FRONTOSTRIATAL WHITE MATTER INTEGRITY RELATIONS WITH 'COOL' AND 'HOT' SELF-REGULATION FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Jesse T. Fischer

August 2018

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ABSTRACT

Traumatic brain injury (TBI) produces microstructural damage to white matter pathways connecting neural structures that support top-down control of prefrontal regions over striatal regions involved in self-regulation (SR). Frontostriatal white matter can be separated into dorsal and ventral pathways, and has been linked to cognitive ('cool') and emotional ('hot') types of SR. The aims of the current study were to (1) evaluate the impact of pediatric TBI, age at injury, and sex on the integrity of dorsal (dorsal anterior cingulate, ventrolateral prefrontal cortex, and dorsolateral prefrontal cortex to caudate) and ventral (medial orbitofrontal cortex and rostral anterior cingulate cortex to nucleus accumbens) frontostriatal pathways assessed 2 months after injury, and on the cool and hot self-regulatory behaviors they are believed to support; and (2) investigate whether the impact of TBI on cool and hot self-regulatory behaviors at 6 months after injury was mediated by the integrity of dorsal and ventral frontostriatal pathways, respectively. The current study used archival data from a prospective, longitudinal study consisting of 84 children and adolescents with TBI (24 uncomplicated mild, 30 complicated mild, 6 moderate, 24 severe) and 55 typically developing (TD) children, aged 8-15. Children with TBI were classified into uncomplicated mild TBI (mTBI), and more severe TBI (sTBI; complicated mild, moderate, and severe TBI). Diffusion tensor tractography was used to map dorsal and ventral white matter pathways. Measures of cool SR included focused and sustained attention (Continuous Performance Task omission errors and reaction time by block), and parent reported attention via the Strengths and Weaknesses of ADHD and Normal Behavior scale. Hot SR measures included risk-taking via Balloon Analogue Risk Task pumps and emotional control via the Behavior Rating in Executive Functioning parent report. Multivariate general linear models (GLM)

showed that, in comparison to TD children, children with sTBI had lower fractional anisotropy (FA) in dorsal pathways connecting bilateral dorsal anterior cingulate to caudate and the ventral pathway linking the right medial orbitofrontal cortex to nucleus accumbens. Children with sTBI also had significantly greater difficulties than healthy children with parent reported cool and hot SR, but not on task perfromance of SR (focused or sustained attention and risk taking). Focused attention, risk taking, and emotional control were significantly correlated with FA of specific dorsal and ventral pathways. Although frontostriatal white matter integrity predicted both cool and hot SR difficulties, only the effect of TBI on focused attention 6 months after injury was mediated by dorsal pathway integrity 2 months post-TBI. Frontostriatal pathways may serve as a biomarker to identify children at risk for specific SR difficulties as well as to assess response to interventions targeted at cool or hot SR. Findings can guide future research on dorsal and ventral neural correlates of SR difficulties following pediatric TBI, and can inform theoretical and clinical understanding of attention and frontostriatal neural circuitry in broader neurodevelopmental populations.

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Introduction

Frontostriatal pathways include anatomical connections between frontal or prefrontal cortices and parts of the striatum (Mori, Wakana, Zijl, & Nagae-Poetscher, 2005), which includes a set of subcortical structures with powerful implications for cognitive (or "cool") and motivational/emotional (or "hot") processes (Arnsten & Rubia, 2012; Casey, 2015; Chiang, Chen, Lo, Tseng, & Gau, 2015; Nigg, 2017; Peterson & Welsh, 2014; Prencipe et al., 2011; Wu, Gau, Lo, & Tseng, 2014). Notably, frontostriatal white matter pathways are believed to be anatomically segregate according to their relationship with self-regulation (SR) – dorsal pathways relate to cool SR and ventral pathways relate to hot SR (Figure 1; Haber, 2011; Haber & Knutson, 2010). Further, frontostriatal pathway changes have frequently been linked to neurobehavioral problems in populations with neurodevelopmental externalizing disorders, such as attention-deficit hyperactivity disorder and conduct disorder (Arnsten & Rubia, 2012; Rubia, 2011). However, there has been very little investigation into the role of frontostriatal pathways in children with acquired disorders such as traumatic brain injury (TBI).

Children and adolescents with TBI experience cognitive, functional, and psychological problems long after injury (Anderson, Godfrey, Rosenfeld, & Catroppa, 2012; Babikian, Merkley, Savage, Giza, & Levin, 2015). Typically, children with complicated mild, moderate, and severe TBI demonstrate more persistent neurocognitive problems whereas a majority of children with uncomplicated mild TBI tend to recover (Babikian & Asarnow, 2009; Babikian, McArthur, & Asarnow, 2013). In particular, individuals with TBI struggle with cool (e.g., attention, vigilance) and hot (e.g., risky decision making, emotional control) aspects of SR (Catroppa, Anderson, Morse, Haritou & Rosenfield, 2007; Fonseca et

al., 2012; Ganesalingam, Sanson, Anderson, & Yeates, 2006; Levin & Hanten, 2005; Li & Liu, 2013; Max et al., 2005). Because both frontostriatal pathways and self-regulation have been implicated post-TBI, further understanding of their interrelations is highly relevant to addressing issues related to difficulties in TBI. This is especially important given that TBI is a leading cause of disability in the United States. An estimated 1.36 million individuals are admitted to the emergency department for TBI, with 500,000 of these between ages of 0 to 19 (Faul et al., 2010; Keenan & Bratton, 2006). Further, estimates point to annual costs for pediatric TBI-related hospitalizations to be over two billion dollars (Shi et al., 2009), and healthcare costs per individual are significantly higher for more severe TBI than mild TBI (Graves, Rivara, & Vavilala, 2015).

TBI is typically a diffuse or multifocal injury, often causing widespread damage to frontal cortex, temporal lobes, subfrontal and parasagittal white matter of the cerebrum, as well as subcortical structures like the basal ganglia (Bigler, 2007; McAllister, 2011; Meythaler, Peduzzi, Eleftheriou, & Novack, 2001). Frontal, temporal, and subcortical regions are at particularly high risk for injury from TBI, including white matter changes in frontostriatal pathways (Bigler, 2016; Hayes, Bigler, & Verfaellie, 2016; Kraus, 2007; Parizel et al., 1998). Damage to frontal lobes (Levin & Hanten, 2005; Levin et al., 2004; Wilde et al., 2012) and frontostriatal pathways (Faber et al., 2016) following pediatric TBI is linked to SR difficulties. However, research differentiating dorsal and ventral frontostriatal pathways, examining differences in their structural integrity, and exploring how differences in structural integrity relate to behavioral outcomes following pediatric TBI remains scarce.

The goals of the present study are to: (1) better characterize white matter integrity changes in dorsal and ventral frontostriatal pathways and in cool and hot self-regulatory

outcomes following TBI in children in comparison to typically developing children; and (2) investigate whether structural changes in pathway integrity mediate differences in SR outcomes in children with TBI and healthy children.

'Cool' Self-regulation of Cognition and 'Hot' Self-regulation of Emotion

In a recent review, Nigg (2017) proposed the terms 'SR of cognition' and 'SR of emotion' that map onto cool and hot top-down processes (Poon, 2018; Rubia, 2011), respectively. Importantly, SR is a broad construct, covering a wide range of complex processes. Measurement of SR thus brings challenges given assessment tools that often tap into related or overlapping constructs. Further, there remains a lack of consensus on how best to conceptualize the many processes that fall under "SR," leading to 'conceptual clutter' in the field (Morrison & Grammer, 2016). Yet fundamentally, SR of cognition, or cool SR, is considered an intrinsic process that includes functions such as focused attention and sustained attention (Nigg, 2017; Peterson & Welsh, 2013; Rubia, 2011). In contrast, SR of emotion, or hot SR, commonly includes top down processes moderating control of emotions and risk-taking propensity (Boyer, 2006; Steinberg, 2008; Poon, 2018). Under cool SR, focused attention refers to the ability to "concentrate attentional resources on a specific task, and be able to screen out distracting stimuli" (Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991, p. 171), and sustained attention refers to the ability to maintain that focus on a task over time (Egeland & Kovalik-Gran, 2010). Though tasks of focused or sustained attention may be straightforward, good performance requires individuals to regulate their own engagement on a specific task, typically absent of reward, and manage tendencies to disengage from monotony of the tasks. Hot SR includes self-control in an emotional context (Casey, 2015; Rubia, 2011), as well as risk-taking, defined as "action that discounts the

probability of negative consequences relative to probability of positive consequences" (Nigg, 2017, p. 371). Thus, individuals faced with a risky decision are tasked with regulating their motivation for a reward in the presence of a potential penalty of some kind. It is well established that children with TBI often experience difficulties with cool and hot SR (Ganesalingam et al., 2006).

Cool and hot SR are empirically measured with both performance tasks and behavioral report. Under cool SR, the Conners' Continuous Performance Test (CPT; Conners et al., 2000) is a classic performance task measuring multiple elements of attention, including focused and sustained attention. The Strengths and Weaknesses of ADHD and Normal Behavior scale (SWAN; Swanson et al., 2001) in contrast, is a parent report of diagnostic criteria for attention deficit-hyperactivity disorder (ADHD) with a specific rating scale for attention difficulties. Under hot SR, risk-taking propensity is often operationalized with performance tasks assessing decision-making in the face of risk, such as the Balloon Analogue Risk Task (BART), which presents increasing financial reward alongside increasing risk of loss (Lejuez, 2002). Riskiness on the BART has been shown to predict to self-reported real-world risk taking, including substance use (e.g., smoking), delinquency (e.g., stealing), and safety (e.g. not using a seatbelt) in pediatric and adult populations, above and beyond demographic factors (Aklin, et al., 2005; Lejuez, Aklin, Zvolensky, & Pedulla, 2003). Additionally, emotion regulation in children is frequently assessed using behavioral reports by parent or teacher, such as the Behavior Rating in Executive Functioning (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000).

Diffusion Tensor Imaging and Dorsal and Ventral Frontostriatal Pathways

White matter maturation increases with development and is thought to improve efficiency of communication between brain regions, supporting complex behaviors and cognition (Barnea-Goraly et al., 2005; Bava & Tapert, 2010; Mills & Tamnes, 2014). Diffusion tensor imaging (DTI) is a structural imaging technique that provides a sensitive measure of microstructural changes to white matter by measuring the diffusion of water molecules in the brain (Arfanakis et al., 2002). Fractional anisotropy (FA) is a measure of the diffusion such that higher FA values generally indicate more dense and consistent ordering of axons, and greater myelination (Moseley & Bammer, 2002; Pierpaoli et al., 2001). Diffusion tensor tractography (DTT) maps white matter pathways using DTI voxel-based values, and has been increasingly used to assess compromised pathway integrity. DTT recreates large pathways by reconstructing fibers by inferring directional information from acquired diffusion metrics, allowing for a fully reformed assessment of white matter pathway integrity rather than depending on individual regions of interest.

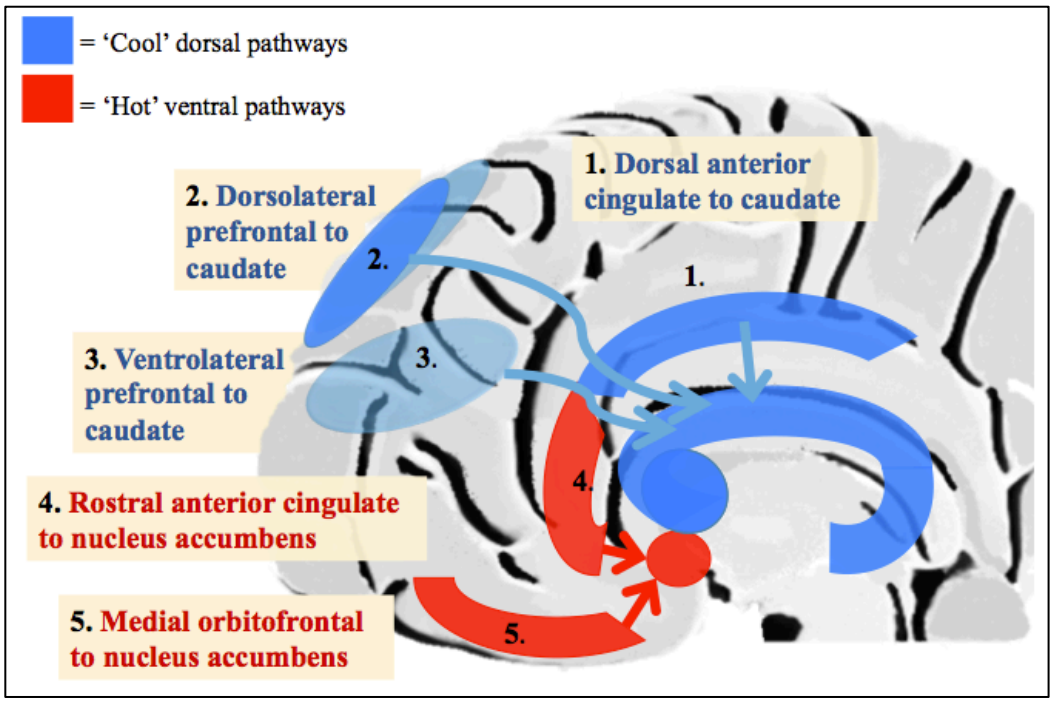

Figure 1. Schematic representation showing sagittal view of dorsal and ventral frontostriatal pathways regulating cool and hot SR, respectively. Anterior (left) to posterior (right) orientation.

Dorsal Frontostriatal Pathways and Cool Self-regulation.

Dorsal and ventral frontostriatal regions have been functionally and structurally *dissociated* in uninjured populations, though research examining these pathways simultaneously is limited. A strong line of research has demonstrated that structural differences in the ventrolateral prefrontal (VLPFC), dorsolateral prefrontal (DLPFC), and dorsal anterior cingulate cortices (dACC) are related to attentional problems (Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012; Konrad & Eickhoff, 2010; Makris, Biederman, Monuteaux, & Seidman, 2009; Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood, & Simonneau, 2011). Further, strong white matter connections exist between dACC and the dorsal striatum (Beckman, Johansen-Berg, & Rushworth, 2009), and between prefrontal cortices and the caudate nucleus (Afifi & Bergman, 1998; Mori et al., 2005; Leh,

Ptito, Chakravarty, & Strafella, 2007). Dorsal pathways of interest in the current study will include these regions (Figure 1).

Recent studies on uninjured children have begun to better differentiate prefrontal regions based on functional specificity. Investigating the white matter pathways branching from varied sections of the prefrontal cortex, Chiang and colleagues (2015) studied adolescents with and without ADHD, finding lower fractional anisotropy in white matter tracts connecting VLPFC, DLPFC, and orbitofrontal cortex to caudate and cingulum that related to worse focused and sustained attention scores on the CPT. Further demonstrating the importance of fronto-caudate pathways in children with and without ADHD, Wu and colleagues (2014) showed that lower scores of focused and sustained attention on the CPT related to lower fractional anisotropy in tracts from DLPFC, VLPFC, and medial prefrontal cortices to the caudate nucleus. Thus, differentiating between frontostriatal pathways branching from varied prefrontal regions using techniques such as DTT can expand on our understanding of their potential functional specificity.

Changes in caudate connectivity, as measured by structural volume, functional activation, and white matter integrity, has been associated with goal-directed action, planning, and has been functionally differentiated from other parts of the striatum such as the putamen and ventral striatum (Grahn, Parkinson, & Owen, 2008). A recent functional MRI study demonstrated BOLD fluctuations in the lateral prefrontal cortex, extending to the dACC and caudate nucleus across both children with and without ADHD (Lin, Tseng, Lai, Matsuo, & Gau, 2015). However, given that direct structural connection of these regions are not assessed in functional studies, investigation of the structural integrity of dorsal and

ventral frontostriatal pathways between these regions and relating these to functional measures can augment our understanding of such brain-behavior relations.

Ventral Frontostriatal Pathways and Hot Self-regulation

Dense anatomical connections exist from the ventral striatum to orbitofrontal and medial prefrontal cortical regions, and these regions are heavily linked to reward and emotion processes (Haber, 2011). Ventral frontostriatal pathways have been functionally related to reward-based learning, specifically between the orbitofrontal cortex and nucleus accumbens in reward anticipation (Galvan et al., 2005). Synthesizing past decades of literature with recent empirical revisions on developmental theories of self-control, Casey (2015) presents a model of the neural network central to the SR of emotion. This network includes the prefrontal cortex, ventral striatum, amygdala, hippocampus, and ventral tegmentum as principal structures. Notably, the ventral striatum consists of the nucleus accumbens and olfactory tubercle, though for parsimony the current study will only consider the nucleus accumbens in pathways of interest. Within Casey's model, research on neural correlates of hot SR such as risk taking and emotion regulation has implicated specific ventral frontostriatal regions. Thus, hot pathways of interest in the current study span from medial orbitofrontal (mOFC) and rostral anterior cingulate cortices (rACC) to the nucleus accumbens (Figure 1).

Structural and functional alterations in ventral frontostriatal regions have been associated with risk taking behaviors and emotional dysregulation in uninjured children (Bjork & Pardini, 2015; Crone, van Duijvenvoorde, & Peper; 2016; Leong, Pestilli, Wu, Samanez-Larkin, & Knutson, 2016; Samanez-Larkin, Levens, Perry, Dougherty, & Knutson, 2012) and those with TBI (Bechara, 2004; Wilde et al., 2012). The ventromedial prefrontal

and medial orbitofrontal cortices are partially overlapping regions that are known to be involved in risky decision making and emotion regulation (Bechara, 2004; Dixon, Thiruchselvam, Todd, & Christoff, 2017). Peper, Koolschijn, and Crone (2013) showed that medial orbitofrontal grey matter volume mediated age-related change in BART performance, such that increases accounted for increases in risky decisions throughout childhood. The rACC and mOFC regions have dense anatomical connections to the nucleus accumbens, and both regions have been linked to hot SR (Bush, Luu, & Posner, 2000; Haber, 2011; Stevens, Hurley, & Taber, 2011).

Changes in the functional activation of ventral frontostriatal regions relate to various aspects of hot SR in healthy children and adolescents and those with ADHD or other neurobehavioral disorders (Crone et al., 2016; Lamm et al., 2014; Mohanty et al., 2007; Rao et al., 2008; Schonberg et al., 2012; Van Leijenhorst et al., 2010*a*; Van Leijenhorst et al., 2010*b*). However, investigations characterizing relations between underlying white matter pathways of frontal or striatal regions and hot SR are scarce and rely largely on adult literature. Further, variations in performance tasks used, and in the regions associated with risk taking and emotion regulation have not been consistent across the literature. A recent study found white matter integrity of the prefrontal cortex, midbrain, and insula pathways to the striatum in healthy adults related to network-wide brain function during risky decision-making via the BART (Kohno, Morales, Guttman, & London, 2017). However, caudate, putamen, and nucleus accumbens structures were grouped together as a seed region for the "striatum" in this study. Differentiating dorsal from ventral frontostriatal pathways may help elucidate specific brain-behavior relations. Leong and colleagues (2016) found higher FA in white matter between the insula and nucleus accumbens in healthy adults related to less risky

choices on a gambling task, introducing emerging evidence of potential fronto-temporal to nucleus accumbens relations with risk taking. In a study of healthy adults, decreased FA in white matter from the medial prefrontal cortex to the ventral striatum was associated with poor decision making motivated by reward (Samanez-Larkin et al., 2012). Despite varied methods and findings, a reasonable conclusion is that risky task performance and emotion dysregulation are associated with decreased volume or compromised white matter integrity in regions associated with relatively hot SR processes.

Cool and Hot Self-regulation Across Development and Sex

Development of attentional capacity varies for particular elements of attention, with sustained and focused attention demonstrating developmental spurts at age 8 and around age 11, respectively (De Luca & Leventer, 2010; McKay, Halperin, Schwartz, & Sharma, 1994). As development continues, sustained attention improves until about 11 (De Luca & Leventer, 2010). Hot self-regulatory capacities also develop in a dynamic manner as children mature. For example, while impulsivity tends to decrease linearly during development (Shulman, 2016), risky decision-making and difficulties with emotional control increase from early childhood to middle adolescence (Casey, 2015; Mata, Josef, Samanez-Larkin, & Hertwig, 2011). A mid-adolescence peak in risky decision making has been shown in studies using reward and loss tasks such as the BART, as well as behavioral report in uninjured children (Braams, van Duijvenvoorde, Peper, & Crone, 2015; Cox, Mills-Koonce, Propper, & Gariépy, 2010; Masten & Cicchetti, 2010; Smith & Thelen, 2003). Even more impactful, risk-taking propensity and SR difficulties early in childhood predict development of later behavioral problems, such as risky sexual behavior (Crockett, Raffaelli, & Shen, 2006), substance use (Tarter et al., 2003), and child psychopathology (Keenan, 2000).

These changes in capacity roughly mirror cortical and subcortical changes in middle childhood and adolescence. Frontostriatal white matter integrity increases across adolescence (Achterberg, Peper, Duijvenvoorde, Mandl, & Crone, 2016). Cortically, middle childhood brings with it steady white matter and myelination increases. While white matter develops gradually, grey matter development peaks at age 11 and 12 before steadily declining as synaptic organization and pruning take place (Ge et al., 2002; Scahill et al., 2003). Cortical areas responsible for affective decision making such as the ventromedial cortex and orbitofrontal cortex continue to mature through late adolescence (De Luca & Leventer, 2010; Hooper, Luciana, Conklin, & Yargar, 2004; Zelazo, 2015). Thus, with continued development, the frontal lobes take on an expanded role in providing top down regulation (Casey, 2015).

Although increasing capacity for adequate SR has been demonstrated in uninjured children and adolescents throughout development (van Duijvenvoorde, Jansen, Visser, & Huizenga, 2010; Huizenga, Crone, & Jansen, 2007), other factors such as sex play a role as well. Generally, males tend to take more risks than females on such tasks (Byrnes, Miller, & Schafer, 1999). However, findings across context are not consistent, and reasons for sex differences in decision-making across development continue to be investigated. The prefrontal cortex matures earlier in adulthood in females, which is heavily involved in hot and cool SR (Powell, 2006, Lebel & Deoni, 2018), and in adolescence there is a peak in cortical activation of the nucleus accumbens, a key structure of reward-linked behaviors (Braams et al., 2015). Sex differences have not been prominently demonstrated in research on children with traditionally “cool” executive functioning difficulties (Houghton et al.,

1999) but sex represents an important factor that may play a role in outcomes following pediatric TBI.

Cool and Hot Self-regulation Following TBI

Cool SR such as focused and sustained attention is negatively impacted following pediatric TBI (Anderson, Anderson, & Anderson, 2006; Anderson & Pentland, 1998; Catroppa & Anderson, 2003; Catroppa et al., 2007; Ganesalingam et al., 2006; Ginstfeldt & Emanuelson, 2010; Kaufman, Fletcher, Levin, Miner, & Ewing-Cobbs, 1993). School aged children and adolescents with TBI show reduced focused and sustained attention in relation to injury comparison groups or typically developing children (Ginstfeldt & Emanuelson, 2010). Greater severity of TBI in children has been linked to more significant problems in these areas (Anderson, Catroppa, Haritou, Morse, & Rosenfeld, 2005a; Anderson, Catroppa, Haritou, Morse, & Rosenfeld, 2005b; Babikian et al., 2015; Levin & Hanten, 2005). A study comparing various elements of attention in school aged children with and without TBI found the TBI group to have lower scores on measures of both focused and sustained attention, but TBI severity was only related to the former and not the latter (Park, Allen, Barney, Ringdahl, & Mayfield, 2009). However, relations between attention and TBI severity remain inconsistent (Taylor et al., 1999; Wassenberg, Max, Lindgren, & Schatz, 2004). Additionally, a majority of children with uncomplicated mild TBI show improved functioning over the year following injury, or do not show significant differences from orthopedic injury in cognitive and behavioral outcomes (Babikian et al., 2011, Babikian, McArthur, & Asarnow, 2013; Kirkwood et al., 2008; Levin et al., 2004; Maillard-Wermilinger et al., 2009). Further, children with complicated mild, moderate, and severe TBI generally show worse quality of life, disability, psychosocial, and neurocognitive outcomes than those with uncomplicated

mild TBI, those without frontal lesions on acute CT scan, or those with orthopedic injury (Iverson, 2006, Levin et al., 2004; Levin et al., 2008; Rivara et al., 2011). Thus, improved characterization of clinical markers and predictors of impairment outside of traditional severity classification would assist in determining those at greater risk for impairment.

Difficulties with hot SR may develop or worsen following pediatric TBI, including emotional dysregulation, risky decision making, and increased risk for externalizing behaviors such as oppositional and conduct disorders (Ganesalingam et al., 2006; McKinlay, Grace, Horwood, Fergusson, & MacFarlane, 2010; Levin & Hanten, 2005; Li & Liu, 2013; Rao, Korczykowski, Pluta, Hoang, & Detre, 2008; Schmidt et al., 2012; Wilde et al., 2012). For instance, Gerring and colleagues (2009) demonstrated that children aged 4 to 19 with severe TBI experienced greater levels of new-onset disruptive and conduct disorders in the year following injury in comparison to normative levels. While greater severity of TBI has generally been associated with greater difficulties in hot SR disruptive behaviors and externalizing problems (Chapman et al., 2010), some studies have not found a link (Ganesalingam et al., 2006; Cole et al., 2008), and children with mild TBI have also demonstrated problems when compared to children without TBI (Dennis et al., 2013; Sesma et al., 2008). Importantly, these studies typically consider mild TBI as inclusive of those with and without hemorrhagic CT findings, though children without parenchymal injury tend to show better post-injury functioning (Levin et al., 2008). Overall, relations between difficulties in hot SR and injury severity have not been consistent; however, greater severity tends to be more commonly linked to worse behavioral outcomes, and it is important to clearly define what constitutes more mild versus more severe TBI.

Frontal and Frontostriatal Damage associated with TBI: Relation to Self-Regulation

Changes in white matter integrity following pediatric TBI have been associated with a range of cognitive difficulties (Roberts, Mathias, & Rose, 2016; Wilde et al., 2010; Treble et al., 2013; Ewing-Cobbs et al., 2008), yet few studies have examined cool or hot SR problems using this imaging method (Faber et al., 2016; Johnson et al., 2011; Wilde et al., 2010). Despite the evidence in uninjured populations reviewed above, there is a lack of research on children with TBI examining how white matter changes to dorsal frontostriatal pathways relate to cool SR. A recent meta-analytic review of DTI findings following pediatric TBI showed that attention difficulties were related to lower FA at least one month post-injury in frontal and cingulate regions (Roberts, Mathias, & Rose, 2016). Still, studies reviewed did not investigate relations between frontostriatal pathways and cool SR. School aged children with moderate to severe TBI demonstrated lower FA in the cingulum, a bundle of white matter fibers attached to the cingulate cortex, that was associated with worse performance on cool SR measures (Wilde et al., 2010).

A small number of studies have investigated ventral frontostriatal regions following pediatric TBI, and even fewer have sought to characterize the relation between anatomical differences and hot SR processes. Lesion studies on adults have demonstrated that damage to the ventromedial prefrontal and orbitofrontal cortices relates to risky decision-making and poor emotional decision making (Bechara, 2004; Hornak et al, 2003). Wilde and colleagues (2012) demonstrated decreased cortical thickness of superior frontal, dorsolateral frontal, orbitofrontal, and anterior cingulate regions in 8-17 year olds 3 months post-TBI compared to orthopedic-injured controls. Additionally, failure of cortical thinning across time in medial frontal and anterior cingulate cortex related to increased problems with emotional control

reported via the BRIEF parent report. Faber and colleagues (2016) recently reported higher diffusion of ventral striatum was correlated with greater executive functioning difficulties in children and adolescents 5 to 15 years following their TBI. Similarly, a study of adults showed lower FA relating to executive functioning in those with severe TBI compared to healthy controls (Shah et al., 2012). However, hot SR measures were not included in these studies, and thus it is unclear whether ventral striatum damage was also related to hot outcomes such as risk taking or emotion regulation. Further, the regions of interest were limited to the ventral striatum, limiting conclusions about potential relations between executive functioning and dorsal pathways. The current study aims to build on this research by including dorsal and ventral frontostriatal white matter pathways simultaneously, as well as behavioral measures of cool and hot SR. Clearly, research on structural changes and emotion regulation and risk taking following pediatric TBI is limited.

Functional activation of ventral frontostriatal regions after TBI has been associated with SR of emotion as well, although evidence is limited, findings are not consistent, and sample sizes are small. A recent review of structural and functional network connectivity of regions serving emotion regulation following mild TBI highlighted disruption in connectivity of the medial prefrontal cortex (van der Horn, Liemburg, Aleman, Spikman, & van der Naalt, 2016). Functional alterations following pediatric TBI have also been demonstrated in the medial prefrontal, ventral or inferior frontal cortices, as well as the rACC have related to hot SR (Chiu et al., 2012; Newsome et al., 2013; Vink et al., 2014). Despite growing literature showing structural and functional changes relating to hot SR, our understanding of such structural changes in children after TBI remains nascent.

Rationale

There is evidence that pediatric TBI, particularly more severe TBI, impacts top down self-regulatory processes. Areas of difficulty include the SR of cognition, or cool SR; as well as SR of emotion, or hot SR (Nigg, 2017; Rubia, 2011). Frontostriatal white matter pathways have been related to cool and hot SR. Children with TBI frequently demonstrate compromised frontal white matter and reduced integrity of frontostriatal pathways (Faber et al., 2016; Roberts et al., 2016; Wilde et al., 2012). Frontostriatal pathways have been investigated extensively in relation to hot and cool processes in children with developmental disorders such as attention-deficit hyperactivity and conduct disorders (Arnsten & Rubia, 2012; Rubia, 2011). However, they have rarely been examined in children with acquired disorders such as TBI.

Regions of the prefrontal, orbitofrontal, and anterior cingulate cortices, have strong anatomical and functional connections to the nucleus accumbens and caudate nucleus (Mori et al., 2005). Frontostriatal white matter pathways between these regions can be anatomically and functionally differentiated via dorsal and ventral pathways (Haber, 2011; Haber & Knutson, 2010). However, there is limited investigation characterizing how cool and hot processes relate to dorsal (Figure 2) and ventral (Figure 3) frontostriatal pathways following pediatric TBI. Further, no studies have investigated whether changes to integrity in these pathways in children with TBI might differentially relate to cool vs. hot SR. At present, little is known whether other variables, such as severity of TBI, age at injury, and sex, influence pathway integrity and/or self-regulatory changes following injury.

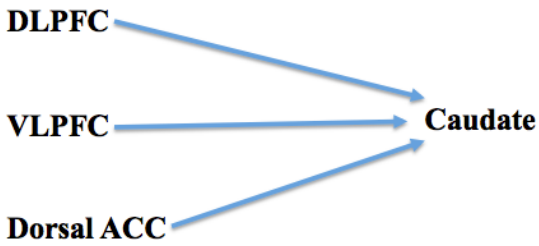

Figure 2. Dorsal frontostriatal "cool" pathways of interest. DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; ACC = anterior cingulate cortex to caudate.

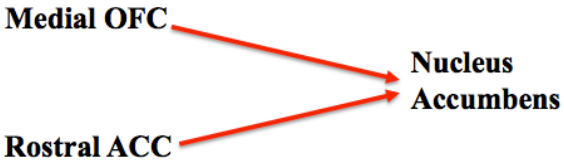

Figure 3. Ventral frontostriatal "hot" pathways of interest. OFC = medial orbitofrontal cortex; ACC = anterior cingulate cortex.

A more comprehensive understanding of how specific pathway changes account for behavioral difficulties following TBI may lead to better-informed models of intervention and treatment planning. Increased knowledge of neural structure-function relations in children with and without TBI could be an important tool for early identification and intervention. Specifically, early identification of those with a potential propensity for cool and hot self-regulatory difficulties may be possible. Notably, recent studies have demonstrated preliminary evidence of post-injury alterations in structural connectivity following intervention such as computerized attention tasks, metacognitive strategy coaching, and aerobic training following TBI (Yuan, Treble-Barna, Sohlberg, Harn, & Wade, 2017a; Yuan et al., 2017b). Thus, improved understanding of underlying neural mechanisms may allow future studies to designate types of personalized intervention.

To address these gaps in the literature, the aims of the current study were to (1) evaluate the impact of uncomplicated mild and more severe pediatric TBI within the context

of age at injury and sex on the integrity of dorsal and ventral frontostriatal pathways assessed 2 months after injury and to the cool and hot self-regulatory behaviors they are believed to support; and (2) investigate whether the impact of mild and more severe TBI on cool and hot self-regulatory behaviors assessed at 6 months after injury was mediated by the integrity of dorsal and ventral frontostriatal pathways, respectively.

Hypotheses

Group differences in frontostriatal white matter.

1) In comparison to typically developing (TD) children, we expected that children with more severe TBI would demonstrate lower FA in dorsal (Figure 2) and ventral pathways (Figure 3) two months post-injury. In addition, we expected a main effect of age such that younger children across groups would demonstrate lower FA than older children. Considering potential sex differences that may account for individual differences in FA, the main effect of sex was also investigated.

Group differences in behavioral problems.

2) In comparison to TD children and controlling for baseline/preinjury behavioral ratings, we expected that children with more severe TBI would demonstrate more problems with cool and hot self-regulatory behaviors assessed by performance tasks and parent-report at 6 months post-injury. In addition, we expected a main effect of age such that cool SR would improve and hot SR difficulties would increase in older children across groups. Further, considering the limited research investigating the influence of sex on cool and hot SR following pediatric TBI, and given the influence of sex on behavioral outcomes across development, we expected that boys across groups would demonstrate greater difficulties than girls with both cool and hot SR.

Associations between white matter integrity and behavioral difficulties.

3) Given that we expected dorsal pathways to relate to cool self-regulatory behaviors, and ventral pathways to relate to hot self-regulatory behaviors, we expected dorsal frontostriatal FA at 2 months to mediate the effect of *Group* on cool self-regulatory problems at 6 months, particularly for children with more severe TBI. Similarly, we expected ventral frontostriatal FA at 2 months to mediate the effect of *Group* on hot self-regulatory problems at 6 months.

Methods

Participants

This study was approved by the Committee for the Protection of Human Subjects (CPHS) in the University of Houston (UH) Institutional Review Board (IRB). Data for this archival study were collected originally in compliance with regulations mandated by the IRB of the University of Texas – Health Science Center at Houston (UT-HSCH), and were part of a National Institutes of Health grant. UH CPHS and UT-HSCH approval and permission from Linda Ewing-Cobbs, PhD, was obtained for this study before any collected data were viewed or obtained. Under the original protocol, participants were initially enrolled in a longitudinal prospective study. A flow chart of sample participation for the current study is presented in Figure 4. Of the 147 (56 TD, 91 TBI) participants originally enrolled in the study, 8 were lost to follow up prior to their 2 month evaluation, leaving 139 participants with either 2 month MRI scan data, 6 month follow up data, or both. Thus, archival data from 84 children and adolescents with varying severity of closed head injury were used for the current study. Additionally, data from 55 TD children also recruited previously through posting of flyers throughout Texas Medical Center were used. 11 children did not receive an MRI due to various reasons: braces, MRI safe metal, helmet, plates, or anxiety. Following

rigorous examination of each scan, an additional 38 cases were excluded from the MRI data due to imaging concerns (due to motion or other artifact, incomplete data, failure to register to the TBSS template), resulting in 98 participants with imaging outcome data (41 TD and 57 TBI). Of the 139 in the current study, 11 more were lost to follow up prior to 6 month evaluations, resulting in 128 participants with behavioral outcomes (52 TD and 76 TBI). Data from three participants' cool SR measures were missing because the participant did not complete the evaluation, and one participant's hot SR measures were missing because the parent report was filled out incorrectly. For mediation analyses, there were 86 participants with both behavioral outcomes and valid MRI scans (38 TD and 48 TBI). Due to motion artifact, one participant's DTI data was valid for ventral frontostriatal pathways but not dorsal pathways. Two-tailed t-tests and chi square analyses showed that the original sample of 147 children did not differ significantly on any of the demographic and injury comparisons as compared to the final sample of 139 children. Given the different sample sizes of those with behavioral data (n = 128) and those with both imaging and behavioral data (n = 86), imaging analyses were run for those with and without behavioral data, and behavioral analyses were run for those with and without imaging data, and each showed similar results.

Inclusionary criteria were: children with TBI admitted to the emergency department or to the Level 1 Trauma Center at UT Health/Children's Memorial Hermann Hospital in Houston, Texas between the ages of 8 and 15, and TD children first assessed between the ages of 8 and 15. Additionally, all children included in the original study were either bilingual or primarily English speaking. Exclusionary criteria were: previous history of brain injury, severe developmental or learning disability, hospitalization for a psychological disorder, history of child protective services intervention (except in the case of family

placement with no abuse or serious neglect), or if they sustained a gunshot wound to the head or other penetrating head injury. These participants have been reported in previous work (DeMaster, Johnson, Juranek, & Ewing-Cobbs, 2017; Fischer, Hannay, Alfano, Swank, & Ewing-Cobbs, 2018); however, the hypotheses presented, the pathways examined, and the outcomes evaluated here, have not previously been reported.

The age range of 8-15 was selected to allow for investigation of injury effects across a broad age range, and allow for investigations of cool and hot SR during the transition into adolescence. The study design allows a wide range of variability in developmental processes, which can add to heterogeneity of outcomes. However, a key benefit of this design is the inclusion of children prior to, during, and following onset of puberty, in order to consider how pubertal stage influences outcomes. Ultimately, this age range allows for inclusion of children at times when cool and hot SR processes continue to develop, adding to potential investigation of how such processes relate to outcomes following TBI, and how cool and hot SR may develop at different trajectories (Perone, Almy, & Zelazo, 2018; Prencipe et al., 2011; Rubia, 2011).

TBI severity is most often clinically assessed using acute injury characteristics. Assessing eye opening, verbal response, and motor response, the Glasgow Coma Scale (GCS) is the most frequently used measure of acute TBI severity (Teasdale & Jennett, 1974). 24 children in the current study had uncomplicated mild TBI, defined as an admission GCS score of 13-15 with no structural injury outside of non-displaced skull fractures on computed tomography (CT) scan; 30 children had complicated mild, defined as an admission GCS of 13-15 with evidence of parenchymal injury on CT scan; 6 children had moderate TBI, defined as an admission GCS score of 9-12, and 24 children had severe TBI, defined as an

admission GCS score of 3-8 (Levin et al., 2008; Williams, Levin, & Eisenberg, 1990). Given the divergent trajectories of recovery and outcomes for those with uncomplicated mild TBI compared to those with more severe TBI (Babikian et al., 2011, Babikian, McArthur, & Asarnow, 2013; Iverson, 2006; Kirkwood et al., 2008; Levin et al., 2004; Levin et al., 2008; Maillard-Wermilinger et al., 2009; Rivara et al., 2012), the current study design classified children with TBI into two severity groups of lesser versus greater degree: the mTBI (n = 24) group included children with uncomplicated mild TBI, while the sTBI group (n = 60) included children with complicated mild, moderate, and severe TBI.

Behavioral Measures

Cool SR. The Conners' Continuous Performance Test (CPT-II) was used to assess attention. The CPT-II is a computerized task where participants were required to press a key every 324 times a letter appears on the computer screen, and to refrain from responding whenever the letter "X" appeared (a total of 36 times). The standard paradigm consists of six blocks, within each target and nontarget stimuli are presented with varying frequency. Research assistants were passively present in the room during presentation. Omission errors, or the number of times a participant fails to respond to a target, were used as a measure of focused attention. Higher scaled scores represent greater number of errors of omission. Hit Reaction Time Change by Block, or the slope of change in reaction time over the six blocks as the task progresses, was used as a measure of sustained attention. Higher scaled scores represent greater difficulty sustaining attention over time. Split half reliability for all of the CPT performance measures range between .73 and .95, while test-retest reliabilities for a 3-month interval were found to fall between .55 and .84 (Conners et al., 2000). Thus, the measure has demonstrated adequate reliability in children aged 6 and older been validated for

clinical and non-clinical child and adolescent populations (Conners et al., 2000; Egeland & Kovalik-Gran, 2010).

The parent-report attention scale from the SWAN was used to assess attention (Swanson et al., 2001). The Inattentive Behavior subscale is the average of Items 1-9, which map onto inattentive symptom diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV). Participants were rated on a 7-point Likert type scale, with ratings ranging from -3 to +3. This scale produces a raw score in which lower scores are indicative of greater problems with attention. Test-retest reliability (*rs* between .71 and .76) and internal consistency (Cronbach's alphas $\geq$.95) of the SWAN has been demonstrated to be high (Lakes, Swanson, & Riggs, 2012; Waschbusch, & Sparkes, 2003). The SWAN has also demonstrated be validity of attention difficulties and impulsivity in clinical and nonclinical samples (Arnett et al., 2013).

Hot SR. The Balloon Analogue Risk Task (BART) was used as a measure of risk taking propensity. Participants completed the BART following nondirective informative directions of the procedure given by a trained research assistant. They were told that after the task, the amount of points they earn would determine the size of their prize reward. For the task, the computer screen presented a small balloon along with a balloon pump, a reset button to save progress labeled "Save Points," the "total earned," and the amount earned on the previous balloon. Participants inflated the balloon by clicking the mouse, earning 1 point per mouse click. Pressing the "Save Points" icon at any time saved earnings from the current balloon after which a new balloon was presented. Earnings were lost if the balloon "popped" before a participant chose to save earnings. Thirty balloons popped at different sizes, after anywhere from 1 to 128 pumps. The order of balloons was constant across participants. A

'pop' sound was emitted when a balloon exploded, and a 'scoring' sound emitted when points were earned. This measure has consistently correlated well with self-report measures of risk-taking (Lejuez, 2002). Test-retest reliability has been shown to be acceptable (.77) (White, Lejuez, & de Wit, 2008) and it has demonstrated acceptable construct validity (Hunt, Hopko, Bare, Lejuez, & Robinson, 2005; Lejuez, 2002). The average number of adjusted pumps, or pumps for unexploded balloons predicts risk-taking propensity, and was used for the current study. Greater number of pumps represents a higher level of risk-taking.

The Behavior Rating in Executive Functioning (BRIEF; Gioia et al., 2000) is an 86-item parent report of everyday executive functioning problems with strong psychometric integrity. The BRIEF has demonstrated greater ecological validity for assessment of executive functioning difficulties related to activities of daily life than performance based measures in children with TBI (Gioia & Isquith, 2004; Vriezen & Pigott, 2002). Test-retest reliability for the BRIEF subscales has been demonstrated to be .81 on average. The Emotional Control subscale was used for assessing emotion regulation in the current study. Higher T scores ($M = 50$, $SD = 10$) indicate greater difficulty with emotion regulation.

Covariate. The current study used the Pubertal Development Scale (Petersen, Crockett, Richards, & Boxer, 1988) to assess pubertal stage of development. This scale is a validated and reliable self-report measure of pubertal status. Child and parent independent ratings of changes associated with puberty were collected, including growth in height, body hair, and skin, and sex-specific changes. Each item was coded on a 5-point scale similar to Tanner staging (Shirtcliff & Essex, 2008), and ratings were averaged to yield a score from 1 (pre-pubertal) to 5 (post-pubertal).

Procedure

In the original study informed written consent was obtained from the child's guardian, in accordance with guidelines established by the UT-Health IRB. Children who were ages 11 and older signed the written adolescent consent while those under 11 signed the written child assent at the 2 month visit.

Participants were scanned at their baseline assessment at University of Texas McGovern Medical School. Children and adolescents with TBI were scanned for their baseline assessment approximately 2 months following injury. Behavioral outcome data were collected from all participants who attended their 6-month follow up. Trained research assistants administered the CPT-II and BART individually with participants in a quiet testing room. The parents completed the BRIEF measure. SWAN ratings were obtained via clinical interview as part of a structured DSM interview. Data on retrospective preinjury functioning for the TBI groups and baseline functioning for the TD group were gathered at a baseline clinical visit using the BRIEF and SWAN, which took place 2 months following injury in the TBI groups. Although correlations between performance task and behavioral report outcomes are generally low to moderate (Allan, Lonigan, & Wilson, 2013; Gerst et al., 2017), the use of multiple methods for the constructs of interest assists in the generalization of results.

Image acquisition. The current study used data that were acquired on a Philips 3T MR scanner with a 32 channel head coil. Participants were scanned at the University of Texas McGovern Medical School. An echo planar imaging sequence (TR = 8700 ms; TE = 67 ms; 65 slices total; square FOV = 240 mm; slice thickness = 2.5 mm) was used for diffusion weighted data collection. High resolution T1-weighted anatomical scans were

collected (TR = 8.1 ms, TE = 3.7 ms, flip angle = 6°, matrix = 256 X 256, slice thickness = 1 mm, and voxel size = 1 mm^3). Toward the end of data collection, the University of Texas scanning facility upgraded the scanner with a Philips 3T Ingenia and 45 of our participants with valid DTI data were scanned after the upgrade. We performed fidelity analysis to match Diffusion-weighted and T1-weighted scanning protocols, however some variations may remain. To account for differences in scanner, scanner change was included as a covariate in all DTI analyses.

Image processing. FreeSurfer 5.3.0 (http://surfer.nmr.mgh.harvard.edu) automated segmentation software was used for parcellation of cortical and subcortical structures (Fischl et al., 2002; Fischl et al., 2004). After standard Freesurfer pre- and post- processing steps, trained research assistants and authors reviewed quality of subcortical parcellation and edited parcellations (particularly subcortical regions) to ensure accurate masks. Using Linear Image Registration Tool (FSL: FLIRT), segmentation maps for each participant were then registered to corresponding diffusion-weighted images, creating the seed regions for DTI analysis. Seed regions were restricted to each participant's anatomy, corresponding to regions listed in Table 1. We generated exclusion masks for DTI analysis corresponding to ventricular regions using the same image-processing pipeline.

FMRIB Software Library (FSL) 5.0.1 (http://www.fmrib.ox.ac.uk/fsl) was used for processing of DTI data, which was performed using the standard DTI pipeline. Eddy Correct was utilized to attenuate participant head movement and eddy current distortions. BET (Brain Extraction Tool; Smith, 2002) was used for skull-stripping to remove non-brain tissue, and brain-extracted images were examined and corrected for quality assurance. Brain masks were edited for DTI analysis, DTIFIT was then used in calculation of FA maps, and Bayesian

Estimation of Diffusion Parameters Obtained using Sampling Techniques (BedpostX) was used to build probability distributions in preparation for tractography,.

The current study used probabilistic methodology to determine fiber orientation and to designate voxels in white matter pathways. The probabilistic approach uses values of each individual voxel to guide where tracts lead. This method is particularly suitable in studying children with TBI or other neurological insults, given that pathway structure and relations to the rest of the cortical and subcortical network may not be as expected. Probabilistic tractography algorithm (FSL: probtrackx) uses voxelwise probability distributions to generate a distribution of pathways connecting specified regions, and this was applied for seed to target fiber tracking. This algorithm has been used for recent investigation of prefrontal to subcortical white matter in children (Ngo et al., 2017). We initiated one-way direction fiber tracking from each voxel in a seed mask to track all paths connecting to the target mask and discarding paths in contact with exclusion masks (see Table 1). Three dorsal pathways were constructed as the seed to termination points of DLPFC to caudate, VLPFC to caudate, and dACC to caudate. Two ventral pathways were constructed with seed to termination points: medial orbitofrontal cortex (mOFC) to nucleus accumbens, and rACC to nucleus accumbens. Thus, for each of the five seed-to-target combinations, we calculated the average FA for each hemisphere along the entire pathway. Fiber tracking within a diffusion space generated 5000 streamline samples (step length = 0.5 mm; curvature threshold = 0.2). Because tract volume varies based on the size of seed regions, we normalized tract maps in order to account for voxel count in seed masks by dividing the number of streamline samples present in the voxels of the tract maps by the way-total. The way-total consisted of the total number of generated tracts from each seed mask that reached at least one of the other masks

and had not been rejected by mask inclusion/exclusion criteria. This approach accounts for within-subject variation across individuals, and has been used in research on pediatric TBI (Johnson et al., 2011) as well as other patient populations (Williams et al., 2013). Tracts were thresholded to voxels with FA values above 0.2 in order to ensure pathways included only white matter.

Statistical Analyses

Data screening strategies and goodness-of-fit checks were conducted before behavioral and DTI analyses were run (Tabachnick, & Fidell, 2001). The dataset was screened for missing data points, and outliers were examined for inclusion or exclusion from the current study. The distribution of the data was tested for normality to determine whether skew and/or kurtosis were demonstrated. Skew and kurtosis were found to be within acceptable limits, with only the CPT Omission Errors demonstrating moderate kurtosis and mild skew. Homoscedasticity and linearity assumptions were examined, error variance and covariance matrix assumptions were not violated, and extreme values were examined and determined to be valid scores and representations of children's functioning. Thus, analyses conducted were appropriate for the current data. Regarding effect sizes, partial eta squared (η_p^2) values were used for measures of effect sizes of multivariate and univariate models, representing the proportion of total variance attributable to the factor of interest, partialling out variance explained by other predictors (Levine & Hullet, 2010). Partial eta squared, in comparison to eta squared, can also improve comparability of effect sizes between studies (Cohen, 1973; Keppel, 1991), and can be benchmarked against Cohen's criteria (Richardson, 2011) of small (.01), medium (.06), and large (.14) effect sizes. Hedges g (g) was used for follow-up pairwise comparisons, in part because it allows for a conservative estimate of

effect size by accounting for variation in sample size across groups with pooled weighted standard deviations (Hedges & Olkin, 1985). Similar to Cohen's measure of effect size, Hedges g can be considered small (.20), medium (.50), and large (.80).

Hypothesis 1

Multivariate general linear model (GLM) procedures were used to determine if FA of bilateral dorsal and ventral frontostriatal pathways differed among the sTBI, mTBI, and TD groups. Independent variables included group membership (TD, mTBI, sTBI), age at injury, sex. The right and left FA of each frontostriatal pathway was the dependent variables. One multivariate GLM was run for each of the five pathways of interest, with each GLM including right and left FA values of a specific pathway, culminating in five GLM procedures. A main effect of age was expected such that younger children would demonstrate lower FA. Scanner change was included as a covariate. When two-way group by sex and group by age interactions were not significant they were trimmed from analyses. Between subject effects were examined to determine if right or left FA were driving significant multivariate findings. For pathways demonstrating multivariate group main effects, Bonferroni-corrected follow-up analyses were performed to further investigate group differences (Field, 2013). Considering the conceptualization of p values as flexible inferential measures, a threshold of $p < .10$ was used for guidance of follow-up univariate analyses (Goodman, 1993), and to examine pairwise relations that would survive corrections for multiple comparisons.

Hypothesis 2

Multivariate GLM procedures were used to determine if cool and hot SR outcome scores differed among the TD, mTBI, and sTBI groups. Group membership, age at injury,

sex, and the group by age interaction were the independent variables, while SR scores were the dependent variables. One multivariate GLM procedure included dependent variables measuring cool SR (CPT Omissions, CPT Reaction Time by Block, SWAN attention scale), and a second multivariate GLM included dependent variables measuring hot SR (BART average number of adjusted pumps, and BRIEF Emotional Control subscale scores). To account for preinjury level of functioning, retrospective ratings of attention (via the SWAN) and emotional control (via the BRIEF) were added to the first and second GLM, respectively. When sex and group by age interactions were not significant they were trimmed from analyses. Follow up univariate analyses were examined to determine which behavioral measures were driving multivariate findings for GLMs with multivariate group differences ($p < .10$). Bonferroni-corrected pairwise comparisons were performed to further investigate group differences.

Hypothesis 3

Pathways demonstrating group differences in FA via Hypothesis 1 as well as correlations between left and right pathway FA and SR outcomes were examined for the construction of mediation models. For correlations involving FA with raw SR outcomes (e.g., BART, SWAN), age was partialled; further Spearman correlations were utilized given the ordinal nature of these scales (Pearson correlations were used for correlations of FA with CPT and BRIEF measures). When both hemispheres of a pathway FA were correlated with an outcome, the mean of right and left hemisphere FA for that pathway was used in the outcome variable's respective mediation analysis (DeMaster et al., 2017). When FA from only one hemisphere of a pathway was significantly related to an outcome, only that hemisphere FA was selected for the mediation model.

Mediational regression analyses were conducted using bootstrapping techniques through PROCESS, a conditional modeling program that utilizes an ordinary least squares-based path analytical framework to test for both direct and indirect effects (Hayes, 2013). Due to the study design employing multiple groups, Hypotheses 3 called for multicategorical mediation models, allowing for the use of a multicategorical independent variable (IV; Hayes & Preacher, 2014). A mediating model is presumed to reflect a causal sequence in which an IV affects a dependent variable (DV) indirectly through a mediator variable in a time-dependent fashion, achievable in this study given that group status was defined prior to measurement of the mediator, which in turn was assessed before measurement of the SR outcomes. Though classic mediation theory assumes a significant total and/or direct effect is required, a growing position in recent years has been that this relation is not necessary in order to examine indirect effects (Preacher & Hayes, 2008; Rucker, Preacher, Tormala, & Petty, 2011) due to several potential factors (e.g., suppression effects). Using this emerging line of thought, the primary statistical factor in mediation is the indirect effect, whether or not there is a direct or even a total effect. With indirect associations, group may be associated with FA, and FA in turn may be associated with SR outcomes. Therefore, this model allows an analysis of frontostriatal white matter integrity as a potential mediator of the direct effect of group on cool and hot SR. Due to the variable selection process discussed above, four mediation models were run in total. For each model, group served as the IV (with the TD group as the reference group), 6-month CPT omission errors, BART pumps, and BRIEF emotional control served as the DVs, and pathway FA at 2 months was entered as the mediators (Figure 5-8). Scanner change was entered as a covariate. All models were subjected to 10,000 bootstrap re-samplings and 95-percentile confidence intervals were

estimated (recommended by Hayes, 2009; Hayes & Preacher, 2014; Preacher & Hayes, 2004, 2008).

Results

Sample characteristics

Table 2 includes sample clinical and demographic data for the TD (n = 55), mTBI (n = 24), and sTBI groups (n = 60). Variables previously demonstrated to relate to brain and behavior were investigated across groups. Distribution of pubertal status and age across the 8-15 age range was comparable across groups. Ethnicity and socioeconomic status, as measured by the Hollingshead-Redlich Index (Weinberg, Dietz, Penick, McAlister, 1974), also did not vary by group. A scanner hardware upgrade during the study recruitment potentially influenced image acquisition for some participants. To account for differences in scanner, we included scanner change as a binary covariate in all white matter analyses. Scanner update was equally distributed in participants with valid DTI data. GCS distribution for the 84 children with TBI included 26.2% in the 3-8 range (n=22), 7.1% in the 9-12 range (n=6), and 66.7% fell in the 13-15 range (n=56).

Hypothesis 1: Group differences in frontostriatal white matter

Table 3 provides descriptive statistics for dorsal and ventral pathways. Investigating group differences in frontostriatal white matter pathways, multivariate GLMs examined the effect of group (TD, mTBI, sTBI), age, and sex on right and left pathway FA, with scanner change as a covariate (Table 4). Group by age and group by sex interactions were non-significant and trimmed from the models. Multivariate group differences were demonstrated for dACC cortex to caudate pathway (bilaterally), with a medium effect size (η_p^2 = .07) (Cohen, 1988, Levine & Hullet, 2010). Follow up Bonferroni adjusted pairwise comparisons

showed that the sTBI group had significantly lower left and right FA than the mTBI group (p = .008; p = .014) and the TD group (p = .046; p = .042), while FA in the mild TBI group did not significantly differ from the TD group ($p > .05$). The effect of age was not significant. The main effect of sex was significant with a medium effect size ($\eta_p^2 = .10$), such that males had lower pathway FA across groups. To investigate whether sex differences were related to pubertal status, pubertal stage of development was added to the GLM via post-hoc analyses, which did not alter findings and it was not related to outcomes $F(89) = .69$, $p = .506$.

Bilateral VLPFC to caudate pathway FA differed across groups (p = .031), demonstrating a medium effect size ($\eta_p^2 = .06$; Cohen, 1988; Levine & Hullet, 2010). Adjusted pairwise comparisons showed the sTBI group had significantly lower left and right FA than the mild TBI group (p = .018; p = .004), but not the TD group ($p > .05$). While those with more severe TBI (sTBI) had lower FA than typically developing children, this difference did not reach statistical significance ($p > .05$). Multivariate main effects effects of age and sex were not significant ($p > .05$).

Multivariate group differences in the mOFC to nucleus accumbens pathway did not meet conventional statistical significance levels (p = .099) despite a small effect size (η_p^2 = .04), and follow up univariate analyses effects indicated this was driven by lower FA on the right side (p = .024). Follow up Bonferroni adjusted pairwise comparisons showed that children with more severe TBI had non-significantly lower right FA than those in the mild TBI (p = .054) and TD groups (p = .074), with medium effect sizes (g = .601; g = .558). The left-sided pathway did not show differences in FA ($p > .05$). The DLPFC to caudate pathway and rACC to nucleus accumbens pathway failed to demonstrate significant group differences.

Multivariate main effects of age and sex were non-significant in these pathways as well (all $p > .05$).

Hypothesis 2: Group differences in cool and hot self-regulation

Descriptive data are presented in Table 5 for baseline/preinjury and 6 month cool and hot SR variables. SWAN, but not BRIEF scores, differed at baseline. On the SWAN, the mTBI group showed worse baseline attention than TD children ($p = .012$). However, scores in the sTBI group did not significantly differ from scores in the mTBI group or typically developing children ($p > .10$). Intercorrelations among SR variables assessed at 6-month follow-up are provided in Table 6.

Investigating behavioral outcomes across groups, two multivariate general linear model analyses examined the effects of group (TD, mTBI, sTBI), age, and sex on cool and hot SR at 6 months, controlling for baseline SWAN ratings (Table 7). Group by age and group by sex interactions were non-significant and trimmed from the models. Multivariate analyses of cool SR showed significant group differences ($p = .006$), with a medium effect size ($\eta_p^2 = .07$). Follow-up univariate analyses demonstrated group differences in cool SR to be driven by parent report of attention at 6 months ($p < .001$), but not by child performance on tasks of sustained and focused attention (p's $> .05$). Bonferroni adjusted univariate pairwise comparisons showed children with more severe TBI had significantly greater cool SR difficulties (parent reported attention) than typically developing children with a large effect size ($p < .001$; $g = .769$), and non-significantly greater difficulties than the mTBI group, with a small effect size ($p = .069$; $g = .199$). A main effect of age was shown, such that younger children across groups demonstrated a greater number of errors on cool SR tasks of focused and sustained attention, with small ($\eta_p^2 = .04$) and medium ($\eta_p^2 = .07$)

respective effect sizes. No significant multivariate main effect of sex was demonstrated ($p > .05$).

Investigating behavioral outcomes in hot SR across groups, multivariate GLM showed significant group differences ($p < .001$), with a medium effect size ($\eta_p^2 = .10$). Follow-up univariate effects demonstrated group differences to be driven by parent report of emotional control at 6 months, with a large effect size ($p < .001$, $\eta_p^2 = .42$), with no group differences in risk-taking task performance ($p > .05$). Bonferroni adjusted follow up analyses showed children with more severe TBI had significantly greater emotional control difficulties than children with mild TBI with a small effect ($p = .012$; $g = .32$) and typically developing children with a medium effect ($p < .001$; $g = .67$). In the multivariate model, as expected, the effect of age was significant, with a medium effect size ($\eta_p^2 = .05$). Univariate effects showed that older children across groups displayed a greater number of adjusted pumps on the BART, indicative of higher levels of risk-taking with a medium effect size ($\eta_p^2 = .05$). No significant multivariate effect of sex was shown.

Hypothesis 3: Mediation models examining white matter and group effects on behavior

Multicategorical mediation models were run to examine whether frontostriatal white matter integrity mediated the direct effects of group (TD, mTBI, sTBI) on 6 month cool and hot SR difficulties, using the TD group as a reference group (Hayes & Preacher, 2014). Associations between FA and 6 month hot and cool SR were used to guide pathways entered into mediation models (Table 8), culminating in four multicategorical mediation models (Figures 5-8). As expected, for children in the sTBI group, there was a significant indirect effect of group on CPT omission errors through the (right) dACC to caudate FA ($B = .115$; Figure 5). Additionally, for the mTBI group, but not sTBI group, the relation between group

and CPT omission errors at 6 months demonstrated a significant indirect effect through mean VLPFC to caudate FA (B = .060; Figure 6). Though the total effect was nonsignificant for these two models, findings meet guidelines consistent with mediation given the significant indirect effects (MacKinnon, Krull, & Lockwood, 2000; Zhao, Lynch, & Chen, 2010). Contrary to expectations, there was no indirect effect of mean FA of rACC to nucleus accumbens pathway on the relation between group and BART pumps at 6 months (Figure 7). An exploratory mediation model was conducted given the positive correlation between higher DLPFC to caudate FA and greater emotional control difficulties, however group failed to demonstrate a significant indirect effect via FA in this pathway (Figure 8).

Discussion

The aim of the current study was to investigate whether changes in white matter integrity following TBI account for difficulties in cool and hot SR in a longitudinal mediational context. The present study is the first to examine both dorsal and ventral frontostriatal white matter integrity in core pathways 2 months following TBI using clinically relevant and theoretically based models of SR. Relative to typically developing children and/or those with uncomplicated mild TBI, integrity was reduced following more severe TBI in bilateral pathways connecting dACC and VLPFC to the caudate, as well as in the pathway connecting the right mOFC with the nucleus accumbens. Children with more severe TBI showed more difficulties than healthy children with parent-reported cool (attention) and hot (emotional control) SR, but not on direct measures of sustained or focused attention and risk-taking. Although lower FA in bilateral rACC to nucleus accumbens pathways was associated with greater risk taking, pathway integrity did not mediate the relation between group and risk-taking. Dorsal frontostriatal white matter integrity assessed 2 months after injury

partially mediated the relation of TBI severity to differences in direct measures of attention at 6 months post-injury. Specifically, lower integrity of the dACC to caudate pathway predicted worse focused attention in children with more severe TBI, while greater integrity of the VLPFC to caudate pathway predicted better focused attention following uncomplicated mild TBI. As such, this study illustrates the importance of dorsal frontostriatal white matter for regulation of attention in TBI similar to other disorders associated with attentional difficulties (Durston, van Belle, & de Zeeuw, 2011; Riley, Moore, Cramer, & Lin, 2011). Findings can guide future research on neural correlates of self-regulatory difficulties following pediatric TBI, and can inform theoretical understanding of attention and frontostriatal neural circuitry in broader neurodevelopmental populations.

Children with TBI showed reduced white matter integrity

The lower white matter integrity in children with more severe TBI relative to those with mild TBI and typically developing children in several core pathways is consistent with the few prior structural imaging studies examining change in frontostriatal structures and pathways. Though post-TBI structural imaging research of dorsal and ventral striatum regions is limited, Faber and colleagues (2016) also found microstructural changes in the ventral striatum following moderate to severe TBI in relation to healthy controls. In a meta-analysis of DTI findings following pediatric TBI, Roberts, Mathias, and Rose (2014) found several studies showing white matter differences in regions overlapping the current study's pathways of interest (anterior corona radiata, cingulate, and orbito-frontal white matter). For instance, microstructural changes have been reported in children with TBI compared to children with bodily injury in the bilateral cingulum bundle (Wilde, 2010), the left cingulum and medial prefrontal white matter (Levin et al., 2011), and right anterior corona radiata

(Adamson et al., 2013). Current findings extend this line of research by showing bilateral reduction in dACC and VLPFC to caudate FA as well as right mOFC to nucleus accumbens FA following more severe TBI, using anatomical and theoretically based models (Casey, 2015). This highlights the importance of MRI structural imaging to serve as a potential biomarker to detect selective changes in frontal and subcortical brain regions following more severe TBI.

Children with TBI showed worse cool and hot self-regulation

After accounting for preinjury functioning, children with more severe TBI showed greater difficulties on parent report measures of cool and hot SR assessing attention and emotional control 6 months following injury, in comparison to those with mild TBI and typically developing children. These findings add to a body of research demonstrating attention, emotional control, and other SR difficulties in children with TBI in comparison to those with orthopedic injury and healthy controls (Anderson et al., 2006; Catroppa et al., 2007; Ganesalingham, Sanson, Anderson, & Yeates, 2007; Ginstfeldt & Emanuelson, 2010; Johnson et al., 2010; Keenan, Clark, Holubkov, Cox, & Ewing-Cobbs, 2018; Li & Liu, 2013; Wade et al., 2010; Wilde et al., 2012; Yeates et al., 2005).

These cool and hot SR difficulties have significant implications for real-world outcomes. Children with more severe TBI have shown executive functioning problems via behavioral ratings and task performance that strongly relate to social functioning difficulties (Ganesalingham et al., 2011; Shultz et al., 2016), and predict lower educational competence and special education placement (Arnett et al., 2013). Similarly, problems with attention and emotional control in uninjured children create clear barriers to academic achievement, and put children at risk for negative outcomes in adulthood, like lower graduation rates (Finn,

Pannozzo, & Voelkl, 1995; Galéra, Melchior, Chastang, Bouvard, & Fombonne, 2009; Merrell & Tymms, 2010, Pingault et al., 2011). Moreover, children with such SR difficulties are at higher risk for substance use and sexual risk-taking (Crockett, Raffaelli, & Shen, 2006; Wills, Walker, Mendoza, & Ainette, 2006). A recent review of intervention following pediatric acquired brain injury highlighted that differential types of intervention were beneficial for cool vs. hot executive functioning, and that greater improvement in functioning occurred when specific types of executive functioning were targeted, rather than cool and hot SR targeted together (Chavez-Arana et al., 2018). In conjunction with our findings of both attention and emotional control difficulties, this underscores the importance of treating self-regulatory difficulties in varying ways.

Age and sex effects on white matter and cool and hot self-regulation

Partial support was demonstrated regarding hypotheses on age and sex effects. Age effects were not demonstrated for white matter integrity, contrary to expectations and prior research showing FA is lower in younger children with and without TBI (Ewing-Cobbs et al., 2016, Lebel & Deoni, 2018). Ewing-Cobbs and colleagues (2016) found robust age effects in school aged children but not adolescents in several association, limbic, and projection pathways; however, white matter change was assessed over time at 3 and 24 months post-injury, allowing for greater power for such examinations. Further, their sample excluded children with uncomplicated mild TBI. The current study includes a smaller DTI sample overall and examined different pathways, potentially limiting age effects. Considering these past findings and given that white matter develops gradually (Achterberg, Peper, Duijvenvoorde, Mandl, & Crone, 2016; Ge et al., 2002; Scahill et al., 2003), future work with larger samples across wider age ranges may stratify across other developmental stages.

Though the current study design of an 8-15 age range allows for inclusion of children during onset of pubertal development, because frontal white matter continues to develop across childhood through adulthood, frontostriatal pathways may demonstrate larger age effects at other age ranges.

Age effects were identified on performance tasks, with older children across groups showing signs of greater risk-taking, and younger children struggling with focused and sustained attention. Younger children experiencing greater difficulties with attention coincides with what is known about developmental improvement in attention and executive functioning capacity across early childhood and adolescence (De Luca & Leventer, 2010; Diamond, 2013; Perone et al., 2018; Zelazo & Carlson; 2012). In contrast, greater risk-taking demonstrated in older children follows the U-shaped slope of reward-seeking and risky behaviors illustrated across development, such that risk-taking and impulsivity increase from early childhood to middle adolescence (Braams, van Duijvenvoorde, Peper, & Crone, 2015; Casey, 2015; Cox, Mills-Koonce, Propper, & Gariépy, 2010; Mata, Josef, Poon, 2018; Samanez-Larkin, & Hertwig, 2011). Given that reward-seeking tendency has been associated with hormonal and pubertal changes during development (Smith, Chein, & Steinberg, 2013), pubertal stage of development was examined for the pathway showing sex effects, but did not predict behavioral outcomes above the effect of age.

Interestingly, boys across groups demonstrated lower white matter integrity than girls along the dACC to caudate pathway; differences were not attributable to age or pubertal stage of development. This falls in line with recent work on typically developing children aged 8-16, which demonstrated males had less advanced development and later maturation of white matter than females, including lower whole brain FA (Seunarine et al., 2016; Asato,

2010; Bava, 2011). Simmonds, Hallquist, Asato, and Luna (2014) studied 8-28 year olds longitudinally and found that males demonstrated significantly more protracted frontal white matter development than females in frontal regions involved in cognitive control. Though males typically have shown lower white matter FA than females across development (Bava, 2011, Herting et al., 2017), others found adolescent boys to have higher FA, which was associated with hormonal influences (Herting, Maxwell, Irvine, & Nagel, 2012). Sex differences in biological outcomes often suggest hormonal or pubertal mechanisms, however pubertal stage of development was not an independent predictor of outcomes. Given that pubertal stage was determined by parent and child consensus, future explorations of white matter and pubertal developmental using specific hormonal indicators following pediatric TBI are warranted. Overall, findings support past work showing sex and age in injured and uninjured children play a role in white matter and behavioral functioning, respectively.

Understanding the protracted development of white matter in boys across typically developing children and those with TBI can inform investigations of sex-specific neural phenotypes. In ADHD, which is more common in boys, a dorsal frontostriatal subtype has been proposed (Durston et al., 2011), and such regions have been targeted with pharmacological intervention (Rubia et al., 2011). Models of risk-taking can benefit from increased understanding of neural mechanisms of the risk-taking peak in middle-adolescence. Notably, impulsive risk-taking increasing with age underscores the importance of prevention and early screening efforts in preadolescence, targeted intervention during middle adolescence (Hennessy & Tanner-Smith, 2014), as well as psychoeducation for caregivers and families (Schoenfelder & Kollins, 2016).

White matter integrity predicted cool and hot self-regulation

Dorsal frontostriatal white matter integrity 2 months following TBI accounted for changes in the relations between group and cool SR task performance at 6 months post-injury (Figures 5-6). Worse focused attention was mediated by lower right-sided FA of the dACC to caudate in children with more severe TBI. Higher FA of VLPFC to caudate predicted better attention performance in children with uncomplicated mild TBI, possibly reflecting preinjury white matter differences or compensatory structural post-injury changes. Findings support prior work showing reduced integrity in frontostriatal regions such as the frontal white matter, cingulum bundle (Wilde et al., 2011; Wilde et al., 2010), caudate, and ventral striatum (Faber et al., 2016) relating to attentional and cognitive control outcomes post-TBI. Though group differences were not demonstrated in task performance, indirect effects still demonstrated the influence of dorsal white matter on focused attention in children with TBI. In contrast, mOFC to nucleus accumbens FA and DLPFC to caudate FA failed to mediate the relation of group to risk taking and emotional control, respectively (Figures 7-8), despite correlations between pathways and outcomes. Potential mediation findings were likely precluded by FA not varying by group in those model pathways. This pattern of findings reinforces recent functional imaging research indicating cool executive functioning relies on dorsal regions while hot executive functioning relies on both dorsal and ventral regions (Nejati, Salehinejad, & Nitsche, 2018).

The current study advances knowledge of frontostriatal relations with behavioral outcomes by longitudinally linking compromised frontostriatal microstructure assessed 2 months after injury to worse attention and risk-taking 6 months after TBI. More broadly, integrity of these pathways predicted future functioning across children with and without

clinical imaging findings post-TBI. In sum, results support evidence that post-acute frontostriatal white matter integrity predicts chronic behavioral outcomes in children with TBI (Faber et al., 2016; Wilde et al., 2011; Wu et al., 2014) and may inform brain-behavior relations for uninjured populations (Chiang et al, 2015; Rubia 2011; Samanez-Larkin et al., 2012). Thus, we present novel support showing altered dorsal frontostriatal white matter pathways in children with TBI across the range of severity, and that those changes predict changes in specific aspects of cool SR.

Findings have research and clinical implications for children with Attention Deficit-Hyperactivity Disorder (ADHD) and other neurobehavioral disorders. The dACC and caudate, along with the white matter connections between them, are centrally involved in SR difficulties associated with ADHD (Chiang et al., 2015; Rubia, 2011; de Zeeuw, Mandl, Hulshoff Pol, van Engeland, & Durston, 2012). Further, the anterior cingulate and prefrontal cortex are associated with key social functioning capacities (Ryan et al., 2016). Chronic difficulties with cool and hot SR following TBI are likely to interfere with social relations, exacerbating or accounting for difficulties children with TBI already experience in social functioning (Catroppa et al., 2014; Ganesalingham et al., 2006; Ganesalingham et al., 2011; Ryan et al., 2016; Shultz et al., 2016). Given the current literature and our findings, knowledge of frontostriatal white matter integrity may aid in prediction of children at-risk for behavioral difficulties. Considering the prominent role of frontostriatal circuitry in children with TBI, ADHD, and other acquired and neurodevelopmental disorders (Bluschke, von der Hagen, Novotna, Roessner, & Beste, 2018; Bradshaw & Enticott, 2001; Myers & Thomas, 2003, Riley et al., 2011), dorsal frontostriatal white matter relations with cool SR may guide pharmacological (Rubia et al., 2011; Rubia, Alegria, & Brinson, 2014; Yarmolovsky,

Szwarc, Schwartz, Tirosh, & Geva, 2017) or behavioral treatment (Chavez-Arana et al., 2018) by serving as a potential biomarker for those most likely to respond or those most at risk. In future studies, interventions targeting SR may enhance microstructural changes in associated pathways of interest (Yuan et al., 2017a; Yuan et al., 2017b).

Interestingly, parent reported cool and hot SR, but not task performance, accounted for most of the variance between groups, yet pathway integrity predicted task performance. Because parent ratings incorporate information from everyday functioning and have been shown to predict diagnostic status in children with ADHD more so than task performance (Toplak, Buciarelli, Jain, & Tannock, 2008), parent ratings may be more sensitive to the effect of injury on broader SR problems. On the other hand, our findings suggest task performance may be more sensitive to the effects of injury on pathway integrity.

Correlations between parent report measures and performance tasks ranged from weakly correlated to non-significant, while parent reported cool and hot SR was moderately correlated (Table 10). A similar pattern is demonstrated across literature on executive functioning (Gerst et al., 2017; Toplak, West, & Stanovich, 2013). Thus, differentiation between cool and hot SR constructs based on parent report is limited by method variance, which can inflate or attenuate relations. However, attention performance measures in the current study were correlated, while attention and risk-taking measures were not, supporting differentiation of cool and hot constructs. Therefore, the current study's parent reports and performance tasks may target different underlying aspects of cool and hot SR, highlighting the importance of including both direct assessment and behavioral ratings in study design (Allan et al., 2013; Toplak, West, & Stanovich, 2013). The use of additional performance tasks assessing varying aspects of cool and hot SR (e.g., higher-order executive functioning

tasks or emotional decision-making paradigms*)*, along with behavior report measures from multiple raters may better target the behavioral constructs and pathways of interest in future studies.

Limitations and future research

The current study is not without limitations. Smaller group sample sizes likely restricted the power of multivariate and meditational analyses. Future work with tighter age bands and larger samples may be better able to stratify and examine age or pubertal stage relations along with brain-behavior outcomes following TBI. FA in the VLPFC to caudate for children with mild TBI was minimally higher than TD children, thus FA differed in sTBI and mTBI groups but not TD groups. The smaller sample size of the mTBI group and the higher variability overall (wider range of values) may have affected the reliability of the estimate for this pathway, likely leading to this finding. Thus, this may reflect sampling variation, preinjury developmental differences, or potential compensatory processes, warranting further research examining white matter differences in uncomplicated mild TBI. An inherent limitation in studies of white matter relations to TBI is the lack of premorbid brain data. The current study therefore cannot rule out developmental differences in FA, which underscores the importance of future research using animal models and controlled environmental studies allowing for "baseline" neuroimaging of at-risk populations (e.g., sports concussion, military blast injury).

The constructs of cool and hot SR encompass broad sets of cognitive and emotional capacities, thus future work can further refine constructs and expand on measures used to more comprehensively assess the different domains. Additionally, the use of cool and hot SR terminology can result in simplification of complex and related processes, thus the

consideration of intercorrelations of measures and pathways are essential. Though children with more severe TBI had relatively worse behavioral ratings of attention and emotional control than mTBI and TD groups, mean scores still fell within the average range 6 months post-TBI. As such, further investigation is necessary regarding clinical implications of group differences. Sleep was not investigated in the current study, however, sleep disturbances are well known risk-factors for SR difficulties in uninjured children (Alfano & Gamble, 2009), and have been linked to internalizing (Fischer et al., 2018) and externalizing behavior problems (Shay et al., 2014) following TBI. Thus, future studies can parse out relations among sleep, SR, and potential neural correlates following TBI. Given the wide range of structures involved in self-regulation, using tractography to examine specific pathways of interest can limit the scope of regions explored. As such, future work might compare findings from tractography of individual pathways with results from structural imaging techniques such as graph theory that allow for examination of the network as a whole. Therefore, knowledge of white matter circuitry may benefit from a network-approach to examinations of brain-behavior relations in conjunction with analysis of a priori pathways (Caeyenberghs et al., 2012; Hayes, Bigler, & Verfaellie, 2016; Sharp, Scott, & Leech, 2014). However, tractography methods were better positioned for the aims of the current study, which used a theoretically driven construction and examination of specific a priori frontostriatal pathways rather than investigation of whole network group differences.

Conclusion

The current study demonstrated that lower FA in specific frontostriatal pathways accounted for differences in cool and hot SR following pediatric TBI. Dorsal pathways were more vulnerable to disruption than ventral frontostriatal pathways after more severe TBI, and

dorsal pathway integrity predicted later attention performance. Importantly, neural mechanisms of cool SR rely on dorsal frontostriatal microstructure, while hot SR may involve on both dorsal and ventral structures (Nejatl et al., 2018; Poon, 2018). Additionally, cool and hot SR may not be easily differentiated by dorsal and ventral pathways following pediatric TBI, due in part to the heterogeneity of TBI, including variability in pre-injury status, injury location, and type of brain injury (e.g., contusion, parenchymal hemorrhage, diffuse axonal injury, etc.). Educators and clinicians have key opportunities to screen for worsening attention and emotional control difficulties in the year following pediatric TBI, as well as tailor interventions to target specific cool and hot SR problems (Chavez-Arana et al., 2018). More broadly, an enriched understanding of frontostriatal brain-behavior relations using structural imaging will inform future research and can lead to improved treatment planning and earlier, better-targeted interventions for children with both developmental and acquired neurological disorders.

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Table 1
Parcellations of frontostriatal pathways of interest

Cool dorsal pathways	
Seed	**Termination**
DLPFC	Caudate
VLPFC	Caudate
DorsalACC	Caudate

Hot ventral pathways	
Seed	**Termination**
MedialOFC	Nucleus accumbens
RostralACC	Nucleus accumbens

Note. DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex; ACC = anterior cingulate cortex; OFC = orbitofrontal cortex. Freesurfer divisions: DLPFC consists of rostral middle frontal and caudal middle frontal; VLPFC consists of pars triangularis, orbitalis, and opercularis; Dorsal ACC consists of caudal anterior and posterior cingulate cortex.

Table 2

Demographics and clinical characteristics by group

	Group			
	Typically developing (n = 55)	mTBI (n = 24)	sTBI (n = 60)	Statistic
Age at baseline in years, M (SD)	12.1(2.4)	12.4(2.3)	12.7(2.3)	$F(2,136)=1.013$, $p=.366$
Males, *n (*%)	63.6%	63.0%	65.0%	$\chi2(2, N=139) = 0.053$, $p=.974$
Hollingstead, M(SD)	38.2 (14.3)	39.1 (13.7)	34.9(13.0)	$F(2,136)=1.201$, $p=.304$
Pubertal Status M(SD)	2.4 (0.9)	2.5 (1.0)	2.5 (0.9)	$F(2,136)=0.301$, $p=.741$
Scanner update, *n (*%)	43.9%	42.1%	50.0%	$\chi2(2, N=98) = 0.433$, $p=.805$
Race/Ethnicity				$\chi2(8, N=139) = 11.656$, $p=.167$
African American	20.0%	20.8%	18.3%	
Asian	5.5%	0.0%	1.7%	
Caucasian	29.1%	33.3%	23.3%	
Hispanic	32.7%	45.8%	53.3%	
Mixed ethnicity	12.7%	0.0%	3.3%	
Months from injury to baseline M(SD)		1.6(0.6)	1.8(1.0)	$t(82)= -0.711$, $p=.479$

Note. mTBI = uncomplicated mild traumatic brain injury; sTBI = complicated mild, moderate, and severe traumatic brain injury.

Table 3
Descriptives for dorsal and ventral frontostriatal fractional anisotropy (FA)

FA M(SD)	Typically developing	mTBI	sTBI
Dorsal pathways			
Right DACC - C	.405 (.024)	.411 (.026)	.390 (.022)
Left DACC - C	.404 (.026)	.413 (.026)	.390 (.024)
Right VLPFC - C	.380 (.020)	.390 (.020)	.372 (.016)
Left VLPFC - C	.381 (.022)	.390 (.020)	.374 (.017)
Right DLPFC - C	.373 (.019)	.369 (.016)	.373 (.019)
Left DLPFC - C	.373 (.020)	.364 (.016)	.368 (.019)
Ventral pathways			
Right RACC - NA	.310 (.024)	.314 (.038)	.303 (.035)
Left RACC - NA	.309 (.023)	.308 (.027)	.304 (.021)
Right MOFC - NA	.341 (.029)	.347 (.037)	.325 (.031)
Left MOFC - NA	.336 (.030)	.339 (.027)	.334 (.031)

Note. DACC-C = dorsal anterior cingulate to caudate; VLPFC-C = ventrolateral prefrontal cortex to caudate; DLPFC-C = dorsolateral prefrontal cortex to caudate; RACC-NA = rostral anterior cingulate to nucleus accumbens; MOFC-NA = medial orbitofrontal cortex to nucleus accumbens; TBI = traumatic brain injury.

Table 4

Multivariate group differences in dorsal and ventral frontostriatal pathways

	Multivariate/Within-subjects effects						Follow-up univariate effects		
Dorsal pathways	Group df (4,182)		Age df (2,90)		Sex df (2,90)		Group df (2,91)	Age df (1,91)	Sex df (1,91)
	F	(*p*) η_p^2	*F*	(*p*) η_p^2	*F*	(*p*) η_p^2	*F* (*p*)	*F* (*p*)	*F* (*p*)
DACC - C	**3.18**	**(.015).07**	0.75	(.474).02	**5.07**	**(.008).10**			
Right							**5.19(.007)*ab***	.20(.660)	1.48(.227)
Left							**5.57(.005)*ab***	.46(.497)	**9.73(.002)**
VLPFC - C	**2.72**	**(.031).06**	1.15	(.323).03	0.48	(.620).01			
Right							**5.50(.006)*b***	3.13(.578)	.97(.327)
Left							**4.14(.019)*b***	1.89(.172)	.52(.475)
DLPFC - C	1.2	(.313).03	0.12	(.887).00	1.93	(.152).04			
Right							0.59(.557)	0.07(.791)	0.32(.857)
Left							1.54(.220)	0.01(.922)	1.53(.219)
Ventral pathways	df (4,184)		df (2,91)		df (2,91)		df (2,92)	df (1,92)	df (1,92)
RACC - NA	0.43	(.789).01	1.45	(.240).03	0.24	(.788).01			
Right							0.69(.503)	.853(.358)	0.25(.618)
Left							.34(.713)	2.72(.103)	0.10(.755)
MOFC - NA	*1.98*	*(.099).04*	0.54	(.587).01	0.85	(.431).02			
Right							**3.90(.024)*ab***	.37(.544)	0.00 (.984)
Left							0.08(.922)	1.00(.319)	1.50 (.224)

Note. DACC-C=dorsal anterior cingulate to caudate; VLPFC-C=ventrolateral prefrontal cortex to caudate; DLPFC-C= dorsolateral prefrontal cortex to caudate; RACC-NA=rostral anterior cingulate to nucleus accumbens; MOFC-NA= medial orbitofrontal cortex to nucleus accumbens; η_p^2=partial eta squared effect size; Bonferroni adjusted pairwise comparisons revealed: *a*=sTBI worse than TD, *b*=sTBI worse than mTBI; ***bolded*=*p*<.05**; *un-bolded*=*p*<.099.

Table 5

Descriptive data for baseline and 6 month cool and hot self-regulation

Measure M(SD)	Typically developing	mTBI	sTBI
Cool self-regulation			
Baseline SWAN Attention	3.4(7.1)	-2.4(10.4)	1.8 (8.0)
6 month SWAN Attention	5.1(8.8)	0.3(9.8)	-1.5 (7.3)
6 month CPT Omission T	52.6(12.6)	57.6(18.3)	56.4 (14.8)
6 month CPT RT by Block T	51.3(9.7)	52.0(9.8)	50.1 (12.0)
Hot self-regulation			
Baseline BRIEF Emotional Control T	48.4(10.1)	52.5(11.4)	48.4(10.9)
6 month BRIEF Emo. Control T	44.1(8.0)	47.4(9.4)	52.0(14.2)
6 month BART Pumps	28.9(12.0)	33.1(15.5)	31.5(13.6)

Note. mTBI = uncomplicated mild traumatic brain injury; sTBI = complicated mild, moderate, and severe traumatic brain injury; T = T score; RT = Reaction Time; Emo. = Emotional.

Table 6
Interrelations between cool and hot self-regulation measures

Measures		CPT Omission	CPT RT by Block	SWAN Attention	BART pumps	BRIEF EC
CPT RT by Block	(*r*)	0.280**	-	0.056	-0.068	-0.093
SWAN Attention	(*r*)	-0.194*	0.056	-	0.129	-0.351**
BART pumps	(*r*)	-0.018	-0.068	0.129	-	-0.003
BRIEF EC	(*r*)	0.093	-0.093	-0.351**	-0.003	-

Note. *df* = 112; *r* = Spearman's Rho controlling for age at baseline. EC = emotional control. RT = reaction time. * = $p<.05$; ** = $p<.01$

Table 7

Multivariate group differences in cool and hot self-regulation

Pathway and hemisphere	Multivariate/Within-subjects effects						Follow-up univariate effects		
	Group df (6,236)		Age df (3,117)		Sex df (3,117)		Group df (2,119)	Age df (1,119)	Sex df (1,119)
	F	(p) η_p^2	*F*	(*p*) η_p^2	*F*	(*p*) η_p^2	*F* (*p*)	*F* (*p*)	*F* (*p*)
Cool SR	**3.14**	**(.006).07**	**3.52**	**(.017).08**	0.78	(.507).02			
CPT Om.							1.41 (.249)	**4.94 (.028)**	0.05 (.823)
CPT RT							0.06 (.945)	**8.68 (.004)**	1.31 (.255)
SWAN							**9.38(.00)*ab***	0.69 (.407)	1.03 (.313)
	df (4,242)		df (2,120)		df (2,120)		df (2,121)	df (1,121)	df (1,121)
Hot SR	**6.19**	**(.000).10**	**3.18**	**(.045).05**	1.47	(.235).02			
BART							0.88 (.354)	**5.73 (.018)**	2.55 (.113)
Emo. Control							**11.80(.00)*ab***	0.44 (.511)	0.56 (.456)

Note. SR = self-regulation; Om. = Omissions; Emo. = Emotional; RT = Reaction Time; Bonferroni adjusted pairwise comparisons revealed: *a* = sTBI worse than TD group, *b* = sTBI worse than mTBI group; ***bolded*** = $p<.05$; *un-bolded* = $p<.086$. η_p^2 = partial eta squared effect size. Only participants with data from all measures included in each model.

Table 8

Correlations guiding mediation models for dorsal pathways

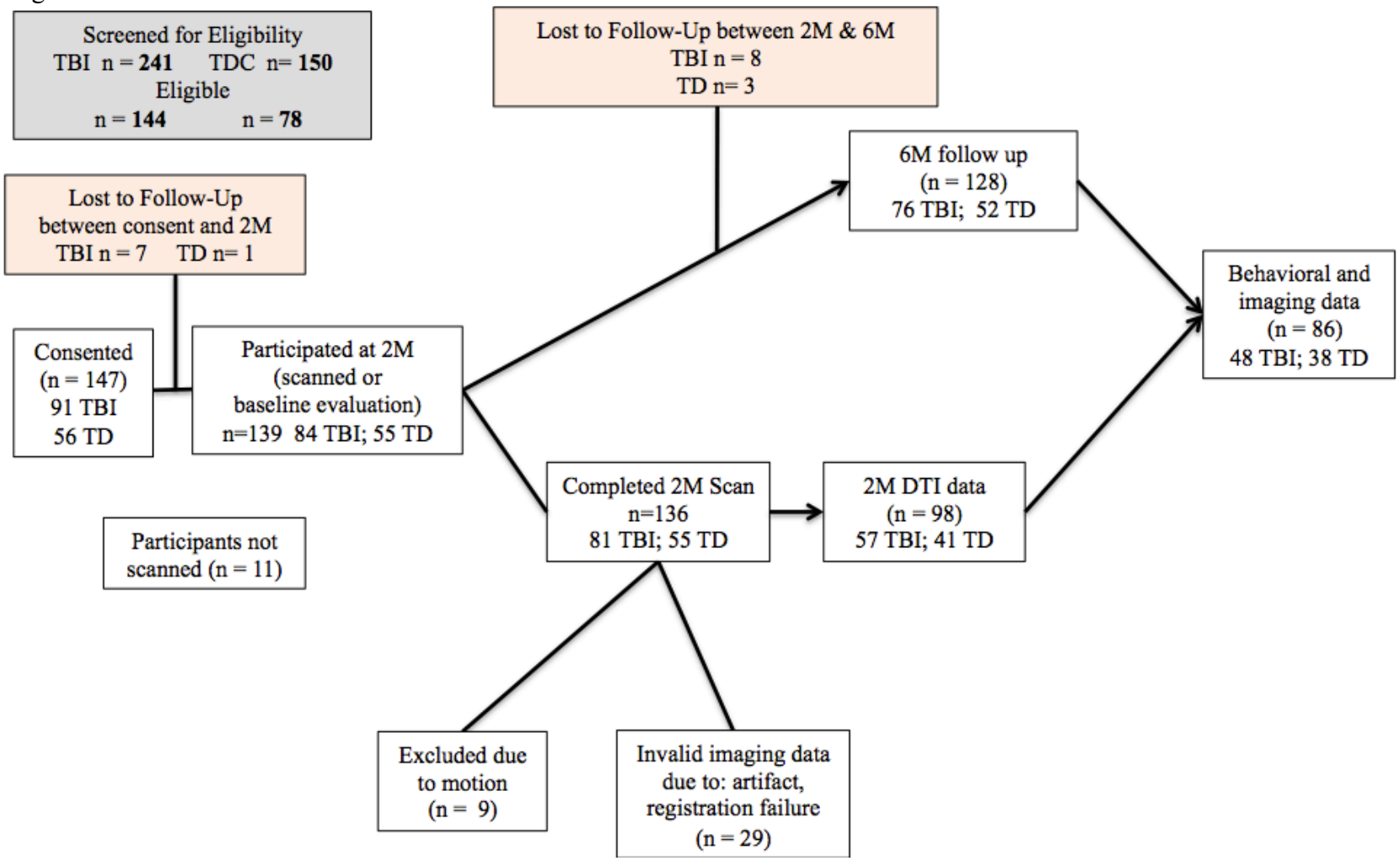
		R DACC-C	L DACC-C	R VLPFC-C	L VLPFC-C	R DLPFC-C	L DLPFC-C
CPT Omissions	(*r*)	-0.321**	-0.162	-0.219*	-0.18	-0.052	-0.116
	p	0.003	0.14	0.045	0.102	0.637	0.292
CPT RT Block	(*r*)	-0.028	-0.016	-0.016	0.07	0.04	-0.028
	p	0.802	0.886	0.884	0.532	0.718	0.806
SWAN Attention	(*r*)	0.13	0.188	0.112	0.199	0.033	-0.017
	p	0.244	0.091	0.315	0.073	0.771	0.88
BART pumps	(*r*)	-0.195	-0.163	-0.156	-0.142	0.069	0.044
	p	0.079	0.144	0.161	0.204	0.54	0.698
BRIEF Emo. Control	(*r*)	-0.126	-0.173	-0.045	-0.069	0.199	0.303**
	p	0.259	0.12	0.689	0.539	0.073	0.006

Correlations guiding mediation models for ventral pathways

		R RACC-NA	L RACC-NA	R MOFC-NA	L MOFC-NA
CPT Omissions	(*r*)	-0.161	-0.114	-0.201	-0.083
	p	0.142	0.303	0.067	0.454
CPT RT Block	(*r*)	-0.035	0.065	0.075	0.01
	p	0.752	0.559	0.502	0.93
SWAN Attention	(*r*)	0.194	-0.14	0.209	0.062
	p	0.08	0.211	0.06	0.58
BART pumps	(*r*)	-0.311**	-0.292**	-0.11	-0.115
	p	0.004	0.008	0.327	0.302
BRIEF Emo. Control	(*r*)	0.068	-0.047	-0.003	-0.028
	p	0.542	0.674	0.979	0.805

Note. DACC-C=dorsal anterior cingulate to caudate; VLPFC-C=ventrolateral prefrontal cortex to caudate; DLPFC-C= dorsolateral prefrontal cortex to caudate; RACC-C=dorsal anterior cingulate to caudate; MOFC-NA = ventrolateral prefrontal cortex to caudate; R = right; L = left; RT = reaction time; * = $p<.05$; ** = $p<.01$.

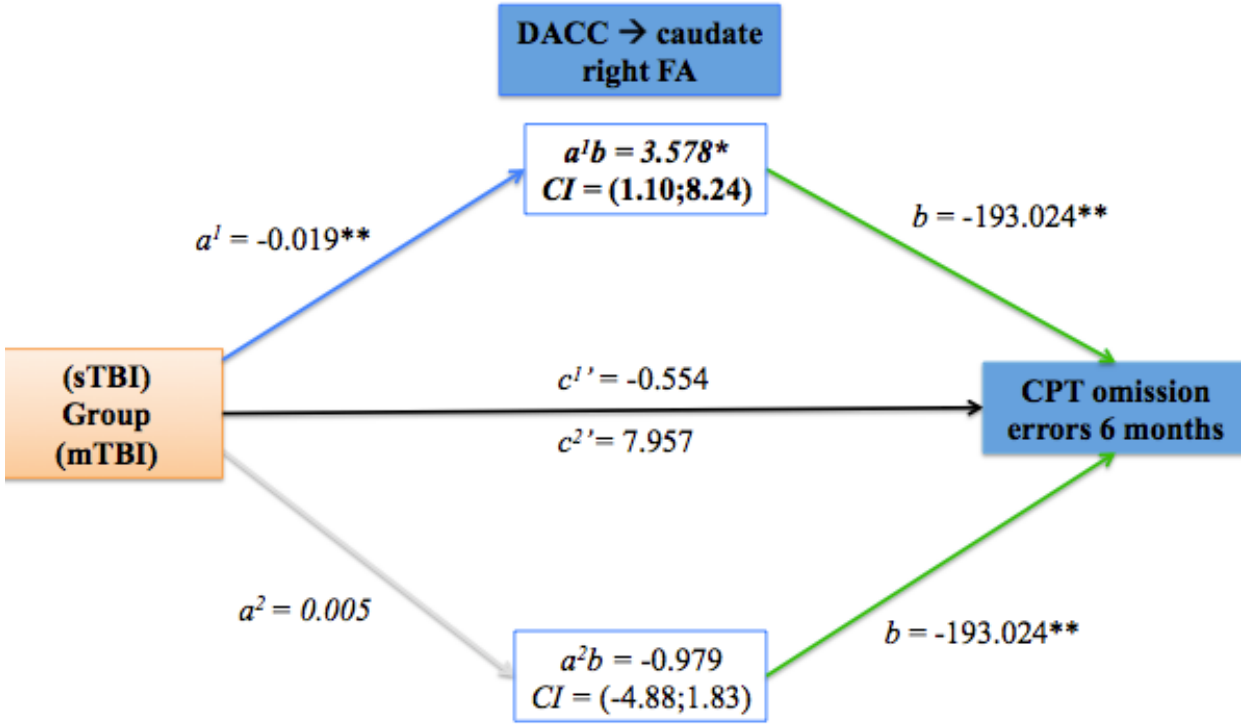
Figure 4



NOTE. Participant flow diagram. 2M = 2 month; 6M = 6 month; TBI = traumatic brain injury; TD = typically developing children; DTI = diffusion tensor imaging.

Figure 5

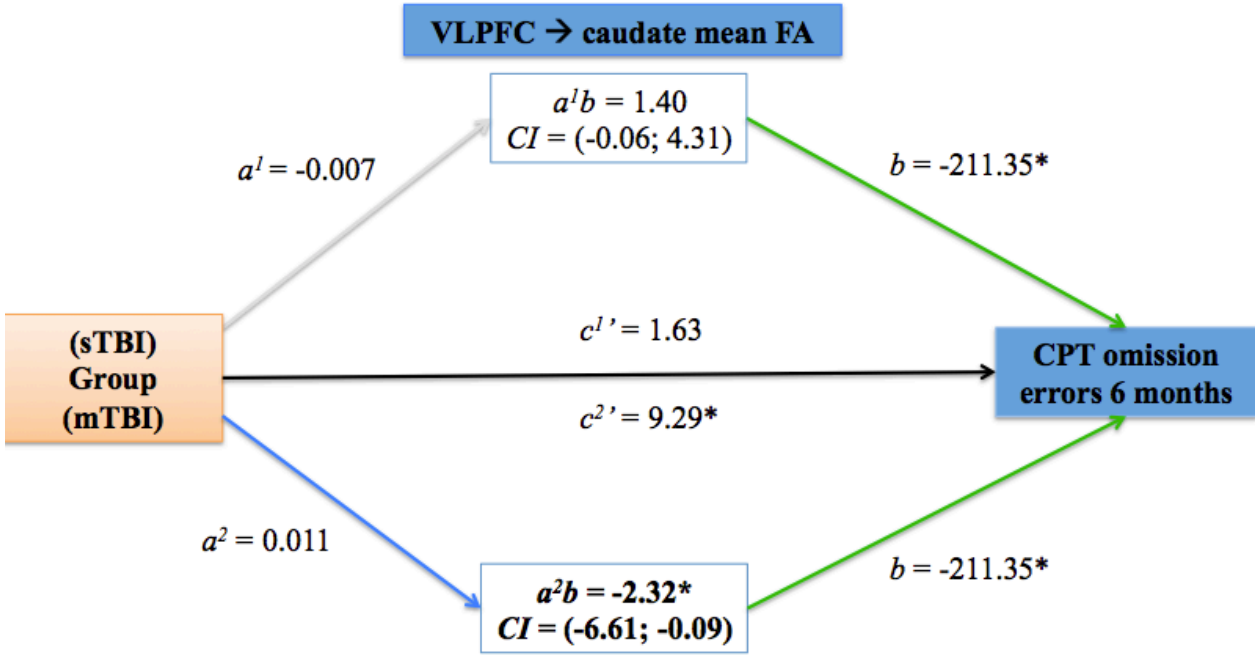
Multicategorical mediation model showing the direct effect of more severe TBI on CPT omission errors mediated by dorsal anterior cingulate cortex to caudate white matter



Note. **For children with sTBI but not mTBI, greater right DACC to caudate FA at 2 months mediated the relation between Group and higher CPT omission errors.** Direct (*c'*) and indirect effects (*ab*) of group on CPT omission errors at 6 months are shown. Path a^1 and c^{1}' indicates sTBI, path a^2 and c^{2}' indicates mTBI, path a_1b = indirect effect of sTBI on CPT omission errors, path a_2b = indirect effect of mTBI on CPT omission errors. Group variable consisted of two dummy coded levels (mTBI, sTBI), while the typically developing group was used as the reference group. Total effects (c) were non-significant $p>.05$. Confidence intervals for both indirect effects are shown. The 95% confidence interval for the indirect effects were obtained through bootstrapping with 10,000 re-samples. DACC = dorsal anterior cingulate cortex; FA = fractional anisotropy; mTBI = uncomplicated mild traumatic brain injury; sTBI = complicated mild, moderate, and severe traumatic brain injury; CI = confidence interval. * = $p<.05$; ** = $p<.01$.

Figure 6

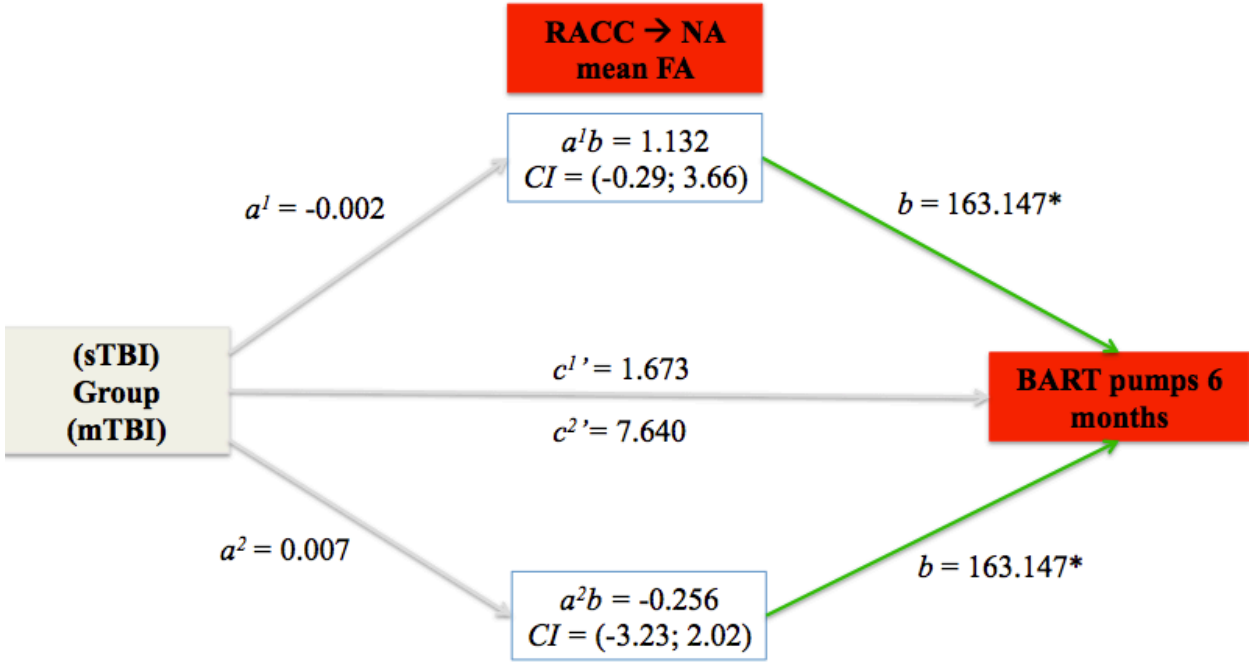
Multicategorical mediation model examining direct and indirect effect of group on CPT omission errors through ventrolateral prefrontal cortex to caudate white matter



Note. **For those with mTBI but not sTBI, results showed greater VLPFC to caudate mean FA at 2 months mediated the relation between Group and fewer CPT omission errors.** Direct (*c'*) and indirect effects (*ab*) of group on CPT omission errors at 6 months are shown. Path a^1 and c^{1}' indicates sTBI, path a^2 and c^{2}' indicates mTBI, path a_1b = indirect effect of mTBI on CPT omission Errors, path a_2b = indirect effect of sTBI on CPT omission Errors. Confidence intervals for both indirect effects are shown. Group variable consisted of two dummy coded levels (mTBI, sTBI), while the typically developing group was used as the reference group. Total effects (c) were non-significant (p>.05). The 95% confidence interval for the indirect effects were obtained through bootstrapping with 10,000 re-samples. VLPFC = ventrolateral prefrontal cortex; FA = fractional anisotropy; mTBI = uncomplicated mild traumatic brain injury; sTBI = complicated mild, moderate, and severe traumatic brain injury; CI = confidence interval. * = p<.05; ** = p<.01.

Figure 7

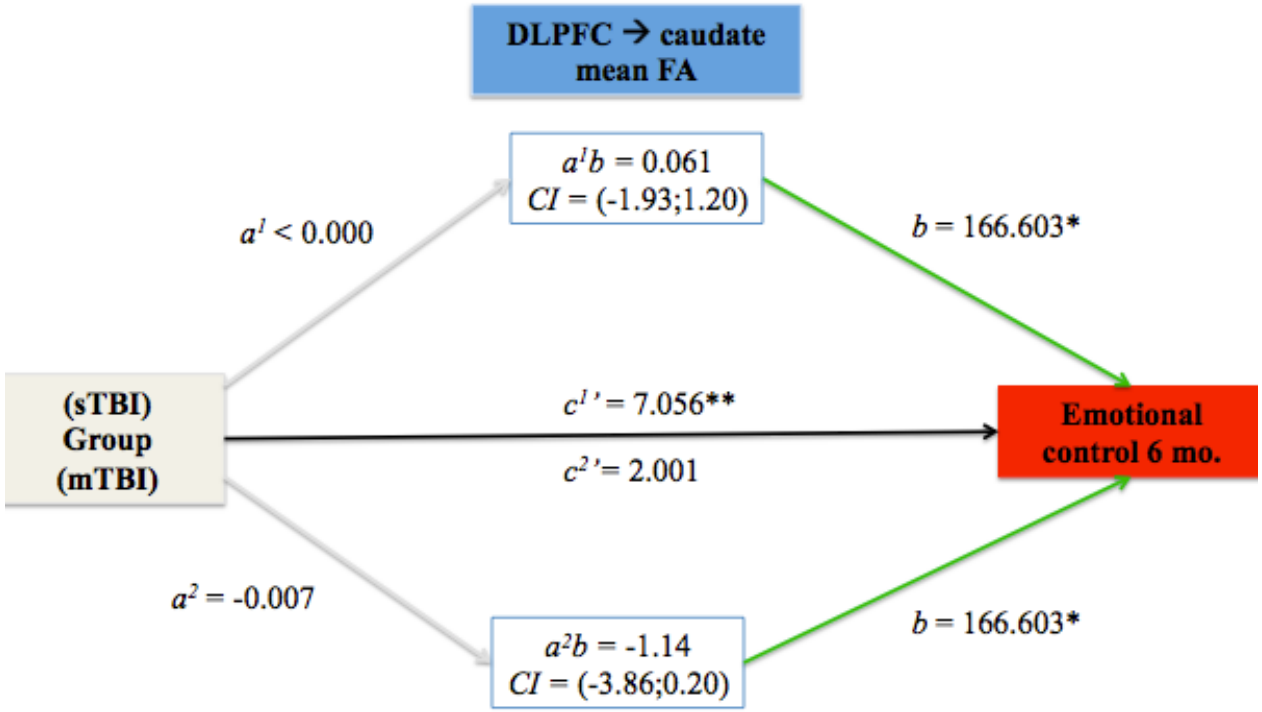
Multicategorical mediation model examining direct and indirect effects of group on BART pumps through rostral anterior cingulate cortex to nucleus accumbens white matter



Note. **Neither significant direct or indirect effects were demonstrated between group and BART pumps though RACC-NA mean FA at 2 months.** Direct (*c'*) and indirect effects (*ab*) of group on BART pumps at 6 months are shown. Path a^1 and c^{1}' indicates sTBI, and path a^2 and c^{2}' indicates mTBI, path a^1b = indirect effect of sTBI on BART pumps; path a^2b = indirect effect of mTBI on BART pumps. Group variable consisted of two dummy coded levels (mTBI, sTBI), while the typically developing group was used as the reference group. Total effects (c) were non-significant (p>.05). Confidence intervals for both indirect effects are shown. The 95% confidence interval for the indirect effects were obtained through bootstrapping with 10,000 re-samples. RACC-NA = rostral anterior cingulate cortex to nucleus accumbens; FA = fractional anisotropy; mTBI = uncomplicated mild traumatic brain injury; sTBI = complicated mild, moderate, and severe traumatic brain injury; CI = confidence interval; mo. = months. * = p<.05.

Figure 8

Multicategorical mediation model examining indirect effect of dorsolateral prefrontal cortex to caudate white matter on the direct effect of group to BRIEF emotional control



Note. **Results showed DLPFC to caudate mean FA at 2 months failed to mediate the relation between group and BRIEF Emotional Control.** Direct (*c'*) and indirect effects (*ab*) of group on BRIEF Emotional Control at 6 months are shown. Path a^1 and $c^{1,}$ indicates sTBI, and path a^2 and $c^{2,}$ indicates mTBI, path a^1b = indirect effect of sTBI on BRIEF Emotional Control, path a^2b = indirect effect of mTBI on BRIEF Emotional Control. Group variable consisted of two dummy coded levels (mTBI, sTBI), while the typically developing group was used as the reference group. Total effect (c) for the sTBI group was significant (p<.01), while the total effect for the mTBI group was nonsignificant (p>.05). Confidence intervals for both indirect effects are shown. The 95% confidence interval for the indirect effects were obtained through bootstrapping with 10,000 re-samples. DLPFC = dorsolateral prefrontal cortex; FA = fractional anisotropy; mTBI = uncomplicated mild traumatic brain injury; sTBI = complicated mild, moderate, and severe traumatic brain injury; CI = confidence interval; mo. = months. * = p<.05; ** = p<.01.

Appendix

Table 1

TBI severity correlations with white matter and behavioral outcomes

TBI severity with dorsal frontostriatal pathways

		Right DACC-C	Left DACC-C	Right VLPFC-C	Left VLPFC-C	Right DLPFC-C	Left DLPFC-C
GCS	(*r*)	0.401	0.204	0.43	0.262	-0.074	0.17
df (52)	*p*	0.003	0.139	0.001	0.056	0.595	0.22

TBI severity with ventral frontostriatal pathways

		Right RACC-NA	Left RACC-NA	Right MOFC-NA	Left MOFC-NA
GCS	(*r*)	0.264	0.057	0.227	0.026
df (52)	*p*	0.054	0.68	0.099	0.852

TBI severity with cool and hot functioning measures

		CPT Omission	CPT RT by Block	SWAN Attention	BART pumps	BRIEF Emotional Control
GCS	(*r*)	-0.03	0.05	0.03	-0.07	-0.04
df (70)	*p*	0.813	0.68	0.791	0.569	0.751

NOTE. Spearman's rho correlations shown, controlling for age at injury and scanner for white matter correlations. TBI = traumatic brain injury; GCS = Glasgow Coma Scale; DACC-C = dorsal anterior cingulate to caudate; VLPFC-C = ventrolateral prefrontal cortex to caudate; DLPFC-C = dorsolateral prefrontal cortex to caudate; RACC-NA = rostral anterior cingulate to nucleus accumbens; MOFC-NA = medial orbitofrontal cortex to nucleus accumbens; RT = reaction time.