Maternal depression during early childhood, persistent aggression into emerging adulthood: neurodevelopmental pathways of risk?

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Despite an accumulation of evidence documenting prospective links between maternal depression and aggression in offspring, the mechanisms underlying this association remain somewhat mysterious. Mothers' depressive symptoms could undermine offspring's learning of stage-adaptive emotion regulation (ER) skills during early childhood (e.g., Seifer, Schiller, Sameroff, Resnick, & Riordan, 1996; Silk, Shaw, Skuban, Oland, & Kovacs, 2006). Some longitudinal studies link maternal depression to disruptions in young children's ER, which has been found to predict elevated aggressive behavior in later childhood and emerging adolescence (e.g., Gilliom et al., 2002; Trentacosta & Shaw, 2009). Neurodevelopmental mechanisms such as altered organization or refinement in cortico-limbic pathways could also play a role in prospective associations between mothers' depression during early childhood and dysregulated aggression in offspring (Callaghan & Tottenham, 2016; Sheikh et al., 2014). To further inform future inquiries into these mechanisms of risk, the present study tested whether maternal depression in early childhood was prospectively linked to persistent patterns of aggression at school entry and in emerging adulthood via disruptions in early ER processes and related patterns of neuroanatomical connectivity. Participants were drawn from a sample of 310 males at elevated risk for disruptive behavior problems based on their gender and low socioeconomic status. Direct paths from maternal depression and preschool-age ER in early childhood to offspring aggression at school-

age were supported. Unexpectedly, aggressive behavior was not found to be stable from the early school-age period into young adulthood across informant and context. Children's aggressive behavior was inversely associated with uncinate fasciculus structural integrity in emerging adulthood, such that higher aggression at school-age predicted lower fractional anisotropy at age 20. Another index of uncinate structural integrity (i.e., mean diffusivity) was positively associated with general antisocial behavior and depressive symptoms in young adulthood. The present findings add new, longitudinal evidence to inform nascent theories for neurodevelopmental mechanisms underlying antisocial behavior and clarify directions for future research endeavors to illuminate other potential neurodevelopmental mechanisms of risk related to mothers' depression.

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1.0 Introduction.

Developmental mechanisms linking mothers' depression to persistent aggressive behavior problems among offspring remain somewhat mysterious, despite abundant inquiry over several decades. Maternal depression occurring during offspring's infancy (Bettes, 1988; Fleming, Ruble, Flett, & Shaul, 1988; Seifer, Schiller, Sameroff, Resnick, & Riordan, 1996) and toddler/preschool years (Breznitz & Friedman, 1988; Gilliom, Shaw, Beck, Schonberg & Lukon, 2002; Goldsmith & Rogoff, 1997; Silk, Shaw, Skuban, Oland, & Kovacs, 2006) is linked to salient risk factors for emerging deficits in young children's emotion regulation (ER). Maternal depression-related disruptions in ER processes with young children predict subsequent increases in offspring aggressive behavior from late preschool through middle childhood and into emerging adolescence (Gilliom et al., 2002; Shaw, Keenan, & Vondra, 1994; Trentacosta & Shaw, 2009). Recent findings regarding the neurodevelopment of affective and behavioral regulatory abilities in early childhood could be uniquely informative as to how offspring incur such persistent patterns of aggression in relation to mothers' depression during early childhood (e.g., possibly via altered development of cortico-limbic connectivity; Callighan & Tottenham, 2016; Sheikh et al., 2014).

However, future efforts to illuminate potential neurodevelopmental mechanisms mediating offspring's risk for persistent aggression in the context of maternal depression during their first years of life require additional, longitudinal evidence regarding the long-term neuroanatomical correlates of exposure to mothers' depression during early childhood and their significance for offspring's emotional and behavioral adjustment. To address this need, the proposed study will

examine whether maternal depression in early childhood predicts persistent patterns of aggression at school entry and in emerging adulthood via disruptions in early ER processes and related patterns of neuroanatomical connectivity. Participants will be drawn from a sample of 310 males at elevated risk for disruptive behavior problems based on their gender and low socioeconomic status. The proposed study will first test a path model linking postnatal exposure to maternal depressive symptoms to offspring's ER strategies during the early preschool period (see Figure 1). Next, a second path model linking maladaptive ER in early childhood to subsequent patterns of aggression in middle childhood will be evaluated (see Figure 2). Third, the proposed study will determine whether the persistence of children's aggression into young adulthood might be mediated by their relative structural integrity in a central neural ER circuit connecting the amygdala and prefrontal cortex (i.e., the uncinate fasciculus), measured earlier in emerging adulthood (see Figure 3). A final path model (see Figure 4) will test direct paths among maternal depression in early childhood, preschool-age emotion regulation, school-age aggression, uncinate fasciculus structural connectivity in emerging adulthood, and young adult aggression. Additionally, this model will test an indirect path by which the prospective association between maternal depression during early childhood and young adult aggression might be mediated by earlier structural connectivity of the uncinate fasciculus in offspring's emerging adulthood (see Figure 4).

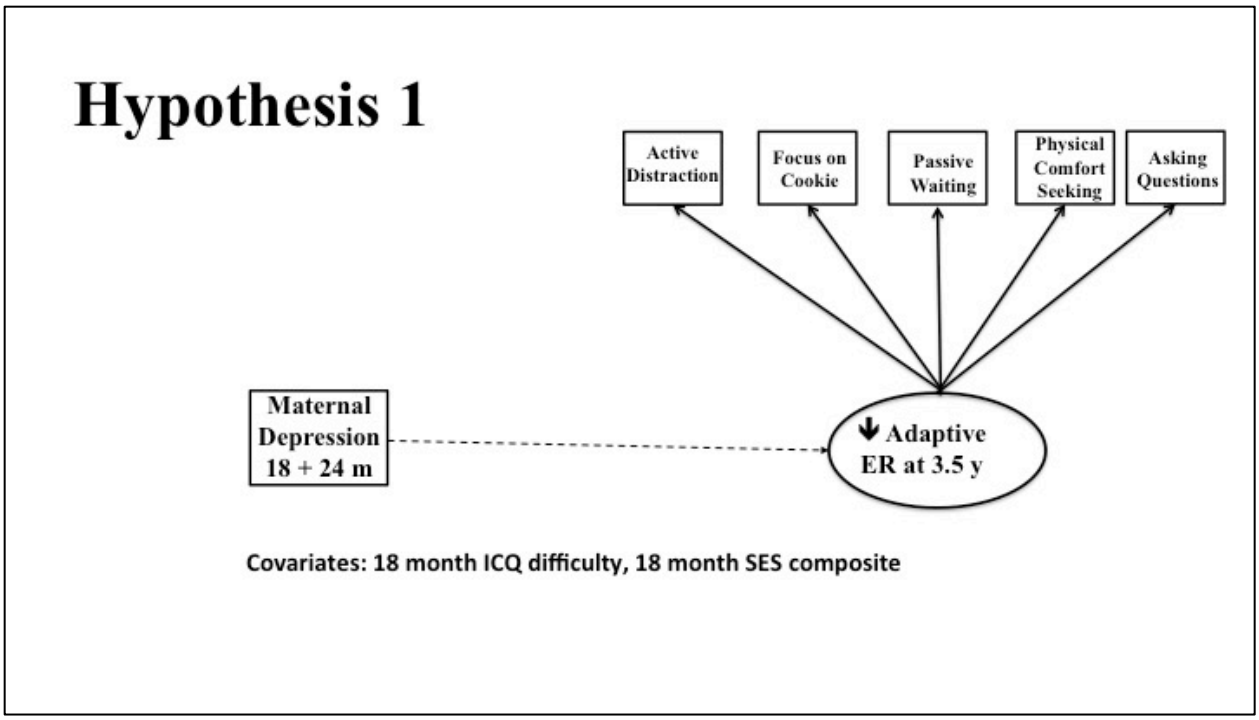

Figure 1 Hypotheses 1- Maternal depression and emotion regulation at preschool-age.

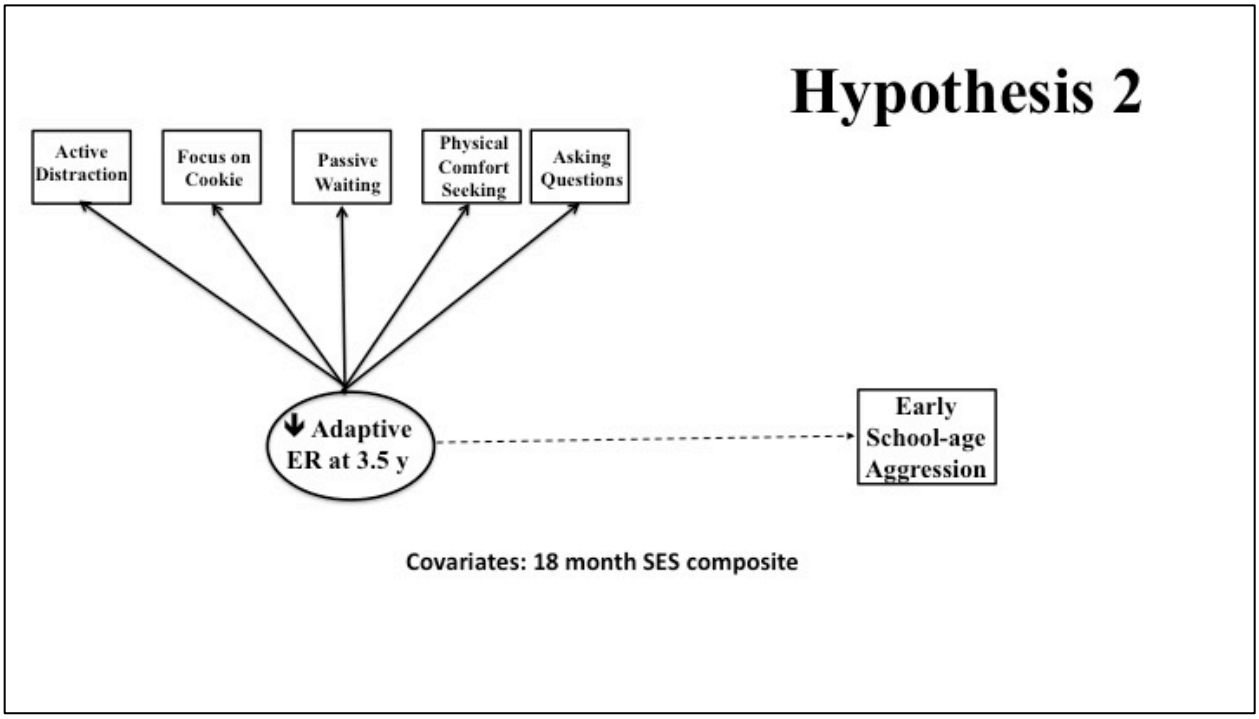

Figure 2 Hypotheses 2- Preschool-age ER strategies in relation to school-age aggression.

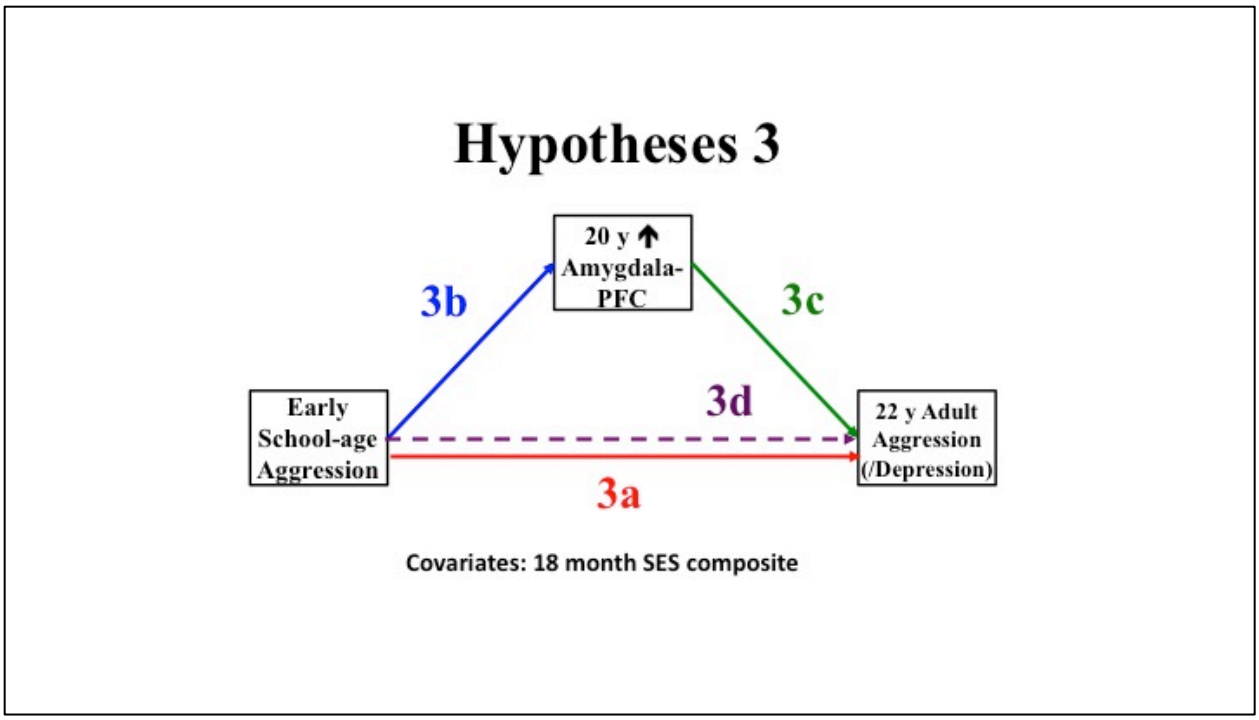

Figure 3 Hypotheses 3- Mediating role of amygdala-prefrontal structure in accounting for possible relations between aggression in early school-age and adulthood.

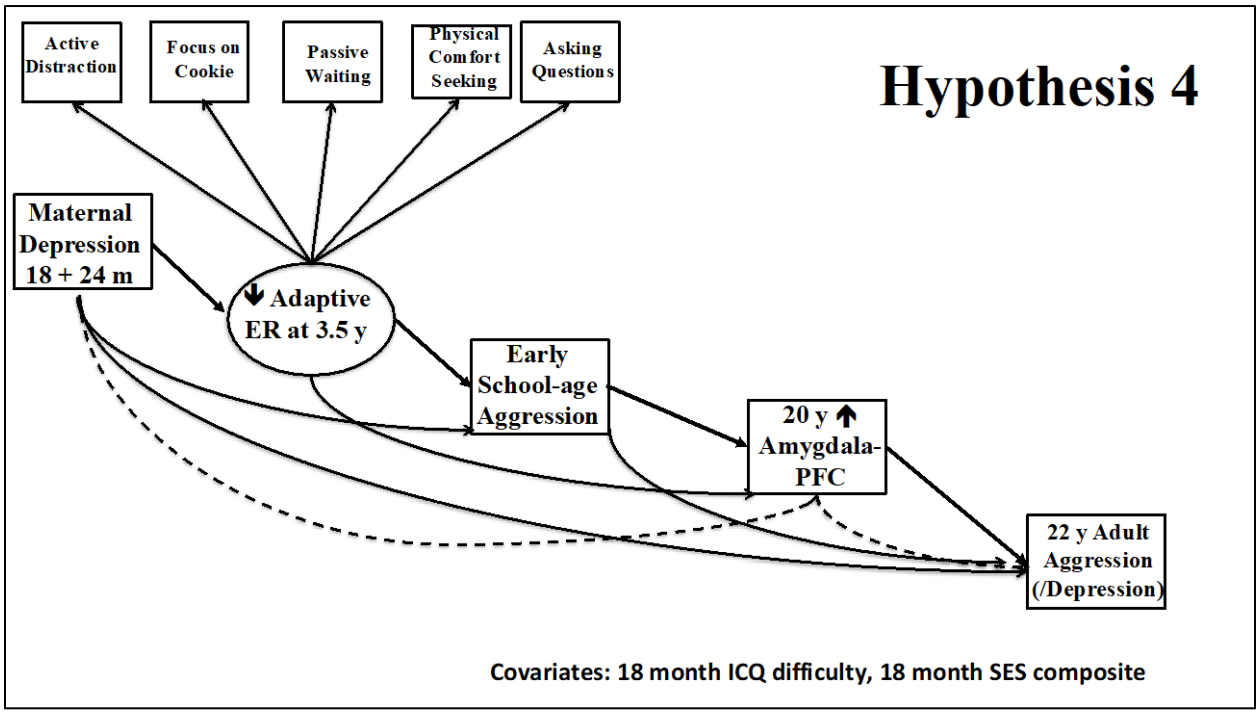

Figure 4 Hypotheses 4- Neurodevelopmental model linking maternal depression and aggression in adulthood.

In sum, the proposed study will clarify prospective relationships among maternal depression in early childhood and select, empirically-indicated behavioral and neurobiological factors at different points in offspring development from the toddler period to young adulthood. Methodological strengths of the study include the use of a high-risk, longitudinal sample of families with male children followed prospectively from offspring infancy into adulthood. This sample is uniquely well-suited to the present research question because it permits the combination of prospective data regarding maternal depression, emerging offspring emotion regulation strategies during early childhood, and aggressive behavior at school-age with young adult magnetic resonance imaging and behavioral data. Thus, these findings will provide new, longitudinal evidence needed to bolster nascent theories for neurodevelopmental mechanisms by which offspring may incur lasting risk for aggressive behavior outcomes in relation to mothers' depression during their first years of life.

2.0 Literature review.

2.1 **Maternal depression during early childhood.**

Depression is alarmingly prevalent and persistent among mothers of young children. Particularly in low-socioeconomic status (SES) samples, as many as 50% of mothers report subclinical elevations of depressive symptoms during the first postpartum months (O'Hara & Swain, 1996). Although mothers' symptoms generally attenuate somewhat by 4-6 months postpartum (Horwitz & Goodman, 2004; Wang, Wu, Anderson & Florence, 2011), a sizable minority of mothers experiencing elevated depressive symptoms at this time still do so upon follow-up two or even three years later (Horwitz & Goodman, 2004; Wang, et al., 2011). As such, roughly 17-33% of mothers display elevated maternal depressive symptoms across offspring's early childhood, a period stretching from infancy into the toddler and early preschool years (Horwitz, Briggs-Gowan, Storfer-Isser & Carter, 2009; Woolhouse, Gartland, Mensah & Brown, 2015). The presence of additional risk factors such as low socioeconomic status appears to increase mothers' likelihood of experiencing such chronically elevated symptoms across offspring's early childhood (Horwitz et al., 2009; Seto, Cornelius, Goldschmidt, Morimoto & Day, 2005; Wang et al., 2011).

Rates of maternal depressive symptoms are generally found to decline from the toddler to early school-age period (Giallo, Cooklin & Nicholson, 2014; Gross, Shaw, Burwell, & Nagin, 2009; Horwitz et al., 2009). Nonetheless, mothers' elevated depressive symptoms during offspring's early childhood (i.e., roughly 18-30 months, or "the terrible two's") have been prospectively linked with parent- and teacher- reports of aggression at school-entry when demands

on children's behavioral self-regulation increase substantially (Shaw, Bell, & Gilliom, 2000). Thus, the considerable prevalence and persistence of depression among mothers of young children (Horwitz et al., 2009) is concerning for mothers but also for offspring's long-term behavioral functioning (Kovacs, Joormann, & Gotlib, 2008; Shaw et al., 2000). Notably, both clinical and subclinical maternal depression have been empirically linked to adverse behavioral outcomes such as childhood aggression among offspring (Cummings, Keller, & Davies, 2005). Therefore, in subsequent sections, "maternal depression" will be used to refer both to categorical/diagnostic and continuous/symptom-based indices of mothers' depression.

2.2 **Maternal depression and early childhood emotion regulation.**

Many risk factors related to mothers' depression have been hypothesized to play a role in its prospective associations with child emotional and behavioral maladjustment, including genetic heritability, impaired caregiving practices, stressful contexts, and, most recently, offspring neuroregulatory dysfunction (Goodman & Gotlib, 1999). Notably, a recent review of 26 studies concluded that prenatal maternal depression only consistently predicts children's later conduct problems and antisocial behavior in the context of maternal depression persisting into the first postnatal year (Waters, Hay, Simmonds, & van Goozen, 2014). Offspring's relative physical and emotional immaturity during the first two years of life may confer unique dependency upon caregivers for stage-salient adaptations such as regulation of arousal or affect during this period (Goodman et al., 2011).

Emotion regulation (ER) includes intrinsic and extrinsic processes related to the monitoring, evaluation, and/or modification of affective or motivational states in service of

homeostatic or higher-level goals (Gross et al., 2007). Emotion regulation strategies have been conceptualized as developing from four, interrelated domains of functioning (i.e., somatic/sensory; cognitive; behavioral; social) with the support of a physiological infrastructure of specific neural circuits (Silk et al., 2006). Evolutionary theories of neurodevelopment posit that genetically-programmed, experience-expectant patterns in early neurodevelopment (i.e., the regionally-specific overproduction of synapses during early childhood) evolve selectively in the presence of species-specific, historically-reliable and –adaptive sources of developmentally-congruous information (e.g., mothers' predictable and contingent touch during infancy; Kolb et al., 2012). During developmentally 'sensitive periods,' the rapid organization and selective strengthening of synaptic connections based on these central environmental inputs are hypothesized to facilitate fundamental ER learning processes such as behavioral and affective response patterns and regulatory contingencies (Kolb & Gibb, 2014).

Many childhood ER strategies involve interactions with caregivers (Parke, 1994; Thompson, 1994). Although constrained in significant ways by developmental considerations even within this period, common ER strategies during early childhood are generally conceptualized as falling on continuums between "passive" and "active," as well as "other-reliant" and "autonomous," respectively (Grolnick, McMenamy & Kurowski, 2006). Passive, other-reliant processes of ER (e.g., infant cries elicit caregiver assistance to change motivational/affective state) may be uniquely adaptive during early infancy. Infants typically display some self-initiated or autonomous ER strategies like gaze aversion, self-distraction, and physical self-soothing by around 6 months (Calkins, Hill & Gross, 2007; Grolnick, Bridges & Connell, 1996; Kopp, 1982, 1989; Stifter & Spinrad, 2002). In the context of typical development from infancy into later parts of early childhood, relatively more passive ER strategies (e.g., self-soothing, gaze aversion, passive

waiting, passive focus on object of distress) have been found to show declining efficacy for down-regulating negative emotion and stronger links to distress as compared with active strategies (e.g., active distraction, shifting attention, manipulating the environment; Buss & Goldsmith, 1998; Calkins et al., 1999; Diener, Mangelsdorf, McHale & Frosch, 2002; Eisenberg et al., 2001; Gilliom et al., 2002).

In the context of risk factors related to maternal depression (e.g., disrupted maternal responsivity) it may be that this dynamic and extended maturational process confers vulnerability to dysregulation in emerging ER circuits (Kolb & Gibb, 2014). Notably, maternal responsivity during the first years of life has been inversely linked to later externalizing behaviors, especially in high-risk samples (e.g., Egeland, Marvinney, Mandelsdorf, & Sroufe, 1989; Shaw et al., 1994). Maternal depression has been linked to disruptions in parenting behaviors critical to dyadic emotion regulation (ER) processes with offspring beginning during infancy (Bettes, 1988; Fleming et al., 1988; Seifer et al., 1996) and continuing through the toddler years (Breznitz & Friedman, 1988; Goldsmith & Rogoff, 1997). More specifically, depressed mothers have been observed to show less consistent, less contingent and generally delayed patterns of responding to infants' gaze, vocalizations and behaviors, as compared with non-depressed mothers (Bettes, 1988; Field, 2010; Fleming et al., 1988). By their first months of life, infants of depressed (versus non-depressed) mothers display relatively delayed cognitive and motor development, less physical activity, and reduced responsiveness to caregiving behaviors such as maternal touch (Cummings & Davies, 1994; Field, 1992; Gotlib & Goodman, 1999; Gotlib & Lee, 1996). By late infancy, depressed mother-infant dyads have been observed to spend less time mutually engaged in shared activities (Goldsmith & Rogoff, 1997) and to demonstrate less sustained attention on a shared object (Breznitz & Friedman 1988). In one prospective sample, both maternal depression and

observations of less effective maternal scaffolding at child age 3 were positively associated with observed child emotional dysregulation and behavior problems one year later (Hoffman, Crnic, & Baker, 2006). However, although depressed mothers were found to use less effective scaffolding, maternal scaffolding did not mediate associations between maternal depression and child emotional dysregulation (Hoffman et al., 2006).

Adaptive ER strategies vary somewhat across the early childhood period, with behaviors such as interpersonal bids for comfort or attention, active distraction, and seeking information about relevant contingencies becoming central during the preschool years (Denham et al., 2003; Gilliom et al., 2002). In contrast to earlier-emerging tendencies toward affective reactivity or arousal (e.g., impulsivity, fearful temperament), such "top-down" emotional and behavioral regulation capacities undergo a protracted period of development from middle childhood through adolescence and adulthood (Bridgett et al., 2015). From toddler to preschool age, low SES boys like those in the present sample typically display declining patterns of emotion-focused self-regulatory strategies (e.g., comfort seeking) and increasing use of proactive cognitive self-regulatory strategies (e.g., distraction; Supplee, Skuban, Trentacosta, Shaw & Stolz, 2011). Toddlers of depressed mothers demonstrate relatively higher proportions of self- (versus other-) directed regulatory behaviors and show higher negative affective expression (Cummings & Davies, 1994; Downey & Coyne, 1990; Gotlib & Goodman, 1999; Gotlib & Lee, 1996; Tronick & Gianino, 1986). Consistent with life history theory (Belsky, Steinberg, & Draper, 1991) suggesting that natural selection might differentially favor developmentally 'slow' or 'fast' life history strategies of adaptation in response to specific environmental influences (e.g., relative predictability of caregiving; Ellis, Figueredo, Brumbach, & Schlomer, 2009), it could be that such disproportionate and/or prematurely-emerging self-directed ER strategies (e.g., self-soothing)

carry an eventual ‘cost’ for offspring’s later emotional or behavioral adjustment. Indeed, in a slightly older sample of children (i.e., ranging in age from 4 to 7 years), Silk and colleagues (2006) found that children of mothers with childhood-onset depression showed different ER strategies as compared with children of never-depressed mothers during a laboratory delay task. Assessed during the preschool period, offspring of depressed mothers were more likely to focus on the delay object or task than offspring of never-depressed mothers. Female offspring of depressed mothers, in particular, were observed to display higher rates of passive waiting and lower rates of active distraction (the most common strategy in this age range) as compared with daughters of non-depressed mothers (Silk et al., 2006).

Consistent with differential susceptibility (DS) theory (Belsky, Hsieh, & Crnic, 1998), infants’ abilities to regulate their own physiological arousal may also evolve from transactional processes between their own affective and reactive predispositions and early socialization experiences. The Tripartite Model for family influences on ER (Morris, Silk, Steinberg, Myers, & Robinson, 2007) postulates that child affective and arousal characteristics such as reactivity or propensity toward negative emotionality could confer differential (i.e., increased or decreased) susceptibility to family environmental contexts such as mothers’ mental health and caregiving (Kochanska, Philibert, & Barry, 2009; Morris et al., 2007). More specifically, children with similar susceptibilities toward increased reactivity to affective challenges may both benefit disproportionately from sensitive caregiving and incur disproportionately higher risk from its absence (Belsky 1997, 2005, 2007). During the preschool and early school-age years, maternal depressive symptoms have been found to interact with children’s autonomic reactivity to predict emerging self-regulatory abilities (Blandon, Calkins, Keane, & O’Brien, 2008). As such, it is

important to consider effects of individual factors such as negative emotionality in prospective associations between maternal depression and offspring ER difficulties (See Figure 1).

In sum, the first years of life constitute a developmental sensitive period for fundamental processes of dyadic emotion regulation (e.g., attachment; Martins & Gaffan, 2000). As such, mothers' depression-related impairments may be especially salient for offspring's emerging affective predispositions and subsequent regulatory adaptations during this time. During early childhood, offspring of depressed mothers may display disproportionate and/or prematurely-emerging self-directed ER strategies (e.g., self-soothing) and/or subsequent impairments in active, cognitive ER strategies (e.g., active distraction) in the late preschool years. Moreover, maternal depression has been hypothesized to predict child behavioral outcomes via their effects on neurobiological and social self-regulatory adaptations during early childhood (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Campbell, Shaw, & Gilliom, 2000; Kovacs, Joormann, & Gotlib, 2008).

2.3 **Impaired emotion regulation and child aggression.**

Children's conduct problems related to emotional dysregulation, such as aggression, have been postulated to emerge as a function of high reactivity to emotionally-salient challenges and inadequate regulatory strategies (Calkins, Smith, Gill & Johnson, 1998; Eisenberg, Fabes, Guthrie, & Reiser, 2000; Fabes et al., 1999). Offspring's emerging ER strategies during early childhood may play an important role in the emergence of later child emotional and behavioral dysregulation. During the preschool years, difficulty with self-directed, cognitive ER strategies (i.e., shifting attention away from emotionally salient stimuli and toward more helpful targets; behavioral

inhibition; Kalpidou, Power, Cherry & Gottfried, 2004; Silk et al., 2006; Stansbury & Sigman, 2000) has been linked to conduct problems such as aggression (Eisenberg et al., 2000). In the present sample of at-risk males, relatively lower use of active distraction (attention shifting, seeking information about contingencies) during a delay-of-gratification task (i.e., waiting for a desired cookie) at preschool-age predicted concurrently higher negative (e.g., angry) affect and prospectively elevated rates of conduct problems with aggression at school-entry (Gilliom, Shaw, Beck, Schonber, & Lukon, 2002). In fact, these same early childhood ER difficulties were then linked to increased peer rejection in late childhood and thereby, indirectly, to antisocial behavior during emerging adolescence (Trentacosta & Shaw, 2009). In sum, early childhood ER difficulties predict behavioral dysregulation (e.g., aggression) well beyond this period.

2.4 **Maternal depression in early childhood, and offspring risk for aggression well-beyond.**

As discussed previously, in multiple, low-income samples, maternal depressive symptoms have been found to peak during the toddler period, before declining from the preschool years into middle childhood (Giallo, Cooklin & Nicholson, 2014; Gross, Shaw, Burwell, & Nagin, 2009; Horwitz et al., 2009). Extant theoretical and empirical evidence suggests that exposure to mothers' depression during early (as opposed to middle, or late) childhood might differentially predict aggression among offspring (Goodman et al., 2011; Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005; Munson, McMahon, & Spieker, 2001). Within a larger meta-analysis of studies linking maternal depression to child psychopathology, the size of associations between maternal depression and child aggression was inversely related to the age of offspring sampled (Goodman et al., 2011). Consistent with this, in the present, longitudinal sample of low-SES males, maternal

depression at 18 and 24 months differentiated teacher reports of clinically-meaningful child aggression at school better than did mothers' depression at ages 3.5 and 5 (Shaw, Bell, & Gilliom, 2000).

Longitudinal evidence further links maternal depression during the toddler years specifically to early-starting and persistent trajectories of aggression among offspring (Kim-Cohen et al., 2005; Munson et al., 2001; Radke-Yarrow, Nottelmann, Martinez, Fox, & Belmont, 1992; Shaw, Gilliom, Ingoldsby, & Nagin, 2003). In the present sample, mothers' depression at 18 and 24 months distinguished parent-reported, early-starting and persistent trajectories of child conduct problems from ages 2 to 10 (Shaw, Lacourse, & Nagin, 2005) and youth-reported persistent trajectories of antisocial behavior from ages 10 to 17 (Shaw, Hyde, & Brennan, 2012). This persistence of offspring aggressive behavior from childhood into adolescence is represented in the direct pathway depicted in Figure 3. Notably, children who display this early-starting/persistent pattern of aggressive behavior are disproportionately characterized by some personal (e.g., difficult temperament) and familial (e.g., adverse caregiving) risk factors (Campbell, Shaw, & Gilliom, 2000) beginning in early childhood. In sum, maternal depression during early childhood has been linked to early-starting and persistent patterns of aggression among offspring. However, on the basis of extant behavioral evidence, alone, it remains unclear *why* offspring should incur risk for such persistent patterns of aggression in relation to maternal depression peaking during their first years of life.

2.5 **The persistence of offspring aggression: neurodevelopmental mechanisms?**

During the toddler years, the overlap of foundational processes like attachment formation with the rapid organization of intrinsic (i.e., neurobiological) self-regulation systems could confer particular, long-term behavioral vulnerability to maternal depression (Radke-Yarrow, Cummings, Leon, & Chapman, 1985; van Ijzendoorn, 1997). Rapid, experience-expectant neurodevelopmental processes in very early childhood could also theoretically increase offspring's susceptibility to maternal depression-related disruptions in responsive caregiving during this period, as fundamental patterns of emotional and behavioral self-regulation are being established (Callighan & Tottenham, 2016).

A recent accumulation of translational findings across a range of species and neuroscience methodologies now suggests basic neurodevelopmental processes by which early adverse caregiving experiences might give rise to long-term patterns of neurobiological, emotional, and/or behavioral dysregulation (Davidson, Putnam, & Larson, 2000; Hyde, Shaw, & Hariri, 2013; Propper, & Moore, 2006). Protracted processes of neural maturation (e.g., axonal elimination, myelination) during early childhood have been hypothesized to enable experience-expectant learning, and support individuals' capacities for adaptive and efficient functioning in their particular environment (Gee et al., 2014). These processes are hypothesized to constitute a mechanism by which species-specific, salient environmental inputs such as caregiving experiences can influence neurobiological and behavioral development.

Like emotional and behavioral adaptations to ER challenges in early childhood, neurobiological alterations in ER circuitry in the context of aggressive behavior have been conceptualized in terms of life history theory (Belsky et al., 1991). More specifically, a life history perspective suggests that children and adolescents adapt to unpredictable conditions contributing

to their own emotional or behavioral dysregulation, particularly aggression, by adjusting their "maturational clock" (Passamonti et al., 2012) in favor of faster microstructural development in central tracts underlying ER (e.g., white matter tracts connecting the amygdala and prefrontal cortex). Although speculative on the basis of currently limited evidence in humans, it is possible that similar processes of neurodevelopmental adaptation in these regions underlie the commonly observed persistence of early-onset aggressive behavior into adolescence and beyond, perhaps especially in the context of maternal depression.

In sum, ample theoretical bases exist for suspecting that atypical neurodevelopmental behaviors may play a role in persistent risk for elevated rates of aggressive behavior as a function of exposure to stage-salient stressors such as maternal depression in the first years of life. Although limited evidence in human samples currently exists to support possible neurodevelopmental mechanisms of risk, a small literature now suggests specific neural systems by which such processes of experience-expectant development might most likely give rise to persistent patterns of emotional and behavioral dysregulation. This literature is reviewed in subsequent sections.

2.6 **Regions of interest: amygdala, prefrontal cortex, and uncinate fasciculus.**

The hypothalamic-pituitary-adrenal (HPA)-axis is responsible for slow-acting, neuroendocrine adaptions (e.g., modulating cortisol levels in the bloodstream; Ordaz & Luna, 2012) to changing environmental and internal conditions (Shirtcliff et al., 2005). The autonomic nervous system facilitates the rapid sympathetic and parasympathetic modulation of metabolic inputs and outputs from organs (e.g., the heart) in service of goals (Ordaz & Luna, 2012). Over the first postnatal year, the gradual maturation of fronto-limbic neural circuits modulating

neuroendocrine and autonomic nervous system regulatory functioning enables infants' progressively more graded and flexible modulation of arousal and stress responsivity (Porges, 2003; Rothbart, Ahadi, & Evans, 2000; Stansbury & Gunmar, 1994). From the early postnatal period, a subcortical, temporal limbic structure called the amygdala plays a central role in learning processes related to ER, initiating neuroendocrine and/or autonomic processes in response to affectively challenging experiences (Davis & Whalen, 2001; Erickson, Drevets, & Schulkin, 2003). Non-human primate studies suggest the amygdala undergoes its most rapid period of structural development during the prenatal and early postnatal period (Belsky & de Haan, 2011), with its intrinsic patterns of connectivity and basic functional capacities likely present by birth (Pine, 2003). The human amygdala displays uniquely rapid patterns of volumetric growth across the first year of life (i.e., increases roughly 100% in size, versus less than 10% in the second year; reviewed in Callaghan & Tottenham, 2016; Uematsu et al., 2012). Moreover, autopsy studies of human infants suggest that within-amygdala myelination is underway by the first months of life and appears mostly 'mature' one year of age (reviewed in Belsky & de Haan, 2011).

Non-human primate studies suggest that the amygdala's bidirectional anatomical connections with temporal and prefrontal/orbitofrontal cortices are likewise in place by birth or soon after (Amaral & Bennett, 2000), and refined during over early infancy (Belsky & de Haan, 2011). Basic neurodevelopmental studies in rodents have found that the amygdala's predominant, efferent connections to the prefrontal cortex precede its incoming projections from the prefrontal cortex in both emergence and myelination during the early postnatal period (Bouwmeester, Smits, & van Ree, 2002; Bouwmeester, Wolterink, & van Ree, 2002; Bridgett et al., 2015; Kim et al., 2011). In contrast to earlier-stabilizing patterns of intrinsic connectivity and myelination, translational evidence from non-human primates suggests that the myelination of the amygdala's

output fibers largely approaches ‘mature’ levels by roughly preschool-age (Belsky & de Haan, 2011; Machado & Bachevalier, 2003).

Functional response properties of the amygdala and prefrontal cortex are hypothesized to be linked to their reciprocal patterns of structural connectivity (Friston & Price, 2001), especially patterns of white matter input and output (Passingham, Stephan, & Kotter, 2002). For example, the amygdala’s ‘bottom-up’ pattern of developing connectivity is hypothesized to play a role in its increasing hierarchical privilege of its threat signaling relative to top-down, prefrontal inhibitory influences during early childhood (Belsky & de Haan, 2011). There is some functional neuroimaging evidence to suggest that patterns of amygdala signaling may be relatively ‘immature’ (i.e., less specialized or selective) during early childhood, as compared with later stages (Callaghan & Tottenham, 2016; Graham, Fisher, & Pfeifer, 2013). Compelling arguments suggest that such immature/less-specific functional contingencies might play a central role in facilitating subsequent plasticity on the basis of early experiences (Callaghan & Tottenham, 2016), as its functional connectivity with the prefrontal cortex increases and patterns of amygdala activation become contextually flexible and selective from early childhood into the preschool and early school-age years (Gabard-Durnam et al, 2014; Monk et al., 2003; Thomas et al., 2001; Todd, Evans, Morris, Lewis, & Taylor, 2010).

Reciprocal patterns of amygdala-orbitofrontal/prefrontal functional connectivity have been implicated in higher-order behavioral and cognitive regulatory processes during early childhood, such as inhibitory control, error detection, and attention shifting, by early childhood (Criaud & Boulinguez, 2013; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). Cross-sectional, functional neuroimaging evidence suggests that the hierarchical contingencies of increasing amygdala-prefrontal co-activation in response to affectively and socially salient visual stimuli (i.e., fearful

faces) reverse in late childhood, shifting from positive to negative, or inverse, patterns of amygdala-prefrontal functional connectivity (Kim et al., 2011; Hare et al., 2008; Perlman & Pelphrey, 2011). Notably, these findings closely parallel developmental patterns of decreasing amygdala reactivity and improved performance on executive functioning tasks (Gee et al., 2013). A recent review concluded that most (but not all; Hare et al., 2008; Moore et al., 2012) studies suggest the amygdala is most robustly responsive to affectively-salient stimuli during early childhood, with decreasing patterns of activation taking place across adolescence and into adulthood (Callaghan & Tottenham, 2016; Decety et al., 2012; Gee et al., 2013). Thus, structural and functional connections between the amygdala and higher-order frontal regions constitute a likely neural system by which early caregiving adversities may influence long-term emotional and behavioral functioning.

2.6.1 **The uncinate fasciculus.**

The uncinate fasciculus (UF, or uncinate) is a long-range, bidirectional white matter pathway connecting (para-) limbic regions, including the amygdala to the ventromedial/orbitofrontal cortex (Catani & de Schotten, 2008; Petrides & Pandya, 2002; Schmahmann et al., 2007; Von Der Heide, Skipper, Klobusicky & Olson, 2013). A recent review of evidence in non-human and human populations concluded that uncinate functioning broadly rests at the intersection of memory and social-emotional processes and is thus central to many ER processes involving autobiographically-informed decision-making—for instance, the flexible, conditional application of affective associations and related response patterns (Von Der Heide et al., 2013). Accordingly, disruption of the uncinate's bidirectional communication pathways could undermine the efficient use and/or concurrent "updating" of learning and memory processes

needed for social-emotional decision-making (Von Der Heide et al., 2013). More specifically, impaired coherence of this fronto-limbic tract might be expected to disrupt individuals' error monitoring and behavioral adaptations in service of higher-level goals, perhaps especially in interpersonal transactions (Von Der Heide et al., 2013). Thus, although the hippocampus holds unique importance for the initial encoding of affective associations (Alvarez & Squire, 1994; Frankland & Bontempi, 2005), altered uncinate functioning might constitute a more likely mechanism for the persistence of emotional and behavioral dysregulation in the context of early life adversities, despite maturational and contextual changes (as posited in Figures 3-4).

In a small, mixed-sex sample of children with traumatic brain injury assessed in late childhood, uncinate coherence was prospectively linked to emotional-behavioral regulation upon follow-up a year later (Johnson et al., 2011). Furthermore, in adult clinical samples (e.g., adults with Kluver-Bucy disconnection syndrome; adults with behavioral-variant fronto-temporal degeneration), structural damage and/or reduced integrity of the uncinate has been linked to decreased behavioral inhibition (Hornberger, Geng, & Hodges, 2011; Lilly, Cummings, Benson & Frankel, 1983) and in some cases, aggressive behavior (Lilly et al., 1983). Among typically developing adults, individual variation in uncinate coherence has been found to differentially predict patterns of ER (Zuurbier, Nikolova, Åhs, & Hariri, 2013) and degree of interpersonal competence (De Pisapia et al., 2014). Of particular interest to the present study (pathways hypothesized in Figures 3 and 4), individual variation in uncinate coherence has been specifically linked to aggressive behavior outcomes in late childhood, adolescence, and adulthood. However, as reviewed in subsequent sections, the manner and degree of these associations varies in important ways with development, perhaps reflecting neurodevelopmental mechanisms of aggression-related

impairment at different stages. These developmental considerations are illustrated in the sections that follow.

2.6.2 **Microstructural development of the uncinate fasciculus.**

The uncinate is present in early childhood and does not display age-related increases in volume after age 5 (Taki et al., 2013). However, this fronto-limbic white matter tract shows protracted maturational patterns in terms of microstructural characteristics, such as changing synaptic density and myelination (Benes, 1994; Huttenlocher & Dabolkar, 1997; Taki et al., 2013). In contrast to the amygdala's more local white matter projections, the integrity of the uncinate increases rapidly from early into late childhood and continues to increase into young adulthood (Wang et al., 2012). More specifically, increasing patterns of fractional anisotropy and decreasing patterns of mean diffusivity are observed in the uncinate from middle to late childhood (Muftuler et al., 2012) and childhood into adolescence (Bashat et al., 2005; Lebel, Walker, Leemans, Phillips & Beaulieu, 2008; Schneider, Il'yasov, Hennig & Martin, 2004; Taki et al., 2013; Zhang et al., 2005). Mean diffusivity in the uncinate decreases in an exponential manner, such that rapid changes over the course of puberty are followed by progressively more gradual decreases through late adolescence (Menzies, Goddings, Whitaker, Blakemore & Viner, 2015), giving rise to adult levels of mean diffusivity by roughly the early twenties (Lebel et al., 2008; Olson, Von Der Heide, Alm & Vyas, 2015). In contrast, fractional anisotropy of the uncinate typically continues to increase in a roughly linear manner through young adulthood before finally assuming its exponentially decreasing, "adult" pattern in the late twenties or early thirties (Lebel et al., 2008; Olson, Von Der Heide, Alm & Vyas, 2015). Fractional anisotropy (FA) reflects water molecules' parallel or "axial" directional diffusivity relative to their diffusion in directions orthogonal to the

preferred direction or long axis (i.e., perpendicular, or 'radial,' diffusivity; Beaulieu, 2002). Mean diffusivity (MD), in contrast, reflects the average magnitude of water diffusion within a tract, both parallel and orthogonal to the "preferred" direction (Pierpaoli & Basser, 1996). Although the biophysical correlates of these indices remain somewhat unclear, relatively greater fractional anisotropy is often inferred to suggest relatively more homogeneous spatial organization of fibers, increased axonal diameter or number, and/or relatively greater parallel myelination (Beaulieu, 2009; Paus, 2010). As such, the indirect inference of these properties from diffusion-weighted (DWI) imaging could be uniquely informative as to the developmental trajectories of central neural ER structures such as the uncinate, and their disruption in the context of difficulties with ER and/or aggression.

2.6.3 **Structural integrity of the uncinate in relation to aggression.**

2.6.3.1 **Late childhood into middle adolescence.**

At present, children's aggression has been examined in relation to the structural integrity of the uncinate fasciculus measured, almost exclusively, at or after emerging adolescence. The sole exception is a cross-sectional study of male and female children with high and low levels of conduct problems scanned during late-childhood (i.e., 9-11 years; Decety, Yoder, & Lahey, 2015). Within this moderately large sample (N = 110), conduct problems were positively related to concurrent axial/parallel diffusivity and inversely related to radial/perpendicular diffusivity of the uncinate (Decety et al., 2015). In the context of typical developmental trends toward increasing fractional anisotropy (i.e., greater relative parallel/axial diffusivity relative to diffusion orthogonal to the preferred direction) and decreasing mean diffusivity from middle to late childhood (Muftuler

et al., 2012), these findings could represent accelerated microstructural development of this tract in relation to conduct problems by late childhood.

However, such a trend would appear to contrast with other neurodevelopmental outcomes observed in relation to aggression during late childhood. For example, in another sample of males scanned during late childhood, relatively increased gray matter volume was found in the medial orbitofrontal cortex/anterior cingulate cortex of children with conduct disorder and callous-unemotional traits versus controls (De Brito et al., 2009). In the context of typical peaks for macro-structural gray matter maturation (e.g., volume/thickness), these findings were hypothesized to represent relatively 'delayed' neurodevelopment. However, the samples' proximity to emerging adolescence complicates the inference of neurodevelopmental alterations from these child populations, as early pubertal development would amplify the heterogeneity of outcomes around the onset of puberty. Although entirely speculative, it could be that precocious, long-term engagement of orbitofrontal/prefrontal projections by the amygdala during childhood, in the context of less developed and organized local connectivity within the frontal regions being recruited, gives rise to these contrasting maturational trends in gray and white matter, respectively, in late childhood among aggressive children. Additional, longitudinal inquiry in child samples of adequate size tested at multiple time points is needed to address these questions (Hermoye et al., 2006; Lebel et al., 2008, 2012; Mukherjee et al., 2001).

Despite somewhat mixed findings (Finger et al., 2012; Haney-Caron, Caprihan, & Stevens, 2014), youth with aggressive behavior problems (in most cases, conduct disorder) generally appear to show relatively enhanced coherence of the uncinate relative to others of their age from early to middle adolescence (Passamonti et al., 2012; Sarkar et al., 2013; Zhang et al., 2014). For example, severe conduct/aggressive problems were linked to relatively increased fractional anisotropy of

the uncinate in a cross-sectional sample of high-risk (i.e., low socioeconomic status) males assessed during middle adolescence (Sarkar et al., 2013). In another, a moderately small sample of emerging-middle adolescents ranging in age from 13 to 16 years, males diagnosed with childhood disorder during their childhood years likewise displayed higher fractional anisotropy and lower radial diffusivity in the uncinate fasciculus as compared with, not only age-and sex-matched controls, but with similarly-aged females with childhood- onset conduct disorder (Zhang et al., 2014). These findings of enhanced uncinate coherence in boys with conduct disorder at emerging adolescence are consistent with those of Decety and colleagues (2015) at a slightly earlier developmental stage, and likewise suggest accelerated white matter maturation. Although speculative, it is possible that contrasting findings of relatively enhanced uncinate fractional anisotropy in males versus females with conduct disorder represent a developmental shift from late childhood into emerging-middle adolescence, as boys' microstructural maturation lags behind that of girls, and could therefore still be in a phase of steeper or more rapid change.

Microstructural alterations related to aggression during early adolescence have been hypothesized to reflect a 'snapshot' of early-accelerating patterns in the development of uncinate white matter coherence (Sarkar et al., 2013). Early or enhanced maturational progressions of axonal pruning and myelination could theoretically predict premature stabilization of active ER networks and connections in childhood (Belsky & de Haan, 2011) and subsequent 'failures' in later processes of refinement during adulthood (Passamonti et al., 2012; Sarkar et al., 2013). While compelling, additional longitudinal research is needed to test such neurodevelopmental theories for explaining these patterns in cross-sectional samples.

It is also important to note that findings in early to middle adolescent samples are not entirely consistent, with null (Finger et al., 2012; Haney-Caron, Caprihan, & Stevens, 2014) and

even contrasting (Haney-Caron et al., 2014) results also reported. For example, in a mixed-sex sample ranging from 12-18 years in age, youth with conduct problems displayed comparable fractional anisotropy but decreased axial/parallel diffusivity of the uncinate relative to controls (Haney-Caron, Caprihan, & Stevens, 2014). In addition to being more widespread and somewhat older in age as compared with the sample assessed by Zhang and colleagues (2014), Haney-Caron's sample (2014) could have been more heterogeneous with regard to youth's age at onset of conduct problems (i.e., not limited to childhood-onset).

It is also unclear whether associations between aggression and uncinate coherence during early adolescence are specific to clinically impaired youth (i.e., diagnosed with conduct or oppositional-defiant disorder), versus sub-clinical or trait-level aggressive characteristics. Evidence from one cross-sectional community sample suggests that the significance, direction and/or regional white matter localization of associations between self-reported/sub-clinical aggressive behaviors and uncinate integrity might differ across dimensions of self-reported aggressive behavior (physical, expressive/verbal) or characteristics (tendencies toward hostile attribution; Peper, de Reus, van den Heuvel & Schutter, 2015). In one, relatively small, mixed-sex, community sample of 10-17-year olds, self-report of antisocial behavior was inversely related to uncinate integrity, albeit, to a lesser degree than were callous-unemotional traits (Breeden, Cardinale, Lozier, Van Meter & Marsh, 2015).

2.6.3.2 **Late adolescence-young adulthood.**

Precocious white matter development in relation to aggression during late childhood and into middle adolescence (Passamonti et al., 2012; Sarkar et al., 2013; Zhang et al., 2014) appears to precede similarly increased uncinate coherence in late adolescence and young adulthood. In a sample of late-adolescent males (mean age 18.5 years), childhood-onset/persistent conduct

disorder was linked to relatively increased fractional anisotropy and relatively reduced radial diffusivity of the uncinate, as compared with controls (Passamonti et al., 2012). Fractional anisotropy of the uncinate typically increases through late adolescence, so these findings provide still further evidence for abnormally accelerated white matter maturation in connection with conduct problems during adolescence, especially those with an early onset (Passamonti et al., 2012).

Uncinate white matter alterations should also be considered in the context of other aggression-related anomalies in functionally-linked regions. For example, the amygdala and orbitofrontal cortex of adolescents with conduct disorder display reduced gray matter volume as compared with that of controls (Fairchild et al., 2011; Huebner et al., 2008; Sterzer, Stadler, Poustka, & Kleinschmidt, 2007). As with enhanced microstructural coherence or integrity of the UF, is possible that these volumetric reductions reflect increased or accelerated gray matter thinning as a "downstream effect" of over-activation and excessive experience-dependent synaptic pruning of these regions. It is even possible that the reciprocal effects of smaller gray matter volume and more efficient white matter myelination of the uncinate are associated with early stabilization and decreased plasticity in central ER circuits in the context of childhood-onset aggression, although purely speculative, based on present evidence.

2.6.3.3 **Adulthood.**

In adult samples assessed from roughly the late twenties onward, contrasting patterns of *reduced* fractional anisotropy of the uncinate have been associated with antisocial behavior, including aggression (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012; reviewed in Von der Heide et al., 2013). Adult-typical reductions of uncinate coherence related to aggression could represent precociously advanced white matter degradation,

as speculated by Passamonti (2012). Disrupted uncinate coherence in adulthood has been hypothesized to play a role in some cognitive ER deficits linked with externalizing problems (e.g., reduced flexibility in updating affectively salient, associative memories; impaired reversal learning and contextually-flexible decision-making; Olson et al., 2015; Von Der Heide et al., 2013). Moreover, lower uncinate integrity has been hypothetically linked to dysregulated (i.e., hyper-) amygdala activation via related reduced amygdala-prefrontal functional connectivity (Pezawas et al., 2005). Indeed, adults' impulsive aggressive behavior has been positively linked with amygdala reactivity and negatively associated with orbitofrontal activation in response to threatening faces (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). Thus, as hypothesized in Figure 3c, disrupted uncinate coherence and/or related deficits could theoretically play a role in the continuity of aggression from childhood into adulthood.

At present, however, evidence for inverse associations between aggressive/antisocial and uncinate microstructural integrity in adulthood is quite limited. Findings were drawn exclusively from forensic (e.g., incarcerated) samples of convicted violent offenders, some of whom were forensic inpatients (Craig et al., 2009; Sundram et al., 2012) and/or also displayed psychopathic traits (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011). It is unclear whether patterns of compromised uncinate microstructural integrity would be found in connection to sub-clinical aggressive characteristics in less severely functionally impaired (e.g., non-forensic) adult samples. In one moderately large sample of typically-developing, young adult males, structural coherence of the uncinate fasciculus did not differ between individuals classified as 'high' versus 'low' in trait physical aggressiveness and anger, respectively (Beyer, Munte, Wiechert, Heldmann, & Kramer, 2014). However, based on the broad age range (18 to 30 years) of this cross-sectional

sample (Beyer et al., 2014), it is possible that these null findings are related to neurodevelopmental heterogeneity in the late-maturing uncinate.

2.6.3.4 **Aggression and uncinate integrity: summary.**

In sum, despite limited and somewhat mixed extant evidence, there are sufficient theoretical bases for suspecting that uncinate coherence underlies patterns of persistent aggression from childhood into adulthood (see Figure 3, Hypothesis 3d). Although results are somewhat mixed, youth with aggressive behavior problems generally displayed relatively enhanced coherence of the uncinate relative to others of their age from late childhood into adolescence (Passamonti et al., 2012; Sarkar et al., 2013; Zhang et al., 2014), while the opposite pattern was observed in samples of violent-offending adults assessed beyond emerging adulthood (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012; reviewed in Von Der Heide et al., 2013). However, given the cross-sectional nature of extant studies, the neurodevelopmental significance of any aggression-related alterations could only be inferred on the basis of evidence regarding typical developmental trajectories of these structures. As such, predominant, 'fast life' neurodevelopmental theories linking altered uncinate coherence and aggression still await empirical validation additional, longitudinal inquiry in larger samples (Von Der Heide et al., 2013).

2.7 **Maternal depression and neurodevelopmental mechanisms of risk in early childhood.**

The human brain displays rapid microstructural development between birth and age 5, with whole-brain fractional anisotropy increases of roughly 200% (most of which is achieved by only

age 2; Dubois et al., 2006, 2008; Hermoye et al., 2006; Mukherjee et al., 2001; Partridge et al., 2005). Longitudinal evidence suggests that the structure of the uncinate fasciculus may be particularly susceptible to display alterations in relation to adverse experiences (e.g., poor or absent caregiving) incurred from the perinatal period throughout early childhood (Eluvathingal et al., 2006). Based on a modest body of translational neuroimaging studies in animal and human samples, Callighan and Tottenham (2016) recently theorized that amygdala-prefrontal circuit connectivity (e.g., via the uncinate) displays particular, experience-expectant plasticity in response to periodic parental inputs during a sensitive period from infancy into early childhood. With increasing self-regulatory abilities and related autonomy from parents, Calligan and Tottenham posit, increasing myelination and decreasing plasticity of the amygdala-prefrontal circuit bring this sensitive period to a close (Callighan & Tottenham, 2016). However, the developmental timing by which this central ER circuit is stabilized is suspected to vary based on the quality of early caregiving, consistent with "fast life" theory (Belsky et al., 1991; Callighan & Tottenham, 2016).

Presently, limited evidence in human samples precludes the discernment of whether similar neurodevelopmental mechanisms could underlie persistent patterns of aggression found among offspring exposed to maternal depression during their early childhood years. A sizable portion of extant studies employed electroencephalography (see Field & Diego, 2008; Peltola et al., 2014 for reviews), a functional neuroimaging methodology with limited potential for the spatial localization of signal. Within a more modest accumulation of potentially relevant structural magnetic resonance imaging (MRI) studies in humans, offspring brain structure is often described in relation to distinct but empirically-linked factors like general familial/genetic risk for depression (Amico et al., 2012), maternal positive affect (Sheikh et al., 2014), or maternal anxiety (Rifkin-Graboi et al., 2015), rather than maternal depression, per se.

Among studies focused on maternal depression, the developmental timing of children's exposure to mothers' symptoms is often omitted or under-specified. For example, some studies operationalize maternal depression in terms of mothers' history of depression at any point during offspring's lifetime (Chen, Hamilton, & Gotlib, 2010), complicating the inference of when children were 'exposed.' Compounding this problem are constrained age-ranges at which offspring neuroanatomical data are amply available. At present, a preponderance of relevant findings arises from offspring scanned neonatally or in infancy (Qiu et al., 2015; Rifkin-Graboi, et al., 2013, 2015), or, conversely, (well) after offspring's late childhood years (Gilliam et al., 2015; Sarkar et al., 2013). As such, mothers' prenatal, perinatal, or very early postnatal affective disorder or related experiences are sometimes tested in relation to offspring brain structure at quite developmentally-distal points, with only limited controls for postnatal risk (i.e., single, isolated reports collected either concurrently, or earlier in development; Sarkar et al., 2014). In sum, theoretical arguments for developmentally-specific mechanisms of risk related to mothers' depression (e.g., prenatal/perinatal risk, versus later coercive parent-child interactions; Goodman & Gotlib, 1999; Patterson, DeBaryshe & Ramsey, 1989), require more, and more methodologically rigorous, studies in human samples. As prospective findings from studies of prenatal maternal depression could have relevance for mechanisms of postnatal risk related to mothers' illness, these studies are discussed briefly, below.

Extant reports of offspring neuroanatomical outcomes during infancy as a function of mothers' perinatal mental health arise, almost exclusively, from the same, large middle-SES birth cohort of mothers and infants, the Growing Up in Singapore Towards Healthy Outcomes cohort (GUSTO; Soh et al., 2013). Most reports from the GUSTO sample focus on maternal mental health during the prenatal period, although prenatal and postnatal maternal depression appear to display

significant stability within the sample (Qiu et al., 2015). Notably, the GUSTO group also tends to report offspring neuroanatomical outcomes in relation to prenatal maternal depression *or* prenatal maternal anxiety, in isolation, despite evidence for their high comorbidity in the sample ($r = 0.781$, $p < .001$; Rifkin-Graboi et al., 2015).

For example, in one report from the GUSTO sample, prenatal maternal depressive symptoms were inversely linked to intrinsic (i.e., within-amygdala) white matter coherence among neonates (Rifkin-Graboi et al., 2013). In a separate report on a different subset of the same sample of neonates, a correlated risk factor, prenatal anxiety, was found to predict similarly reduced fractional anisotropy of the uncinate fasciculus, among other regions (Rifkin-Graboi et al., 2015). Moreover, although prenatal maternal depression was not the independent variable of interest in the latter report, the authors noted that prenatal maternal depression also predicted reduced white matter integrity within the neonate dorsolateral prefrontal cortex (Rifkin-Graboi et al., 2015). Together, these reports indicate that prenatal maternal depression was linked to reduced coherence within the neonate amygdala and parts of the prefrontal cortex in the GUSTO sample. Among a smaller subset of the same infants scanned again at 6 months, prenatal maternal depression was reportedly linked to relatively stronger resting functional connectivity, but comparable structural connectivity, of the amygdala and prefrontal cortex in infancy (Qiu et al., 2015). The authors noted that prenatal maternal depression's association with enhanced functional amygdala-prefrontal connectivity persisted controlling for mothers' reports of their depressive symptoms at offspring age 3 months (Qiu et al., 2015).

In sum, these reports from the GUSTO sample indicate that prenatal maternal depression was linked to reduced coherence within the amygdala and prefrontal cortex during the first days of life (Rifkin-Graboi et al., 2013, 2015). A correlated risk factor, prenatal maternal anxiety, was

linked to similarly reduced white matter integrity of the uncinate and other regions among neonates in the same cohort (Rifkin-Graboi et al., 2015), but no microstructural alterations of this amygdala-prefrontal tract were evident in relation to prenatal maternal depression at offspring at 6 months (Qiu et al., 2015). However, prenatal maternal depression did appear to predict relatively increased resting functional amygdala-prefrontal functional connectivity at this point in infancy after controlling for mothers' postnatal symptoms at one earlier time point (Qiu et al., 2015).

This evidence yields preliminary clues as to how prenatal maternal depression might impact long-term patterns of functional and structural organization of the amygdala and prefrontal cortex. Gross amygdala structure (i.e., volume) is nearly intact by mid-gestation, but prenatal maternal depression is only posited to gain salience for offspring neurodevelopmental outcomes after this period (Nikolić & Kostović, 1986). Theoretically, it could be that the experience-expectant integration of prenatal/very early postnatal environmental input related to mothers' depression (e.g., altered prenatal neuroendocrine environment) generate reduced patterns of intrinsic coherence in the amygdala and/or functionally-linked structures like the prefrontal cortex integrates (Rifkin-Graboi et al., 2013), or precociously increased co-activation of these regions (Qiu et al., 2015). Although small in number, taken together, extant evidence in human samples suggests that prenatal maternal depression and/or associated prenatal risk could lead to early alterations in white matter coherence, rather than volume, within central, amygdala-prefrontal networks. However, any behavioral correlates of such neuroanatomical alterations in very early development, if present, remain unknown.

Even more inferentially challenging are studies that test such associations with offspring neurodevelopment at more developmentally-distal time points. For example, in a separate, prospective sample, prenatal maternal depressive symptoms predicted enhanced prefrontal cortical

thinning and increased externalizing behavior among school-age offspring, with associations between mothers' prenatal depression and offspring's externalizing mediated by prefrontal reductions (Sandman, Buss, Head, & Davis, 2015). However, because of the methodological considerations reviewed earlier, it is unclear whether macrostructural alterations of the prefrontal cortex were incurred concurrently or as a down-stream consequence of mothers' prenatal depression, or correlated risk factors.

Early amygdala and, possibly, amygdala-prefrontal alterations may play a role in infant tendencies toward reactivity to novelty or stress. However, it is far more likely that infant characteristics related to the regulation of their own physiological arousal emerge in interaction with early socialization experiences. It may be that adaptive, early parenting experiences such as synchronous parenting are particularly beneficial—and, perhaps, their absence, particularly problematic—for infants with genetic and/or prenatal susceptibilities, such as exposure to maternal depressive symptoms in utero (Belsky & de Haan, 1998). Potential prenatal risk mechanisms associated with mothers' depression might therefore be most appropriately considered in light of their potential role in later transactional processes of risk related to postnatal maternal depression during early childhood.

Lebel and colleagues (2015) have conducted the only study specifically focused on direct links between maternal depression during the perinatal period and offspring brain coherence in early childhood. In a moderately large, community sample, Lebel (2015) assessed maternal depressive symptoms in each trimester of pregnancy and 3 months postpartum. Offspring then underwent structural MRI scanning during early childhood (mean age of 3.6 years; Lebel et al., 2015). Although base rates of prenatal maternal depressive symptoms were moderately low in the sample, second trimester maternal depressive symptoms were prospectively linked to increased

coherence (i.e., lower diffusivity) of some white matter fibers emanating from the inferior frontal cortex, including part of the lateral uncinate. Notably, these prenatal associations were no longer significant when mothers' postnatal depressive symptoms (i.e., at 3 months) were taken into account. Controlling for prenatal symptoms, mothers' postnatal depression also prospectively predicted increased white matter integrity of fiber tracts projecting from other (i.e., superior) frontal regions, including an even broader, more temporal expanse of the uncinate (Lebel et al., 2015). In addition, both prenatal and postnatal maternal depressive symptoms were independently linked to gross reductions of cortical thickness in frontal regions, replicating patterns of cortical thinning observed in relation to prenatal maternal depression in older child samples (Sandman et al., 2015). Both patterns of microstructural and macrostructural alterations observed in connection with maternal depressive symptoms were likewise posited to represent relatively early trajectories of brain maturation, perhaps as a function of premature myelination and synaptic pruning of 'unused' prefrontal-amygdala connections (Lebel et al., 2015). The authors further speculate that such precocious development could potentially constrain the potential for later, more extended processes of plasticity in development (Lebel et al., 2015).

Only one another study has reported on related outcomes in child offspring, and only incidentally. This retrospective study by Sarkar and colleagues (2014) linked maternal reports of prenatal stressful life events to structure of the uncinate fasciculus, and included maternal depression at child age 17 months as a covariate (Sarkar et al., 2014), finding non-significant trends between maternal depression and structural coherence of the uncinate fasciculus when children were between ages 6 and 9. Although only a nonsignificant trend, the results are consistent with that of Lebel and colleagues (2015), suggesting links between postnatal maternal depression and

precocious white matter development of the uncinate might continue through the early school-age period. However, additional empirical validation in larger samples is needed.

In one other prospective, mixed-sex sample, maternal history of childhood-onset depression predicted reduced resting amygdala-PFC connectivity and reduced positive functional connectivity between the amygdala and other limbic regions including the hippocampus, as well as less effective coping with negative affect at age 9 (Luking et al., 2011). As previously discussed, this study design precludes the inference of developmentally-specific mechanisms of risk related specifically to mothers' depression. Although entirely speculative, it could be that Luking's findings are an intermediate expression of an atypically early, ongoing developmental "switch" from positive (i.e., amygdala-driven) to negative (i.e., prefrontal-driven) amygdala— prefrontal connectivity prior to preadolescence (Gee et al., 2013). As the amygdala and hippocampus are consistently, modestly co-activated from school entry into preadolescence (Guyer et al., 2008), their reduced positive connectivity could possibly reflect precociously mature patterns of amygdala co-activation.

Still other studies have examined long-term neuroanatomical correlates of exposure to maternal depression during childhood, although the developmental timing of mothers' illness across this period is unclear. For example, increased amygdala volumes and elevated basal glucocorticoids were observed in 10-year old, male and female offspring chronically exposed to maternal depression from birth to 7 years of age (Lupien et al., 2011). In the present longitudinal sample of boys at high risk for externalizing problems, moderately elevated trajectories of maternal depression from 1.5 years to 10 years of age predicted increased amygdala:hippocampal volume ratios and increased aggression in emerging adulthood, with evidence for full mediation of maternal depression-offspring aggression links by brain structure (Gilliam, Forbes, Gianaros,

Erickson, Brennan et al., 2015). As amygdala structural development, including myelination of output fibers, is almost entirely complete by 3 years of age, it seems likely that these later-observed outcomes probably reflect risk incurred at an earlier stage (Belsky & de Haan, 2011). Perhaps especially in the presence of early childhood influences on amygdala coherence, it may be that these larger volumes are a more distal reflection of relatively more diffuse, less selective, and less efficient fiber organization of the amygdala by late childhood, although such speculations await further longitudinal inquiry in which the timing of maternal depression is more clearly specified.

2.7.1.1 **Summary.**

Evidence for early pathways to emotional dysregulation through the interaction of maternal depression and neurodevelopmental processes in the organization of ER abilities in infancy and toddlerhood are impeded by the lack of prospective studies of fronto- limbic development in younger samples as a function of mothers' depression. At present, it is only possible to infer on the basis of typical developmental trajectories and developmental periods for emerging abilities where processes may have been disrupted. There is some, preliminary evidence to suggest that exposure to maternal depression in very early childhood predicts precocious trajectories of cortico-limbic white matter maturation (see Figure 4, hypothesis 4b), perhaps via adverse, "downstream" effects for later, more extended neurodevelopmental processes of plasticity. Based on cross-species evidence regarding emerging neurodevelopmental pathways in very early childhood processes related to ER, one could speculate that such adaptations could facilitate the early emergency of self-directed capacities for evaluation and response to intrinsic and extrinsic stressors. However, evidence for concurrent or later behavioral correlates of neuroanatomical alterations in the context of early adverse caregiving is sparse at present. Thus, even compelling theories for neurodevelopmental pathways of risk for emotional dysregulation and related

aggressive behavior problems in relation to mothers' depression during early childhood must be tentative on the basis of extant evidence.

3.0 Method.

3.1 **Participants.**

Participants were drawn from the Pitt Mother & Child Project (PMCP), a longitudinal sample of low-income boys in Pittsburgh, Pennsylvania (Shaw, Gilliom, Ingoldsby, & Nagin, 2003). Beginning in 1991, infant boys from 310 families were selected for their high risk for developing problem behaviors, especially aggression, as a function of 1) their male sex; 2) their family's eligibility for participating in WIC (Women, Infants, and Children) Nutritional Supplement Program Clinics based on income regulations; and (3) the presence of at least one other child living at home. Two-thirds of mothers had 12 or fewer years of education, and mean per capita income was $2,892 per year. Youth were prospectively followed from 1991-2014 with the goal of identifying factors associated with vulnerability and resiliency in child development (Shaw, Gilliom, Ingoldsby, & Nagin, 2003). Retention rates were consistently high throughout the study. For example, at age 20, the sample retention rate was 83%, with 258 participants completing behavioral measures and 186 participants completing the MRI scan. The PMCP sample is also ethnically diverse (53% of children are White; 36% African American; 5% Biracial; 6% other).

3.2 **Procedures.**

3.2.1 **Assessment protocol.**

This study utilized mother, other-observer, and youth self-report data collected from family assessments conducted at participants' homes and/or in our laboratory at the University of Pittsburgh when children were ages 1.5, 2, 3.5, 20, and 22 years old. Reports were obtained from multiple family members including primary caregivers (usually, but not always, mothers) and alternate caregivers. This study focused on a large subset of participants for whom primary caregivers were mothers at early childhood assessments (age 18 and 24 months). Mothers' report of child behavior from child ages 5.5-6 years was utilized in addition to teacher reports of child behavior from target ages 6 to 7 years. Youth magnetic resonance imaging (MRI) and, finally, self-report of behavior in young adulthood was incorporated from laboratory assessments conducted at ages 20 and 22, respectively.

3.2.2 **Measures.**

3.2.2.1 **Maternal depression.**

Ratings of mothers' depressive symptoms were obtained from maternal self-report on the Beck Depression Inventory (BDI; Beck, Steer & Garbin, 1988) at offspring ages 18 and 24 months. The BDI is a 21-item self-report questionnaire that is a well-established and widely used to measure depressive states. Mothers rated each item based on severity (i.e., 0 to 3) based on how they had been feeling in the past six months. Mothers' total symptom ratings at offspring age 18

and 24 months were summed to generate a score for maternal depressive symptoms in offspring early childhood (α =.67 in current sample).

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3.2.2.2 **Family socioeconomic status.**

A demographics questionnaire was administered during the age 18-month home visit including questions about parental education, occupational status and income. These items were used to create a composite measure of family's early SES that was included as a covariate in some analyses. Socioeconomic status is included as a covariate (as opposed to a primary predictor variable) in the present study because it is thought to be less proximal and directly salient to children's developing emotion regulation, specifically during the early childhood years as compared with more theoretically stage-salient and proximal variables (e.g., maternal depression, parenting.

3.2.2.3 **Infant negative emotionality.**

Maternal report of infants' negative emotionality (i.e., difficultness factor) at 18 months of age from the Infant Characteristics Questionnaire (ICQ), "How Babies Are" (Abridged; Bates, Freeland, & Lounsbury, 1979) was also included as a covariate in some analyses in Hypotheses 1

and 4 to account for initial child negative emotionality. More specifically, scores on 10 traits rated from 1 (easy) to 7 (difficult) were summed to create a "fussy-difficulty" temperament factor from which infant negative emotionality at 18 months of age was inferred.

3.2.2.4 **Child preschool ER.**

Children's emotion regulation in early childhood was examined using a 3-minute, cookie wait-task (Marvin, 1977) videotaped during the age 3.5 laboratory assessment. For this task, the assessment room was cleared of all toys and activities, and mothers were asked sit at a table and complete questionnaires. After selecting the child's favorite cookie from several choices, mothers were presented with the cookie of choice in a clear bag and told to hold the bag in view of their child (but out of reach) for three minutes while they completed a questionnaire, during which time the examiner left the room. After the 3-minute delay, the examiner signaled the mother to give the cookie to the child. Boys' regulatory strategies were coded by trained research assistants from videotapes according to principles drawn from Grolnick and colleagues (1996) and adapted by Gilliom et al. (2002). More specifically, across 18 intervals of 10 seconds (i.e., 3 minutes), boys' frequency of different regulation strategies (i.e., active distraction, passive waiting, physical comfort seeking, focus on delay object, and information gathering) were coded, with inter-rater reliabilities ranging from 0.64 to 0.79. For the purposes of the current study, preschool-aged children's ER efficacy was initially evaluated in terms of four potential, theoretically-informed latent factor structures based on extant studies from multiple samples incorporating these observed measures (Chang, Shaw, & Cheong, 2015; Chang, Shelleby, Cheong & Shaw, 2012; Gilliom et al., 2002; Silk, Shaw, Forbes, Lane & Kovacs, 2006; Silk, Shaw, Skuban, Oland & Kovacs, 2006; Trentacosta & Shaw, 2009). As described in the Data Analyses section, this literature, first, and model evaluation indices, second, ultimately suggested that preschool-age ER should be

operationalized in terms of a latent factor score incorporating children's adaptive (i.e., active distraction, including goal-directed behavior that does not involve gathering information directly relevant to the task at hand, such as fantasy play, exploration of the room, or active engagement in mature conversation with mother) and maladaptive (i.e., focus on the cookie, as by trying to retrieve the cookie through persuasion, whining, or force) ER strategies and observed emotional regulation (i.e., displayed anger—both peak rating of intensity, and total time angry during observation). It was hypothesized that this latent factor would account for a significant portion of the variance in each of these observed variables, and that these variables would be correlated with one another.

3.2.2.5 **Child Aggression at Early School-age.**

Child aggression was assessed using parent- and teacher- reports of child behavior, collected at 5.5-6 and 6-7 years of age, respectively. In both cases, higher scores indicated higher parent and/or teacher ratings of problem behavior. First, parent-report of child aggressive behavior was assessed using the Child Behavior Checklist (CBCL/4-18; Achenbach, 1991), a 113-item questionnaire that is well-established and widely used to assess child problem behavior. Respondents rated each item on a scale of 0 (not true), 1 (somewhat or sometimes true), and 2 (very true or often true) based on their child's behavior within the past 6 months. The 20-item Aggression factor was utilized (α = .87 and α =.89 at 5.5 and 6 years of age, respectively, in the current sample). Second, youth's aggressive behavior was examined using the Teacher Report Form (TRF) 5-18; Achenbach, 1991), another widely-used and well-established questionnaire of the same length, likewise assessing child problem behavior. Teachers rated each item in the same manner as mothers, based on their student's behavior within the past 6 months. Twenty-five items from the Aggressive Behavior factor were utilized (α = .96 at both 6 and 7 years of age in current

sample). For the purposes of this study, child aggression during the early school-age years was operationalized using a latent factor including each of these four ratings (two from mothers, two from teachers) of children's aggressive behavior collected when children were between 5.5 and 7 years of age.

3.2.2.6 **Amygdala-PFC white matter coherence.**

At age 20, 186 participants were eligible and able to complete diffusion tensor imaging (DTI) on a 3T Siemens Tim Trio scanner at the University of Pittsburgh Magnetic Resonance Imaging (MRI) Research Center. Participants were first introduced to MRI procedures through use of a simulator, then instructed to lie still with their eyes closed during a ten-minute, structural MRI scan. Axial, 2D-DTI bipolar scans with the following parameters were acquired: time-to-repetition (TR) = 13600 ms; time-to-echo (TE) = 91ms; field of view = 256x256; frequency = 96; phase = 96; 64 slices of 2.5mm thickness, each. Diffusion sensitizing gradient encoding was applied in 61 uniform angular directions with a diffusion weighting of b=1000 s/mm^2. Eight reference images with no diffusion gradient (b = 0) were also obtained.

To correct for head motion and gradient coil eddy currents (Horsfield, 1999), a fully-automated, preprocessing script (FLIRT; Jenkinson & Smith, 2001) was used to extract all reference (i.e., non-diffusion-weighted, or b = 0) images, conduct an approximate, non-linear registration of these images with all the DT images, and calculate the diffusion tensor using a simple least squares fit of the tensor model to the diffusion data. From resulting eigenvalues describing diffusion strength in the primary, secondary and tertiary diffusion directions for each subject, this script generated separate files for multiple indices of tract coherence or integrity, including fractional anisotropy (FA) and mean diffusivity (MD; Basser et al., 1994; Pierpaoli and Basser, 1996). Resulting FA and MD files for each subject were then opened in FMRIB Software

Library's Tract-Based Spatial Statistics (TBSS; Smith, 2006) and another, fully-automated, brain extraction tool (BET; Smith, 2002) was applied to reference images to exclude non-brain voxels.

To correct for potential warping in subjects' FA images, non-linear registration then aligned all subjects' FA images to a single, "most typical" (i.e., minimum mean distance of this subjects' warping to all other subjects warping) subject's FA image. Then, the linear and nonlinear registration step registered FMRIB FA files to standard-space (i.e., 1 x 1 x 1 mm^3 MNI152 space). To facilitate adequately robust statistical analyses, TBSS then generated a skeletonized, mean FA image based on the mean white matter at the centers of all uncinate-fiber bundles in the subjects. Each subject's respective FA data were then projected onto this "skeleton" and visually inspected to ensure proper registration of the mean FA skeleton onto participants' white matter. Young adults' relative uncinate fasciculus integrity was operationalized in terms of the fractional anisotropy (FA) and mean diffusivity (MD) of this amygdala:prefrontal white matter tract.

Univariate linear modeling was applied to examine child/adult aggression in relation to subjects' mean FA and MD across each voxel included in an uncinate "skeleton." This skeleton-based (versus whole-brain) approach served, in part, to correct for multiple comparisons, by reducing the number of tests conducted.

3.2.2.7 **Young Adult Aggression (/Depression).**

Young adult offspring's self-report of aggressive behavior was assessed at age 22 using a modified version of the Self-Report of Delinquency (SRD; Elliott et al., 1985). Fifty-three, developmentally appropriate items were drawn from the SRD, a self-report questionnaire that assesses the frequency with which an individual has engaged in specific antisocial behaviors during the prior year on a 3-point scale (0 = never, 1 = once/twice, 2 = more often). These items were summed to generate a general, total score, such that higher total score is indicative of

relatively more frequent antisocial behavior (α = .85 in the present sample at age 22). This general score included items concerning both reactive types of aggressive behavior (i.e. acts of aggression typically carried out without planning or fore-thought such as '[hitting] someone with the idea of hurting them') and proactive types of aggressive behavior (i.e. acts of aggression typically carried out with forethought and/or in service of a goal, such as, '[using] a weapon, force, or strong arm methods to get money'). Next, seven items focused specifically on reactive aggression (i.e. not proactive aggressive or other kinds of problem behavior) were summed to generate a 'reactive aggression' factor (α = .66 in the present sample at age 22). Young adults' self-report of depressive symptoms at age 22 was also obtained using Beck Depression Inventory (BDI—the same measure used to assess maternal depression in early childhood; Beck, Steer & Garbin, 1988). Total depressive symptoms reported by the young men at age 22 were summed and included as an additional dependent variable (α = .861) in Hypotheses 3-4.

3.3 **Data analytic plan.**

First, bivariate correlations were examined among all discrete variable (including covariates) from the study's four hypotheses to assess the manner of their respective associations from a univariate framework (summarized in Table 1). Then, multivariate measurement and sequential path models for the four main study hypotheses were conducted using structural equation modeling (SEM) in Mplus (Muthén & Muthén, 2017). To address expected non-normality in some study variables, maximum likelihood estimation with robust standard errors (MLR) was utilized. This maximum likelihood parameter estimator generates a chi-square test statistic and standard errors that are robust to non-normality, using a 'sandwich' estimator (Muthén

& Muthén, 2017). For each hypothesis, the two study covariates (i.e., composite of family's early SES, and mother's report of infants' negative emotionality, respectively, from initial, 18-month assessment) were planned to be included on all paths when a significant association was found with any of the main variables in the hypothesis being tested (1-4).

Table 1 Bivariate correlations and descriptive statistics.

	SES	NE	MD18m	MD24m	MD T	P Anger	T Anger	Distract	Foc D	66m M	72m T	72m M	7y T	L FA	R FA	L MD	R MD	SRD T	R Agg	Int Agg	BDI T
SES	1																				
NE	-.018	1																			
MD18m	-.097	.090	1																		
MD24m	-.018	.184**	.672**	1																	
MD T	-.040	.136*	.917**	.912**	1																
P Anger	-.076	.109	.125	.050	.081	1															
T Anger	-.121	.170**	-.047	-.083	-.084	.605**	1														
Distract	.035	.073	-.024	-.012	-.005	-.317**	-.392**	1													
Foc D	-.050	.046	.051	-.085	-.04	.634**	.665**	-.516**	1												
66m M	-.090	.293**	.270**	.291**	.337**	.083	.051	-.101	.028	1											
72m T	-.072	.013	.105	.099	.102	.164*	.160*	-.183*	.237**	.268**	1										
72m M	-.138*	.213**	.272**	.251**	.280**	.173*	.138*	-.165*	.099	.695**	.278**	1									
7y T	-.112	.048	.080	.167*	.130	.024	.024	-.101	.029	.308**	.574**	.320**	1								
L FA	.065	-.063	-.122	-.072	-.104	-.118	-.08	.055	-.085	-.171	-.130	.014	-.066	1							
R FA	-.034	-.021	-.131	-.048	-.095	-.160	-.003	.047	-.052	-.130	-.117	.037	.098	.818**	1						
L MD	-.006	-.143	.052	-.129	-.048	.045	.059	-.061	.158	.014	-.141	.015	-.037	-.419**	-.411**	1					
R MD	.052	-.069	.133	-.057	.037	.108	-.021	-.040	.139	-.066	-.085	-.041	-.179	-.354**	-.469**	.777**	1				
SRD T	.108	.013	-.028	.041	.024	.054	-.098	-.039	.025	.038	-.171*	.011	-.050	-.067	-.076	.165*	.128	1			
R Agg	-.065	.018	-.003	.057	.033	.032	-.089	-.124	.000	.017	.024	.067	.132	-.103	-.072	.034	.012	.601**	1		
Int Agg	-.059	.027	.019	.052	.041	.035	-.068	-.151*	.005	-.016	-.007	.048	.086	-.076	-.064	.056	.052	.575**	.950**	1	
BDI T	.008	-.039	-.041	-.060	-.079	-.088	-.153*	.130	-.073	-.031	.059	.001	.020	-.016	-.016	.136	.112	.300**	.284**	.252**	1
N	310	302	303	302	294	247	257	254	254	234	207	262	173	154	154	154	154	245	245	245	245
M	23.34	23.31	9.07	7.58	16.41	.88	15.52	10.92	4.25	10.55	7.89	10.86	8.49	.47	.47	.00018	.00017	61.77	8.56	7.4	5.19
SD	9.25	6.49	6.87	6.27	11.67	.91	31.92	5.14	4.32	6.61	10.02	6.81	10.83	.03	.02	.000005	.000006	7.00	1.15	1.0	7.12

*$p<.05$; **$p<.01$; SES= 18-month family socioeconomic status; NE= 18-month ICQ Difficulty; MD18m= 18-month maternal BDI sum; MD24m= 24-month maternal BDI sum; MDT= Early childhood total maternal BDI sum; P Anger= Peak anger in preschool-age ER task; T Anger= Total time angry in preschool-age ER task (in seconds); Distract= time spent using active distraction in preschool-age ER task (in seconds); Foc D= time spent focused on delay Object in preschool-age ER task (in seconds); 66m M= Mother-rated aggression on CBCL at 66 months; 72m T= Teacher-rated aggression on CBCL at 72 months; 72m M= Mother-rated aggression on CBCL at 72 months; 7y T= Teacher-rated aggression on CBCL at 7 years; L FA= Left uncinate fractional anisotropy at age 20; R FA= Right uncinate fractional anisotropy at age 20; L MD= Left uncinate mean diffusivity at age 20; R MD= Right uncinate mean diffusivity at age 20; SRD T = total antisocial behavior on SRD at age 22; R Agg= reactive aggressive items endorsed on SRD at age 22; Int Agg= interpersonal aggression items endorsed on SRD at age 22; BDI T= total symptoms on BDI at age 22; N= number of participants; M= Mean; SD= Standard deviation.

4.0 Results.

4.1 **Descriptive statistics and bivariate correlations.**

Descriptive statistics including means and standard deviations for the study's primary variables and covariates, as well as their bivariate inter-correlations are summarized in Table 1. As expected, mothers' total depressive symptoms on the BDI at 18 and 24 months were significantly correlated (r = .67, p < .01). Although mothers were recruited as part of a high-risk community sample, mothers' distribution of BDI scores (i.e., mean totals of 9.07 [*SD*=6.87] and 7.58 [*SD*=6.27] at 18 and 24 months, respectively) generally fell within the range of patients diagnosed with minimal to mild clinical depression based on guidelines from the Center for Cognitive Therapy (i.e., minimal depressive symptoms < 10, ≥ mild- moderate depression, 10-18 symptoms; Beck, Steer, & Garbin, 1988).

Raw scores (versus *t* scores) on the CBCL aggression factor were used for all models because the former provide relatively greater variability. Consistent with previously published findings from a large longitudinal community sample (Koot & Verhulst, 1991), children's scores on the CBCL aggression factor were significantly correlated (r = .27-.70, p's < .01) across the ages sampled (child ages of 5.5, 6 and 7 years), with strongest longitudinal associations found between reporters of the same 'type' (within rater-type r's = .70-.57, p's < .01 for mothers' and teachers' reports, respectively). Not surprisingly based on the high-risk nature of this sample, mother's mean ratings on both the child age 5.5 and 6 year- measures of the CBCL Aggressive behavior factor

were more than 1 *SD* above those previously reported by mothers of a large normative sample of US boys aged 6-11; see Table 1; Braet, Callens, Schittekatte, Soyez, Druart & Roeyers, 2011). Although raw scores were utilized in analyses, they were converted to *t* scores based on Achenbach's normative sample (Achenbach, 2001) for ease of interpretation in making the following comparisons. At ages 5.5 and 6 years, the mean *t* scores for the domain-specific aggression factor as rated by mothers in the present sample were 56.38 and 56.95, respectively, more than half a standard deviation higher than the normative average. Based on the general guideline of *t*-scores ≥ 65 or roughly 93rd percentile being defined as borderline to high (borderline-clinical cutpoint) for the CBCL's domain-specific scales (Achenbach & Rescorla, 2001), roughly 7% of children would be expected to have borderline to high clinical scores on the Aggression factor at ages 5.5 and 6, respectively. In the current sample, these figures were 16 % at both ages based on maternal reports.

In young adulthood, the negative-skew distribution of young men's overall endorsement of their own delinquent behavior was generally consistent with patterns in the extant literature (including a similarly aged sample of male urban youth from same area; Sibley, Pelham, et al 2010).

Bivariate correlations relevant to the first hypothesis that mothers' depressive symptoms during early childhood would predict observed factors of child emotion regulation (ER) at age 3.5 were not supported, with no significant correlations evident across all indicators of ER (focus on delay object, active distraction, time angry and peak anger). However, as hypothesized, these four indices of ER at preschool age were all significantly correlated (*r's* absolute values ranging from .317-.665, all *p's* < .01).

Bivariate correlations examining associations between preschool-age ER indices and school-age aggression were partially supportive of Hypothesis 2, albeit not consistently across reporter and age. For example, both peak anger and total time angry in the cookie task in preschool were positively associated with levels of child aggression at age 6 as rated by both mothers and teacher (*r's* = .138-.173, *p's* < .05), but not at ages 5 and 5.5. Preschool-aged children's use of active distraction during the cookie task was inversely related to later aggression according to both mother and teachers—but again, only at the age 6 assessment (*r's* = -.165-.183, *p's* < .05). Finally, focus on delay object was positively related to teachers' (but not mothers') reports of children's later aggression at age 6 (*r* = .237, *p* < .01).

Although not specified in hypotheses 1 or 2, it was also noteworthy that mothers' depressive symptoms across early childhood (18 months, 24 months, composite) were positively related to their later reports of their children's aggression at ages 5.5 and 6 years (*r's* = .251-.337, *p's* < .01), but mothers' depressive symptoms at 24 months (not 18 months or combined) was only related to later teacher report of children's aggression at age 7; *r* = .167, *p* < .05.

Regarding key variables from Hypotheses 3-4, mostly nonsignificant associations (with the exception of one, modestly significant association in the opposite direction expected) were found between mothers' and teachers' ratings of children's school-age aggression and young adults' later report of antisocial behavior and depressive symptoms). Only trend-level associations were noted between children's aggression at school-age, as rated by mothers, and their later uncinate fasciculus fractional anisotropy at age 20 (with trends in the opposite direction tentatively hypothesized). In terms of prospective associations between the indices of youth's relative uncinate fasciculus integrity at age 20 and self-report of antisocial behavior and depressive symptoms at age 22, modest significant and trend-level correlational results suggested that

different indices-- left (and to a lesser degree, right) uncinate mean diffusivity—were positively related to general delinquency (i.e., not reactive or interpersonal aggression) and depressive symptoms in young adulthood. No significant associations were observed between fractional anisotropy of the uncinate and later behavioral outcomes. Finally, with regard to the path model specified in Hypothesis 4, no significant associations were evident between maternal depression in early childhood and later adult behavior outcomes in offspring at age 22.

4.2 **Path models testing central hypotheses.**

The central analyses for Hypotheses 1-4 were all conducted using structural equation modeling (SEM) with MLR estimation in Mplus 8 (Muthén & Muthén, 2017). Specifically, SEM was used to test the hypotheses that: 1) maternal depressive symptoms at 18 and 24 months would predict less adaptive observed indices of emotion regulation (ER) in children at age 3.5; 2) children with less adaptive ER at preschool age would display more aggression in early school-age as reported by mothers and teachers; 3) the continuity of aggression between early school-age and self-report of delinquent (especially, aggressive) behaviors in early adulthood (age 22) would be mediated by relative coherence of the uncinate fasciculus as assessed earlier at age 20; and 4) direct paths between maternal depression in early childhood, emotion regulation at preschool-age, school-age aggression, and adult aggression would be significant and moreover, a significant indirect effect through amygdala:prefrontal structural connectivity would mediate the prospective association between maternal depression in early childhood and adult aggression at age 22.

Bivariate correlations suggested mostly non-significant associations between family SES in early childhood and the central study variables, with the exception of a modest but significant

association in an unexpected direction with later child aggression as rated by mother at age 6. As such, in all subsequently presented analyses that include the school-age aggression variable, pathways were modeled with the inclusion of the covariate of family SES at 18 months.

Child negative emotionality at 18 months (as operationalized in terms of mother's ratings of infants' difficulty on the ICQ) was used as a second covariate to account for possible effects of child temperament from correlated contextual factors such as mothers' depression (e.g., $r = .184$, $p < .01$ with mothers' 24-month rating of depressive symptoms in this sample). Bivariate correlations supported the significance of theorized, potential associations between children's negative emotionality as rated by mothers at age 18 months and indices of later ER at preschool age (i.e., positively related to time angry, $r = .170$, $p < .01$), as well as aggression at school-age (i.e., mothers' ratings of children's aggression at both time points; *r's* = .213-.293, *p's* < .01). However, the inclusion of this covariate consistently resulted in errors related to non-positive definiteness of covariance matrices and unacceptable model fit indices when testing Hypotheses 1-2, unless complex and theoretically tenuous modifications were made to the model (e.g., imposing questionable permissions or restrictions on its covariance with other variables). Theory and some exploratory analyses suggested error messages and poor fit indices might be due to significant, shared variance explained by the subjective nature and shared specific reporter (mom) between mothers' perspectives of their infants' difficult temperament and, later, of their children's aggressive behavior. Nonetheless, the removal of mothers' report of negative emotionality from exploratory analyses (i.e., examining teachers' report of later aggression in isolation from mothers' report) failed to improve model fit and permit interpretation of parameters when the ICQ covariate was present. As such, the results of analyses taking into account this planned covariate are not included in subsequent sections.

4.2.1 **Hypotheses 1: Maternal depression and emotion regulation at preschool-age.**

Before testing the first set of central hypotheses, the measurement model for the latent variable representing the construct of preschool-age emotion regulation was first examined. Four potential, theoretically-based models were considered in operationalizing ER in terms of latent factor(s) from among the following indicators observed in the cookie task: active distraction, passive waiting, physical comfort seeking, focus on delay object, information gathering, total time angry, and peak anger across observation. First, a confirmatory factor analysis was conducted in which all of the five child ER *strategy use* ratings (i.e., active distraction, passive waiting, physical comfort seeking, focus on delay object, information gathering-- and not the two indices of observed *anger*) were loaded onto a single latent preschool-ER variable, yielding inconclusive loadings and generally unsatisfactory fit of the model (i.e., non-positive-definite psi matrix message, significant chi-square and mediocre fit indices). The erroneous results and generally unsatisfactory fit of this model were not entirely unexpected, based on previously reviewed evidence for developmental shifts in the relative salience and efficacy among the different ER strategies across the early childhood period (Buss & Goldsmith, 1998; Calkins & Hill, 2007; Diener, Mangelsdorf, McHale & Frosch, 2002; Eisenberg et al., 2001; Grolnick et al., 1996; Kopp, 1982, 1989; Stifter & Spinrad, 2002).

Second, confirmatory factor analysis yielded improved fit indices but still problematic and uninterpretable loading of four of these five child ER strategies (i.e., active distraction, focus on delay object, information gathering, passive waiting). As a result, and because all four of these factors have been previously found to be associated with varying but significant degrees of subsequent increases or decreases in coder impression of anger (Gilliom et al., 2002), they were aggregated into one single latent variable. Standardized loadings of the four indicators on one

latent variable could not be computed, although information gathering appeared qualitatively to share little variance with the other three ER variables.

Finally, based on theory and evidence linking active distraction and focus on delay object to children's frustration tolerance across multiple, mixed-sex samples at different points in childhood (Chang, Shaw, & Cheong, 2015; Chang, Shelleby, Cheong & Shaw, 2012; Silk, Shaw, Skuban, Oland & Kovacs, 2006; Trentacosta & Shaw, 2009), two models were tested. First, preschool-aged children's active distraction, focus on delay object, peak anger and total time angry were included (with peak anger and time angry allowed to covary based on their substantive associations of their content). As shown in Figure 5, confirmatory factor analysis of a model including these four indices of ER loaded onto a single latent variable indicated significant factor loadings and good fit to the data ($\chi 2$ (*df* =1) =2.17, *p* = .14; *CFI* =.996; *TLI* = .976; *RMSEA* = .067; *SRMR* =.01). Second, a two-factor model was tested that additionally included passive waiting (along with active distraction) as a 'behavioral distraction' factor and loaded focus on delay object and the two correlated indices of observed anger onto a second 'emotional dysregulation' factor. Passive waiting was added based on incorporating this factor in some prior work using the same task (Silk, Shaw, Forbes, Lane & Kovacs, 2006; Silk, Shaw, Skuban, Oland & Kovacs, 2006), but not selected because of problems with the latent variable covariance matrix and therefore its interpretability. Thus, based first on theory and second on model fit, the one factor, four-indicator measurement model for the construction of the emotion regulation latent variable, as depicted in Figure 5, was selected for use in subsequent path models. However, as these four variables more aptly represent indices of behavioral control and regulatory capacities than ER per se, the term 'behavioral regulation (or, BR)' will be utilized in place of 'emotion regulation' in subsequent sections to describe this latent variable.

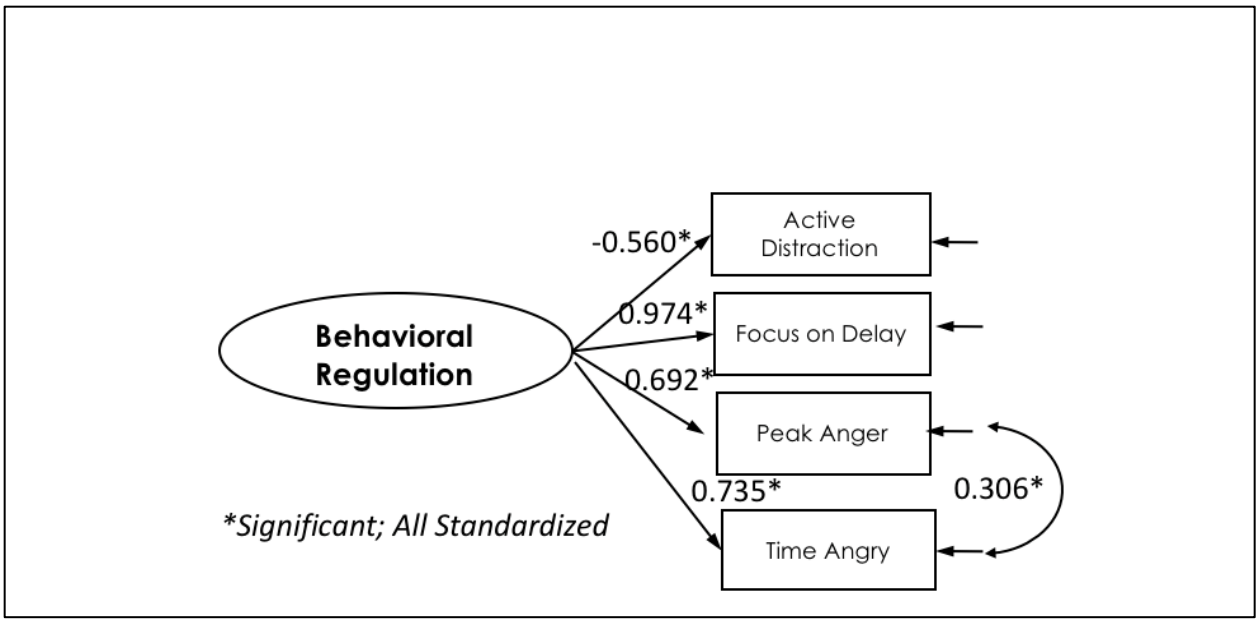

Figure 5 Hypotheses 4- Neurodevelopmental model linking maternal depression and aggression in adulthood.

Next, still in SEM, a path model was tested to examine associations between maternal depression in early childhood and the age 3.5 behavioral regulation (BR) variable, including SES as a covariate (see Figure 6). This model was found to provide an acceptable fit to the data, $\chi 2$ (*df* =7) =10.21, *p* = .18; *CFI* =.99; *TLI* = .98; *RMSEA* = .04; *SRMR* =.02. As depicted in Figure 6, this model indicates a non-significant path from total maternal depressive symptoms across early childhood to the BR construct at preschool age and a now- (with maternal depression included in the model) significant path between family SES at 18 months and the preschool BR. It is worth noting that the unexpected negative association between higher SES and less adaptive BR strategies is only present when maternal depression is included in the model and not in univariate analyses. Path models examining the relation between maternal depression and BR independently demonstrated a similarly non-significant path coefficient, suggesting that Hypothesis 1 should be rejected.

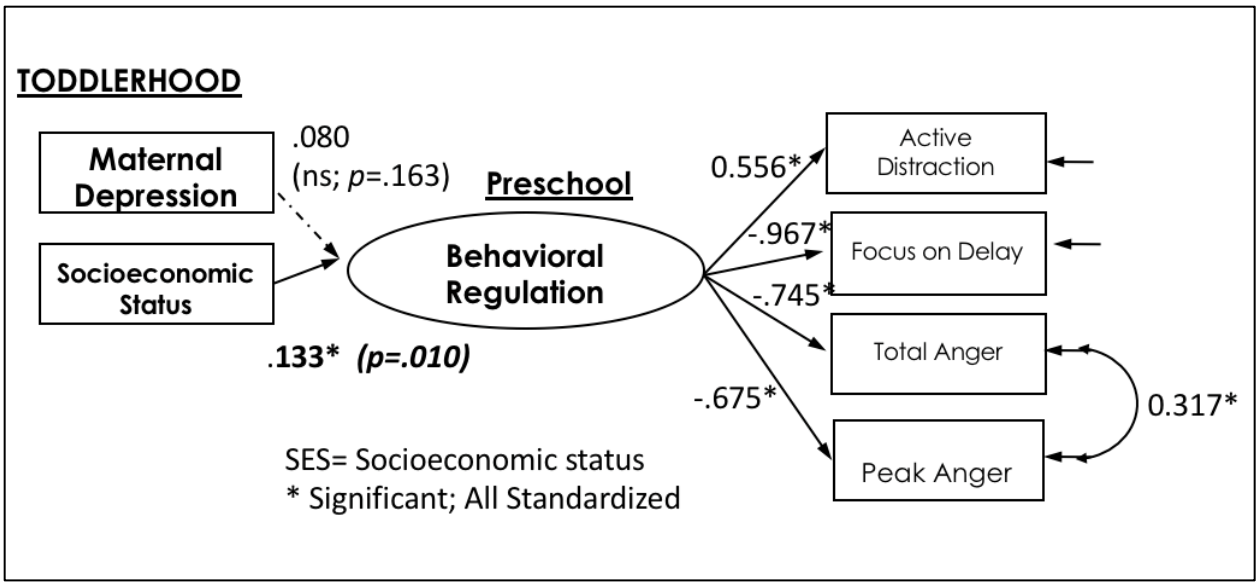

Figure 6 Maternal depression in early childhood and behavioral regulation at preschool-age.

4.2.2 **Hypotheses 2: Preschool-age behavioral regulation strategies in relation to school-age aggression.**

A measurement model for school-age aggression as a construct was first tested in SEM, by which school-age aggression was operationalized as a latent factor incorporating four indicators of maternal and teacher reports of aggressive behavior at age 5.5, 6, and 7 years. Based on the strength of previously mentioned theory and evidence for shared covariance between reporter-type (mother, teacher) across time points (Verhulst & Koot, 1991), mothers' and teachers' reports of children's aggressive behavior were allowed to be correlated with one another despite the specification problems this introduces for the measurement model when considered in isolation. Nonetheless, satisfactory loadings of the indicators on this factor were confirmed and consistently observed in subsequent path models incorporating this latent variable.

As shown in Figure 7, a direct pathway from the factor score on the behavioral regulation (BR) construct in preschool-age to the school-age aggression factor was tested with SES included

as a covariate. This model provided an acceptable fit to the data, $\chi 2$ (*df* =23) =26.38, *p* = .28; *CFI* =.99; *TLI* = .99; *RMSEA* = .02; *SRMR* =.04 and suggested a significant direct pathway by which less adaptive BR in preschool predicted higher levels of children's later aggressive behavior in early school-age (β=.239, *p*=.049). This model accounted for trend-level, inverse associations between early childhood SES and later child aggression. This pathway was significant with and without the inclusion of SES as a covariate, and therefore suggests that Hypothesis 2 was supported.

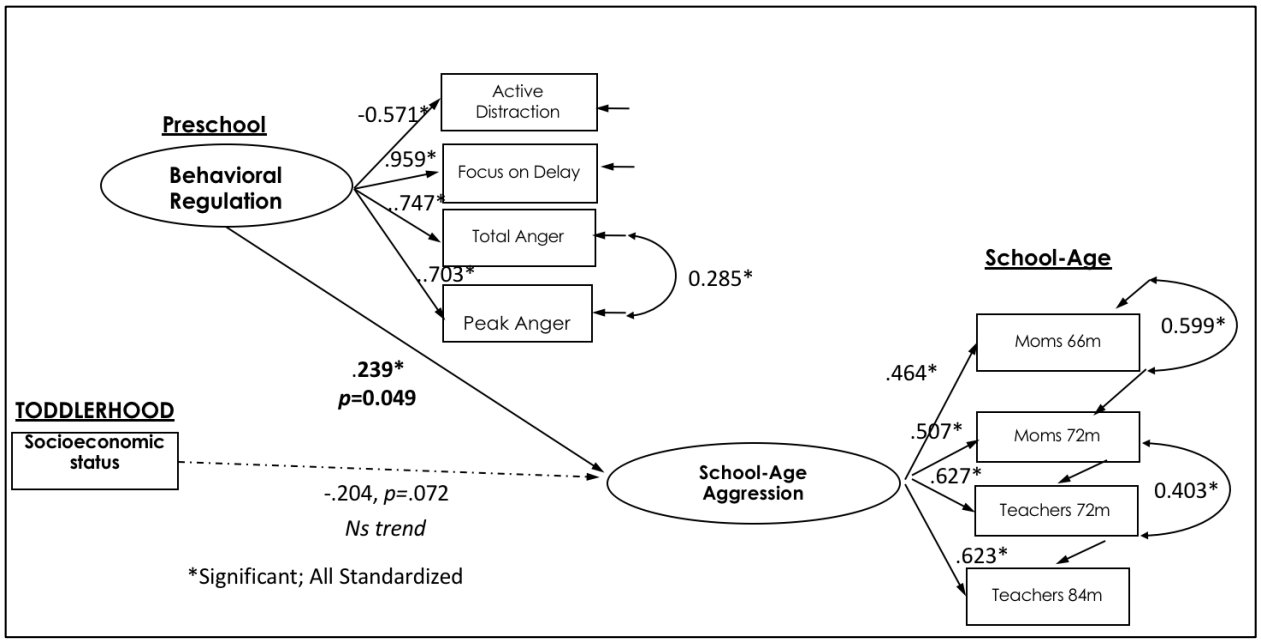

Figure 7 Behavioral regulation at preschool-age and school-age aggression.

4.2.3 **Hypotheses 3: Mediating role of amygdala-prefrontal structure in accounting for possible relations between aggression in early school-age and adulthood.**

In SEM, analyses first tested direct associations among children's aggression in the early school-age period (operationalized in child aggression latent variable as described, above), emerging adults' relative uncinate fasciculus integrity at age 20 (as inferred from left and right fractional anisotropy and mean diffusivity averaged across this tract), and young adults' self-reported aggressive behavior and depressive symptoms at age 22. The latent variable representing children's aggression at school-age as rated by mothers and teachers did not significantly predict young adult self-report of overall delinquency, aggression, or depressive symptoms at age 22, with or without the inclusion of earlier family SES as a covariate. As such, Hypothesis 3a should be rejected.

Regarding Hypothesis 3b, path models testing direct associations between the school-age aggression factor and indices of relative uncinate fasciculus integrity at age 20 (via left and right fractional anisotropy and mean diffusivity averaged across this tract) indicated mixed results. More specifically, school-age aggression was significantly and inversely associated with both left and right fractional anisotropy of the uncinate fasciculus at age 20 (L: β=-.276, p=.028; R: β=-.284, p=.036) in isolation and with SES included as a covariate (see Figure 8; model fit indices good for both left and right, $\chi 2$ (df =23) =4.48-4.60, p = .60-.61; *CFI* =1.00; *TLI* = 1.01-1.02; *RMSEA* = .00; *SRMR* =.03). This significant prospective association was in the opposite direction hypothesized. In contrast to the findings regarding fractional anisotropy of the uncinate, children's aggression at school-age did not predict left or right uncinate mean diffusivity (log-transformed due to very small values and related near-zero variance). Thus, Hypothesis 3b should be retained with regard to associations between childhood aggression and one possible index of the relative

microstructural integrity of the uncinate fasciculus at age 20 (left and right fractional anisotropy) but not the other (left and right mean diffusivity).

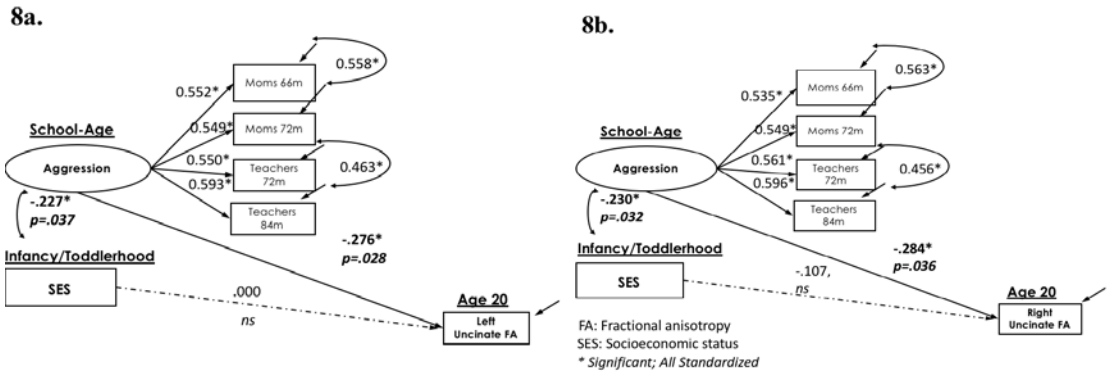

Figure 8 School-age aggression and fractional anisotropy of the uncinate fasciculus in emerging adulthood.

Next, direct pathways hypothesized in 3c were tested between indices of uncinate fasciculus microstructure at age 20 and young adults' self-report of antisocial behavior and depressive symptoms at age 22. Again, results were mixed, with a contrasting but ultimately somewhat theoretically complimentary pattern emerging to those found in Hypothesis 3b. More specifically, relatively increased left mean diffusivity of the uncinate fasciculus at age 20 was positively linked to youth self-report of general delinquency (β=.167, p = .017) and depressive symptoms (β = .137, p = .031), but not aggression, at age 22.

Aside from a non-significant trend in the same direction for the direct pathway between right mean diffusivity of the uncinate at age 20 and depressive symptoms at age 22 (β=.108, p=.089), all other associations between uncinate integrity at age 20 and behavioral outcomes age 22 were not supported. Thus, results of Hypothesis 3c are likewise mixed, supporting some direct pathways from some indices of uncinate fasciculus microstructure to some adult behavioral outcomes (left mean diffusivity, delinquency/depression) and not others.

Had Hypotheses 3a-c been supported and thus, the theoretical prerequisites for possible mediation been satisfied, Hypothesis 3d would have aimed to assess the potential mediating contribution of uncinate integrity in mediating associations between aggressive behavior from middle childhood to young adulthood. However, these prerequisites for mediation were not met. Moreover, exploratory testing of possible indirect pathways from school-age aggression to age 22 behavioral outcomes through age 20 uncinate structure (even in the absence of a main effect) yielded no significant indirect effects, with or without SES added as covariate. As such, Hypothesis 3d was not tested.

4.2.4 **Hypotheses 4: Neurodevelopmental model linking maternal depression and aggression in adulthood.**

In the original, full neurodevelopmental cascade model, elevated rates of maternal depressive symptoms during offspring's early childhood were expected to predict their maladaptive behavioral regulation (BR) strategies in preschool years, which were in turn expected to be linked to increased aggressive behavior during early school-age. With the predicted persistence of elevated aggressive behavior from school-age into young adulthood, maternal depression in early childhood was ultimately hypothesized to have long-term, positive associations with offspring's aggression into young adulthood (i.e., at age 22). In addition to this direct association, it was thought that earlier maternal depression and offspring aggression in young adulthood would be indirectly related through their respective direct associations with offspring amygdala: prefrontal connectivity (assessed earlier in emerging adulthood, around age 20).

As previously reported in the results from Hypotheses 1-3, however, several of the direct pathways originally advanced did not achieve statistical significance. Even among those direct

pathways evident, patterns of significant associations were unexpectedly complex in some cases. For example, results of Hypotheses 3 suggested that two indices of uncinate microstructural integrity (fractional anisotropy, mean diffusivity) were differentially related to earlier child and later adult behaviors, such that childhood aggression predicted relatively lower fractional anisotropy of the uncinate, while *greater* mean diffusivity of the uncinate, in contrast, predicted different adult behavioral outcomes (i.e., depression, general delinquency). As such, the prerequisite main effects for assessing formal mediation were not supported. Moreover, the results of bootstrapping analyses yielded no evidence for significant indirect effects in Hypothesis 3. Thus, the results of Hypotheses 1-3 provide limited support for retaining some of the central pathways included in the full neurodevelopmental cascade model.

As expected based on the results of Hypotheses 1-3, comprehensive models incorporating the main study variables from all four hypotheses, with or without covariates, all featured several pathways that did not achieve significance. Moreover, the results reviewed above and those of Hypotheses 1-3 provided no empirical justification for including any originally-hypothesized indirect effects in comprehensive models. As such, these comprehensive models provided limited information beyond what might be inferred from the results of their respective pathways in Hypotheses 1-3. Nonetheless, one example of such a comprehensive model, in which all theoretically and empirically defensible direct pathways are retained, is presented in Figure 9. For the purpose of testing a comprehensive model close to that originally specified in Hypothesis 4, pathways from maternal depressive symptoms in early childhood, to behavioral regulation (BR) and aggression factors at preschool- and early school-age, to left fractional anisotropy at age 20 (an index of uncinate coherence at age 20), and self-reported reactive aggression at age 22 were examined in one model, with early childhood socioeconomic status entered as a covariate. This

model provides a good fit to the data, $\chi 2$ (df = 45) =43.751, p = .5249; *CFI* =1.000; *TLI* = 1.003; *RMSEA* = .000; *SRMR* =.046. Consistent with results of Hypotheses 1-3, maternal depression in early childhood was not related to BR at preschool-age but was associated with increased aggression at early school-age as rated by mothers and teachers (with SES included as a covariate; β=.408, p=.000). The association between preschool-age BR and early school-age aggression (also controlling for SES in early childhood) was likewise present but weakened to a trend (i.e., p=.056). In contrast, with earlier results including maternal depression in this model, the association between the covariate of SES and preschool-age BR now achieves significance in a theoretically-expected direction. Moreover, school-age aggression is significantly, negatively associated with left uncinate fractional anisotropy at age 20 (β=-.235, p=.045). However, the associations between reactive aggression and left fractional anisotropy are not significant.

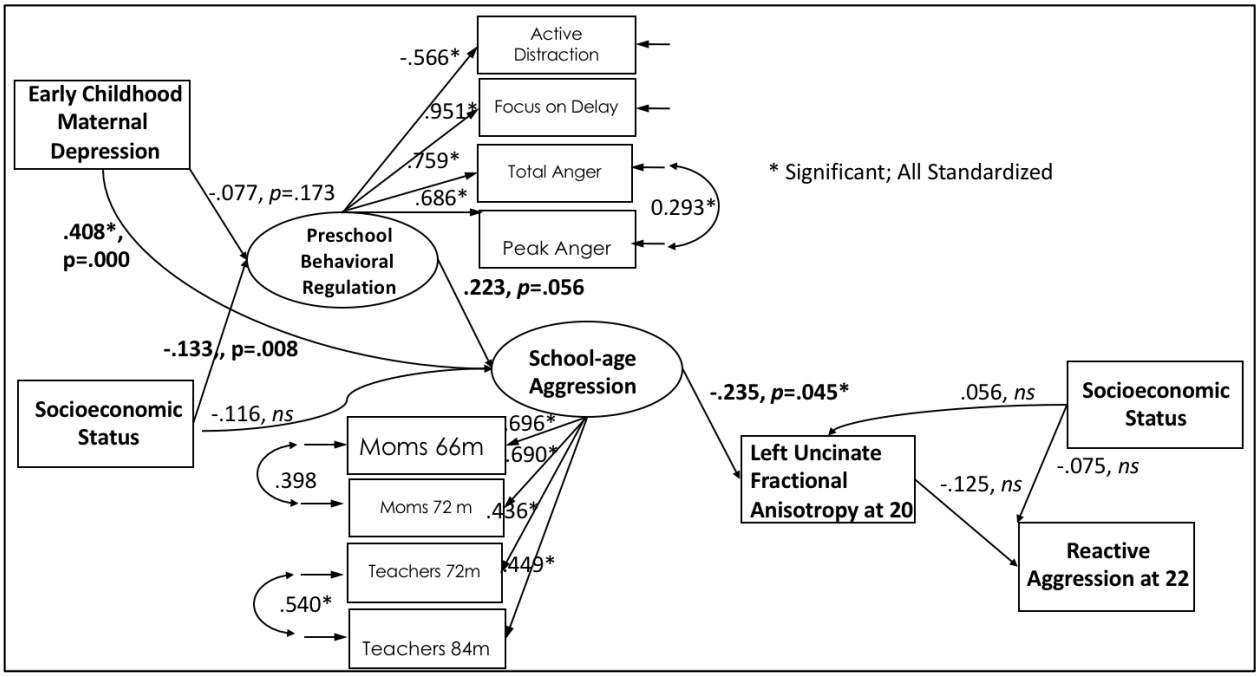

Figure 9 Partial comprehensive model.

5.0 Discussion.

The purpose of the present study was to test whether maternal depression in early childhood would predict persistent patterns of aggression in offspring from early school-age into emerging adulthood through alterations in early emotion regulation (ER) and behavioral regulation (BR) processes as well as related patterns of neural connectivity, respectively. Contrary to hypotheses, mothers' depressive symptoms during offspring's early childhood were not significantly associated with offspring behavioral regulation (BR) at preschool-age. As expected, however, both maternal depression in early childhood and offspring's relatively less age-adaptive BR at preschool-age separately predicted increased aggression in early-school age across context and informant. In contrast to predictions, children's aggressive behavior at early-school-age and their self-report of aggression in young adulthood were not significantly associated. Aggressive behavior at school entry was, however, prospectively and inversely linked to fractional anisotropy of the uncinate fasciculus (or, UF) in emerging adulthood (i.e., at age 20). This inverse association was in the opposite direction to that originally hypothesized based on theory and limited extant evidence in human samples (Passamonti et al., 2012; Rogers, Gonzalez, Baker, Clanton, Pauli et al., 2017; Sarkar et al., 2013; Zhang et al., 2014). Contrary to expectations, fractional anisotropy of the uncinate at age 20 was not significantly related to young adults' self-report on any of the behavioral outcomes assessed at age 22, including general antisocial behavior, reactive or interpersonal aggression, or depressive symptoms. Rather, a different index of relative uncinate structural integrity or diffusivity (i.e., mean diffusivity) at age 20 was positively linked to young adults' self-report of antisocial (but not specifically reactive or interpersonally aggressive) behavior and depressive symptoms at age 22.

5.1 **Maternal depression during early childhood, offspring behavioral regulation, and aggression.**

Contrary to hypotheses, maternal depression in early childhood was not significantly related to children's more adaptive behavioral regulation (BR) strategies at preschool. However, analyses of bivariate correlations suggested that mothers' ratings of child negative emotionality at 18 months were significantly related to maternal depression in early childhood (i.e., $r = .136$, $p < .05$). It could be that this relatively 'purer' index of children's own negative emotionality (versus their later patterns of observed passive-active ER strategies at preschool-age or related indices of BR) could be relatively more sensitive to earlier or concurrent family factors such as maternal depression (Kochanska, Philibert, & Barry, 2009; Morris, Silk, Steinberg, Myers, & Robinson, 2007). Additional examination of bivariate correlations in the present study does indicate that children's negative emotionality as rated by mothers at age 18 months was modestly related to objective raters' coding of their children's later time spent displaying angry affect at preschool-age ($r = .170$, $p < .01$), supporting the predictive validity of this index across time and method.

However, children's negative emotionality alone did not predict their overall behavioral regulation factor score or their likelihood of using adaptive or maladaptive active and passive emotion regulation strategies, respectively. It is noteworthy that some extant evidence suggests that maternal depressive symptoms may interact with children's autonomic reactivity to predict emerging self-regulatory abilities (Blandon, Calkins, Keane, & O'Brien, 2008). Although not tested in the present study, it is possible that maternal depressive symptoms might interact with offspring characteristics such as their reactivity or negative emotionality during infancy or toddlerhood in predicting children's emerging emotion or behavioral regulation strategies (and not just their affective correlates as indicated by displayed anger) around preschool age. More

specifically, it could be that children with relatively greater negative emotionality at infancy are relatively more susceptible to ongoing, stage-salient socialization experiences such as maternal psychopathology or correlated factors such as disrupted sensitivity of parenting, consistent with differential susceptibility (DS) theory (Belsky, Hsieh, & Crnic, 1998). Nonetheless, it is unclear whether, if present, any long-term behavioral correlates of such earlier transactional processes between infants' susceptible temperaments and environmental stressors such as maternal depression during early childhood would be observable in terms of their preschool-age emotion or behavioral regulation strategy use. It is also possible that maternal depression-related functional impairments such as maladaptive emotional or behavioral strategy use, or dysregulated affect might not yet have come 'on line' developmentally by preschool-age, and could be evident later on, at school entry or beyond, as has been found in another, female sample of offspring of depressed mothers (Silk et al., 2006).

Consistent with theoretical models and evidence for children's aggressive behavior problems' bases in emotional or behavioral regulation difficulties (Calkins, Smith, Gill & Johnson, 1998; Eisenberg, Fabes, Guthrie, & Reiser, 2000; Fabes et al., 1999), offspring behavioral regulation (BR) in preschool was significantly associated with later aggression at school age in the expected directions (Eisenberg et al., 2000; Kalpidou, Power, Cherry & Gottfried, 2004; Silk et al., 2006; Stansbury & Sigman, 2000). This direct path between BR and offspring aggression at school-age is consistent with previous findings in this sample inversely linking use of active distraction and concurrent negative affect as well as later conduct problems at school-entry (Gilliom et al., 2002).

Relatively strong, positive associations were found between maternal depression in early childhood and offspring aggression at early school-age across informant and context, consistent

with a growing accumulation of evidence for prospective associations between maternal depressive symptoms in early childhood and offspring aggression around the transition to school (Cummings, Keller, & Davies, 2005; Kovacs, Joormann, & Gotlib, 2008; Shaw, Bell, & Gilliom, 2000). Although not tested as part of the central hypotheses of this study, exploratory analyses suggested that maternal depression and behavioral regulation each separately predicted offspring aggression, albeit to varying degrees, using both parent and teacher reports of child aggression. More specifically, when maternal depression, preschool-age BR, and SES (as a covariate) were all included in one model, maternal depression still strongly predicted children's scores on the aggression factor at school-age across informant, whereas the association between BR in preschool and aggression in early school-age became a non-significant trend. Exploratory analyses further suggested that the interaction between maternal depression and preschool BR did not contribute a significant amount of variance above that already explained by each variable.

Rather, it could be that other risk factors related to mothers' depression and disrupted behavioral regulation, like genetics, impaired caregiving practices, and stressful contexts, also play a role in influencing prospective associations (Goodman & Gotlib, 1999), such that the continuity of disrupted BR processes from the first postnatal years into preschool-age or beyond depends on parenting being impacted by depression. The present study did not include observations or caregiver reports of theoretically salient parenting practices in early childhood (e.g., contingency of responsiveness; Kolb et al., 2012) along with ratings of mothers' depressive symptoms, although these were collected at multiple assessments during offspring's childhood. It is possible that stage-salient parenting practices in infancy or early childhood might mediate or moderate any associations between exposure to maternal depression and offspring BR in early childhood. For example, parenting practices could moderate maternal depression's association with later

aggression, based on evidence that maternal responsivity during infancy and the toddler period has been inversely linked to later externalizing behaviors (e.g., Egeland, Marvinney, Mandelsdorf, & Sroufe, 1989; Shaw et al., 1994, 1998; 2003, 2012) and more serious, even violent, forms of antisocial behavior in adolescence (Sitnick et al., 2017). Finally, it is perhaps worth noting that maternal depressive symptoms at 18 months were significantly and positively related to children's later aggression at early school-age regardless of whether mothers' or teachers' reports were utilized for the latter (β=.347, p= .000 for just mothers' report and β=.179, p= .017 for just teachers' reports, respectively, controlling for earlier SES).

5.2 **Persistence of offspring aggression.**

Although their prospective association across reporters (parent/teacher versus self) and an extended period of time (i.e., roughly sixteen years) was expected to be significant, albeit modest in magnitude, it was nonetheless unexpected that children's aggression at school-entry, based on parent and teacher reports, was not significantly associated with their later self-reports of reactive or interpersonally aggressive behavior in young adulthood (i.e., at age 22). Like similar considerations during early childhood as described above, it is possible that correlated contextual risk factors (and not just aggressive behavior, in isolation) act to modulate continuity of underlying affective or behavioral dysregulation, including aggressive behavior. For example, in the present sample of low-income males, relatively lower use of active distraction during the delay-of-gratification task at preschool-age predicted increased peer rejection in late childhood, and thereby was prospectively but indirectly associated with youth reports of antisocial behavior at age 15 (Trentacosta & Shaw, 2009). Consistent with normative developmental transitions in children's

social contexts and spheres of influence, it could be that with waning relative salience of direct parent-child interactional quality and increased peer influence, such extra-familial social or school contexts play an increasingly important role in the continuity of aggression beyond childhood.

In the context of the broader theoretical and empirical literature on aggression, the present findings may be somewhat specific to particular subsets of aggressive behavior or populations at risk for showing these behaviors. For instance, the present sample differs in important ways from the higher-SES samples used to inform extant theories and evidence on childhood aggression related to the presence of callous-unemotional behavior (Blair, 2001). For example, aggressive behavior in more privileged samples might be expected to be more strongly related to personal (i.e., callous-unemotional traits) biological (i.e., brain structure) factors (versus other contextual indices of risk), as compared with the same behaviors in a high-risk sample like that of the present study. In fact, in the present sample of high-risk male youth, callous-unemotional traits have been less consistently associated with trajectories of persistently high antisocial behavior (Hyde, Burt, Shaw, Donellan, and Forbes, 2015).

5.3 **Neurodevelopmental processes in the persistence of offspring aggression into adulthood?**

Elevated scores on the child aggression factor at school entry were prospectively linked to relative reductions in left and right uncinate fasciculus fractional anisotropy (FA) at age 20 in the present study. Uncinate FA, which is generally inferred as reflecting water molecules' parallel or "axial" directional diffusivity relative to a preferred direction or long axis (Beaulieu, 2002), typically continues to increase linearly into young adulthood before starting an exponentially

decreasing trend toward the end of the third decade of life (Lebel et al., 2008; Olson, Von Der Heide, Alm & Vyas, 2015). As such, relatively lower uncinate FA in emerging adulthood among those who previously showed relatively higher rates of aggression during early school-age could reasonably be suspected to represent a 'snap shot' of their present, relative structural immaturity in this tract at this time. As this study included indices of uncinate microstructural integrity exclusively at age 20, it is only possible to speculate about whether precocious or enhanced maturational progressions would have been observed earlier in childhood (Belsky & de Haan, 2011). It has been hypothesized that the uncinate integrity is delayed in attaining structural refinement until adolescence or adulthood, with some evidence supporting this idea based on extant findings (Passamonti et al., 2012; Sarkar et al., 2013). More specifically, multiple studies of relatively younger youth samples have linked aggressive behavior to relatively enhanced coherence or integrity of the uncinate during early to middle adolescence (Passamonti et al., 2012; Rogers, Gonzalez, Baker, Clanton, Pauli et al., 2017; Sarkar et al., 2013; Zhang et al., 2014). However, the extant literature is both limited and inconclusive, as results are mixed with some finding opposing or null associations between youth aggression and uncinate integrity (Finger et al., 2012; Haney-Caron, Caprihan, & Stevens, 2014). For example, some studies report inverse associations between conduct problems and axial or parallel diffusivity of the uncinate in middle adolescent, mixed-sex samples (Breeden, Cardinale, Lozier, Van Meter & Marsh, 2015; Haney-Caron, Caprihan, & Stevens, 2014).

Theoretically, it is possible that patterns of aggressive behavior and/or the repeated situational consequences of such behavior (i.e., punishment, reciprocation, related neuroendocrine response tendencies), repeated over the course of childhood and beyond, could disrupt uncinate functions. This includes top-down communication between higher-order prefrontal regions and the

limbic system, resulting in impaired abilities to use cognitive and contextual cues to modulate learned responses emotional responses (Von Der Heide et al., 2013). However, additional, multi-modal neuroimaging research is needed to clarify whether these or other possible mechanisms operate in tandem between childhood aggressive behavior and reduced UF fractional anisotropy later in development. Finally, it is perhaps noteworthy that while the general school-entry aggression factor, incorporating mother and teacher ratings of children's aggression, was significantly linked to left and right uncinate FA, exploratory analyses suggested this association was mostly accounted for by mothers' (versus teacher's) reports on child behavior. Although subtle, this distinction could be meaningful in that mothers' perceptions of their school-aged offspring as aggressive or difficult (whether or not this subjective impression is related to mothers' past or concurrent depressive symptoms) could be uniquely salient for offspring's long-term neurodevelopment.

In the present sample, higher mean diffusivity of the left uncinate in emerging adulthood was significantly related to offspring's general report of antisocial behavior (including aggression but also other disruptive or rule-breaking behaviors), as well as depressive symptoms at age 22 (with non-significant trends for the right UF in the same direction). Very generally, this pattern suggests that relatively more diffuse (i.e., parallel/axial and perpendicular/radial to the preferred or long axis; Pierpaoli & Basser, 1996) movement of water molecules in all directions throughout the uncinate prospectively predicted young adults' self-report of some behavioral outcomes (i.e., general antisocial behavior, depressive symptoms, but not reactive or interpersonal aggression) at age 22. Extant evidence suggests that mean uncinate diffusivity generally decreases exponentially across puberty into adolescence and more gradually as youth approach late adolescence (Menzies, Goddings, Whitaker, Blakemore & Viner, 2015). As such, the positive association between

uncinate mean diffusivity at age 20 and general antisocial behavior and affective symptoms at age 22 could, like the finding of reduced fractional anisotropy in relation to earlier aggression, be interpreted to reflect a relatively less mature adult levels of uncinate mean diffusivity in emerging adulthood (Lebel et al., 2008; Olson, Von Der Heide, Alm & Vyas, 2015).

Although somewhat unexpected in direction, these associations with different indices (FA, MD) of uncinate structural integrity are not without precedent in the limited extant literature. Albeit in a much younger sample, a recent study in a large, population-based, cross-sectional sample of mixed-sex ten-year olds found that uncinate FA was negatively associated with antisocial behaviors (i.e., CBCL items related to stealing, destroying others' things, as opposed to physical aggression, irritability, or disobedience; Bolhuis, Muetzel, Stringaris, Hudziak, Jaddoe et al., in press). In contrast, mean diffusivity of the uncinate and other diffuse brain regions was positively linked to antisocial behaviors in this preadolescent sample. In contrast, this study found no concurrent associations between the aggression domain-specific scale and FA or MD of the uncinate or other regions (Bolhuis et al., in press).

Our finding of inverse associations between uncinate diffusivity and antisocial behavior as well as depressive symptoms in adulthood are generally consistent with findings from adult samples of reduced fractional anisotropy (i.e., increased diffusivity, or reduced coherence) in connection with antisocial behavior (Craig et al., 2009; Hoppenbrouwers et al., 2013; Motzkin et al., 2011; Sundram et al., 2012; Von Der Heide et al., 2013). The present findings are less consistent with those previously found in youth and relatively younger emerging adult or late adolescent samples in which childhood-onset/persistent conduct disorder has been associated with relatively increased integrity (i.e., increased fractional anisotropy, reduced radial diffusivity) of the uncinate (Passamonti et al., 2012). A recent meta-analysis by Waller et al., (2017) included a

plausible theory that increased diffusivity in the uncinate and elsewhere among adults with antisocial behavior could still represent developmental delays at this stage, even if excessive or precociously increasing structural integrity might have occurred in the uncinate at earlier developmental points. More specifically, depending on when developmental trends in adolescence give way to adult developmental processes, adult-typical reductions of uncinate coherence related to aggression could represent delayed or dysfunctional trajectories of normative axon pruning (Waller, Dotterer, Murray, Maxwell & Hyde, 2017). In contrast, such patterns could also be consistent with precociously advanced white matter degradation, as speculated by Passamonti (2012). Regardless, additional prospective research in samples across this age range is needed to clarify the developmental timelines and directions of these associations for inference.

A recent meta-analysis found that associations between antisocial behavior and patterns of greater diffusivity in the uncinate fasciculus and also across a range of tracts (i.e., inferior fronto-occipital fasciculus, cingulum, corticospinal tract, thalamic radiations, corpus callosum) in adult samples (Waller et al., 2017). Notably, results of this meta-analyses were less conclusive with regard to findings in youth samples (Waller et al., 2017). Despite presently inconclusive evidence for the regional specificity of disruptions in white matter diffusivity to the uncinate in connection with aggressive behavior, there is reason to suspect that relatively immature or increased mean diffusivity of the uncinate could play a role in dysregulated behavioral or emotional control. Although the functional bases of such structural alterations are not entirely clear, relatively lower uncinate integrity has been hypothesized to predict hyper-activation in the amygdala via reduced amygdala-prefrontal functional connectivity (Pezawas et al., 2005). While somewhat limited in number, extant studies in adult clinical samples generally suggest that reduced structural integrity of the uncinate predicts disrupted behavioral inhibition (Hornberger, Geng, & Hodges, 2011; Lilly,

Cummings, Benson & Frankel, 1983), and sometimes, increases in related aggressive behavior outcomes (Lilly et al., 1983).

Nonetheless, it is important to note that reduced behavioral inhibition could either predict or reflect symptoms of many adult behavioral and emotional problems (e.g., antisocial behavior more generally) or related patterns of functional impairment (e.g., low vocational or educational attainment). Consistent with this premise, the present study's original hypotheses that altered uncinate integrity would specifically predict aggressive (and especially reactive or interpersonally aggressive behaviors) were not upheld by the results of analyses. This null finding compliments those from a moderately large sample of typically-developing, young adult males, in which structural coherence of the UF was not found to differentiate between individuals classified as 'high' versus 'low' in trait physical aggression or anger, respectively (Beyer, Munte, Wiechert, Heldmann, & Kramer, 2014). However, our study differed from that of Beyer and colleagues (2014) in that it utilized a higher-risk sample and included relevant contextual risk factors in development and adult behavior outcomes. Additionally, the present findings linking reduced uncinate coherence with higher instances of general antisocial behavior and depressive symptoms are somewhat consistent with a finding that FA in the right UF was inversely related to psychopathy (Sobhani et al., 2015; Wolf et al., 2015) and relative expression of interpersonal-affective (Wolf et al., 2015) and lifestyle-antisocial (Hoppenbrouwers et al., 2013) behavior.

5.4 **Maternal depression in early childhood and adult offspring behavior.**

In contrast to empirically-informed hypotheses that maternal depression would predict early-starting and persistent trajectories of aggression among offspring in adulthood (Kim-Cohen

et al., 2005; Munson et al., 2001; Radke-Yarrow, Nottelmann, Martinez, Fox, & Belmont, 1992; Shaw, Gilliom, Ingoldsby, & Nagin, 2003), the present study did not find predicted associations between maternal depression during the toddler years and young adult behavioral outcomes (multiple types of antisocial behavior, including aggression, and depression). In previous studies from the present sample, mothers' depression at 18 and 24 months was linked to early-starting persistent trajectories of child conduct problems from early to late childhood (Shaw, Lacourse, & Nagin, 2005) as well as from late childhood into adolescence (Shaw, Hyde, & Brennan, 2012). Moreover, moderate elevations of maternal depressive symptoms throughout childhood were previously linked to reactive aggression earlier at age 20 and altered development of limbic structures at this time point (Gilliam et al., 2015). It is unclear why such long-term, prospective associations between maternal depression in childhood and later aggressive behavior were not confirmed in offspring at age 22. Notably, the Gilliam et al. study (2015) operationalized maternal depressive symptoms in terms of relative elevations of mothers' trajectories throughout childhood (up to age 10), whereas the present study only considered mothers' depression through the toddler years. Thus, it is possible that maternal depressive symptoms during offspring's early childhood do not predict offspring aggressive behavior outcomes past adolescence unless impairment continues later into the childhood years. It also could be that from emerging into young adulthood, young men's likelihood of certain behavioral expressions (e.g., reactive aggression) of possible underlying emotional or neuroregulatory deficits related to early psychosocial risk might be reduced. In predicting young adult adjustment, the likelihood of expressing such underlying regulatory dysfunctions might be more dependent on other kinds of emotional or behavioral outcomes not assessed in the present study, such as anxiety.

5.5 **Neurodevelopmental mechanisms of risk related to maternal depression during early childhood.**

The present study did not find the expected prospective associations between exposure to maternal depression in early childhood and offspring white matter coherence in the uncinate during emerging adulthood. These hypotheses were based on compelling life history theories positing that children might have evolved to adapt to adverse contextual stressors through precocious development of behavioral and neural self-regulatory processes (Belsky et al., 1991; Passamonti et al., 2012). However, this theory is presently limited by sparse evidence in human samples, especially with regard to specific timing (i.e., mostly only prenatal or very early postnatal exposure) of exposure to childhood adversity and mode or target for examination of child brain structure.

To our knowledge, only two extant studies have documented associations, albeit modest, between postnatal maternal depression and precocious white matter development of brain regions, including the uncinate, in offspring scanned during early childhood and the early school-age period (Lebel et al., 2015; only trend-level, Sarkar et al., 2014). In contrast, another very recent study concluded that exposure to maternal depressive symptoms during pregnancy (but *not* in early childhood) was associated with higher mean diffusivity (MD) in the left uncinate fasciculus among a large, mixed-sex sample of six to nine-year-old children (El Marroun, Zou, Muetzel, Jaddoe, Verhulst et al., 2017). Findings from the present study generally suggest that maternal depression-related disruptions in uncinate microstructural developmental trajectories may not persist into young adulthood without the presence of persisting maternal depression continuing through later childhood. Previous findings in this sample linked moderate elevations of maternal depressive symptoms from 1.5 years to 10 years of age to increased amygdala: hippocampal volume ratios

and aggression in emerging adulthood (Gilliam et al., 2015). In addition to assessing maternal depressive symptoms across childhood (and not only in early childhood), the latter study differs from the present in its exclusive focus on structural characteristics (i.e., gross volume, versus microstructure) of earlier-maturing limbic regions (i.e., the amygdala and hippocampus). Thus, it is unclear whether structural or functional characteristics of later-maturing, top-down connections with prefrontal regions might moderate or mediate any associations between structural alterations of these earlier developing structures and behavioral outcomes in young adulthood (i.e., by age 22).

At present, there is insufficient evidence to predict whether bidirectional connections between the limbic and prefrontal tracts might be expected to appear relatively less or more 'refined' in terms of microstructural integrity at specific ages in the context of different timing and types of childhood adversity. One very recent cross-sectional study examined associations between retrospective reports of childhood maltreatment and trait anger in young adulthood (i.e., mean age 19 years) (Kim, Elliott, d'Arbeloff, Knodt, Radtke et al., in press). The authors found that microstructural integrity of the uncinate moderated the strength of this association, such that increased relative uncinate coherence was related to weaker associations between childhood maltreatment and trait anger. In addition to providing some corroborative support for the role of uncinate white matter integrity in adult trait anger, this study raises the question of whether alterations in uncinate white matter diffusivity might be related to other kinds of adverse childhood events, beyond exposure to mothers' depressive symptoms.

5.6 **Limitations and future directions.**

The present study had many strengths, including the use of a prospective, longitudinal design and multiple informants as well as methodologies (self-report, parent-report, teacher-report, observational, neuroimaging). However, it also has several limitations. The present low-income, community sample of males was selected based on child's age, gender, the family's income (i.e., qualifying for WIC), and having another sibling living at the family's residence. As such, findings may not be generalizable to higher SES or mixed-sex samples or living in an urban versus suburban or rural community. In fact, these findings should be generalized with caution because of evidence suggesting possible sex differences in neurodevelopmental mechanisms and expression of risk related to maternal psychopathology (Zhang, Gao, Shi, et al., 2014).

The present findings should also be interpreted with consideration of the limitations of deterministic tractography methods applied across a region, such as the uncinate that contains multiple, crossing fiber bundles with different orientations. Repeated interrogation of the present hypotheses using alternate methodologies for interpretation of diffusion tensor indices (i.e., voxel-based or specialized for crossing-fiber regions) would enhance their interpretability and provide greater potential for specifying characteristics, such as directions and connections of uncinate white matter fibers. The present study utilized average fractional anisotropy (FA) and mean diffusivity (MD) across the entire tract, bilaterally. Microstructural characteristics such as axon diameter, density, branching and myelination cannot be directly inferred from more distal indices like FA and MD (Beaulieu, 2002). Rather, their common interpretation as general indices of possible structural integrity, directional strength of connectivity, and degree of diffusivity are not directly or straightforwardly linked to such anatomical characteristics and should not be cited as evidence for such features (Jones, Knösche, & Turner, 2013).

The present study is not immune to limitations related to the current, relatively nascent state of neuroscientific inquiry in human samples. Despite a burgeoning literature based on diffusion tractography imaging methods over nearly two decades of inquiry, the tractography indices (i.e., fractional anisotropy, mean diffusivity) utilized in the present study and in most of the literature in human samples have serious limitations for the reliable and accurate inference of neuroanatomical characteristics. In the future, the incorporation of novel diffusion methods and models may hold promise for clarifying issues around replicability, time-series intra-class correlation of indices, and interpretability of results, including the present findings (Dell'Acquaa, and Catania, 2012).

As previously noted, the present findings do not clarify the specificity of associations between different indices of behavior and altered diffusivity of the uncinate. It is possible that the uncinate is one of several regions for which altered structural coherence might be found in connection with youth behavior or correlated risk factors. The addition of whole-brain analyses and case-control approaches would help to clarify the specificity of the associations reported in the present study. Finally, multi-modal imaging studies are needed to illuminate possible functional correlates of uncinate structural alterations such as those reported in the present study in connection with youth behaviors.

In sum, the present study aimed to clarify possible neurodevelopmental pathways in prospective associations between maternal depression in early childhood and long-term difficulties with emotional and behavioral dysregulation among offspring. Findings generally supported more developmentally-proximal and direct associations between early childhood maternal depression and preschool-age behavioral regulation and childhood aggression later at school-age across informant and context. Likewise, different offspring behavioral outcomes (childhood aggression

and general antisocial behavior as well as depressive symptoms in young adulthood) were differentially associated with two indices, suggesting generally reduced uncinate coherence, specifically relatively lower fractional anisotropy and relatively increased mean diffusivity. In contrast, findings did not support main effects by which maternal depression in early childhood predicted long-term and persistent patterns of offspring aggression into their adulthood. These findings also were inconsistent with hypothesized indirect effects of uncinate microstructure in mediation of this association even in the absence of all hypothesized main effects. However, this study provides some evidence that disrupted uncinate coherence may be implicated in different types of aggressive and other problem behavior at different points in development. Additional, prospective, multi-modal research is needed to evaluate the mechanisms underlying this possible brain-behavior association.

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