Published in final edited form as:

Int J Dev Neurosci. 2012 May ; 30(3): 207–215. doi:10.1016/j.ijdevneu.2011.08.006.

Inhibitory Control after Traumatic Brain Injury in Children

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Abstract

Inhibitory control describes a number of distinct processes. Effortless inhibition refers to acts of control that are automatic and reflexive. Effortful inhibition refers to voluntary, goal-directed acts of control such as response flexibility, interference control, cancellation inhibition, and restraint inhibition. Disruptions to a number of inhibitory control processes occur as a consequence of childhood traumatic brain injury (TBI). This paper reviews the current knowledge of inhibition deficits following childhood TBI, and includes an overview of the inhibition construct and a discussion of the specific deficits shown by children and adolescents with TBI and the factors that mediate the expression of these deficits, including injury-related variables and the expression of pre- and post-injury attention-deficit/hyperactivity disorder. The review illustrates that inhibitory control processes differ in terms of measurement, assessment, and neurological underpinnings, and also that childhood TBI may selectively disrupt particular forms of inhibition.

Keywords

TBI; inhibitory control; effortful inhibition; effortless inhibition

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1. Introduction

The ability to exert acts of control – to ignore distraction, to attend selectively, to prevent an action from being executed, or to stop an action in progress – is an important adaptive function. Inhibitory control is a key component of behavioral self-regulation that interacts with other executive-cognitive processes, such as working memory, to guide adaptive interactions with the environment (Fuster, 2002; G. D. Logan, 1994). A variety of brain-based disorders, including childhood traumatic brain injury (TBI), disrupt inhibitory control.

Childhood TBI can lead to poor inhibitory control in both the acute and chronic phases of injury. Our understanding of inhibitory control in pediatric TBI is broad, in the sense that it has been demonstrated on a wide range of tasks, but insufficiently deep, in the sense that more studies have described the existence of deficits than have analyzed the underlying mechanisms of inhibitory control. In this paper, we review what is currently known about inhibitory control after childhood TBI, beginning with a general overview of the inhibition construct and then focusing on select forms of inhibitory control that are commonly disrupted following TBI, ending with a general discussion of the putative neural correlates of inhibitory control and future directions for further research. Three questions are of particular interest:

1. Do children with TBI show global inhibitory control deficits following their injury, or are some forms of inhibition more vulnerable than others to the effects of brain trauma?
2. How are inhibitory control deficits within childhood TBI groups moderated by injury-related variables, such as age and TBI severity?
3. What are the similarities and differences, behavioral and neural, between inhibitory control deficits after childhood TBI, in children with and without secondary attention-deficit/hyperactivity disorder (S-ADHD), and those typical of developmental or primary attention-deficit/hyperactivity disorder (P-ADHD)?

While there is consensus that inhibitory control is part of a set of shifting, overlapping, and developmentally volatile skills collectively referred to as “executive function”, the purpose of this review is to probe the ability to inhibit an action, rather than to review the spectrum of executive function and the place of inhibitory control within it. Many of the tasks used to assess different inhibition process involve multiple dimensions, and in the work described below, we aim to identify the core processes involved directly in inhibiting an action.

2. What is Inhibitory Control?

A variety of different processes are subsumed under the term, *inhibitory control* (see Figure 1). It may refer to effortless, automatic forms of inhibition involving a reflexive-type response to exogenous stimuli (stimulus orienting). For example, repeatedly saccading to the same stimulus location in response to a flash of light causes the response to become gradually slower, as if to avoid a previously attended location, thereby resulting in an increased probability of attending to novel stimuli that may appear in the environment (i.e., inhibition of return) (Klein, 2000). More commonly, *inhibitory control* refers to effortful,

voluntary forms of control, whereby one acts in accordance with current instructional set or previous experiential contingencies. Effortful inhibition can be further subdivided into a number of different processes.

Interference control is the ability to perform an act while ignoring distracting, competing, or conflicting information. One example of a task requiring interference control is the Stroop task, which requires one to name the color of the ink a colour word is written in while inhibiting the impulse to read the word (Stroop, 1935). The interference control in this task comes from the requirement to perform a controlled act (colour naming) while ignoring a well-practiced, automatic act (word reading). The flanker task is also used to assess interference control. As in the Stroop task, one is required to attend to a target while ignoring interfering or distracting material that flanks it (B. A. Eriksen & C. W. Eriksen, 1974). The antisaccade task, in which an individual is instructed to look away from a target and instead saccade to its mirror position (Munoz & Everling, 2004) is also used to measure the ability to substitute a non-automatic, controlled response for a more automatic, practiced one.

Response flexibility refers to the ability to shift among the features of a stimulus to which one will respond. Tasks such as the Wisconsin Card Sorting Task (WCST; (Berg, 1948) and the Children's Category Test measure this form of inhibitory control. Shifting may occur within a stimulus dimension, as in the WCST (intra-dimensional shift; e.g. inhibit responding to red shapes and instead respond to blue shapes) or between stimulus dimensions (extra-dimensional shift; e.g. inhibit responding to the shape of items and instead respond to the number of items present). Poor response flexibility is indexed by perseverative behaviour, where participants continue to use the previous response set and fail to shift their attention towards the newly salient rule.

Cancellation involves inhibiting or stopping an already initiated or ongoing action; for example, stopping the swing of a baseball bat as the pitch leaves the strike zone. The stop signal task is commonly used to assess this type of inhibitory control: participants respond to a visually presented "go signal" and cancel or interrupt their responses when they hear an auditory "stop signal" that is presented at varying intervals following the go signal (G. D. Logan, 1994; G. D. Logan & Cowan., 1984). Inhibitory control is estimated by the latency of inhibitory control, or the stop signal reaction time (SSRT), with longer SSRT denoting slower or less efficient inhibitory control (G. D. Logan, 1994).

Restraint refers to withholding or preventing a prepotent response before it is initiated. Typical "first-person shooter" video games often involve this type of inhibitory control, requiring gamers to shoot at one type of target (the bad guy), but refrain from shooting at another target (innocent bystanders). The generic form of restraint inhibition tasks includes the Go/No-Go and continuous performance tasks, where inhibitory control is indexed by the amount of commission errors made to a "no-go" stimulus. Restraint can also refer to delaying of a prepotent response; on the Gordon Delay Task, participants are instructed to respond to a target only if it followed a preceding target by a specified time interval (Gordon, 1983).

3. Development of Inhibitory Control

Different inhibitory control abilities follow different developmental trajectories. Inhibition of return is apparent between the 3rd and 6th month of life (Clohessy, MI Posner, & MK Rothbart, 2001; Johnson, 1995), coinciding with the onset of the ability to efficiently direct saccades to specific locations in space (J. Schatz, Craft, D. White, Park, & Figiel, 2001). Effortful inhibition on the other hand, shows a more protracted rate of development. Generally, these processes are immature in young children, with linear increases in performance observed throughout childhood and adolescence, with some processes improving well into adulthood. Age-related improvements in effortful inhibition are thought to reflect maturation of frontostriatal circuitry which includes non-linear decreases in cortical gray matter accompanied by linear increases in myelination (JN Giedd et al., 1999; Gogtay et al., 2004; Sowell, PM Thompson, C. J. Holmes, Jernigan, & AW Toga, 1999).

Increased interference control is apparent by middle childhood. The “Stroop effect” (colour-word interference) appears around the age of 8 years, or when children have acquired the reading skills required to easily read colour words (MacLeod, 1991). Although the Stroop effect declines throughout childhood and adolescence, it is evident in adulthood as well (MacLeod, 1991). The Stroop task has been modified for children under the age of 6 utilizing objects that had been coloured inappropriately (Prevor & Diamond, 2005), with colour-object interference noted in early childhood (between the ages of 3 and 8 years; (La Heij & Boelens, 2011; Prevor & Diamond, 2005) and disappearing by late childhood (around age 12; (La Heij & Boelens, 2011). Similarly, interference control on flanker tasks appears around age 4 with adult levels of control reached between the ages of 7 to 10 years (Ridderinkhof, van der Molen, Band, & Bashore, 1997; Rueda, Michael I Posner, Mary K Rothbart, & Davis-Stober, 2004). Improvements in antisaccade performance coincide with the development of efficient voluntary control of automatic saccades (Velanova, Wheeler, & Luna, 2009), with greater accuracy in generating an antisaccade noted from childhood to young adulthood (e.g., (Klein & Foerster, 2001; Velanova et al., 2009).

The ability to shift behaviour between one rule to another is apparent by age 5 (Zelazo, 2006). The WCST imposes qualitatively different cognitive demands on children depending on age (Bujoreanu & Willis, 2008). A linear increase in the number of categories achieved on the WCST occurs between the ages of 6 to 11 years, with performance plateauing by early adolescence (Bujoreanu & Willis, 2008; Somsen, 2007). The performance of younger children is enhanced by decreasing distraction to correct feedback, while older children perform optimally with an increase in attention to error feedback (Somsen, 2007). Moreover, the performance of younger, but not older, children is greatly affected by the order of criterion presentation (Bujoreanu & Willis, 2008).

Cancellation and restraint inhibition have somewhat different developmental trajectories. The latency to cancel a response becomes faster throughout childhood and adolescence, with only limited slowing in older adults (Williams, Ponesse, RJ Schachar, GD Logan, & Tannock, 1999). Improvements in cancellation are thought to be independent of improvements in the speed of motor output (as measured by the reaction time to go stimuli),

with differences noted in their developmental trajectories (Williams et al., 1999). Restraint inhibition, in contrast, reaches adult levels around age 12 years (Johnstone et al., 2007).

4. Inhibitory Control and TBI

It is clear that the inhibitory control construct is multi-faceted. Each type of process is measured by distinct cognitive and behavioral paradigms and follows different, but overlapping developmental trajectories. The functional and developmental diversity of inhibitory control is paralleled in the variability in inhibitory control abilities after childhood TBI, in which some inhibitory control processes are more disrupted than others. Effortful forms of inhibitory control appear more vulnerable to impairment following childhood TBI than more automatic forms of inhibitory control (see Table 1). Poor inhibition of return has been documented in adults with TBI within weeks of the injury (Mayer et al., 2009), but intact abilities to engage and disengage from stimuli have been found in the chronic phase of injury (Bate, Mathias, & Crawford, 2001) suggesting intact reflexive or effortless inhibitory control abilities. No studies to date have examined inhibition of return abilities following childhood TBI.

Regardless of the status of effortless inhibition, there is an extensive body of work studying effortful inhibition and results fairly consistently showing impairment after childhood TBI. Like their non-injured peers, children with TBI exhibit Stroop colour-word interference both soon after the injury and 12 months post-injury (Harvey S Levin et al., 2008). However, poorer interference control relative to healthy participants has been shown in adolescents with chronic TBI (Ward, Shum, McKinlay, Baker, & Wallace, 2007). Relative to healthy controls, children with chronic TBI exhibit poor performance on a flanker task during interference but not during facilitation and neutral conditions (Harvey S Levin, G. Hanten, L. Zhang, P. R. Swank, & J. Hunter, 2004), lending further support to findings of an intact ability to orient attention and use salient information to guide goal-directed behaviour, but poor interference control.

Impaired response flexibility, as measured by performance on the WCST, is evident in children with TBI, especially those with lesions involving the left frontal lobe (HS Levin et al., 1993). Moreover, a mixed sample of adolescents and young adults who had incurred a TBI in childhood exhibit poor performance on the Children's Category Test (Aaro Jonsson, Smedler, Leis Ljungmark, & Emanuelson, 2009; Horneman & Emanuelson, 2009), suggesting impaired response flexibility. However, the WCST and Children's Category Test involve a number of processes unrelated to inhibitory control, such as working memory, divided attention, the ability to form abstract concepts, and the ability to utilize feedback to guide subsequent decisions. Ewing-Cobbs and colleagues (2004) utilized the spatial reversal task to assess cognitive flexibility following childhood TBI. In this task, the child must develop a response set to find a hidden reward in a particular location, and then must suddenly reverse this response set towards a different spatial location. Children with moderate and severe TBI and controls performed equally well on this task (Ewing-Cobbs, Prasad, Landry, Kramer, & DeLeon, 2004), suggesting an intact ability to inhibit a previous rule and shift adaptively. TBI incurred in adulthood leads to impaired antisaccade performance (a greater number of prosaccade errors; (Kraus et al., 2007), but no study to

date has explored this phenomenon in children. Further research is required to elucidate whether children with TBI can adaptively inhibit then shift their behavior in accordance with changing environmental demands.

Childhood TBI in both acute and chronic phases of recovery is also associated with deficient cancellation inhibition, indicated by slower or less efficient SSRT on the stop signal task (Konrad, S Gauggel, Manz, & Schöll, 2000a, 2000b; Leblanc et al., 2005)(Sinopoli, R Schachar, & Maureen Dennis, 2011). Utilizing a restraint version of the stop signal task where the presentation of the go and stop signals occur concurrently (thus signalling for the restraint or withholding of the “go response”; (Russell Schachar et al., 2007), we showed that children with TBI do not make more commission errors than controls, despite slowed SSRT to the stop signal (Sinopoli et al., 2011). Other studies have reported increased commission errors: Levin and colleagues (2004) showed that children with severe TBI in the chronic phase of recovery made more commission errors on a Go/No-Go flanker task. Similarly, Konrad and colleagues (2000a) reported that children with TBI make an increased number of commission errors, but this an effect was found only with a long delay between the onset of the go and no-go stimuli, which suggests delay aversion rather than restraint as the impaired process.

5. Factors affecting Effortful Inhibitory Control Following Childhood TBI

A number of factors can influence the manifestation of inhibitory control deficits after childhood TBI. Within TBI groups, these factors include those intrinsic to the child (age at test, premorbid behaviour), factors related to the injury itself (severity of injury, age at injury), factors related to attentional deficits that occur following the injury, and factors related to the motivational value of a stimulus (see Table 1).

5.1 Injury related variables

It is important to examine whether injury-related variables mediate the effects of childhood TBI on inhibitory control. To the extent that they do so, it is possible to use research findings to guide rehabilitation based on individual differences as well as group characteristics.

Ratings of severity are generally based on scores on the Glasgow Coma Scale (GCS; (Teasdale & Jennett, 1974). Ranging from 3–15, GCS scores were developed to provide an objective means to record the conscious state of an individual along three dimensions (motor, eye, and verbal responses). Severe injuries are classified by GCS scores of 3–8, moderate injuries by scores of 9–12, and mild injuries by scores of 13–15. Although children with more severe injuries tend to have the greater neuropsychological deficits (Yeates, 2009), the relationship between GCS severity classification and inhibition performance is not consistent. While children with severe TBI exhibit less resistance to distractors than those with mild or moderate injuries (M Dennis, Guger, Roncadin, M Barnes, & R Schachar, 2001); (Harvey S Levin et al., 2004), TBI severity is unrelated to speed of cancellation inhibition (Russell Schachar, Harvey S Levin, Jeffrey E Max, Purvis, & S. Chen, 2004); (Sinopoli et al., 2011) or to speed and accuracy of restraint inhibition (Sinopoli et al., 2011). The lack of a consistent relationship between inhibition performance

and severity ratings may be attributed to the fact that GCS scores vary over time since impact and with the physiological characteristics of the injury, so that severity classification depends on when it is assessed (Yeates, 2000). Moreover, categorizing severity based on initial GCS scores ignores injury variables such as the presence of edema, hemorrhaging, or localized hematomas, which may be arguably more important to the establishment of injury severity than the traditional GCS coding (see (Bigler, Ryser, Gandhi, Kimball, & Wilde, 2006; Harvey S Levin et al., 2008).

Given that inhibition processes develop throughout childhood, and in some cases, throughout adolescence and young adulthood, the various forms of inhibition may be differently disrupted by TBI depending on the age at which the child was when the injury occurred. Age at injury and time since injury are significant predictors of interference control, with better performance noted in children with an older age at injury and longer time since injury (M. Dennis, Wilkinson, Koski, & Humphreys, 1995); (M Dennis et al., 2001). Younger children with TBI exhibit poorer cancellation performance on the stop signal task relative to older children with TBI, but age at TBI generally does not predict cancellation performance (Russell Schachar et al., 2004); (Sinopoli et al., 2011). Although there is evidence showing that time since injury is not related to cancellation deficits (Russell Schachar et al., 2004); (Sinopoli et al., 2011), Leblanc and colleagues showed that deficits in cancellation inhibition present in the acute phase of injury resolve by one year post-TBI, with younger children with TBI exhibiting the greatest resolution of inhibitory control deficits. However, because the Leblanc et al. (2005) study included only children with TBI after age five, the results may not generalize to the full age at injury range.

Restraint inhibition also improves with increased time since injury, although fewer improvements are observed in children with more severe TBI (Wassenberg, Jeffrey E Max, Scott D Lindgren, & A. Schatz, 2004), in line with the Levin et al. (2004) study that only examined children with severe injuries. However, age at injury and time since injury do not predict the speed of restraint inhibition or the number of commission errors made by children with chronic TBI (Sinopoli et al., 2011), suggesting that injury-related variables are poorly predictive of the long-term ability to withhold a response.

5.2 Secondary ADHD and its relation to inhibitory control

Children with TBI commonly exhibit deficits in attention both before and after the injury. Although 10–19 % of children with TBI exhibit a pre-injury diagnosis of P-ADHD (JP Gerring et al., 1998; JE Max et al., 1998; Slomine et al., 2005), approximately 15–20% of survivors develop *de novo* ADHD symptoms (i.e., S-ADHD; (JP eGerring et al., 1998; J. Gerring et al., 2000; E. H. Herskovits et al., 1999; Jeffrey E Max, Russell J Schachar, Harvey S Levin, Ewing-Cobbs, Sandra B Chapman, Maureen Dennis, Saunders, & Landis, 2005a, 2005b; Slomine et al., 2005; Yeates et al., 2005). S-ADHD is the most common psychiatric disorder in children with TBI (JE Max et al., 1998), manifesting as early as 6 months post-injury and persisting into the chronic phase of recovery (H. Levin et al., 2007; Jeffrey E Max, Russell J Schachar, Harvey S Levin, Ewing-Cobbs, Sandra B Chapman, Maureen Dennis, Saunders, & Landis, 2005a, 2005b). Pre-injury variables associated with the emergence of S-ADHD include lower socioeconomic status, greater psychosocial

adversity and adaptive functioning, poorer family functioning, and poorer socialization and communication skills (JP Gerring et al., 1998; H. Levin et al., 2007; Jeffrey E Max, Russell J Schachar, Harvey S Levin, Ewing-Cobbs, Sandra B Chapman, Maureen Dennis, Saunders, & Landis, 2005a, 2005b).

Some key questions about the significance of a S-ADHD diagnosis following childhood TBI remain unclear. Do children with a S-ADHD diagnosis have more deficits than those without? P-ADHD is associated with characteristic inhibitory control deficits, including cancellation and restraint (e.g., (Russell Schachar et al., 2007; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) that are thought to reflect frontostriatal dysfunction associated with the disorder (e.g. (Aron & Poldrack, 2005). Does S-ADHD - an acquired condition - reflect cognitive and neural abnormalities closely similar to those in children with P-ADHD? To address these questions, it is helpful to compare the performance of children with S-ADHD and P-ADHD on the same inhibitory control tasks.

Neither the presence of pre-injury P-ADHD nor the emergence of post-injury S-ADHD affects WSCT performance in children with TBI (Slomine et al., 2005), although the lack of a control group in this study make any conclusion tentative. Restraint inhibition, as measured by the percentage of responses inhibited during the restraint version of the stop signal task, is similar in children and adolescence with TBI, S-ADHD, and non-injured controls (Sinopoli et al., 2011). On the other hand, children with P-ADHD without TBI inhibit a fewer percentage of responses to the no-go signal relative to controls, suggesting a restraint deficit present only in children with the developmental form of ADHD (Sinopoli et al., 2011). Congruent with these findings, S-ADHD soon after TBI is associated with a greater number of errors of omission, but not errors of commission (Wassenberg et al., 2004), suggesting that acute-phase restraint inhibition does not predict attention problems in the chronic phase of injury.

Children with greater pre-injury behavioral difficulties, such as short attention spans and over-activity, were more likely than those without such difficulties to exhibit poor cancellation inhibition on the stop signal task following TBI (Russell Schachar et al., 2004). However, the diagnosis of P-ADHD pre-TBI does not significantly affect the acute-phase cancellation deficit (Leblanc et al., 2005). In the chronic phase of injury, children with S-ADHD exhibit longer SSRT on the stop signal task than typically developing controls, with performance similar to those with TBI without S-ADHD (Konrad, S Gauggel, Manz, & Schöll, 2000a, 2000b); (Sinopoli et al., 2011). However, Schachar and colleagues (2004) found that a cancellation deficit relative to children with TBI without S-ADHD was present in children with S-ADHD if they also had a severe TBI.

Cancellation performance in both P-ADHD and S-ADHD groups has been assessed in a few studies (Konrad, S Gauggel, Manz, & Schöll, 2000a, 2000b); (Sinopoli et al., 2011). Although the Konrad et al. (2000a, 2000b) studies revealed poor cancellation in both children with P-ADHD and S-ADHD, performance was not directly compared between groups. In a direct comparison of both groups, we recently reported that children with P-ADHD exhibit a stronger deficit on the cancellation version of the stop signal task than do children with S-ADHD (Sinopoli et al., 2011). A similar finding was discovered on the

restraint version of the stop signal task in terms of the speed of inhibitory control (Sinopoli et al., 2011). Whereas youth with P-ADHD make more commission errors than controls, those with S-ADHD did not show this restraint inhibition impairment (Sinopoli et al., 2011). No studies have reported similarities or differences between ADHD groups in terms of interference control or response flexibility.

The direct comparison of children with S-ADHD and P-ADHD on the same inhibitory control tasks informs underlying mechanisms. Similar performance between groups would imply that S-ADHD is associated with deficits that mimic the P-ADHD endophenotype of poor inhibitory control (see (Crosbie, Prusse, C. L. Barr, & Russell J Schachar, 2008), which would inform both the brain bases of inhibition deficits in P-ADHD and of inhibitory control processes in general. To the extent that the groups show distinct inhibitory control profiles would suggest then that S-ADHD after TBI may also be thought of as distinct from P-ADHD, both in terms of associated behavioral impairments and underlying mechanisms. The data provide some support for this view, and suggest that developmental (P-ADHD) and acquired (S-ADHD) forms of ADHD have distinct inhibitory control profiles, with children with P-ADHD exhibiting deficits in both cancellation and restraint, and those with TBI and S-ADHD exhibiting a selective and less severe cancellation deficit. That cancellation is impaired in S-ADHD suggests that this behaviour may represent a phenocopy of P-ADHD behaviour.

S-ADHD is typically associated with the inattentive subtype (Max et al., 2005a, 2005b; Levin et al., 2007), whereas the combined and inattentive subtypes are both common in P-ADHD (Larsson et al., 2011). It is not clear whether a priori subtyping of participants with ADHD affects performance on inhibitory control tasks: whereas some studies have shown that children with P-ADHD, combined subtype, exhibit poorer inhibitory control relative to those with the inattentive subtype and healthy controls (e.g., Desman, Petermann, & Hampel, 2008; Mulas et al., 2006; Rhodes et al., 2005), other studies have shown similar inhibition deficits between subtypes (e.g., Bedard et al., 2003; Huang-Pollock et al., 2007; Scheres et al., 2001). Although controversial (see Adams et al., 2008), recent arguments (Diamond, 2005; Solanto, 2002) have suggested that children with P-ADHD, inattentive subtype, are characterized by a slow, cautious response tendency that may negatively affect inhibitory control, reflecting a dopaminergic deficit in the prefrontal cortex. These children may also have difficulty processing environmental cues (Desman et al., 2008), which may also negatively affect inhibition performance by limiting the efficacy of error feedback to guide subsequent action. In contrast, the poor inhibition performance exhibited by children with P-ADHD with hyperactivity/impulsivity may reflect an excess of dopamine in the striatum (Solanto, 2002). Further studies are needed to clarify whether children with S-ADHD exhibit a response style similar to children with P-ADHD, inattentive subtype, rather than those with the hyperactivity/impulsivity. These results would inform the nature of inhibition deficits in S-ADHD and would lend a greater understanding to the potential brain bases underlying different ADHD subtypes.

5.3 Reward and Inhibitory Control

Acts of inhibitory control do not occur within a motivational vacuum. Slamming on the brakes in response to a red light is done to avoid a car accident or a ticket. For a child, acting in a controlled manner may generate a reward in the form of praise or a tangible reward such as a cookie; indeed, behavior is often performed in order to avoid a punishment or to gain a reward.

But how do rewards affect inhibitory control? At a developmental level, inhibition and reward systems are both immature in children (e.g., (Geier & Luna, 2009; Rubia, A. B. Smith, E. Taylor, & Michael Brammer, 2007). At a behavioral level, reinforcement can both facilitate and hinder inhibitory control, depending on the strength and direction of the reinforcer. At a neural level, rewards may directly influence the interaction between inhibitory control and motivational centers in the brain, or may alter the activity in other brain centers that integrate inhibition and motivation (Padmala & Pessoa, 2010).

In typically developing children and adolescents, rewarding successful inhibitory control increases the speed of cancellation and restraint inhibition without affecting the speed of response execution (Sinopoli et al., 2011). Only two studies to date have examined the effect of rewards on inhibitory control abilities in children with TBI. Rewards facilitated the speed of cancellation and restraint inhibition, without significantly affecting the speed of “go” responses (Konrad, S Gauggel, Manz, & Schöll, 2000b) (Sinopoli et al., 2011). The degree to which rewards improve inhibitory control is similar between TBI and S-ADHD groups, with both groups continuing to exhibit impairments relative to controls (Konrad, S Gauggel, Manz, & Schöll, 2000b) (Sinopoli et al., 2011).

6. Putative neural substrates of inhibitory control

The discussion of neural substrates of inhibitory control, below, is limited to effortful inhibition (specifically, to cancellation and interference control), not only because the neural substrates of these forms of inhibitory control are relatively well understood, but also because deficits in these functions seem to be more robustly evident in children with TBI compared to other inhibitory control difficulties. Much of the following information on putative neural substrates is derived from the adult literature, although some developmental studies and studies specifically examining pediatric TBI lesions are also discussed.

When the environment changes and salient stimuli are detected, nigrostriatal and mesolimbic dopamine neurons are activated and the subsequent dopamine release converges with glutamatergic output from the orbitofrontal cortex and amygdala on dendritic spines in the dorsal and ventral striatum (Horvitz, 2002). Dopamine acts to “gate” basal ganglia processing of the glutamatergic sensorimotor and incentive-related information in the striatum by enhancing strong signals and dampening weak signals (see (Horvitz, 2002). While the active suppression of motor responses is largely undertaken by such activity in the basal ganglia (Mink, 1996), successful cancellation (and restraint) also involve activation of the inferior frontal gyrus (IFG; e.g., (Chevrier, Noseworthy, & Russell Schachar, 2007; S Konishi et al., 1999).

The IFG may be part of a network that arouses attention when salient information, such as a stop signal, is detected in the environment (Downar, Crawley, Mikulis, & Davis, 2002). The IFG may also signal when inhibitory control demands increase or when previously learned information needs to be inhibited as task demands change (S Konishi et al., 1999; E. E. Smith & Jonides, 1998). Thus, the role of the IFG in cancellation may be to direct attention toward the stop signal to improve the efficiency of inhibition while decreasing the prepotent drive on go responses. Because restraint places a high cognitive demand on response preparation and selective attention prior to the presentation of the no-go stimulus (Johnstone et al., 2007; Kelly et al., 2004), successful restraint may rely predominantly on a top-down control system driven by regulatory structures such as the dorsolateral (H Garavan, Ross, K Murphy, Roche, & Stein, 2002; Kelly et al., 2004; V Menon, NE Adelman, CD White, GH Glover, & AL Reiss, 2001), mid frontal, and dorsal premotor prefrontal cortices (Kelly et al., 2004; Watanabe et al., 2002). Thus, the bottom-up “saliency detection” and “behavioural updating” system associated with the bilateral IFG may interact with a top-down control system to result in successful restraint inhibition.

Interference control appears to rely predominantly on more medial and dorsal areas of the frontal lobes. Utilizing flanker tasks, conflict-related activity during incongruent trials is associated with activity in the bilateral dorsal anterior cingulate cortex, posterior medial frontal cortex, and dorsolateral prefrontal cortex (Botvinick, Braver, Barch, Carter, & Cohen, 2001; MacDonald, Cohen, Stenger, & Carter, 2000; Ochsner, Hughes, Robertson, Cooper, & Gabrieli, 2009). Similar activations have been noted during interference control trials of the Stroop task (Nancy E Adelman et al., 2002; Bush, Shin, J. Holmes, Rosen, & Vogt, 2003), as well as activity in parietal regions important for attentional orienting (Kaufmann et al., 2005). The dorsal anterior cingulate cortex seems to be important for conflict monitoring, error detection, and expectancy violation, whereas the posterior medial frontal cortex may be important for signalling the need for interference control, and the dorsolateral prefrontal cortex may be involved in implementing the control processes and maintaining task goals (e.g., (Botvinick et al., 2001; MacDonald et al., 2000; Miller & Cohen, 2001; Ochsner et al., 2009; Ridderinkhof et al., 1997). There is also evidence for recruitment of ventrolateral areas of the prefrontal cortex, including the IFG, when resolving conflict on both flanker and Stroop tasks (Mincic, 2010; Ochsner et al., 2009). The IFC may act to “bridge” (Mincic, 2010) the bottom-up saliency detection systems with top-down attentional control to facilitate interference control, as in the hypothesis presented above.

The neural circuits for effortful inhibition continue to mature into adulthood. For instance, activity of the IFG is greater in adults than in adolescents during successful inhibition on the stop signal task, with linear progressive changes occurring in response to successful stopping from ages 10–42 years in the bilateral inferior prefrontal cortex and caudate nucleus (Rubia et al., 2007). Improvements in the speed of cancellation (SSRT) may be related to increased recruitment of the IFG with age, which would increase the saliency of the stop signal, thereby improving cancellation (Chikazoe et al., 2009). Increased maturation of the frontostriatal system is related to improvements in restraint, with linear progressive changes observed in the striatum and inferior and mesial prefrontal cortices correlated with successful no-go trials (Liston et al., 2006; Rubia et al., 2006). In particular, the maturation

of cognitive control centers in the prefrontal cortex may promote developmental changes in restraint and interference control (Nancy E Adleman et al., 2002; Kelly et al., 2004).

It may be hypothesized that damage to any of the brain regions discussed above would disrupt inhibitory control processes following childhood TBI, especially given that these neural substrates of inhibitory control continue to develop across childhood and adolescence. In adult patients with TBI, damage to the right IFG (Aron, P. C. Fletcher, Bullmore, Sahakian, & Robbins, 2003), right medial frontal lobe (Floden & Stuss, 2006), and basal ganglia (Rieger, Siegfried Gauggel, & Burmeister, 2003) results in impairments on the stop signal task (cancellation inhibition), and damage to the left supplementary motor areas, premotor cortex, and right ventrolateral prefrontal cortex results in poorer performance on the Go/No-Go task (restraint inhibition; Picton, et al., 2007). Surprisingly, there is a relative dearth of information regarding the relationship between lesion location and inhibition deficits in children with TBI. Injury to the frontal lobes does not predict interference control (M Dennis et al., 2001) or cancellation performance (Leblanc et al., 2005). However, the neural basis of inhibitory control after childhood TBI needs to be investigated with more detailed forms of neuroimaging, such as diffusion tensor imaging that will allow fibre tracts to be more clearly delineated and related to functional outcomes (e.g., (Ewing-Cobbs et al., 2008).

7. Conclusions and Future Directions

Inhibitory control is not a unitary construct. Each form of inhibitory control follows different, but overlapping developmental trajectories, and involves different, but overlapping neural areas in the frontal cortex and basal ganglia. The effects of childhood TBI on these processes appear to be specific to particular aspects of effortful inhibition. This is not to suggest that no form of automatic inhibition is affected by TBI or that automatic and effortful forms of inhibition do not interact to generate acts of control. But it is the ability to exert voluntary control over actions that seems especially vulnerable to the effects of childhood TBI. A number of factors influence the expression of deficits following TBI, including age at injury, time since injury, the emergence of post-injury ADHD symptoms, and the presence of reward. While we understand a number of features of inhibitory control deficits, our knowledge is far from complete. Important future avenues of study include lesion correlates of inhibitory control deficits following TBI, long-term effects of childhood TBI on inhibition abilities, and how TBI-related inhibitory control deficits specifically affect everyday function of children and adolescents.

A key question is not so much *whether* children with TBI exhibit poor inhibitory control, but *why* they do so. Recent advances in the cognitive probing of inhibitory control in normal populations have provided some potentially fruitful avenues for answering this question in children with TBI. In the course of an inhibitory control probe like the stop signal task, trial-by-trial fluctuations in performance occur that reflect, not only random variation, but also adjustments of various kinds (Bissett & Gordon D Logan, 2011). Some adjustments occur over a brief time frame, such as that from one trial to the next, while others build up over longer time frames extending over several trials. Some adjustments are a reaction to failed inhibition, such as the slowing after signal respond trials (Schachar et al., 2004), but others

are proactive, occurring even before an error has been made, such as proactive slowing of response execution in anticipation of stop signals (Verbruggen & Gordon D Logan, 2009). Current research in childhood TBI is studying what these performance fluctuations reveal about the underlying processes involved in successful and unsuccessful inhibitory control in these children.

Why is it important to seek a fuller understanding of the behavioral and neural underpinnings of inhibitory control after childhood TBI? Poor inhibitory control in the “real world” can lead to decreases in adaptive functioning, poor psychosocial outcomes, and decrements to academic, vocational, and social successes. Poor self-regulation of behaviour in children with TBI is associated with impaired social and behavioural function (Ganesalingam, Sanson, Anderson, & Yeates, 2007). By identifying the processing underlying inhibition deficits associated with TBI, as well as the factors that mediate the expression of these deficits, future studies can delineate the types of intervention and rehabilitation required to improve these difficulties, thereby helping to improve the quality of life of children with TBI.

Acknowledgments

Funding to Katia J. Sinopoli was provided by the Ontario Neurotrauma Foundation to (2007-ABI-PHD-565, The Regulation of Thoughts and Actions in Children Following Traumatic Brain Injury). This research was also supported by an NIH 1RO1 grant to Keith O. Yeates and Maureen Dennis (HD04946, Social Outcomes in Pediatric Traumatic Brain Injury).

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Highlights

- Inhibitory control denotes a number of distinct, interrelated processes
- Childhood traumatic brain injury (TBI) can lead to deficits in inhibitory control
- Specific inhibitions deficits emerge as a result of childhood TBI
- Deficits are often moderated by a number of variables (e.g., post-injury ADHD)

Figure 1. Inhibitory control processes

Inhibitory control can be divided into automatic, reflexive, or *effortless inhibition*, and voluntary, goal-directed, or *effortful inhibition*. Effortless inhibition includes the sub-process of stimulus orienting. Effortful inhibition includes interference control, response flexibility, response cancellation, and response restraint. Children with TBI appear to be vulnerable to deficits in effortful inhibition, with consistent impairments noted in interference control, cancellation, and restraint inhibition.

Table 1

GROUP	IMPAIRED	INTACT	FACTORS AFFECTING INHIBITORY PROCESS
TBI	Interference control <ul style="list-style-type: none"> • Stroop Task • Flanker Task • Antisaccade Task^a Response Flexibility <ul style="list-style-type: none"> • WCST^b • Children's Category Task^b Cancellation/Restraint <ul style="list-style-type: none"> • Go/No-Go 	Stimulus Orienting <ul style="list-style-type: none"> • Inhibition of Return^a Response Flexibility <ul style="list-style-type: none"> • Spatial Reversal Task Restraint <ul style="list-style-type: none"> • Restraint Stop Signal Task 	Severe Injuries <ul style="list-style-type: none"> • Interference Control Age at Injury <ul style="list-style-type: none"> • Interference Control • Cancellation Time since Injury <ul style="list-style-type: none"> • Interference Control • Cancellation • Restraint Rewards <ul style="list-style-type: none"> • Cancellation • Restraint
S-ADHD	Cancellation ^d	Response Flexibility <ul style="list-style-type: none"> • WCST Restraint ^d <ul style="list-style-type: none"> • Restraint Stop Signal Task 	Unknown

Legend: TBI = Traumatic Brain Injury; S-ADHD = Secondary Attention-Deficit/Hyperactivity Disorder; WCST = Wisconsin Card Sorting Task

^a Further research is needed to confirm this finding in children with TBI

^b These tasks may confound response flexibility with a number of other processes, such as working memory, divided attention, the ability to form abstract concepts, and the ability to utilize feedback to guide subsequent decisions

^c This effect was only found in children with severe injuries

^d Children and adolescents with S-ADHD exhibited normal restraint inhibition on the restraint version of the stop signal task, but impaired cancellation performance on the stop signal task. In contrast, children with developmental or primary ADHD (P-ADHD) exhibited poor restraint and a more severe cancellation deficit in comparison to youths with S-ADHD.