BA32)(^1)</th>
<th>APFC (BA10)</th>
<th>dACC (BA32)(^2)</th>
<th>dACC (BA32)(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress exposure composite</td>
<td>(.43^*)</td>
<td>(.28)</td>
<td>(.60^{**})</td>
<td>(.31)</td>
<td>(-.01)</td>
</tr>
<tr>
<td>Executive function composite</td>
<td>(-.31)</td>
<td>(-.29)</td>
<td>(.04)</td>
<td>(-.10)</td>
<td>(-.18)</td>
</tr>
<tr>
<td>N-back total number of errors</td>
<td>(-.06)</td>
<td>(-.19)</td>
<td>(-.26)</td>
<td>(-.12)</td>
<td>(-.16)</td>
</tr>
<tr>
<td>N-back overall average RT</td>
<td>(.05)</td>
<td>(.03)</td>
<td>(-.09)</td>
<td>(.20)</td>
<td>(-.24)</td>
</tr>
<tr>
<td>Child secondary control coping</td>
<td>(-.66^{***})</td>
<td>(-.59^*)</td>
<td>(-.88^{***})</td>
<td>(-.23)</td>
<td>(-.22)</td>
</tr>
</tbody>
</table>

*p = .10; **p < .05; ***p < .01*
Multiple linear regressions were conducted to test the third hypothesis that group status (adolescents of depressed mothers) and greater stress exposure would predict secondary control coping, with activation in a priori ROIs would account for these associations (Table 5). In each of the five regressions, group status was entered at Step 1 and stress exposure was added at Step 2. While group status was not a significant predictor of secondary control coping at Step 1, stress exposure significantly predicted children’s coping ($\beta = -0.52$, $t = -2.22$, $p < .045$) at Step 2. At Step 3, activation in each of the significant a priori ROIs was added to the regression equations. In Step 3, activation in the DLPFC ($\beta = -0.52$, $t = -2.30$, $p < .04$), dACC1 ($\beta = -0.49$, $t = -2.32$, $p < .05$), and APFC ($\beta = -0.89$, $t = -5.06$, $p < .01$) were significant independent predictors of adolescents’ secondary control coping. Further, in these three regressions, activation in these regions accounted for the association between stress exposure and coping such that stress exposure was no longer a significant independent predictor of secondary control coping. The other ROIs in the dACC (dACC2, dACC3) did not predict coping.

### Discussion

The current study provides one of the first examinations of associations among chronic stress exposure, executive function, brain activation, and secondary control coping in
adolescent offspring of mothers with and without histories of depression using multi-
method, multi-informant measurement of these constructs. Due to the limited evidence
regarding functional neural differences in this specific population, and the heterogeneity
of findings regarding functional neural differences in similar populations (children and
adults with a history of depression), exploratory analyses regarding the association
between stress exposure, executive function, coping, and neural activation in response
to a working memory task were conducted. Adolescents of depressed mothers demon-
strated greater activation in the APFC and both greater and less activation than controls
in distinct areas within the dACC in response to the N-back working memory task in
comparison to adolescents of nondepressed mothers. Across both groups, activation of
the regions identified in whole group analyses (DLPFC and dACC\(^1\)) was positively
correlated with stress exposure and negatively correlated with secondary control coping.
Similarly, activation of the dACC\(^1\) was negatively correlated with secondary control
coping. Finally, regression analyses revealed that DLPFC, dACC (dACC\(^1\)), and APFC
activation were significant predictors of adolescents’ secondary control coping and
accounted for the association between higher levels of stress exposure and less use of
secondary control coping.

Consistent with previous research (e.g., Robinson et al., 2015), activation was found
in the DLPFC and dACC during an executive function task at both the whole group
and between-group levels. Specifically, examination of responses to the N-back task
across the groups, measured by examining the contrast of the most challenging condi-
tion (3-back) and the baseline condition (0-back), revealed activation in a priori ROIs:
the DLPFC (BA9) and two areas in the dACC (BA32). Additionally, examination of
responses to the N-back task between groups revealed two other significant ROIs within
the dACC (BA32) as well as activation in the APFC (BA10). The DLPFC and dACC
have been implicated not only in general executive function (including working mem-
ory), but also specifically in response to the N-back task (e.g., Owen et al., 2005).
Interestingly, the varied pattern of findings reported in the current study in the dACC is
consistent with findings among meta-analyses examining similar processes in children
and adults with depression. For example, a meta-analysis by Hamilton et al. (2012)
found that adults with a history of depression demonstrated hyperactivation of the
dACC compared to controls in response to a negatively valenced task. However, a
meta-analysis by Miller et al. (2015) found hypoaactivation of the dACC in children with
a history of depression in response to an executive function task.

With regard to the first hypothesis, adolescents of depressed mothers demonstrated
differential activation in identified a priori regions in response to the working memory
task when compared to adolescents of nondepressed mothers. While the adolescents of
depressed mothers demonstrated less activation in one area within the dACC (dACC\(^2\))
and the APFC, they also demonstrated greater activation in a second area within the
dACC (dACC\(^3\)). It is notable that these differences in activation were observed despite a
lack of statistically significant differences in accuracy on the N-back among the groups.
This study was likely underpowered to detect such differences, with only 16 participants
(and eight in each group). Of note, however, adolescents of mothers without a history
of depression made a mean of 3.5 errors out of 48 trials and children of depressed
mothers made a mean of 6 errors out of 48 trials on the most difficult condition (3-
back). Further, the greater activation displayed by adolescents of depressed mothers in
the dACC may reflect a compensatory effect, whereby adolescents are employing greater effort to achieve the same performance. In contrast, instances where they demonstrated less activation (dACC and APFC) may suggest that these regions are not necessary to performance in this sample (Price & Friston, 1999, 2002). It is also possible that the groups were not equated on performance for this task or that a more difficult task would provide more opportunity for variance in performance for both groups.

Second, we hypothesized for both adolescents of mothers with and without a history of depression, activation in the PFC in response to a working memory task would be related to stress exposure, executive function, and secondary control coping. Notably, activation of the APFC, DLPFC, and one of dACC (dACC) regions were all inversely related to reports of adolescents’ use of secondary control coping. There was also a pattern that approached significance for a positive association between stress exposure and DLPFC activation, though this should be interpreted with caution due to the small sample size. These findings build upon previous research demonstrating links between brain function, executive function, and coping in children and adolescents (e.g., Campbell et al., 2009; Robinson et al., 2015).

Finally, in partial support of our hypotheses, findings indicated that while stress exposure was related to adolescents’ secondary control coping, activation in the DLPFC, dACC, and APFC in response to the N-back task each accounted for this relation. Contrary to our hypotheses, group status did not significantly predict use of secondary control coping. In contrast to between-group analyses, whole group regression analyses provided further evidence that greater activation in DLPFC, dACC, and APFC accounted for the association between exposure to chronic stress and less use of adaptive coping. These findings suggest that as children are exposed to increasing levels of stress, the brain regions responsible for executive function and coping may have to activate more to accomplish the same task or produce the same performance than in less stressed adolescents. These findings also have implications for coping with stress. Hyperactivation of the DLPFC has been reported in previous studies using a similar population (i.e., depressed children and adolescents) (Miller et al., 2015). Children with a history of depression demonstrated more activation in the DLPFC in response to negatively valenced tasks in comparison to controls (Miller et al., 2015). 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 cognitive tasks, such as working memory. Further, the findings suggest that chronic stress is associated with brain activation in areas associated with working memory and secondary control coping, as coping was predicted by levels of stress but not by maternal depression history.

These findings have several implications. First, group differences in activation in regions of the PFC in response to the working memory task were observed between adolescents of depressed mothers and children of mothers without a history of depression, which suggests that adolescents of mothers with a history of depression are uniquely impacted neurologically by their mothers’ depression history, even when these differences are not observable in corresponding behavioral differences (e.g., Foland-Ross et al., 2015). Adolescents of depressed mothers in the current study demonstrated hypoactivation of the APFC; they exhibited both hypoactivation and
hyperactivation within the dACC. This pattern suggests that differences in brain activation may be specific to subregions even within the PFC and that further examination of brain activation (e.g., connectivity) might elucidate the potentially complex and multifaceted effects of stress on the brain. When examining these processes across groups, however, greater activation was associated with more stress, suggesting differential effects of parental depression and chronic stress on the developing brain.

Second, this study provides further evidence of the association between brain function and coping. Secondary control coping was significantly related to activation in prefrontal regions identified by whole group analysis. That is, activation in the brain regions stimulated by a working memory task across both groups (the DLPFC and dACC) and one of the regions identified by between-group analyses (the APFC) was negatively correlated with use of secondary control coping. This suggests that greater activation of these regions during a working memory task is associated with less use of secondary control coping skills, which are thought to rely on executive functions such as working memory. Finally, while group status (adolescent of depressed mothers versus mothers without a history of depression) did not predict adolescents’ coping, exposure to stress was a significant predictor, suggesting that it is chronic stress has a significant effect on adolescents’ coping, regardless of maternal depression status. When brain activation in each ROI was entered into these regressions, however, the three ROIs that were significantly correlated with coping (DLPFC, dACC, and APFC) accounted for the association between stress exposure and less use of adaptive coping. This indicates that the neurological effects of stress play an important role in the dual process by which stress impacts individuals: (1) stress directly puts individuals at increased risk for psychopathology and other adverse health outcomes and (2) also impedes adaptive coping through the deleterious effects of stress on brain regions responsible for executive functions foundational to adaptive coping strategies. These processes warrant further investigation and have potential implications for both prevention and treatment of psychopathology and other negative health outcomes in individuals exposed to chronic stress.

Future research may build upon these research questions in a number of ways. First, the current study is limited by a small sample size, and therefore power to detect significant effects is limited and interpretation of significant effects should be treated with caution (e.g., Button et al., 2013). Future research examining these questions with a larger sample of at-risk children and adolescents is needed. In addition, participants in the current study showed low numbers of errors on the more difficult levels of the N-back task. Future studies examining these processes may benefit from an executive function task with a higher ceiling and greater variance in participants’ performance. Further, mothers’ depressive histories were evaluated from retrospective reports, and future research examining prospective associations will be important. 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 adolescents’ stress exposure. It is possible that different sources of chronic stress have different effects on executive functioning, coping, and psychopathology. Similarly, adolescents 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 that may present different associations between these constructs.
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 secondary control coping skills (e.g., cognitive reappraisal) represent a potential neural pathway by which stress impairs coping and put children and adolescents at risk. These processes merit future investigation for further understanding of the pathways by which stress impairs coping. Research examining these associations has implications for intervention with at-risk populations, including children of depressed parents.

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References


