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Sleep and Emotional Functioning in Childhood: Neural Correlates and Psychological Outcomes

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# Sleep and Emotional Functioning in Childhood: Neural Correlates and Psychological Outcomes

By

Brooke L. Reidy
B.S., B.A., Washington & Lee University, 2010
M.A., Emory University, 2014

Advisor: Patricia A. Brennan, Ph.D.

An Abstract of
a dissertation submitted to the Faculty of the Graduate
School of Emory University in partial fulfillment
of the requirements for the degree of
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## Abstract

A growing body of literature implicates sleep as an influential factor in child mental health. Childhood sleep problems can persist for years and have been shown to predict the incidence of various forms of psychopathology, including anxiety disorders and depression. Mood and anxiety disorders are characterized by increased emotional responsivity and disrupted emotional regulation, processes that have also been linked to reduced childhood sleep duration at a behavioral and neurobiological level. Emotion responsivity / regulation may therefore represent an underlying mechanism in the sleep – mental health relationship. That said, much remains to be learned about associations between neural correlates of emotional responsivity/regulation and other, more objective measures of childhood sleep behavior. Research is also needed to more broadly understand the role of sleep as a mental health risk process, particularly for vulnerable populations of children. Study 1 examined persistent childhood sleep problems as a novel risk mechanism involved in the intergenerational transmission of anxiety. Results demonstrated that persistent childhood sleep problems mediated the association between maternal and child anxiety in the school-aged period. Study 2 explored the underlying neural mechanisms linking actigraphy-assessed sleep duration and fMRI measures of child emotional functioning in a school-aged sample. Exploratory analyses comparing fMRI output with actigraphy and/or maternal report measures of sleep quality and variability of sleep duration were also conducted. Results provided limited evidence linking childhood sleep problems and neural activation measures of emotion responsivity / regulation, but suggested that more persistent sleep problems may be more robust in terms of their associations with fMRI measures of emotional functioning in healthy children. Clinically, more persistent childhood sleep difficulties may also represent an important health intervention target for children at familial high risk for anxiety.

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# Sleep and Emotional Functioning in Childhood: Neural Correlates and Psychological Outcomes

In recent decades, growing research and public interest have focused on understanding the role of sleep in human health. Sleep has been linked to a variety of outcomes including: learning and cognitive performance (Goel, Basner, Rao, & Dinges, 2013), memory consolidation and synaptic plasticity (Krueger, Frank, Wisor, & Roy, 2016), brain metabolism (Xie et al., 2013), health quality (Strine & Chapman, 2005), and mortality risk (Buxton & Marcelli, 2010). As such, sleep is increasingly being recognized as an active bio-behavioral process that is critical to promoting daily functioning, bodily homeostasis, and general well-being (Okun, 2011).

This growing appreciation for the influential role of sleep on health comes at a time in which sleep disturbance is an increasingly pervasive cultural phenomenon. As many as 20% of American adults are now getting less than 6 hours of sleep on average per night (National Sleep Foundation, 2009), with over 25% of adults reporting symptoms of insomnia in the past year (Hossain & Shapiro, 2002; Morphy, Dunn, Lewis, Boardman, & Croft, 2007; LeBlanc et al., 2009). Longitudinal examinations of child sleep trends across cohorts also demonstrate that children are getting less and less sleep across generations due to increasingly late bedtimes and unchanged wake times (Iglowstein, Jenni, Molinari, & Largo, 2003). These findings are complemented by research revealing relatively high prevalence rates of childhood difficulties initiating and maintaining sleep (Fricke-Oerkermann et al., 2007; Owens, Spirito, McGuinn, & Nobile, 2000; Spruyt, O'Brien, Cluydts, Verleye, & Ferri, 2005), and suggest that children are increasingly at risk for insufficient or otherwise inadequate sleep.

In addition to their implications for physical health and functioning, these high prevalence rates of sleep problems are concerning in terms of their potential mental health

impact, particularly across development. Childhood sleep difficulties are associated with increased risk for numerous psychiatric disorders characterized by altered emotional responsivity and/or dysregulation, including depression (Gregory, Rijsdijk, Lau, Dahl, & Eley, 2009; Bylsma, Morris, & Rottenberg, 2008), anxiety (Gregory et al., 2005; Carthy, Horesh, Apter, Edge, & Gross, 2010), and post-traumatic stress (Cloitre, Miranda, Stovall-McClough, & Han, 2005). Sleep difficulties in childhood are also positively associated with youth aggression (Aronen, Paavonen, Fjallberg, Soininen, & Torronen, 2000) and predict substance use in adolescence (Wong, Brower, Fitzgerald, & Zucker, 2004). Both of these behavioral issues have been linked to emotion regulation difficulties (Poon, Turpyn, Hansen, Jacangelo, & Chaplin, 2015). Given this, poor childhood sleep may represent a transdiagnostic risk factor for emotion-related disorders.

The clinical implications of identifying how, when, to what extent, and for whom sleep difficulties emerge are therefore significant. In particular, ongoing research investigating the impacts of sleep problems on children's emotional health and development – as well as the underlying mechanisms involved - are particularly important, as this work can provide novel insights to inform early sleep-related health interventions for at-risk children.

**Sleep and Emotion in the Context of Child Development**

In early childhood, sleep is marked by rapid nocturnal consolidation and maturation (Sadeh, 2013), and is characterized by long (~13-14 hours) average daily duration (Galland, Taylor, Elder, & Herbison, 2012; Iglowstein et al., 2003). Average total sleep duration then decreases from ~12 hours in the preschool period to ~ 9 hours in the school-aged period, and then ~8 hours in adolescence (Galland et al., 2012; Iglowstein et al., 2003). Although research has demonstrated that childhood sleep duration is highly variable in the short-term, children

show high levels of long-term stability in their patterns of sleep duration, such that children who have shorter average sleep duration in early childhood continue to have short duration later in life and young children with longer average sleep duration continue to have longer sleep duration (Jenni, Molinari, Caflisch, & Largo, 2007). These findings suggest that sleep duration patterns in children likely reflect, in part, biologically determined sleep needs (Jenni et al., 2007).

Age-related changes in sleep duration correspond to significant brain and behavior changes that occur in the context of children's emotional development. At the time when children require the most sleep, basic features of emotional development (e.g., accurate emotional identification and emotion processing) emerge (Shonkoff et al., 2004) as infants begin to categorize and habituate to different emotional face stimuli (Quinn et al., 2013). This is accompanied by considerable development and fine tuning – both behaviorally and neurally – of children's abilities to recognize and understand other's facial expressions (Nelson, 2013). In the toddler and preschool years, children become increasingly aware of their own behavior and emotional responses and demonstrate increasing insight into other's emotions (Saarni, 2011). Social engagement also increases, and is accompanied by considerable cognitive development (Feldman & Eidelman, 2009). The preschool years are also considered to be a period of "blossoming" in the brain that is characterized by increased brain volume and myelination (Brown & Jernigan, 2011).

In the school-aged period, developmental changes in sleep duration become more gradual. Age-related changes in gray and white matter volume (Giedd et al., 1999), neural activation associated with emotional appraisal (McRae et al., 2012), and increased emotional and social regulation (Zeman, Cassano, Perry-Parish, & Stegall, 2006; Rosso, Young, Femia, & Yurgelun-Todd, 2004) are evidenced across childhood and adolescence. However, by school-

age, children demonstrate an expanded understanding of emotions and are able to anticipate, express, and manage emotions in a social context (Shonkoff et al., 2004).

**Sleep Difficulties and Child Emotional Functioning**

In addition to the temporal relationships between changes in child sleep duration and childhood's social and emotional maturation, studies demonstrate associations between sleep difficulties - particularly reduced sleep duration - and alterations in children's mood, emotional responsivity, and emotion regulation. Childhood sleep difficulties are associated with increased daytime affective dysregulation (Legenbauer, Heiler, Holtmann, Fricke-Oerkermann, & Lehmkuhl, 2012); likewise, child sleep restriction is associated with more intense self-reported feelings of anger, sadness, and fear in response to emotional stimuli (Leotta, Carscadon, Acebo, Seifer, & Quinn, 1997). Recent neuroimaging research involving school-aged children has also shown that decreased sleep duration is associated with increased neural responsivity to emotional stimuli in brain regions implicated in emotion generation; this work further demonstrated that child sleep duration is positively associated with emotion-dependent functional connectivity between the amygdala and brain regions implicated in emotion regulation (Reidy, Hamann, Inman, Johnson, & Brennan, 2016).

Collectively, these findings implicate sleep difficulties as a risk factor for increased emotional reactivity and impaired emotion regulation in childhood. This research also indicates that sleep may be an influential factor impacting children's brain development, particularly as related to children's social-emotional functioning. That said, there is a general scarcity of fMRI literature examining associations between sleep/sleep difficulties and neural correlates of emotion responsivity and/or regulation in children, particularly in middle childhood. Rigorous translational research is needed to examine periods of neurocognitive and social-emotional

development that may be sensitive to sleep. Additionally, prospective longitudinal studies are needed to examine the long-term neural and behavioral effects of sleep/sleep problems on children's emotional development (Dahl, 2007).

**Establishing Childhood Sleep Problems as an Emotional / Mental Health Risk Process**

As highlighted above, sleep problems in childhood are a risk factor for many mental health disorders. That said, several studies have demonstrated bidirectional relationships between sleep and various forms of child psychopathology, as well as relationships between sleep problems, emotion regulation strategies, and co-occurring affective disorders (Shanahan, Copeland, Angold, Bondy, & Costello, 2014; Palmer, Oosterhoff, Bower, Kaplow, & Alfano, 2018). Studies examining relationships between sleep and anxiety, or anxiety/depression tend to provide stronger evidence for sleep as a predictor of anxiety; however, studies have demonstrated that childhood/adolescent internalizing problems do predict insomnia symptoms in adulthood (see Willis & Gregory, 2015; Goldman-Mellor et al., 2014). Longitudinal research is therefore needed to disentangle the nature of these associations across development, and to examine childhood sleep problems as a mechanism that accounts for children's mental health risk in the context of other known risk factors.

Another conceptual issue to be addressed when establishing childhood sleep as a risk factor for mental health issues relates to our understanding of the long-term effects of persistent vs. acute sleep difficulties. Several studies demonstrate that sleep difficulties can persist on the order of years and affect a relatively large percentage (12-26%, depending on the reporting source) of children (Paavonen, Solantaus, Almqvist, & Aronen, 2003; Fricke-Oerkermann et al., 2007). Persistent sleep difficulties have been specifically associated with increased risk for anxiety in adulthood (Gregory et al., 2005). Chronic sleep restriction to 4 - 6 hours of sleep per

night can also result in cognitive performance deficits that are comparable to those seen after two days of total sleep deprivation (Van Dongen, Maislin, Mullington, & Dinges, 2003). Collectively, this work suggests that persistent, even more mild-moderate sleep problems can result in impairments associated with more severe acute sleep disturbance. However, ongoing research is needed to investigate the relative impact of acute and persistent sleep problems on children's emotional functioning.

As research also continues to examine the neurobiological underpinnings of emotional responsivity/regulation as a mechanism linking sleep and mental health, it is critical that this work integrate multiple child sleep measures in order to identify the types of childhood sleep problems that are most associated with altered emotional responsivity and regulation at the neural level. Sleep is a complex physiological process that is best characterized using a multi-method assessment. As such, future studies should strive to incorporate sleep measures tapping different aspects of sleep (e.g., sleep efficiency, general quality, variability) using objective (e.g., actigraphy, polysomnography) and subjective reports of sleep behavior, which likely tap different aspects of child sleep problems (Scher & Asher, 2004).

**Current Studies**

Given the above mentioned gaps in the literature, the two studies that form the basis of the current dissertation investigated the relationship between childhood sleep problems and emotional functioning. The first of these studies prospectively investigated the effects of persistent childhood sleep problems and emotional health in the context of pediatric anxiety, a highly prevalent and pervasive mental health condition presenting in the preadolescent period. In particular, this study used longitudinal data from a clinical high-risk sample of children to examine the role of persistent preschool and school-aged sleep problems in the intergenerational

transmission of anxiety. The second study focused on the neural mechanisms underlying the relationship between childhood sleep and emotional responsivity and regulation. This fMRI study incorporated a multi-method assessment of childhood sleep duration, variability, and quality, to examine associations between different sleep measures with neural activation in response to emotional stimuli, as presented in the context of cognitive control tasks. In this way, the current dissertation provides a unique opportunity to both examine the broader clinical impact of chronic sleep difficulties, as well as the underlying mechanisms that result in more acute sleep-related changes on emotional functioning.

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# Persistent sleep disturbance as an early risk mechanism underlying the maternal intergenerational transmission of anxiety

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## Abstract

Childhood anxiety represents a persistent and prevalent mental health problem with lasting detrimental effects on functioning. Research demonstrates an intergenerational transmission of anxiety from mother to child. However, much remains to be learned about the bio-behavioral processes underlying this phenomenon. Given this, the current study investigated persistent childhood sleep problems as a novel risk mechanism involved in the intergenerational transmission of anxiety. Data were obtained from a community high-risk cohort of 185 mother-child dyads when children were preschool-aged, and then again as part of a school-aged follow up. Structural equation modeling was used to examine relationships between maternal history of anxiety and school-aged anxiety symptoms (measured via maternal and alternate caregiver report), and also to examine the potential mediating role of persistent sleep problems (i.e., maternal-reported sleep problems across the preschool and school-aged period) in this relationship, while accounting for other potentially confounding factors (e.g., SRI exposure, early life stress exposure). Results revealed that maternal history of anxiety predicted child anxiety in the school age period ($\beta$ = .196, $p$ =.022). Persistent childhood sleep problems also predicted school-aged child anxiety ($\beta$ = .754, $p$ =.001), over and above the effects of maternal anxiety, early life stress, and SRI exposure. Indirect effects models supported persistent childhood sleep problems as a mediator in the relationship between maternal and school-aged anxiety, when controlling for the effects of early life stress, SRI exposure, and/or preschool-aged anxiety. These findings implicate persistent childhood sleep problems as a potentially important health intervention target for children who are at familial high-risk for anxiety.

## Persistent sleep disturbance as an early risk mechanism underlying the maternal intergenerational transmission of anxiety

Anxiety disorders are characterized by the persistent and excessive perception and/or anticipation of threat in one's environment (American Psychiatric Association, 2013), and are associated with feelings of physical tension and arousal, worried thoughts, and behavioral avoidance of potentially anxiety-provoking situations (American Psychological Association [APA], 2018). Anxiety disorders often emerge early in life and represent the most commonly occurring form of psychopathology among children and adolescents (Beesdo, Knappe, & Pine, 2009). Lifetime prevalence rates of youth anxiety disorders typically range from 15-20% (Beesdo et al., 2009), although epidemiological research has suggested that rates of adolescent anxiety disorders can exceed 30% (Merikangas et al., 2010). Prevalence rates for youth anxiety disorders vary across development and by disorder (Copeland, Angold, Shanahan, & Costello, 2014). However, a growing body of research demonstrates that high levels of childhood anxiety symptoms persist through development and can predict the incidence of other forms of psychopathology later in life (Letcher, Sanson, Smart, & Toumbourou, 2012; Bittner et al., 2007). When taken together with the significant health consequences (Bardone et al., 1998; Copeland et al., 2014) and long-term psychosocial impairment associated with anxiety disorders (Merikangas et al., 2010; Settipani & Kendall, 2013; Mychailyszyn, Mendez, & Kendall, 2010; Essau, Lewinsohn, Olaya, & Seeley, 2014), youth anxiety represents a significant public health issue (Busko, 2008).

Although relatively understudied when compared to maternal depression (see Goodman et al., 2011), intergenerational transmission of anxiety from mothers to children is increasingly supported in the literature (Li, Sundquist, & Sundquist, 2008). Longitudinal research suggests

some specificity for maternal depression and maternal anxiety as risk factors for the respective emergence of child depression and anxiety (Moffitt et al., 2007; Beesdo, Pine, Lieb, & Wittchen, 2010). Maternal anxiety has also been linked to poorer treatment response among children receiving psychotherapy for anxiety disorders (Cooper, Gallop, Willetts, & Creswell, 2008). Given this, considerable research effort has focused on identifying mechanisms underlying the intergenerational transmission of anxiety as a means of informing early interventions for at-risk children and families.

**Risk Mechanisms Involved in the Intergenerational Transmission of Anxiety: The Role of the Prenatal Environment and Parenting**

Children of twins studies have provided evidence to support genetic influences on the respective incidence of maternal and child anxiety; however, this work has also revealed a primarily environmental transmission of anxiety from parent to child (Creswell & Waite, 2015; Eley et al., 2015). Research focused on mental health risks associated with the prenatal environment have repeatedly demonstrated that prenatal maternal anxiety is associated with increased risk for child behavioral and emotional problems, including anxiety (Van den Bergh & Marcoen, 2004; O'Donnell, Glover, Barker, & O'Connor, 2014). Maternal antenatal anxiety has also been linked to altered fetal cortisol metabolism (O'Donnell et al., 2012), newborn brain development (Rifkin-Graboi et al., 2015), and altered hypothalamic-pituitary-adrenal (HPA) axis functioning in adolescent offspring (Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008); however, this literature is complicated by the fact that some mothers with anxiety are treated with serotonin reuptake inhibitor (SRI) medications in pregnancy, which can also impact children's early brain activity (Videman et al., 2016), stress physiology (e.g., basal cortisol levels; Oberlander et al., 2008), and internalizing behavior problems (Hanley, Brain, &

Oberlander, 2015). Differentiating maternal anxiety from other early childhood stress exposures also complicates these findings, as studies have repeatedly linked early childhood experiences of life stress with the development of multiple forms of psychopathology, including anxiety (Beesdo et al., 2009; Chu, Williams, Harris, Bryant, & Gatt, 2013; Phillips, Hammen, Brennan, Najman, & Bor, 2005; Burkholder, Koss, Hostinar, Johnson, & Gunnar, 2016).

A substantial literature has also focused on the role of parenting as an environmental mechanism underlying the intergenerational transmission of anxiety. Several factors associated with parenting, including mother's negative expectations for children's ability to navigate stressful tasks, overly protective, intrusive, or critical parenting approaches, and accommodation of children's anxious behavior, have been implicated in the intergenerational transmission of anxiety (see Lebowitz, Leckman, Silverman, & Feldman, 2016 for a review; Creswell, Apetroaia, Murray, & Cooper, 2013). However, some research suggests that parenting of anxious youth does not differ between anxious and non-anxious mothers for younger children (i.e., in middle childhood; Waite & Creswell, 2015). When taken together with findings demonstrating that youth anxiety may actually predict some negative parenting behaviors in mothers (Silverman, Kurtines, Jaccard, & Pina, 2009), the extent to which parenting behaviors serve as an early risk process underlying the intergenerational transmission of anxiety remains unclear. As such, additional research is needed to clarify and identify other environmental processes that may serve as an early marker of – and potential intervention target for – anxiety among children at high familial risk.

**Persistent Childhood Sleep Problems as a Novel Risk Mechanism Involved in the Intergenerational Transmission of Anxiety**

One understudied factor that could represent such a risk process is childhood sleep difficulties. Poor sleep in childhood is increasingly implicated as a transdiagnostic mental health problem. Persistent childhood sleep difficulties are symptoms of a variety of psychological disorders, and are associated with increased risk for internalizing problems, including anxiety (Shanahan, Copeland, Angold, Bondy, & Costello, 2014; Willis & Gregory, 2015). Childhood sleep disturbance has also been linked to several known risk factors for childhood anxiety, including maternal psychopathology (O'Connor, Heron, Glover, & Alspac Study Team, 2002; Goldberg et al., 2013), prenatal SRI exposure (Oberlander et al., 2010), and early life stress exposure (Mannering et al., 2011; Kelly, Marks, & El-Sheikh, 2014). Sleep disturbance has also been associated with neural alterations that resemble, at least in part, those seen among individuals with anxiety disorders (Pace-Schott et al., 2017; Leahy & Gradisar, 2012; Reidy, Hamann, Inman, Johnson, & Brennan, 2016a). Poor sleep quality is also associated with altered HPA-axis functioning in children (Hatzinger et al., 2008). Given that childhood sleep difficulties are also often influenced by environmental factors – including parenting strategies – that disrupt healthy sleep hygiene (Mindell, Meltzer, Carskadon, & Chervin, 2009), childhood sleep difficulties may represent a cross-cutting bio-behavioral risk process that influences other mechanisms previously implicated in the development and maintenance of youth anxiety.

Importantly, research has demonstrated that, for some children, sleep problems can persist across development and have lasting negative physical and mental health effects. In the school-aged period, persistent difficulties with sleep initiation range can affect almost a quarter of children (Fricke-Oerkermann et al., 2007). Magee and colleagues (Magee, Gordon, & Caputi, 2014) revealed that over 10% of young children (i.e., children assessed from infancy to 6/7 years of age) had persistently short sleep duration, which was associated with poorer physical,

emotional, and social health than typical sleepers. Our group demonstrated that persistent childhood sleep problems predicted youth health quality in young adulthood, over and above the effects of early adversity, chronic childhood illness, maternal depression, lifetime youth depression, and chronic youth stress (Reidy et al., 2016b). Research has also demonstrated that when controlling for child sex, socioeconomic status, and childhood internalizing problems, persistent school-aged sleep problems predicted anxiety – but not depression – in young adulthood (Gregory et al., 2005). Given this, persistent sleep problems may represent a particularly salient risk process that impacts children early in life and leaves them vulnerable to developing anxiety and other adverse health conditions. Remarkably, no previous study has examined sleep disturbances as a potential risk mechanism for the intergenerational transmission of anxiety, particularly in the context of other risk factors associated with this population (e.g., early childhood anxiety symptoms, early life stress exposure, SRI exposure). Such work could have far reaching implications for prevention and early intervention efforts, as childhood sleep behavior represents a malleable intervention target for which there are an increasing number of evidenced-based treatments.

**Current Study**

To address these gaps in the literature, the current study examined the role of persistent childhood sleep problems in the intergenerational transmission of anxiety using longitudinal data collected from a cohort of 185 mother-child dyads. Specifically, the current study used data collected at an initial preschool visit and a school-aged follow-up to test hypotheses that 1). maternal history of anxiety will predict childhood anxiety in the school-aged period, and 2). persistent childhood sleep problems will serve as a mediator in the relationship between maternal

and childhood anxiety, when also accounting for the effects of other potential risk factors associated with this at-risk population (e.g., SRI exposure, early life stress exposure).

## Method

### Participants

Participants were drawn from a sample of 219 mother-child dyads, 178 of whom were recruited through the Emory Women's Mental Health Program (WMHP), a treatment referral and research center for women who experience mental illness during pregnancy and/or the postpartum period. Mothers recruited from the WMHP were initially enrolled in a study investigating the effects of prenatal mood disorders and were evaluated at multiple time points across pregnancy and the postpartum period. An additional 41 mother-child dyads were recruited from the community at the time of the initial visit of the present study. At this initial "preschool" visit, children's ages ranged from 2.5-5.5 years.

Mothers recruited from the WMHP did not differ from community controls in terms of mother's age, child's age, mother/child ethnicity, mother's marital status, mother's education level, number of hours worked per week by mother, and number of adults in the household. Sixty-five percent of children in the current sample were exposed to psychotropic medications in utero (antidepressants: 30.6%; anti-epileptic drugs: 18.3%; anti-psychotics: 9.6%; anti-epileptic and anti-psychotic medications: 7.3%). Community control mothers did not take psychotropic medications during pregnancy, as verified by obstetrical records.

Of the mother-child dyads initially recruited for the preschool visit of the present study, 185 (85%) completed follow-up measures when children were of school age (i.e., 5 to 11 years). Alternate caregivers also provided follow-up information. To be included in the final sample, a child's mother or alternate caregiver must have completed a Child Behavior Checklist (CBCL;

Achenbach & Rescorla, 2001) at follow-up. Mothers in the final sample had attained a significantly higher education level than those lost to follow-up ($p = .015$), but did not differ in terms of maternal age, or history of mood or anxiety disorders. In general, the final sample of mothers in this study represented a highly educated group, with 33.5% of women completing college and 42.7% of women completing graduate school. The majority of mothers (82.7%) were married, while 8.1% of women were divorced, 1.6% of women were separated from partners, and 6.5% of women had never been married. Children included in the final sample did not differ significantly from the 34 children not included on initial measures of youth anxiety/depression and sleep problems, nor did they differ by age, race/ethnicity, or gender. The final child sample was 51.4% male, and was predominately Caucasian (78.4%); 8.1% African American, 10.3% Biracial, and 2.2% Hispanic.

**Procedure**

Mother-child dyads participated in an initial laboratory visit at Emory University when children were of preschool age. During this "preschool" visit, children completed several measures of behavioral and cognitive functioning while mothers completed interviews about their mental health history, as well as questionnaires about their current mood and anxiety symptoms. Mother's also reported on life stressors experienced by the family since their child's birth, and completed questionnaires regarding their child's sleep, mood, and behavior.

For the "school-age" follow-up, data were collected via REDCap, a secure online database used by research institutions for data collection. Mothers who participated in the preschool visit were contacted via email about taking part in a new study with their child. Emails included a hyperlink to REDCap measures; mothers were instructed to click on the link and read consent information. If mothers agreed to all study details, they were then asked to complete a

series of online questionnaires about their child's behavior. Participants were not required to complete all questionnaires in one sitting and were re-contacted if measures were left incomplete for more than 30 days. In addition to obtaining maternal reports, data was also obtained from an alternate caregiver (e.g., father, grandparent) through REDCap.

Both portions of this study were approved by the Institutional Review Board of Emory University. Mothers provided informed consent for their and their children's participation in the initial visit of the present study. Families who completed the school-aged assessment had previously given permission to be re-contacted for future studies and had provided their contact information for follow-up. Both mothers and alternate caregivers provided consent for their participation in the follow-up portion of the study. Families were compensated for each portion of their study involvement.

**Measures**

**Sleep.** During the preschool visit, child sleep problems were measured using maternal responses to 7 sleep items that comprise the Sleep Problems subscale of the Achenbach Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) for ages 1.5-5. Specifically, mothers were asked to report the extent or frequency to which their child has trouble getting to sleep, doesn't want to sleep alone, has nightmares, is overtired, etc. Scores were summed, such that higher scores reflected increased endorsement of sleep problems among children. Internal consistency for this subscale was $\alpha = .743$. Additionally, mothers reported on the number of hours their child slept on the night prior to their laboratory visit.

As part of the school-aged follow-up, mothers and alternate caregivers completed the 113-item CBCL for ages 6-18, and responded to 6 sleep-related items of interest (i.e., does your child have nightmares, have trouble sleeping, sleep less than others, sleep more than others, feel

overtired, walk or talk in his/her sleep). This 6 item sleep measure had a modest internal consistency (maternal report $\alpha$ = .553, alternate caregiver report $\alpha$ = .551). CBCL sleep items have been used in previous research examining sleep and child anxiety (Alfano, Beidel, Turner, & Lewin, 2006) and have been linked to some objective (actigraphy, EEG) measures of sleep physiology (Gregory et al., 2011). Individual sleep items (i.e., "sleeps less than other children") and CBCL sleep composite scores have also been linked to child emotional and behavioral difficulties (Gregory, Van der Ende, Willis, & Verhulst, 2008; Becker, Ramsey, & Byars, 2015). Research also demonstrates convergent validity with other sleep measures, including the Child Sleep Health Questionnaire and the SDIS Sleep Disturbances Indexes (Becker et al., 2015).

**Child Anxiety.** Children's symptoms of anxiety were assessed during the preschool and school-age visits using maternal responses to relevant items on the CBCL for ages 1.5-5, and then again as part of the school-aged follow-up using maternal and alternate caregiver responses to the 113-item CBCL for ages 6-18. The CBCL has high established reliability and internal consistency and has been widely used to assess internalizing and externalizing behavior problems in children and adolescents (Achenbach & Rescorla, 2001). Additionally, at the school-age follow-up, mothers completed the Pediatric Anxiety form of the Patient-Reported Outcomes Measurement Information System (PROMIS)—a measure developed by the National Institute of Health (NIH) to screen children for early signs of anxiety. The parent proxy version of this instrument was used for this study. The PROMIS-Anxiety measure includes 15 items regarding typical symptoms of childhood anxiety (e.g., "In the past 7 days, my child felt nervous."). Each item is coded as occurring "never" (1) in the past 7 days, "almost never" (2), "sometimes" (3), "often" (4), or "almost always" (5). Raw scores range from 0-60; higher scores reflect higher levels of child anxiety. Of note, two sleep-related items (i.e., "My child worried when he/she

went to bed at night" and "My child woke up at night scared") are included on the PROMIS-Anxiety scale; these were not included in analyses to ensure that sleep items were not driving any associations between childhood sleep problems and anxiety in the current sample.

**Maternal Anxiety.** At the initial preschool visit, a trained interviewer administered the *Structured Clinical Interview for DSM-IV (SCID;* First, Spitzer, Gibbon, & Williams, 2002) to assess mother's current and lifetime history of Axis I psychological disorders. As part of this interview, information was obtained regarding mother's lifetime history of anxiety disorders. Maternal anxiety was coded as being present if mothers endorsed criteria on the SCID-IV for one of the following disorders: agoraphobia, panic disorder, social anxiety, obsessive compulsive disorder, post-traumatic stress disorder, generalized anxiety, substance-induced anxiety, or an otherwise unspecified anxiety disorder.

**Prenatal SRI Exposure.** Maternal SRI medication use during pregnancy was collected prospectively and verified by treating psychiatrists and research nurses. Exposure was measured in terms of number of weeks exposed, and was standardized to 40 gestational weeks (typical length of pregnancy).

**Stressful Life Events**. Child exposure to early life stress was measured during the preschool assessment using mother's responses to the Life Events Schedule (LES). The LES consists of 57 potentially stressful events that may have been experienced by the family a). since the child's birth and b). in the past six months. Mothers were required to rate the extent to which each event endorsed was negative or positive. Responses ranged from -3 (Extremely Negative) to 3 (Extremely Positive). Given this, stressful life events scores were weighted to reflect the potential positive or negative impact of life events on the family. To account for the potential

impact of chronic life stress on the child, weighted totals of life events experienced by the family since the child's birth were used in the current study.

## Data Analytic Plan

Structural equation modeling (SEM) was used to test the primary study hypotheses using SPSS AMOS 23.0 software. SEM is a statistical modeling technique that facilitates hypothesis testing at the construct level. Constructs are referred to as latent variables in SEM, and are derived by extracting the common variance from multiple measured variables related to the construct of interest (Kline, 2011). In the current study, a latent measure of persistent childhood sleep problems was created using maternal-reported child sleep behavior in the preschool and school-aged periods, as well as maternal reported child sleep duration for the night prior to the preschool assessment. To ensure consistency of direction of measured sleep variables, maternal reported child sleep duration was reverse scored so that fewer hours of sleep reflected more sleep disturbance. All measured sleep variables were standardized prior to running SEM models. Maternal and alternative caregiver reports of child anxiety problems on the CBCL, as well as maternal reported child anxiety on the PROMIS-Anxiety scale, were also used to create a latent outcome variable of school-aged anxiety.

SEM model fit was evaluated using a combination of absolute and incremental fit indices, including the likelihood-ratio chi-square ($\chi 2$) index, the comparative fit index (CFI), and the root-mean-square error of approximation (RMSEA). In the current analyses, a non-significant $\chi 2$ indicated non-discrepant fit between the population covariance and the covariance predicted by the tested model (Kline, 2011). The CFI assesses the improved fit of the tested model relative to an independence (null) model, and ranges in value from 0-1. Values over .90 indicates adequate model fit and over .95 indicates good fit (Hu & Bentler, 1999). For the RMSEA, which measures

the relative 'poorness' of tested model fit, values under .08 indicates adequate model fit and under .06 indicates good fit (Hu & Bentler, 1999).

Demographic factors (i.e., child gender, child ethnicity, parity, parent education, and maternal age) were assessed as potential confounds by testing them as predictors for persistent child sleep problems and child anxiety at school age. Several other potential confounds associated with this familial high risk sample (early exposure to life stress, early indicators of youth anxiety and prenatal SRI exposure) were also tested as predictors of our latent factors for persistent childhood sleep problems and child anxiety in the school aged period. To test our first hypothesis, maternal anxiety was entered as a predictor of our latent measure of child school-aged anxiety. To test our second hypothesis, a SEM model was first run with our latent factor for persistent childhood sleep problems as the primary predictor of our latent measure of child school-aged anxiety. Maternal anxiety and additional confounding factors were then entered into the primary SEM model examining associations between persistent childhood sleep difficulties and child anxiety in the school-aged period; these variables were entered as predictors of both latent factors. Mediation models were formally tested by calculating user defined estimands that represented indirect effects of maternal anxiety on child anxiety through the impact of persistent sleep. Bootstrapping was performed to produce bias corrected 95% confidence intervals for indirect effects in these models.

## Results

**Preliminary Analyses.** In the current sample, 47.6% of mothers had a history of an anxiety disorder. Descriptive statistics for primary measures of child sleep problems, school-aged anxiety, as well as our potential confounds of early life stress exposure, prenatal SRI exposure, and preschool-aged child anxiety symptoms can be found in Table 1. Preschool-aged

child anxiety was highly skewed and was log transformed prior to analyses. Correlations between measures included in subsequent SEM models can been found in Table 2; childhood sleep variables were significantly intercorrelated, as were school aged anxiety variables. Of note, although our measure of childhood life events stress exposure was not correlated with all individual measures of school-aged anxiety and childhood sleep problems, life events stress exposure, prenatal SRI exposure, and preschool-aged child anxiety significantly predicted to latent factors for persistent sleep problems and school-aged child anxiety (see Table 3). No demographic factors (e.g., child gender, child ethnicity, maternal age) were established as significant confounds.

**Maternal Anxiety as a Predictor of School-Aged Child Anxiety.** SEM models examining maternal anxiety as a predictor of our latent factor for child school-aged anxiety had good fit ($\chi^2$ [2, 185] = 1.466, $p$ = .481; CFI =1.000; RMSEA = 0.000, 90% CI: .000-.133) and the path from maternal to child anxiety was significant ($\beta$ = .196, $p$ =.022), supporting our first hypothesis.

**Sleep as a Mediator in the Relationship Between Maternal and Child Anxiety.** Our subsequent predictive model included a latent measure of persistent childhood sleep problems as a primary predictor of child anxiety at school age and also had good fit ($\chi^2$ [2, 185] = 6.459, $p$ = .596; CFI =1.000; RMSEA = 0.000, 90% CI: .000-.075). Here, persistent childhood sleep problems significantly predicted anxiety problems for children at school age ($\beta$ = .762, $p$ =.001). Persistent childhood sleep problems continued to predict childhood anxiety at school age when maternal anxiety, early life events stress and prenatal SRI exposure were added as additional predictors of both latent factors ($\beta$ = .754, $p$ =.001; see Figure 1 for model fit information). In this tested model, maternal anxiety, life events stress exposure, and prenatal SRI exposure

significantly predicted persistent childhood sleep problems, but did not predict child anxiety symptoms in the school-aged period.

An indirect effects model examining the path linking maternal anxiety to persistent childhood sleep problems (A) and the path linking persistent childhood sleep problems to school aged anxiety symptoms (B) showed good model fit ($\chi^2$ [21, 185] = 15.289, $p$ = .808; CFI =1.000; RMSEA = 0.000, 90% CI: .000-.040) and demonstrated that persistent sleep problems mediated the association between maternal anxiety and childhood anxiety at school age, when also accounting for the effects of life events stress exposure and prenatal SRI exposure (A x B = .386, 95% Bias-Corrected CI: .034-1.013, $p$ = .023). In this model, the path linking life events stress to persistent childhood sleep problems (A) and the path linking persistent childhood sleep problems to school-aged anxiety symptoms (B) was also examined, and revealed that persistent childhood sleep problems mediated the association between early stress exposure and school-aged child anxiety (A x B = -.031, 95% Bias-Corrected CI: -.070 - -.013, $p$ < .001). Indirect effects calculated for the path linking SRI exposure to persistent childhood sleep problems (A) and the path linking childhood persistent sleep problems to school-aged anxiety was not significant (A x B = .009, 95% Bias-Corrected CI: .000- .024, $p$ = .052), and as such, did not provide evidence of childhood sleep problems as a mediator in the prenatal SRI exposure – child anxiety relationship.

Of note, adequate model fit was not obtained when preschool measures of child anxiety were included in the SEM model displayed in Figure 1. However, a separate SEM model including preschool anxiety symptoms, maternal history of anxiety, and our latent factor of persistent childhood sleep problems as predictors of youth anxiety in school age did demonstrate adequate fit ($\chi$2 [14, 185] = 20.313, p = .121; CFI =.982; RMSEA = 0.050, 90% CI: .000-.093) and revealed that persistent childhood sleep problems also predicted school aged anxiety ($\beta$ =

.587, p =.005) over and above the effects of maternal anxiety and early childhood anxiety symptoms (See Figure 2). The indirect effect of maternal anxiety on youth school age anxiety via persistent sleep problems was also significant in this model (A x B = .566, 95% Bias-Corrected CI: .107-1.627, *p* = .017), which controlled for the effect of early childhood anxiety symptoms on youth school age anxiety.

## Discussion

In the first study to examine the role of persistent childhood sleep problems in the intergenerational transmission of anxiety, we demonstrated that persistent childhood sleep problems (i.e., sleep problems across the preschool and school-aged period) mediate the association between maternal anxiety and school aged child anxiety symptoms, as well as the association between early life stress and school aged child anxiety. These findings suggest that persistent childhood sleep difficulties may represent an early mental health risk indicator for those at familial high risk.

The results of the current study have significant treatment implications, as early sleep-focused health interventions may therefore be protective in terms of reducing long term risk for developing anxiety and other forms of child psychopathology. Behavioral treatments for young children have been repeatedly shown to be effective in improving various aspects (e.g., sleep-onset latency, night waking frequency, night waking duration) of childhood sleep; however, sleep intervention research with children often lacks longitudinal follow-up, and has largely failed to examine health and psychosocial outcomes associated with treatments for pediatric insomnia (Meltzer & Mindell, 2014). Given this, future research is needed to examine the effects of sleep interventions in the context of mental health conditions and their development across childhood and adolescence.

Certainly, early sleep-focused interventions necessitate parental/caregiver involvement, and several studies have demonstrated that various parenting related sleep-hygiene practices (e.g., having a parent present for sleep onset, reading to a child as a part of his/her bedtime routine, having a consistent bedtime routine for a child, setting an early vs. late bedtime) influence preschool and school-aged children's overall sleep duration (Owens, Jones, & Nash, 2011; Mindell et al., 2009). Studies have demonstrated that positive daytime parent-child interactions in infancy are linked to increased night-time sleep among preschool-aged children (Bordeleau, Bernier, & Carrier, 2012). Parental enforcement of home rules that promote child self-care has also been linked to healthier sleep patterns (e.g., longer sleep duration, earlier bedtime) in school aged children (Spilsbury et al., 2005). The present study did not examine the interplay of sleep and parenting in the intergenerational transmission of anxiety, as the goal of the current paper focused more on establishing sleep as a novel risk mechanism. However, research should prospectively examine the interplay of child sleep and parenting behaviors in future investigations of the environmental intergenerational transmission of anxiety. Additionally, given that early interventions focused on education about healthy sleep hygiene and children's sleep needs may – in and of themselves - represent a targeted health focused parenting intervention, future research should also investigate the effects of behavioral interventions for childhood sleep problems on other parenting practices, as well as on parent-child interaction more broadly.

Future research should also investigate the underlying neurobiological mechanisms that are associated with the risk conferred by persistent childhood sleep problems. As previously described, research has linked altered HPA-axis and brain functioning to childhood sleep problems, as well as childhood anxiety. Future studies examining sleep in the intergenerational

transmission of anxiety should include endocrine and neuroimaging measures as a means of understanding the physiological changes that occur in the context of persistent sleep difficulties, and that may leave children – particularly those at high-familial risk – vulnerable to developing anxiety. Given the overlap in genetic factors associated with childhood sleep problems and mood and anxiety difficulties (Gregory et al., 2011), future studies could also examine the role of genetic factors linked to sleep disturbance in the intergenerational transmission of anxiety.

A more thorough examination of the timing and severity of maternal anxiety is also critical to furthering our understanding of how - and for whom – persistent sleep problems serve as an early mental health risk indicator for children of anxious mothers. Considerable research efforts have focused on the impact of antenatal anxiety on child outcomes, given that prenatal exposure to maternal anxiety has been shown to have both short and long-term impacts on child development and behavior (Van den Bergh, Mulder, Mennes, & Glover, 2005; Field, 2017). That said, study findings have been mixed in terms of specific prenatal timing effects (see Van den Bergh et al., 2005). Additionally, given that childhood sleep could be disrupted by postnatal exposure to maternal anxiety and stress, as well as associated environmental factors (e.g., poverty, relationship discord in the home) that could give rise to maternal anxiety, future research is necessary to better understand the specific timing and/or pattern of maternal anxiety symptoms that confers the most risk for negative child outcomes, including persistent sleep disturbances.

Importantly, future research should also build on the current findings by taking a multi-method approach to investigating the types and properties of sleep difficulties that are most strongly linked to the development of anxiety in children at familial-high risk. The current study focused solely on maternal reports of child sleep problems. Maternal reported child sleep

problems on the CBCL have – as previously highlighted – been linked to objective (EEG) measures of night arousals and total sleep time (Gregory et al., 2011). Maternal reported child sleep duration has also been associated with actigraphy measures of total sleep time (Iwasaki et al., 2010). That said, agreement between maternal-reported sleep patterns and actigraphy measures are inconsistent, and suggest that these measures characterize different aspects of sleep for young children (Werner, Molinari, Guyer, & Jenni, 2008; Holley, Hill, & Stevenson, 2010; Belanger, Simard, Bernier, & Carrier, 2014). Sleep is generally understood to be a complex physiological process that crosses multiple levels of analysis and cannot be defined by a single measure (Krueger, Frank, Wisor, & Roy, 2016); given this, it is imperative that future studies incorporate a multi-method assessment of sleep that includes more objective measures of various sleep variables (e.g., sleep latency, duration, and efficiency). Examining sleep patterns at more frequent intervals across development will also facilitate a more comprehensive understanding of the long term health effects of persistent childhood sleep problems.

The current study represents an important initial step in establishing persistent childhood sleep problems as an early risk mechanism involved in the intergenerational transmission of anxiety. There are several lines of research to be pursued in the future to better understand the underlying pathways linking sleep to the development of anxiety in children who are at familial high-risk. These lines of research may have significant implications for child mental health outcomes, as early childhood sleep represents a malleable intervention target for which there are effective behavioral treatments.

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**Table 1.** Descriptive Statistics for Primary Variables of Interest: Childhood Sleep Problems, School-Aged Anxiety, and Potential Confounding Factors.

| Variable | Mean | SD |
|---|---|---|
| *Sleep Measures* | | |
| Maternal Reported CBCL Sleep Problems, Preschool Measure | 3.179 | 2.777 |
| Maternal Reported CBCL Sleep Problems, School-Aged Measure | 0.800 | 1.201 |
| Maternal Report, Number of Hours Child Slept on Night Prior to Preschool Visit | 10.024 | 1.368 |
| *School Aged Anxiety Measures* | | |
| Maternal Reported CBCL Anxiety Symptoms | 1.816 | 2.407 |
| Alternate Caregiver Reported CBCL Anxiety Symptoms | 1.725 | 2.234 |
| Maternal Report on PROMIS-Anxiety Scale | 9.343 | 9.430 |
| *Potential Confounding Factors* | | |
| Maternal Reported CBCL Preschool Anxiety Symptoms | 2.766 | 2.408 |
| Life Events Stress Exposure Ratings Since Pregnancy | -.070 | 8.225 |
| SRI exposure, in terms of weeks of pregnancy | 16.530 | 19.246 |

**Table 2.** Correlations Table for Primary Variables of Interest, Known Predictors of School-Aged Anxiety

| **Variable** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. Maternal Reported CBCL Sleep Problems, Preschool | --- | | | | | | | | | |
| 2. Maternal Reported CBCL Sleep Problems, School-Age | .388** | --- | | | | | | | | |
| 3. Maternal Report, Number of Hours Child Slept on Night Prior to Preschool Visit | -.281** | -.174* | --- | | | | | | | |
| 4. Maternal Reported CBCL Anxiety Symptoms, School Age | .404** | .469** | -.243** | --- | | | | | | |
| 5. Alternate Caregiver Reported CBCL Anxiety Symptoms, School Age | .212* | .254** | .003 | .472** | --- | | | | | |
| 6. Maternal Report on PROMIS-Anxiety Scale, School Age | .276** | .384** | -.208** | .627** | .430** | --- | | | | |
| 7. Maternal History of Anxiety | .197** | .159* | -.141 | .168* | .172* | .110 | --- | | | |
| 8. Life Events Exposure Since Pregnancy | .124 | .061 | -.009 | .086 | -.018 | .099 | .105 | --- | | |
| 9. Maternal Reported CBCL Anxiety Symptoms, Preschool Age | .654** | .297** | -.153* | .511** | .315** | .257** | .166* | .084 | --- | |
| 10. Prenatal SRI exposure | .128 | .197** | -.152* | .315** | .194* | .173* | .275** | .001 | .157* | --- |

Anxiety.
*p < .05 ** p < .01 (two tailed)

**Table 3.** SEM Fit Statistics and Results: Life Events Stress Exposure and Prenatal SRI Exposure Predicting Persistent Childhood Sleep Problems, School Aged Anxiety

| ***Predictor Variable*** | ***Chi Square*** | ***CFI*** | ***RMSEA (90 % CI)*** | **β** | ***p*** |
|---|---|---|---|---|---|
| *Persistent Childhood Sleep Problems as Outcome* | | | | | |
| Life Events Exposure Since Pregnancy | *$X^2$ (d.f = 2, N=185) = 2.133, p=.344* | *.997* | *.019 (.000 - .149)* | -.346 | *.005* |
| Prenatal SRI Exposure | *$X^2$ (d.f = 2, N=185) = 3.408, p=.182* | *.969* | *.062 (.000 - .171)* | .265 | *.020* |
| Preschool Aged Child Anxiety | *$X^2$ (d.f = 1, N=185) = 1.356, p=.244* | *.997* | *.044 (.000 - .207)* | .541 | *.001* |
| *School Aged Child Anxiety as Outcome* | | | | | |
| Life Events Exposure Since Pregnancy | *$X^2$ (d.f = 2, N=185) = 1.680, p=.432* | *1.000* | *.000 (.000-.139)* | -.232 | *.008* |
| Prenatal SRI Exposure | *$X^2$ (d.f = 2, N=185) = 2.772, p=.250* | *.995* | *.046 (.000-.198)* | .336 | *<.001* |
| Preschool Aged Child Anxiety | *$X^2$ (d.f = 1, N=185) = 0.249, p=.618* | *1.000* | *.000 (.000-.155)* | .567 | *<.001* |

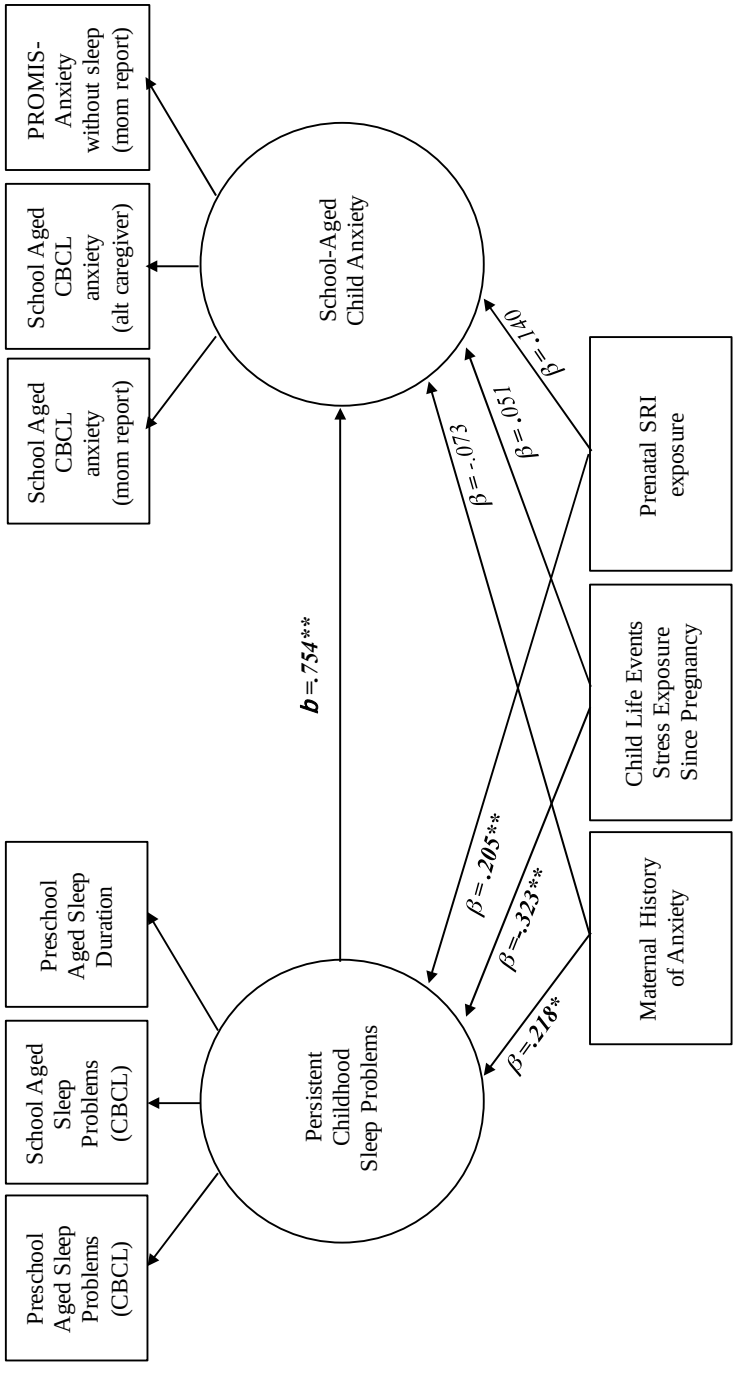


Figure 1. SEM Model with Persistent Childhood Sleep Problems Predicting School-Aged Child Anxiety, in the Context of Maternal Anxiety, Child Early Life Stress Exposure, and Prenatal SRI Exposure.

Model Summary and Fit Statistics: $\chi^2$ [22, 185] = 17.954, p = .709; CFI =1.000; RMSEA= 0.000, 90% CI: .000-.048
*p < .05 ** p < .01, *** p<.001 (Regression weights above bolded if significant)

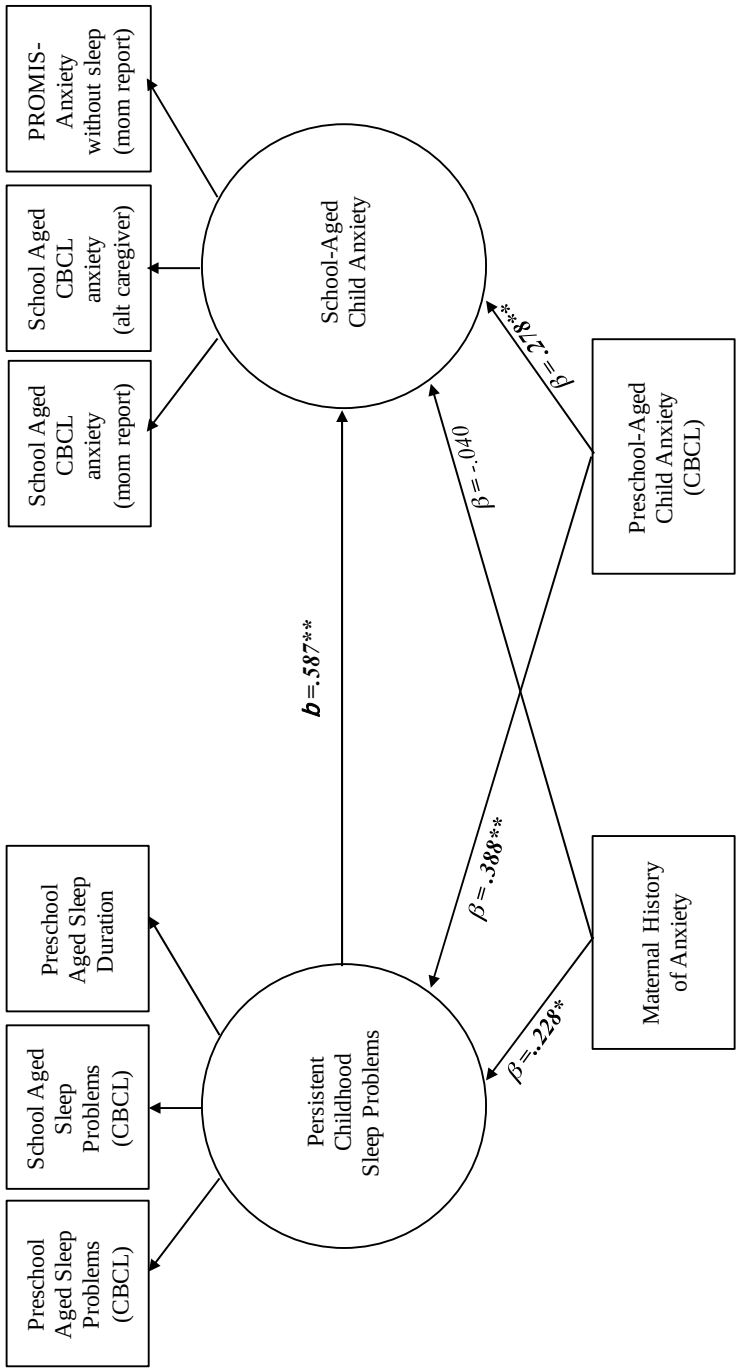


Figure 2. SEM Model with Persistent Childhood Sleep Problems Predicting School-Aged Child Anxiety, in the Context of Maternal Anxiety and Preschool Aged Child Anxiety

*p < .05 ** p < .01, *** p<.001 (Regression weights above bolded if significant)

# Associations Between Childhood Sleep and Neural Correlates of Emotion Responsivity and Regulation

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Abstract

A growing body of literature demonstrates associations between sleep and emotional functioning. Adult functional neuroimaging (fMRI) studies have shown that reduced sleep duration is associated with altered amygdala and reward circuitry activation when processing emotional stimuli, as well as altered amygdala and prefrontal activation in the context of emotion regulation tasks. Recent research in our lab suggests similar associations exist between maternal reported sleep duration and brain activity in school-aged boys. Using a community sample of 32 school-aged children (ages 7-10), the current study extended this work by examining associations between sleep and fMRI activation to emotional faces during two affectively laden executive functioning (response inhibition, working memory) tasks. Sleep was assessed by maternal report as well as actigraphy measures of quality, duration and variability. In contrast to our predictions, significant associations were not found between actigraphy measures of child sleep duration and fMRI measures of emotional responsivity and regulation. Only maternal reported sleep problems over the past six months were associated with left insula and left inferior frontal gyrus activation when viewing fearful faces in the context of a working memory task. Given this, the current study provides limited evidence linking childhood sleep problems and neural activation measures of emotion responsivity / regulation. More persistent sleep problems may be more robust in terms of their associations with fMRI measures of emotional functioning in healthy children.

# Associations Between Childhood Sleep and Neural Correlates of Emotion Responsivity and Regulation

Sleep is increasingly implicated as an influential factor in human mental health. Sleep disturbance is a symptom of several psychiatric disorders, and is implicated in the etiology and maintenance of internalizing disorders such as depression and anxiety (Vgontzas et al., 2012; Morphy, Dunn, Lewis, Boardman, & Croft, 2007). In childhood, sleep problems have been linked to increased risk for emotional and behavior problems (Gregory & Sadeh, 2012; Reid, Hong, & Wade, 2009; Sivertsen et al., 2015), as well as increased risk for anxiety, depression (although findings for this condition are mixed), and oppositional defiant disorder later in life (Shanahan, Copeland, Angold, Bondy, & Costello, 2014; Greene, Gregory, Fone, & White, 2015; Gregory et al., 2005). Given the transdiagnostic nature of sleep problems, as well as the societal burden of mood and anxiety disorders (Whiteford et al., 2013; Kessler et al., 2009; Lépine & Briley, 2011), a growing body of research has investigated the processes by which sleep problems may confer risk for psychopathology across the lifespan.

## Emotional Responsivity and Regulation: Underlying Mechanisms in the Sleep - Mental Health Relationship

A growing body of research implicates emotional responsivity and emotion regulation as mechanisms linking sleep and mental health. Emotional responsivity refers to the extent to which individuals experience emotion in response to affective stimuli (Mathews & Barch, 2010), whereas emotion regulation refers to the processes people use to monitor, evaluate, and modulate emotions to successfully achieve their goals and adapt to different environments (Thompson, 1994). Emotion regulation strategies are thought to influence the extent to which emotional responses to one's environment evolve into more enduring mood states; as such, it is

hypothesized that individuals with emotion regulation difficulties may – over time – become more vulnerable to dysfunctional and/or distressing moods (e.g., depressed, irritable, anxious) and associated mental health conditions (Watling, Pawlik, Scott, Booth, & Short, 2017). This is supported by a growing body of research demonstrating that maladaptive emotional regulation strategies are associated with the presence of internalizing disorders such as depression and anxiety (Aldao, Nolen-Hoeksema, & Schweizer, 2010).

Interestingly, sleep problems can negatively impact mood and daily functioning (Scott, McNaughton, & Polman, 2006; Wong et al., 2013), and have been shown to disrupt processes involved in emotion responsivity and regulation. Studies of healthy adults demonstrate that sleep deprivation is associated with increased physiological and impulsive behavioral responses to negative picture stimuli, relative to positive and/or neutral stimuli (Franzen, Buysse, Dahl, Thompson, & Siegle, 2009; Anderson & Platten, 2011). Sleep loss has also been linked to increased negative emotional reactions to disruptive daily life events, and dampened positive emotional reactions to goal-congruent daily events (Zohar, Tzischinsky, Epstein, & Lavie, 2005). Similarly, poor sleep quality - a multifaceted construct encapsulating concerns regarding daytime fatigue, restlessness in sleep, reduced sleep time and/or difficulties initiating or maintaining sleep (see Harvey, Stinson, Whitaker, Moskovitz, & Virk, 2008) - is associated with impaired emotion regulation abilities (i.e., cognitive reappraisal), even when controlling for stress and symptoms of anxiety and depression (Mauss, Troy, & LeBourgeois, 2013). Although some of this work has demonstrated that sleep loss can lead to elevated baseline positive affect (Zohar et al., 2005), these findings collectively suggest that in the context of poor sleep and/or sleep loss, individuals may perceive situations more negatively than when well-rested, and may have more difficulty managing emotional reactions to these experiences.

Similar findings have been demonstrated among children and adolescents. Experimental research has shown that childhood and adolescent sleep restriction results in increased negative affect in response to challenge (Berger, Miller, Seifer, Cares, & Lebourgeois, 2012), decreased positive affect (Talbot, McGlinchey, Kaplan, Dahl, & Harvey, 2010) and emotional responsivity to positive emotional stimuli, and decreased self- and parent-reported emotional control abilities (Vriend et al., 2013; Baum et al., 2014). Poor childhood sleep quality has also been linked to emotion processing deficits across early adolescence (Soffer-Dudek, Sadeh, Dahl, & Rosenblat-Stein, 2011). It should be noted that some studies demonstrate reduced positive affect following adolescent sleep restriction, rather than changes in the experience of negative affect (see Palmer & Alfano, 2017; Talbot et al., 2010). Therefore, further research is needed to understand how, and to what extent, sleep difficulties impact the processing and experience of negative and positive emotions across different phases of child development.

**Neural Substrates of Emotion Responsivity/ Regulation and Sleep Disturbance**

Sleep loss and emotional responsiveness/regulation also appear to be linked at a neurobiological level. Functional neuroimaging studies have repeatedly implicated fronto-limbic connectivity in the regulation of emotion (Ray & Zald, 2012). Specifically, limbic regions of the brain (e.g., the amygdala) are implicated in the initial evaluation of the salience and valence of emotional stimuli, whereas prefrontal and anterior cingulate activation is implicated in the top-down modulation of these neural responses (Banks, Eddy, Angstadt, Nathan, & Luan Phan, 2007; Hare et al., 2009; Mohanty et al., 2007; Ochsner, Bunge, Gross, & Gabrieli, 2012; Frank et al., 2014). A bulk of this literature has focused on neural responsivity to emotional face stimuli; this work suggests that when compared to neutral faces, emotional responses to fearful, sad, and happy faces are associated with increased amygdala activation, whereas insular activation is

implicated in the processing of negative (e.g., angry, disgusted) face stimuli, and the anterior cingulate is implicated in the processing of happy faces (Fusar-Poli et al., 2009).

Importantly, an emerging literature has revealed that sleep restriction/reduction is associated with alterations in amygdala and prefrontal activation in response to negative – and in some cases, positive emotional stimuli, decreased fronto-limbic functional connectivity, as well as decreased functional connectivity between the amygdala and the anterior cingulate cortex (Gujar, Yoo, Hu, & Walker, 2011; Yoo, Gujar, Hu, Jolesz, & Walker, 2007; Motomura et al., 2013). These findings complement research demonstrating that increased self-reported sleep duration is associated with higher emotional intelligence, greater negative resting state functional connectivity between the amygdala and ventromedial prefrontal cortex, and reduced levels of depression and anxiety symptoms (Killgore, 2013). Although there is not strong evidence linking sleep quality to neural activation in the context of emotion regulation (Minkel et al., 2012), poor sleep quality has been shown to moderate the associations between amygdala activation in response to fearful face stimuli and internalizing symptoms in young adults (Prather, Bogdan, & Hariri, 2013). These findings lend support to the hypothesis that emotion related-neural mechanisms may underlie the associations between sleep and psychopathology.

**Neural Correlates of Sleep and Emotional Functioning in Children**

From a developmental psychopathology perspective, investigations of the neural correlates of sleep difficulties and emotional responsivity across childhood are of particular importance, as this work could provide critical information about early vulnerabilities to mental health disorders, including anxiety and depression. Surprisingly, very few studies have examined associations between child sleep problems and emotional responsivity and regulation at the neural level. A few fMRI studies have examined sleep and brain function in non-clinical

adolescent samples; however, this work has largely focused on the effects of sleep problems (e.g., sleep quality, restricted sleep duration) on circuitry involved in reward processing, decision making, and working memory (Telzer, Fuligni, Lieberman, & Galvan, 2013; Holm et al., 2009; Hasler et al., 2012; Beebe, DiFrancesco, Tlustos, McNally, & Holland, 2009). One recent fMRI study by Carlisi and colleagues (Carlisi, Hilbert, Guyer, and Ernst, 2017) examined sleep and emotional responsivity to fearful face stimuli in anxious and healthy adolescents. In healthy adolescents, these researchers demonstrated that self-reported sleep duration was negatively associated with dorsal anterior cingulate (dACC) and hippocampal activation and positively associated with connectivity between the dACC and dorsomedial prefrontal cortex, as well as connectivity between the hippocampus and the insula. In anxious youths, associations were found in the opposite direction (Carlisi et al., 2017).

In one of the first studies to investigate the relationship between sleep and neural correlates of emotional responsivity in pre-adolescent children, our group demonstrated that parent-reported child sleep duration was negatively associated with activation in the bilateral amygdala, left insula, and left temporal pole when viewing negative (i.e., fearful, disgust) vs. neutral faces and bilateral orbitofrontal, right anterior cingulate, and left amygdala activation when viewing happy vs. neutral faces (Reidy, Hamann, Inman, Johnson, & Brennan, 2016). We also demonstrated that greater sleep duration was associated with increased positive functional connectivity between the bilateral amygdala and prefrontal cortex (Reidy et al., 2016). These findings generally mirrored findings in the adult literature (e.g., Yoo et al., 2007; Gujar et al., 2011); however, this study was limited by a relatively small, all-male sample with behavioral difficulties, and relied solely on maternal-report measures of child sleep duration.

The paucity of literature described above highlights the need for ongoing research to understand relationships between childhood sleep difficulties and neural correlates of emotional responsivity and regulation. In general, current child – and in large part adult - studies examining brain functioning and sleep have focused on sleep duration (manipulated via sleep restriction or measured via subjective report). Measures of sleep duration and quality are thought to characterize different aspects of sleep difficulty, as are objective (e.g., polysomnography, actigraphy) vs subjective (e.g., parental report) assessments of sleep (Werner et al., 2008; Holley, Hill, & Stevenson, 2010; Belanger et al., 2014; Scher & Asher, 2004). Given this, there is a critical need for studies to explore what specific aspects of sleep problems are – or are not – associated with altered emotion processing in children. As highlighted in the adult literature, there is still much to be understood about the extent to which sleep problems influence emotional responsivity and regulation in the context of negative vs. positive environmental stimuli. Given that initial neuroimaging studies have primarily investigated relationships between sleep and emotional functioning in clinical or clinically high-risk samples, future research is needed to examine these relationships in community samples of healthy children.

**Current Study**

The current study addressed several gaps in the literature by examining short-term prospective associations between sleep and the neural correlates of emotional responsivity and regulation in a sample of male and female school-aged children (ages 7-10). Extending our previous findings (Reidy et al., 2016), we collected objective measures of sleep duration, efficiency, variability, and quality to investigate the relationship between neural measures of emotional responsivity and different aspects of sleep difficulties. Focusing on selected brain regions of interest that are implicated in the generation and regulation of emotion, we predicted

that reduced sleep duration would be associated with increased amygdala activation when viewing emotional vs. neutral faces and increased insula activity in response to negative faces. We also anticipated that reduced sleep duration might be linked to altered inferior frontal gyrus and anterior cingulate activation in the context of affectively laden executive functioning tasks. As a more exploratory aim, the current study also examined associations between measures of child sleep quality and variability and neural activation in response to positive and negative face stimuli, in the context of affective fMRI task conditions requiring increased cognitive control.

## Method

### Participants

Forty-nine children (ages 7-10 years) and their mothers were enrolled in the current study. Mother-child dyads were recruited through the Emory University Child Study Center participant database. To be included in the present study, children had to be right-hand dominant, medically healthy, psychotropic medication naïve, and metal free. Children also had to have complete scan data for two functional MRI tasks, as well as data from at least one sleep-related measure to be included in the present study. The 32 children that were included in the final sample did not differ from excluded participants in terms of child age, gender, or ethnicity, nor by maternal age or education. The final sample was 50% male and was majority Caucasian (65.4% of those reporting). Children's mean age was 9.27 years (SD = 1.13 years). Mean maternal age was 41.38 years (SD = 5.41 years). Mothers in this sample were highly educated; of those reporting, 88.5 % endorsed graduating from college and/or pursuing an advanced degree.

### Procedure

The current study consisted of two 1.5-2-hour long visits – one initial laboratory visit and a follow-up scanning visit – that took place over a week period at Emory University. After providing parental informed consent and child assent during the initial laboratory visit, mothers

completed questionnaires regarding their child's sleep and health behaviors while children completed a brief cognitive testing battery. Families also completed a mock scanning session as a means of familiarizing children to the scanning environment prior to their scanning visit. During the mock scan session, children practiced remaining still in the mock scanner for several minutes, and completed practice trials of the behavioral task they would complete during scanning.

During the 7-day period prior to the scheduled scanning visit, mothers completed sleep diaries for their children. Each night, children also wore actigraphs to provide a more objective measure of child sleep quantity and quality. During the second lab visit, mothers returned sleep data for their child and completed additional measures regarding their current mental health and their child's mood and behavior. At this time, children completed a structural, resting state, and two functional MRI scanning runs: one scan run required children to complete an affective response inhibition task; the other required children to complete an affective working memory task. Families were compensated for their participation. This study was approved by the Institutional Review Board of Emory University.

**Measures**

**Maternal Report Measures of Childhood Sleep.** At the initial laboratory visit, mothers completed the Child's Sleep Habits Questionnaire (CSHQ), a 45-item questionnaire that assesses for potential child sleep behavior problems over the course of the past week. Specifically, mothers reported their child's typical bedtime, sleep duration, number of night awakenings, as well as the frequency (i.e., rarely, sometimes, or usually) with which their child engages in various sleep behaviors (e.g., "child sleeps about the same amount each day," "child complains about problems sleeping," "child seems tired"). Responses to 33 key items on the CSHQ were used to generate eight problem subscale scores – Bedtime Resistance, Sleep Onset Delay, Sleep

Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep Disordered Breathing, and Daytime Sleepiness. These items are also summed to generate a composite Total Sleep Disturbance score (Owens, Spirito, McGuinn, & Nobile, 2000). Higher scores (which can range from 33 – 99) on the CSHQ indicate more childhood sleep problems. The CSHQ has been shown to have acceptable test-retest reliability and internal consistency coefficients, and has been successfully used to discriminate sleep-disordered from healthy individuals (Lewandowski, Toliver-Sokol, & Palermo, 2011; Owens et al., 2000).

Mothers also completed the 113-item Achenbach Child Behavior Checklist (Achenbach & Rescorla, 2001) for ages 6-18, a widely used measure of children's emotional and behavior problems. Specifically, mothers responded to 6 sleep-related items of interest (i.e., does your child have nightmares, have trouble sleeping, sleep less than others, sleep more than others, is overtired for no reason, or talks/walks in sleep). Item responses ranged from 0 (not true) to 2 (very/often true), where higher scores indicated higher levels of sleep problems over the past six months. Although not a formal subscale, CBCL sleep items and composite scores have been used in previous research examining sleep and child emotional and behavioral problems (Gregory, Van der Ende, Willis, & Verhulst, 2008; Becker, Ramsey, & Byars, 2015), and have been linked to some objective (actigraphy, EEG) measures of sleep physiology (Gregory et al., 2011). Research also demonstrates convergent validity between a CBCL sleep composite and other sleep measures (e.g., Child Sleep Health Questionnaire, the SDIS Sleep Disturbances Indexes; Becker et al., 2015). This 6 item sleep measure had a modest internal consistency ($\alpha = .663$).

**Actigraphy.** Actigraphs were used to assess child sleep patterns for 7 days prior to the scan visit. Children wore Micro Motionlogger Sleep Watch (Ambulatory Monitoring Inc., Ardsley, NY) actigraphs on their non-dominant wrist at night, and were asked to mark their

bedtime and wake time by pressing an event button on the side of the watch. Actigraph watches then measured body movements in 1-minute epochs (using zero crossing mode) throughout the sleep cycle. Actigraph raw data were downloaded and prepared for analyses using ACTme software in the ActionW2.7 program. Data was trimmed to remove extraneous data prior to the first night of sleep and following wake time on the final morning. Down time (indicating bedtime) was established using children's evening event button press. If no event marker was present, information provided by parents on a supplementary sleep diary was used to establish bedtime. If there were concerns about the accuracy of maternal reported bedtime on the sleep diary, the down time marker was placed when the child put the watch on for the night. A second down time marker, signifying wake time, was placed where activity levels were above a suggested threshold for 5 consecutive minutes. This marker was also established as needed using children's event marker button press and via sleep diary information.

The Sadeh algorithm was used for sleep-wake identification each night. This method for establishing actigraph sleep parameters is widely used in the literature and shows good agreement with sleep-EEG measures (i.e., polysomnography [PSG]) of nocturnal sleep time in children; more modest measures of specificity using actigraphy vs PSG have also been shown (Sadeh, Sharkey, & Carskadon, 1994; Sadeh, Acebo, Seifer, Aytur, & Carskadon, 1995; Meltzer, Montgomery-Downs, Insana, & Walsh, 2012). Actigraph output included estimations of children's mean sleep duration and efficiency over the sleep assessment window, which generally took place over 7 nights. To assess variability of sleep duration, Mean Square of Successive Differences (MSSD) was calculated using actigraph mean sleep duration output from each night of assessment. Intra-individual variability in sleep duration has been linked to

increased risk for depressive symptoms, and as such may provide novel information about links between sleep and emotion regulation (Bei, Wiley, Trinder, & Manber, 2016).

As highlighted above, mothers completed a daily sleep diary regarding children's bedtimes, estimated sleep onset latency (i.e., time to fall asleep), and estimated waking times. Additionally, information was provided about days in which children were sick and/or had taken any medications during the 7-day sleep assessment period. This information was used to address potential confounds in the data and to clean actigraphy data where indicated.

**Emotion Responsivity and Regulation.** Neural measures of child emotional responsivity and regulation were obtained during one run of an affective go/no-go task, as well as one run of an N-back working memory task. These tasks were selected as a means of examining children's neural responses to emotional stimuli under conditions requiring executive functions/top-down cognitive control. During the affective go/no-go task, participants viewed happy or neutral face stimuli that were surrounded by different colored picture frames (i.e., blue, yellow, orange). Participants were required to respond as quickly as possible to stimuli surrounded by one of two target picture frame colors ("go trials"), while refraining from responding to faces surrounded by the non-target picture frame color ("no-go" trials). Target and non-target frame colors were counterbalanced. Happy and neutral facial expressions were matched, with 120 randomized trials (stimulus duration 1000ms; mean ISI 2000ms). Studies using similar paradigms have demonstrated that this task can be successfully used in young children and adolescents to discriminate age-based differences in emotional reactivity and control (Hare et al., 2009; Tottenham et al., 2009).

During the N-back task, children viewed neutral and fearful faces while completing two different memory load conditions. In the low memory load (0-back) condition, children were

instructed to press respond with a button press whenever a target face appeared on the screen. In the high memory load (1-back) condition, children were asked to respond with a button press whenever two of the same face stimulus were presented in a row (i.e., when a face stimulus matches the face stimulus that was previously presented). The fMRI paradigm utilized a 2 (memory load condition) x2 (emotional face condition) factorial block-design with 13 blocks, each consisting of 14 trials, that generally alternated between emotion and memory load condition. Of note, the 7$^{th}$ block of this task was always a low memory load block with neutral face stimuli. In each task block, task instructions lasted for 3000 ms and were followed by a 1000 ms fixation cross; each trial was then comprised of a 500 ms face stimulus and a 1000 ms fixation cross. Children completed one of two counterbalanced versions of this task. Schematic diagrams of both go/no-go and N-back task designs are shown in Figure 1.

**Scanning Acquisition Parameters**

Scanning was completed on a 3T Siemens Magnetom Trio scanner in the Facility for Education and Research in Neuroscience (FERN) at Emory University. Whole-brain structural T1 images were acquired with a gradient-echo T1-weighted pulse sequence (TR =2.30s, TE=30ms, 1x1x1mm voxel size), which allowed the subsequent superposition of functional imaging results with anatomy. EPI functional scans were acquired sequentially (TR =2.00s, TE=30ms, 3x3x3mm voxel size), with 30 3-mm axial slices.

## Data Analytic Plan

Prior to running analyses, behavioral data were assessed for data entry errors, outliers, and missing or otherwise problematic responses using SPSS 24.0. Several demographic variables (e.g., child age, gender, cold and allergy/asthma medication usage) were examined as potential confounds in the relationship between childhood sleep problems and neural activation during N-

Back and Affective Go /No-Go tasks. Identified confounds (i.e., significant predictors of neuroimaging activation output) were controlled for in subsequent analyses.

Functional neuroimaging data was analyzed using Statistical Parametric Mapping (SPM12; Friston et al., 1994) and FSL software. Data were preprocessed for image realignment, normalization to a standard EPI template using SPM12's unified segmentation and normalization method, spatial smoothing, and artifact removal and motion correction. Slice timing was conducted for Affective Go / No-Go data prior to realignment; however, this step was not completed for N-Back data, as this preprocessing step may have interacted with motion during the block design task. Normalization parameters were derived by segmenting each participant's T1-weighted anatomical brain image using the Montreal Neurological Institute (MNI) template. These normalization parameters were then applied to the respective participant's functional images. Data were then spatially smoothed using a Gaussian filter (FWHM = 6 × 6 × 6 mm). Independent Components Analysis–Based Automatic Removal of Motion Artifacts (ICA-AROMA) was used to correct for any motion-related artifacts in the data. ICA-AROMA takes the fMRI time series and breaks it down into maximally differential components. This is then used to identify and remove components in the fMRI data associated with motion via a non-aggressive de-noising option (Pruim et al., 2015).

Data were then extracted for quality control checks in SPM12, and the running of first and second level models. Second level models were run to examine neural activation that corresponded to emotion contrasts for each task (i.e., examining neural activation in response to a happy or fearful face, relative to activation in response to a neutral face), as well as neural activation associated with the interaction of the emotion contrast with each task of interest. The interaction contrasts were used to isolate activation in response to emotional stimuli that was

associated with task conditions characterized by increased cognitive control (e.g., high working memory load vs. low working memory load in the N-Back task). Regions of interest (ROIs) were selected for the amygdala, anterior cingulate cortex, left insula, and left and right inferior frontal cortex. Specifically, ROIs for the amygdala were created using the WFU PickAtlas (see Maldjian, Laurienti, Kraft, & Burdette, 2003) from the AAL atlas ROIs. Spherical (6 mm radius) ROIs for the other above mentioned regions were created in WFU PickAtlas using coordinates from reviews concerning the neural underpinnings of emotional responsivity and regulation (Frank et al., 2014; Fusar-Poli et al., 2009; McRae et al., 2012). Parameter estimates of ROI-averaged values were then extracted from second-level contrast images using the Rex Toolbox in SPM (manual found at: http://web.mit.edu/swg/rex/rex.pdf). Extracted data was then included in SPSS-based analyses to examine associations with actigraphy and maternal reported sleep measures.

## Results

**Preliminary Analyses.** Descriptive statistics for primary measures of child sleep problems, as well as our potential confounds of cold or allergy/asthma medication use, can be found in Table 1. Actigraphy measures of average child sleep duration and MSSD for sleep duration were significantly skewed and were Windsorized prior to analyses. Resulting measures demonstrated child sleep durations ranging from 6.9 hours – 9.51 hours per night. Of note, sleep efficiency was quite good, ranging from 84.8 – 99.7 percent. Maternal reported sleep problem ratings on the CBCL were generally low, with 75% of ratings being 0 or 1. Scores on the CSHQ were consistent with those seen in other community samples of school-aged children (Owens et al., 2000). Correlations between maternal reported measures of sleep quality were significant. In terms of actigraphy measures, sleep duration was significantly associated with individual

variability of sleep duration and sleep efficiency. Sleep efficiency and variability of sleep duration were not associated. However, maternal reported sleep problems on the CSHQ and actigraphy measures of sleep efficiency were associated in the expected direction (see Table 2).

Neural activation measures did not evidence notable skew. Potential demographic factors (i.e., children's age, gender), as well as child cold and asthma/allergy medication usage, were significantly associated with neural contrast output for at least one of our established ROIs. Actigraphy measures of sleep duration variability were higher for minority children ($F(1,22) = 11.012$, $p = .003$) and for girls ($F(1,27) = 4.636$, $p = .040$). Child age was also negatively associated with actigraphy measures of sleep duration ($r = -.518$, $p = .004$). Given this, child age, gender, ethnicity, and medication usage were included as covariates in subsequent analyses.

**Sleep duration and neural correlates of emotion responsivity and regulation.** A series of partial correlations were run to examine associations between actigraphy measures of sleep duration and neural correlates of emotional responsivity, as measured by emotion vs. neutral contrasts for N-Back and Go / No-Go task data. In contrast to our predictions, sleep duration was not significantly associated with activation in any of the pre-determined ROIs for these contrasts. Similarly, no associations between child sleep duration and ROI activity were found in the context of contrasts focused on the interaction between emotion and task.

**Exploratory analyses examining emotion responsivity/regulation and measures of sleep quality and variability.** Across emotion and emotion x task contrasts, significant associations were not found between ROI output and measures of sleep duration variability or sleep efficiency. Sleep quality, as measured using the CSHQ, was also not associated with any ROI measures for emotion and emotion x task contrasts. The only significant associations demonstrated were between maternal reported child sleep problems on the CBCL and activation

in the left inferior frontal cortex for the interaction between working memory on the N-Back task and emotional responsivity to fearful faces ($r$ = .546, $p$ = .013; see Figure 2 for bivariate association). Associations were also demonstrated between CBCL sleep items and the Left insula for this N-Back task x emotion contrast ($r$ = .468, $p$ = .037; see Figure 3 for bivariate associations).

## Discussion

Extending findings from our previous work, the present study examined associations between child sleep problems (measured via actigraphy and maternal report) and neural correlates of emotional responsivity and regulation in a community sample of school-aged children. In contrast to our primary hypothesis, findings from the current study did not demonstrate associations between child sleep duration and activation in the amygdala or left insula in response to emotional face stimuli. Likewise, associations were not demonstrated between sleep duration and amygdala, insular, anterior cingulate, or inferior frontal activation in response to emotional stimuli during tasks requiring increased cognitive control.

These results are surprising, considering the growing body of research demonstrating associations between reduced sleep duration and emotional functioning. These results are also perplexing when our group's previous findings (Reidy et al., 2016) regarding child sleep duration and emotional responsivity are taken into account, particularly given the similarities in the age, mean sleep duration, and sleep duration range of these two study samples. Notably, our previously published study utilized data from an all-male sample that was selected for potential behavior problems (i.e., if they were considered to be "a handful" by their parents). The current community sample represented a highly resourced group of male and female children who evidenced potentially restricted range of sleep measures not assessed in our previous study (e.g.,

sleep efficiency). Although measures of child sleep duration and quality did not differ by gender in the current study, children's intra-individual variability in sleep duration was higher among girls. Gender was controlled for in the present analyses; however, it will likely be beneficial for future investigations to probe gender differences in sleep and emotion responsivity/regulation in more detail. Given the concerns about restricted range of sleep variables in the current study, future investigations in this line of research should select participants to represent a wide range of sleep difficulties, as a means of ensuring adequate data variance. The current study may also have been underpowered to detect sleep and neural associations due to the loss of data resulting from motion, and larger samples may be needed to detect effects.

The two significant findings linking sleep and emotion responsivity/regulation in the current study were positive associations between maternal reported sleep problems on the CBCL and left inferior frontal gyrus/left insula activation that was associated with viewing fearful faces under high working memory load. Given that studies have implicated increased inferior frontal gyrus activation in the effective top-down regulation of emotions (Frank et al., 2014; McRae et al., 2012), one might expect this activation to be decreased in the context of sleep difficulties. However, some research has also implicated the inferior frontal gyrus in emotion recognition and emotion contagion, and as such, may also be implicated in emotion generation (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009).

The findings related to sleep problems and left insula activation in response to fearful faces are generally consistent with studies linking reduced sleep duration to insula activation in response to negative stimuli. These findings also map on to research linking insula activation to reduced sleep duration in the context of a working memory task (Beebe et al., 2009). As such, this finding may provide evidence to support links between maternal reported sleep quality and

increased activation of brain regions implicated in emotional generation. However, the fact that actigraphy measures of sleep duration were not associated with insula activation in this study is puzzling and suggests the potential for Type I error for this finding.

Although the actigraphy measures of sleep were highly correlated, only one maternal report measure of sleep was associated with these more objective measures. As such, maternal measures may be capturing different information and/or be confounded by other factors that affect maternal perception of child's functioning. Of note, the CBCL was the only measure of sleep used in this study which focused on more enduring sleep difficulties (i.e., over the course of the past six months), suggesting that persistent sleep problems may be a more robust indicator of neural factors related to emotional responsivity and regulation in healthy children. Research has demonstrated that across early and middle childhood, sleep problems can persist for years and are associated with increased risk for anxiety disorders (Reidy et al., Manuscript in Preparation; Gregory et al., 2005). Persistent short sleep duration has also been linked to poor self esteem and – albeit less reliably – depressive symptoms among children (Fredriksen, Rhodes, Reddy, & Way, 2004; Roberts, Roberts, & Duong, 2009). That said, other research has implicated current sleep problems, and not persistent problems, as being more predictive of risk for childhood emotional problems (Paavonen, Solantaus, Almqvist, & Aronen, 2003). Future longitudinal research is needed to clarify the role of emotion responsivity and regulation in the association between persistent sleep problems and psychopathology. This may be particularly relevant for studies of healthy child populations, and – in the long-term, may provide novel insights leading to improved identification of children at increased mental health risk.

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**Table 1.** Descriptive Statistics for Primary Sleep Variables of Interest, Plus Potential Confounding Factor of Child Medication Use

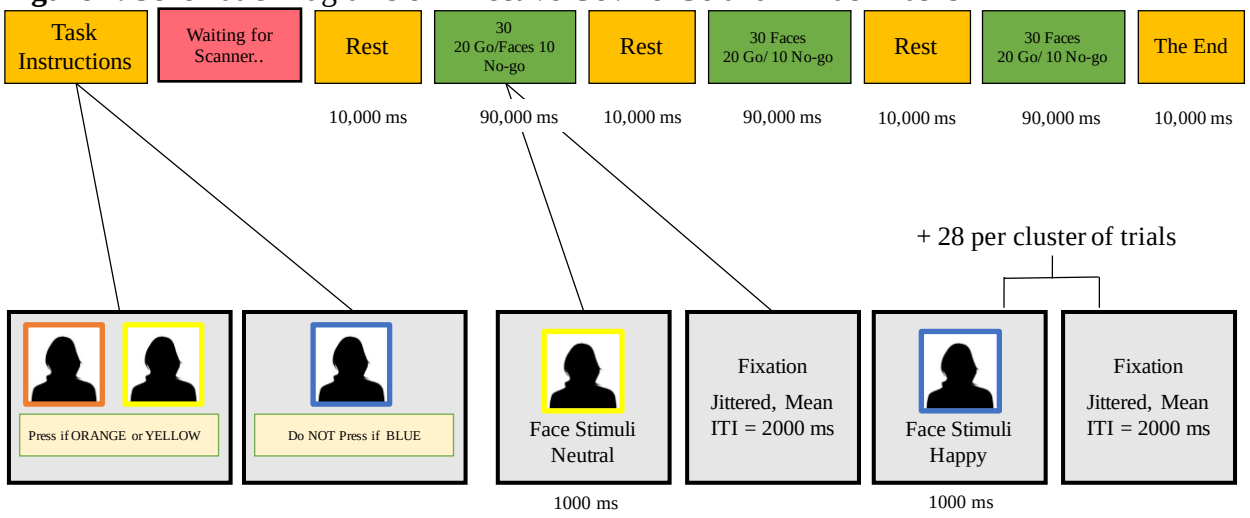
| Variable | Mean | SD |
|---|---|---|
| *Sleep Measures* | | |
| Actigraphy Average Sleep Duration | 500 (min) | 62.57 |
| Actigraphy MSSD, Sleep Duration | 7319.22 (min) | 12144.52 |
| Actigraphy, Average Sleep Efficiency | 93.45 % | 4.17 |
| Maternal Reported Child Sleep Problems, CSHQ | 43.16 | 6.38 |
| Maternal Reported Child Sleep Problems, CBCL | 1.09 | 1.51 |
| Days Taking Cold or Allergy/Asthma Medication During Sleep Assessment | 1.55 | 2.47 |

**Table 2.** Inter-correlations Among Sleep Variables

| **Variable** | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| 1. Actigraphy, Mean Sleep Duration | --- | | | | |
| 2. Actigraphy, MSSD Sleep Duration | -.534** | --- | | | |
| 3. Actigraphy, Sleep Efficiency | .459* | -.310 | --- | | |
| 4. Maternal Reported Sleep Problems, CBCL | -.289 | .041 | -.213 | --- | |
| 5. Maternal Reported Sleep Problems, CSHQ | -.377** | -.195 | -.280 | .491** | --- |

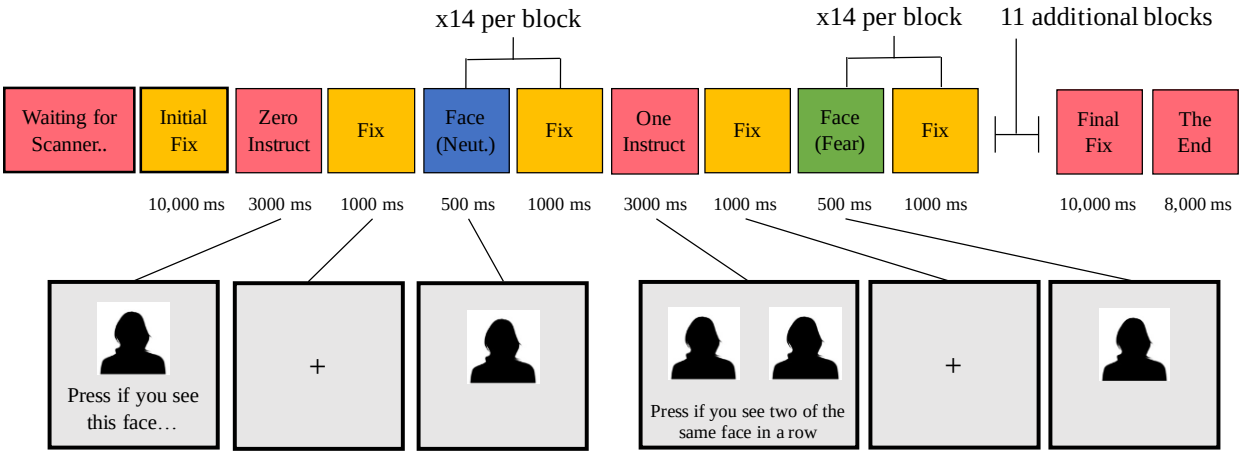
* $p < .05$, ** $p < .01$

**Figure 1.** Schematic Diagrams of Affective Go /No-Go and N-Back Tasks



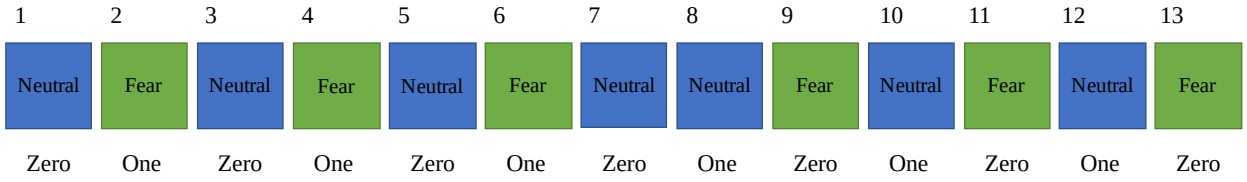

**Go /No-Go TASK DESIGN**

(Counterbalanced Version 3 Illustrated)




Version 2 Block Organization

Block Number:




**NBACK TASK DESIGN**

(Counterbalanced Version 2 Illustrated)

**Figure 2.** Scatter Plot of Association Between CBCL Maternal Reported Sleep Problems and Neural Activation in Working Memory x Emotion Contrast in the Left Inferior Frontal Cortex

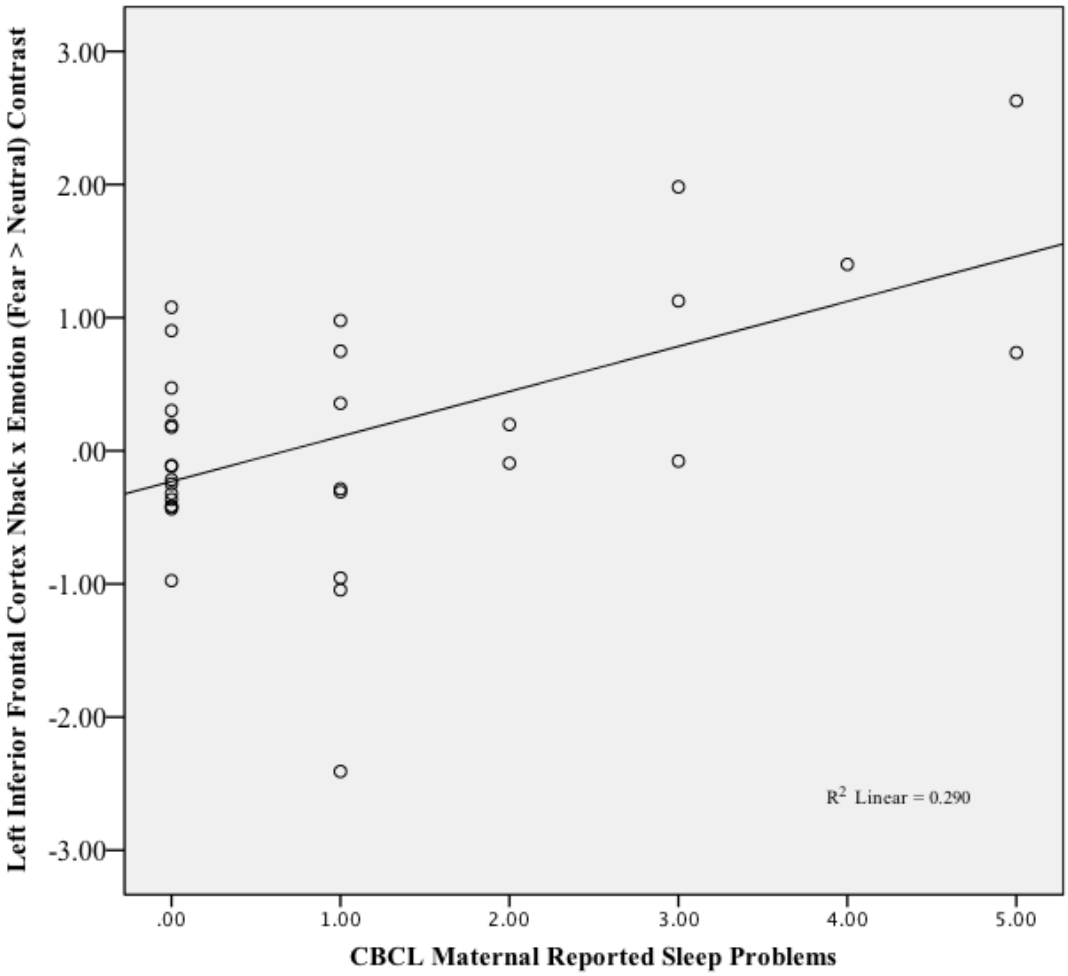
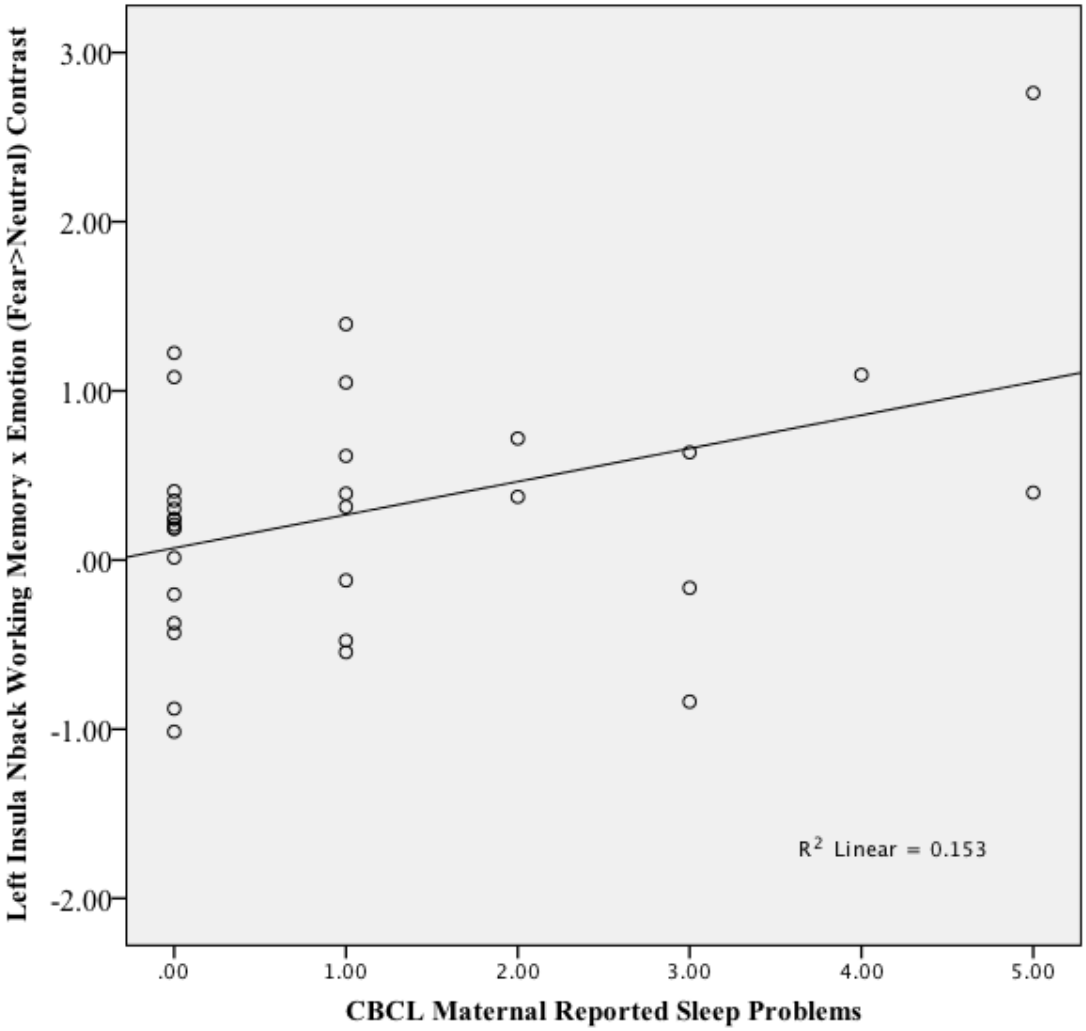


**Figure 3.** Scatter Plot of Association Between CBCL Maternal Reported Sleep Problems and Neural Activation in Working Memory x Emotion Contrast in the Left Insula



## General Discussion

The current dissertation projects took distinct approaches to address gaps in the literature concerning the relationship between childhood sleep problems and emotional functioning. The first study focused on the overarching clinical implications of associations between sleep and emotional well-being in children, investigating persistent childhood sleep problems as a novel risk mechanism involved in the intergenerational transmission of anxiety. Results of this study suggest that persistent childhood sleep problems in the preschool and school-aged period do represent a bio-behavioral process by which anxiety may be transmitted from mother to child. As previously discussed, these findings highlight the potential protective value of early sleep-related health interventions for children at risk for developing an anxiety disorder. From an implementation science perspective, future studies should extend this work by investigating the physical and mental health benefits of behavioral sleep interventions provided to children flagged for family history of anxiety in outpatient primary care settings.

Given that the data collection period in study one focused on a time in development characterized by considerable brain maturation and cognitive, social, and emotional growth, these findings could also have important implications for how persistent sleep problems influence developmental trajectories for children who are otherwise vulnerable to developing anxiety. Ongoing research that investigates the role of sleep in the intergenerational transmission of anxiety at different time points in development will facilitate our understanding of potential sensitive periods by which sleep may influence the biopsychosocial determinants of children's mental health.

Study two focused on more proximal associations between child sleep in school-age period and neural correlates of emotion responsivity and regulation, and utilized a multi-method

assessment of child sleep behavior that included both maternal report and actigraphy measures. Results did not corroborate current findings in the literature regarding short sleep duration and increased neural activation in response to affective stimuli, and there were concerns that the analyses in this study were underpowered to detect associations between our primary variable of interest. That said, it is interesting to note that in this study, only maternal reports of children's sleep difficulties over the past six months (i.e., per the Achenbach CBCL) were associated with neural activation in brain regions linked to emotion generation and regulation. This measure provides a relatively general assessment of sleep quality, but, as highlighted in study one, does appear to tap into clinically meaningful sleep difficulties among school-age children.

Maternal report and objective measures of sleep are thought to characterize different aspects of child sleep behavior; it appears some of this may be explained by the fact that measures like the CBCL reflect more persisting trends in children's sleep behavior, as opposed to providing acute measures of various sleep parameters (as with actigraphy). Comparing CBCL and objective measures of sleep as part of a prolonged, or repeated-measures sleep assessment could provide novel information about the aspects of sleep that characterize persistent sleep problems in otherwise healthy children. Including measures that characterize different stages of sleep will also be helpful, particularly for future fMRI studies investigating associations between childhood sleep and emotion responsivity / regulation, as research has repeatedly implicated REM sleep in emotion regulation (van der Helm et al., 2011; Rosales-Lagarde et al., 2012). REM sleep alterations have also been observed in depressed and anxious adults (Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013; Fuller, Waters, Binks, & Anderson, 1997); although similar findings have not been consistently demonstrated in pediatric anxiety and major depressive disorder (Forbes et al., 2008), including measures of REM sleep could provide novel

information about sleep-related changes in fMRI measures of emotional responsivity / regulation that are associated with increased risk for psychopathology.

Taken together, the current studies suggest that persistent childhood sleep problems contribute to anxiety among school aged-children, particularly those at familial high risk for anxiety, and highlight the potential mental health benefits of early sleep-related health interventions for children with sleep problems and a family history of anxiety. Although the current findings implicate persistent childhood sleep difficulties as an early mental health risk indicator, more research is needed to understand the neurobiological mechanisms linking sleep, emotional functioning, and mental health in children. The current studies call for ongoing research that includes and expands upon multi-method sleep assessment in studies that examine associations between persistent sleep problems and emotion responsivity / regulation, particularly at a neural level. A more systematic, multi-method approach to sleep assessment will codify the literature and facilitate a better understanding of the specific aspects of sleep that are associated with behavioral and neural indices of emotion responsivity and regulation.

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