Neural and behavioral mechanisms of proactive and reactive inhibition

Heidi C. Meyer and David J. Bucci

Department of Psychological and Brain Sciences, Dartmouth College, Hanover, New Hampshire 03755, USA

Response inhibition is an important component of adaptive behavior. Substantial prior research has focused on *reactive* inhibition, which refers to the cessation of a motor response that is already in progress. More recently, a growing number of studies have begun to examine mechanisms underlying *proactive* inhibition, whereby preparatory processes result in a response being withheld before it is initiated. It has become apparent that proactive inhibition is an essential component of the overall ability to regulate behavior and has implications for the success of reactive inhibition. Moreover, successful inhibition relies on learning the meaning of specific environmental cues that signal when a behavioral response should be withheld. Proactive inhibitory control is mediated by stopping goals, which reflect the desired outcome of inhibition and include information about how and when inhibition should be implemented. However, little is known about the circuits and cellular processes that encode and represent features in the environment that indicate the necessity for proactive inhibition or how these representations are implemented in response inhibition. In this article, we will review the brain circuits and systems involved in implementing inhibitory control through both reactive and proactive mechanisms. We also comment on possible cellular mechanisms that may contribute to inhibitory control processes, noting that substantial further research is necessary in this regard. Furthermore, we will outline a number of ways in which the temporal dynamics underlying the generation of the proactive inhibitory signal may be particularly important for parsing out the neurobiological correlates that contribute to the learning processes underlying various aspects of inhibitory control.

An essential feature of adaptive behavior is the ability to meet the changing demands of complex environments. Of particular importance is the inhibition of responses that are inappropriate or maladaptive. Over the past decade it has become well established that successful inhibitory control involves both "reactive" and "proactive" control mechanisms (Braver et al. 2007; Jaffard et al. 2007, 2008; Aron 2011; Braver 2012). Research regarding the former largely emphasizes the cessation of a motoric process, specifically as a reaction to a cue or event in the environment (a so-called stop-signal) that occurs *after* the response process has been initiated. In contrast, proactive inhibition involves a preparatory process that influences whether the response will be initiated in the first place. Unlike reactive processes, proactive inhibition can also be initiated by endogenous factors (Chikazoe et al. 2009b; Verbruggen and Logan 2009a,b; Aron 2011). In addition, proactive inhibitory control can be generated in advance and can extend across time. By comparison, reactive inhibition occurs only in the temporal proximity of the stop-signal. Proactive inhibition is also different from reactive inhibition in that it is mediated by a stopping goal, which is a representation in working memory of the desired outcome of inhibition that includes information about how and when inhibition should be implemented (Verbruggen and Logan 2009a; Hughes et al. 2014; Wessel and Aron 2014; Best et al. 2016). Stopping goals may be defined according to the immediate context or retrieved from short-term or long-term memory.

With these distinctions in mind, we begin this article by reviewing what is currently known about the neural circuits and systems related to reactive and proactive inhibition (definitions of key terms used through the article are noted in Table 1). We note that although there appears to be some overlap in the substrates underlying reactive and proactive inhibition, this may be due in part to the presence of both reactive and proactive processes in the behavioral procedures that have been used to date. We then discuss how other aspects of cognitive function can influence inhibitory processes and how the temporal dynamics of proactive inhibition might be used to isolate this process. This is followed by consideration of the behavioral and neural mechanisms through which learning can contribute particularly to proactive inhibitory control, and we describe behavioral paradigms that may be useful in furthering studying the role of learning in proactive inhibition. We close by describing how impairments in proactive and reactive inhibition manifest in various forms of mental illness.

Neural substrates of reactive and proactive inhibition

Reactive inhibition

Reactive inhibition commonly refers to the cue-triggered stopping of a response that has already been initiated (Aron 2011). This is most commonly studied using the stop-signal task (SST; Logan and Cowan 1984; Logan 1994), which provides an index to assess the efficiency of response inhibition. In this procedure, a "go-signal" is presented on all trials, to which the individual makes a particular behavioral response (e.g., keyboard or lever press). Occasionally, a "stop-signal" is presented after a go-signal has occurred; in this instance, the response must be aborted. The measure of interest is the stop-signal reaction time (SSRT), which serves as a quantitative estimate of the time needed to abort

Corresponding author: david.j.bucci@dartmouth.edu

Table 1. Definitions of key terms

Stopping goal: A representation in working memory of the desired outcome of inhibition that includes information about how and when inhibition should be implemented.

Inhibitory cue: A salient cue indicating that a response should be inhibited.

Proactive inhibition: Inhibitory control mechanisms engaged prior to the initiation of a response.

Reactive inhibition: The cessation of a motor response that is already in progress (e.g., in response to a stop-signal).

Stop-signal: An inhibitory cue indicating that the response to a previously presented cue (specifically a cue indicating that a response should be initiated) should be aborted.

Negative occasion setter: An inhibitory cue indicating that the response to an upcoming cue should be withheld.

Reactive epoch: The time period in an experimental paradigm during which the outcome is either to emit or omit a response.

Delay: Temporarily withholding a response tendency, with the intention of completing the response after a designated period of time.

an already-initiated response. Shorter SSRTs are associated with better reactive inhibitory control (Aron et al. 2004a; Aron and Poldrack 2006; Duann et al. 2009).

The neural systems underlying reactive stopping have been comprehensively reviewed elsewhere (Eagle et al. 2008b; Chambers et al. 2009; Chikazoe 2010; Ridderinkhof et al. 2011; Bari and Robbins 2013a; Aron et al. 2014). Briefly, based primarily on studies using the SST, the overarching consensus is that sensory information about a stop-signal is processed by frontal cortical regions that generate and issue a stopping command that is sent to the basal ganglia to interrupt the incipient response. The frontal regions of particular importance for reactive inhibitory control are the right inferior frontal cortex (rIFC; Aron et al. 2003, 2004a,b, 2007a, 2014; Chambers et al. 2006; Chikazoe et al. 2009a; Swann et al. 2009; Neubert et al. 2010; van Belle et al. 2014; Cai et al. 2016) and presupplementary motor area (pre-SMA; Floden and Stuss 2006; Nachev et al. 2007, 2008; Picton et al. 2007; Chen et al. 2009; Mars et al. 2009; Swann et al. 2009; Hikosaka and Isoda 2010; Neubert et al. 2010; Sharp et al. 2010; Cai et al. 2014a). In addition, numerous lines of evidence now support the basal ganglia, particularly the subthalamic nucleus (STN), as the target of rIFC and pre-SMA for the implementation of reactive inhibitory control (Aron and Poldrack 2006; Eagle et al. 2008b; Isoda and Hikosaka 2008; Li et al. 2008; Ray et al. 2012; Alegre et al. 2013; Schmidt et al. 2013). Finally, the premotor (Mattia et al. 2012) and primary motor cortex (Stinear et al. 2009; Swann et al. 2009) are the last cortical sites involved in this circuit before movement commands descend the cortico-spinal tract.

The standard stop-signal paradigm has great utility for explicitly cueing the need for reactive inhibitory processes. However, real-world stopping goals incorporate a template of features that reflect the complexities of the surrounding environment. Interestingly, the "stopping network" outlined above has recently been extended to account for response patterns in a paradigm that may better reflect inhibition as it manifests in daily life. In the Complex-Stopping Task, participants are required to respond as quickly as possible to a go-signal, consisting of a sequence of arrows that vary on five dimensions. Conversely, if all five dimensions of the current stimulus match the prototype determined prior to the testing block (i.e., the "stopping template"), participants are required to inhibit responding (Wessel and Aron 2014). Similar patterns of brain activity were found during this task compared to the standard SST. This indicates that the network supporting reactive inhibition generalizes across tasks with vary-

ing complexity, and further validates the utility of the standard SST for approximating real-world stopping behavior.

Proactive inhibition

Fewer studies have focused on the brain substrates of proactive inhibitory control, and those studies that have done so have primarily used modified SSTs that include additional signals that indicate a stop-signal is pending, or otherwise provide information about the probability of a stop-signal occurring during a set of trials. Perhaps not surprisingly then, there appears to be significant overlap in the brain systems that are reported to underlie proactive and reactive inhibition. Indeed, proactive inhibition has been shown to engage brain networks that include the rIFC, pre-SMA, STN, and striatum (Hester et al. 2004; Vink et al. 2005a; Chikazoe et al. 2009a; Chen et al. 2010; Jahfari et al. 2010; Zandbelt and Vink 2010; Swann et al. 2012; Aron et al. 2014; Cunillera et al. 2014; Verbruggen et al. 2014b; Cai et al. 2016; but see Zandbelt et al. 2013a,b) with downstream effects on primary motor cortex excitability (Duque and Ivry 2009; Sinclair and Hammond 2009; Stinear et al. 2009; Claffey et al. 2010).

At the same time, differences are apparent in the laterality to which these brain systems are engaged. For example, the reactive network involves a right-lateralized frontoparietal circuit involved in stimulus-driven attentional control (Corbetta and Shulman 2002; Corbetta et al. 2008), action control (Goodale and Milner 1992; Rizzolatti and Matelli 2003), and action intention (Andersen and Buneo 2002). Conversely, circuits common to both reactive and proactive inhibition appear to be bilaterally organized (Li et al. 2006; Congdon et al. 2010; van Belle et al. 2014), which may be better suited to incorporate information obtained from a variety of sensory, cognitive, and limbic sources. Furthermore, the overlap between these networks may be best characterized by contributing to conflict resolution, maintenance of task sets, and action control more generally. van Belle et al. (2014) found that networks important for proactive and reactive inhibition overlapped primarily in the dorsolateral prefrontal cortex (dlPFC). However, the dlPFC has previously been implicated for inhibitory control that is conditional on a certain set of circumstances (such as a specific context) as opposed to more generalized stopping processes (Chikazoe et al. 2009a; Jahfari et al. 2010; Swann et al. 2012), suggesting that dlPFC may implement task rules rather than behavioral inhibition per se.

Basal ganglia circuits in proactive and reactive inhibition

A potentially fruitful avenue for research may be to focus on distinguishing the neural substrates underlying proactive and reactive inhibitory processes at the level of basal ganglia circuits. For example, the differential implementation of reactive and proactive inhibitory control processes may be mediated by switching between the indirect and hyperdirect basal ganglia pathways of movement, respectively (Aron et al. 2007b; Isoda and Hikosaka 2008; Jahfari et al. 2011). Functionally similar to the indirect pathway, the hyperdirect pathway is a cortico-subthalamo-pallidal circuit that has the net effect of inhibiting thalamic neurons, which in turn are unable to activate the motor cortex (Utter and Basso 2008). However, the hyperdirect pathway bypasses the striatum to quickly convey direct excitatory effects from motor-related cortical areas to the globus pallidus (Nambu et al. 2002). As a result, the hyperdirect pathway is particularly well suited to mediate reactive inhibition. Successful inhibition of a response depends on the competition between these pathways and the direct pathway, which induces downstream excitatory effects on the motor cortex (Aron and Poldrack 2006; Dunovan et al. 2015). The ultimate output of the basal ganglia depends on the integration of several signals that promote or inhibit behavior (Alexander et al. 1986; Albin

et al. 1989; Burle et al. 2004; Narayanan and Laubach 2006; Narayanan et al. 2006; Bryden et al. 2012).

Nevertheless, the similar findings to date regarding the systems associated with reactive and proactive inhibition could simply reflect that the two processes are closely intertwined. Indeed, converging lines of evidence suggest that even standard SST or Go/No-Go procedures can actually involve both proactive and reactive components (Verbruggen and Logan 2009a,b; Aron 2011; Criaud et al. 2012). For instance, several studies have demonstrated that response speed is altered following errors or stop-trials (Emeric et al. 2007; Verbruggen and Logan 2009b; Bissett and Logan 2012a,b). Specifically, the latency to respond during a go-trial has been shown to decrease after successive go-trials and increase after successive trials with a stop-signal (Emeric et al. 2007), suggesting that processing the outcome of one trial may subsequently influence responding on another. Although there are many possible explanations for these findings, one implication is that proactive inhibitory processes interact closely with reactive stopping behavior, as described further in the following section.

Interaction between proactive and reactive processes

The potential interaction between reactive and proactive processes is apparent in the Horse-Race Model (Logan and Cowan 1984), a long-standing theoretical perspective regarding inhibitory control. In a standard inhibition paradigm, subjects are instructed to perform go-trials as quickly as possible, yet attempting to stop whenever they hear the stop-signal. The Horse-Race Model theorizes that when the stop-process finishes before the go-process, the response is inhibited, whereas when the go-process finishes before the stop-process, the response is made (Logan and Cowan 1984). Based on this perspective, proactive inhibitory control that results in response slowing may increase the chance that a response can be inhibited (Logan and Cowan 1984). In line with this, behavioral and brain imaging data indicate that a stronger preparatory process helps to withhold a response (Chikazoe et al. 2009b; Verbruggen and Logan 2009b; Benis et al. 2014; Castro-Meneses et al. 2015). One intriguing theory is that the stopping network utilized for reactive stopping could be potentiated in advance—that is, proactively controlled (we refer the reader to Aron 2011 for a more detailed model). Support for this view comes from evidence that key components of the stopping network are not only activated exogenously (in response to a stop-signal) but also endogenously (in anticipation of a possible stop-signal).

Proactive recruitment of the stopping network can increase the chance of successful stopping (Vink et al. 2005a; van Gaal et al. 2008; Chikazoe et al. 2009a Jahfari et al. 2010; Swann et al. 2013; Wessel et al. 2013; Zandbelt et al. 2013b). Furthermore, preparing to stop in advance of a stop-signal has been associated with reduced activity in behavioral inhibition-related regions during the implementation of inhibition, suggesting a priming of these regions that supports later stopping efficiency (Chikazoe et al. 2009b; Verbruggen and Logan 2009b). Indeed, the stopping network may act to "brake" motor output, without stopping it completely. Subsequently, if stopping is required, it will occur more quickly (Aron 2011). Using the Conditional Stop-Signal Task (De Jong et al. 1995), Jahfari et al. (2010) examined the neurocognitive mechanisms that underlie the "response delay effect" (slower reaction times to a go-signal in a context where participants anticipate they might need to stop). They found that this effect is at least partly explained by an active braking mechanism that proactively suppresses the initiated response without canceling it completely, possibly involving a mechanism that is similar to that used to stop responses completely. In line with this, where-

as reactive stopping signals are supported by early (phasic) STN responses, proactive stopping signals are mediated by a more sustained (tonic) STN activity that also predicts subjects' inhibitory performance during the SST (Benis et al. 2014). One possibility is that weak activation of the stopping network can brake motor output, whereas strong activation will block motor output completely (Aron 2011, Aron et al. 2014). However, the extent to which braking occurs probably depends on areas outside of the stopping network as well. For example, activation of rIFC may potentiate a dormant inhibitory connection between sensory cortices relevant to the modality of the stop-signal and the motor system that will facilitate stopping if the stop-signal is subsequently presented (Wiecki and Frank 2013; Chiu and Aron 2014; Verbruggen et al. 2014b; Kenemans 2015).

Cognitive and motivational influences on inhibition

Further complicating the dissection of proactive from reactive inhibition processes is that the generation of stopping goals and the implementation of inhibitory control require a range of other cognitive and motivational processes (Jaffard et al. 2007, 2008; Rushworth and Taylor 2007; Boulinguez et al. 2008, 2009; Eichele et al. 2008; Chatham et al. 2012). In addition, stopping goals themselves may differ in accordance with the differential cognitive demands of tasks used to study inhibition. Yet, most studies primarily focus on the absence of a response under conditions where a response would otherwise be emitted, whereas other cognitive and motivational processes that likely contribute to inhibition are often excluded from consideration. Indeed, mounting evidence challenges the idea of response inhibition as an isolated function (Munakata et al. 2011; Aron et al. 2014) and posits that inhibitory control is modulated significantly by other processes (Munakata et al. 2011; Chatham et al. 2012; Criaud and Boulinguez 2013) as illustrated in the three examples that follow.

Attention

Attentional processes contribute extensively to the implementation and success of behavioral inhibition (Chatham et al. 2012; Aron et al. 2014; Verbruggen et al. 2014b). Indeed, the efficient detection of meaningful cues in an environment, such as a stop-signal, is essential for effective inhibitory control (Chatham et al. 2012). Furthermore, inhibitory control is influenced by saliency of signals indicative of either Go or Stop behavior (Wardak et al. 2012). At the same time, irrelevant stimuli must be filtered out. This requires learning which parts of the environment are most relevant, as well as down-regulating attentional processes directed toward irrelevant stimuli. Importantly, when distracters are expected, stimulus-driven attention can be down regulated (Corbetta et al. 2008), reducing the likelihood that a distractor will disrupt the process of inhibiting a behavioral response.

Preparatory changes in the function of acetylcholine (ACH) or norepinephrine (NE) systems may be critical to both enhancing and attenuating the level of attention directed to a cue in the environment. An increase in ACH release enhances performance in a variety of paradigms measuring behavioral control by enhancing the ability to detect and attend to relevant visual stimuli (Luntz-Leybman et al. 1992; Acri et al. 1996; Blondel et al. 2000; Semenova et al. 2003; Young et al. 2013). ACH is also involved in latent inhibition, indicating that it can also modulate decreases in attention when a stimulus is irrelevant (Rochford et al. 1996). In addition, several studies have documented involvement of prefrontal NE activity in inhibitory control (e.g., Eagle et al. 2008a; Robbins and Arnsten 2009; Bari et al. 2011). The NE system can optimize cognitive function relative to the state of the environment and the individual at the time of testing (Usher et al.

1999; Aston-Jones and Cohen 2005). Indeed, NE is involved in setting basal levels of cortical activity and enhancing stimulus-evoked neural responsiveness in both sensory and motor areas (Foote and Morrison 1987; Berridge and Waterhouse 2003). As a result, changes in NE levels alter responsivity to behaviorally relevant cues that can trigger a sudden change in, or an interruption of, ongoing behavior (Aston-Jones and Cohen 2005; Bouret and Sara 2005; Dayan and Yu 2006).

Interestingly, there is evidence that attentional processes mediated by rIFC may contribute to the maintenance of task-relevant information such as the detection of novel or infrequent stimuli (i.e., a stop-signal; Chikazoe et al. 2009b; Duann et al. 2009; Hampshire et al. 2010; Sharp et al. 2010; Erika-Florence et al. 2014) or the detection of changes in response contingency (Mullette-Gillman and Huettel 2009). Evidence along these lines has prompted controversy in recent years about whether the stopping network truly reflects inhibitory control, rather than mere attention (Chatham et al. 2012; Erika-Florence et al. 2014). However, emerging evidence continues to support a functional and anatomical differentiation within rIFC and areas that implement attentional monitoring and inhibitory control functions (Chikazoe et al. 2009b; Verbruggen et al. 2010; Levy and Wagner 2011). Specifically, the ventral posterior part of rIFC contributes primarily to global and reactive inhibition process whereas the dorsal part of rIFC is involved more in attentional processes, including cue detection (Chikazoe et al. 2009b; Verbruggen et al. 2010; Cai and Leung 2011). In addition, a recent meta-analysis differentiated the functional role of rIFC in the implementation of inhibitory control from the adjacent right anterior insula (rAI), which is part of a salience network critical for detecting behaviorally significant events (Cai et al. 2014b). At the systems level, the distinct but intrinsically linked functions of inhibition and attention are likely facilitated by parallel cortico-cortical and corticostriatal circuits that include both functional subdivisions of rIFC along with the rAI (Cai and Leung 2011). In summary, the anatomical proximity of the stopping network to regions involved in the maintenance and updating of task-relevant information may be used to bias brain systems that represent task-relevant response patterns (Derrfuss et al. 2004).

Expectancy

The extent to which proactive inhibitory control is implemented can vary dynamically with expectations about environment. For example, knowledge about the probability of occurrence of a stop-signal can modulate an individual's ability to inhibit movement (De Jong et al. 1995; Vink et al. 2005a; Jaffard et al. 2007; Verbruggen and Logan 2009b; Boy et al. 2010; Cai et al. 2011; Zandbelt et al. 2013b). This has been studied by modifying the standard SST to include cues that indicate the probability of a stop-signal occurring (Verbruggen and Logan 2009b; Bisset and Logan 2012b; Federico and Mirabella 2014). These experiments have demonstrated correlations between reaction time (on go-trials) and the probability of a stop-signal being presented (Vink et al. 2005a; Chikazoe et al. 2009b; Verbruggen et al. 2010). In particular, slower reaction times are found when the proportion of stop-signals increases (Logan and Burkell 1986; Verbruggen and Logan 2009b).

In addition, a recent study showed that proactive inhibitory control depends not only on the processing of contextual cues indicating stop-signal probability, but also on the subjective interpretation of these cues (i.e., stop-signal expectation; Vink et al. 2015). These processes differently engage parts of the frontostriatal network. Specifically, the expectation of having to stop is associated with activity in dorsal premotor cortex, SMA and striatum. These data suggest that the striatum is involved in forming predic-

tions when an inhibitory signal is present, consistent with studies reporting striatal activity when the occurrence of a stop-signal is highly predictable (Vink et al. 2005a; Aron and Poldrack 2006; Zandbelt and Vink 2010) and with studies showing increased ventral striatum and SMA activity during the expectation of reward (Figee et al. 2013; Hoogendam et al. 2013). In contrast, rIFC and right inferior parietal cortex (rIPC) activity are modulated by probability cues, but not stop-signal expectation (Vink et al. 2015). Thus, rIFC and rIPFC may be related to the processing of contextual cues that indicate the probability of a stop-signal occurring whereas the striatum incorporates this information into a prediction of what will happen.

The continuous maintenance of stopping goals that is required for proactive inhibition is resource consuming, and often slows response times (Logan and Burkell 1986; Verbruggen and Logan 2009b; Jahfari et al. 2010). Interestingly, there is evidence that individuals are able to switch between controlled inhibition of a response (i.e., anticipated suppression of the neuronal processes underlying movement initiation) and automatic processing (i.e., reactive inhibition) depending on their expectations of upcoming events (Jaffard et al. 2008; Hikosaka and Isoda 2010; Criaud et al. 2012; Verbruggen et al. 2014b). This dynamic adjustment of response patterns is often associated with a phenomenon referred to as the "speed-accuracy trade-off" (Wickelgren 1977; Gold and Shadlen 2002; Wang 2008; Bogacz et al. 2010a,b; Heitz 2014), because engagement of proactive inhibitory control mechanisms has been associated with reductions in erroneous responses (Boulinguez et al. 2008; Wardak et al. 2012). However, there is little research into the factors that mediate how an individual *learns* to distinguish the circumstances that dictate the use of reactive versus proactive inhibitory control processes.

Motivation

Internally generated factors, such as motivation, also critically influence the development of behavioral goals, including those goals that relate to inhibiting a response (Leotti and Wager 2010). A key element in establishing motivational level is the anticipated reinforcement associated with a given response pattern. According to the dual mechanisms of control framework (Braver et al. 2007; Braver 2012), proactive control will only be utilized if the cost/benefit tradeoff is favorable. This computation depends on both the ease of actively maintaining goal representations in advance of their utilization, as well as on internal estimates of how beneficial or valuable the consequences of such a control strategy are for task performance (Braver et al. 2007; Locke and Braver 2008; Jimura et al. 2010; Savine et al. 2010). Thus, changes in the reward expectations are one example of how motivational factors may adjust the threshold for generating a top-down inhibitory signal.

Motivation may mediate the extent to which cues in the environment are used to guide behavior. For example, changes in cue salience as a result of motivational factors can directly influence the attentional mechanisms deployed to detect inhibitory cues (Raymond and O'Brien 2009; Pessoa 2014). Furthermore, dopaminergic inputs to the nucleus accumbens (NAC) mediate the attribution of incentive-salience to reward cues, which in turn invigorates approach toward these cues (Berridge and Robinson 1998). Dopamine also acts in NAC to integrate and filter incoming information (Floresco 2007), which is important for regulating behavioral responses, including the inhibition of responses that may interfere with the goals of an individual. In this way, NAC likely plays an integral role in suppressing inappropriate actions and facilitating proactive inhibitory control (Floresco 2015). The orbitofrontal cortex (OFC) is also of particular relevance in mediating the contributions of motivation to

inhibitory control. The OFC is implicated in representing contingencies and expectations between predictive cues and reward outcomes (Hikosaka and Watanabe 2000; Schultz et al. 2000; McClure et al. 2004; Cox et al. 2005; Galvan et al. 2005; Hosokawa et al. 2005; Delamater 2007; Ostlund and Balleine 2007; Wallis 2007; Padoa-Schioppa and Cai 2011; Schoenbaum et al. 2011; Rudebeck et al. 2013; Moorman and Aston-Jones 2014). In addition, OFC activity has been associated with the regulation of reward-related impulses (Elliott et al. 2000; Chudasama and Robbins 2003; O'Doherty et al. 2003).

Moving forward: isolating proactive from reactive inhibitory processes

The body of literature described thus far illustrates the complexity and inherent challenges in studying and dissecting the neural substrates that contribute to proactive versus reactive inhibitory processes, perhaps even calling into question the utility of distinguishing between them. One conclusion is simply that proactive and reactive inhibitions are supported by the same neural systems and mechanisms. Recruitment of a common neural network both for stop-processing prior to the presentation of a stop-signal and for implementation of the stopping process could indicate that the same structures are engaged in a variety of distinctive ways to inhibit behavioral responding. Another possibility is that distinguishing between the systems underlying proactive and reactive inhibition has proven difficult because the behavioral tasks to date are not ideally suited for isolating one from the other, or from the multitude of other cognitive process that likely modulate proactive inhibition. The remainder of the article considers how fundamental differences between proactive and reactive inhibition could be exploited to design procedures that allow for the study of proactive processes in particular.

The temporal dynamics of proactive inhibitory control

The relative timing of informative events, such as the occurrence of salient environmental cues, varies between different inhibitory control tasks and these temporal dynamics may be exploited as an avenue for disambiguating the neural correlates of proactive and reactive inhibitory control. Figure 1 illustrates the generation of a proactive inhibitory control signal as it manifests in a number of commonly used paradigms to study inhibition. All inhibition tasks include a "reactive epoch" (RE), that is usually stimulus-associated. During the RE, the outcome is either to *emit* or *omit* a response. In many cases, the outcome depends on the degree to which proactive inhibitory control processes have been engaged (Chikazoe et al. 2009b; Verbruggen and Logan 2009b; Benis et al. 2014; Castro-Meneses et al. 2015). We propose two main orthogonal axes on which these processes can vary. The first axis is the level of awareness that an individual has for the need to engage inhibitory control processes. This awareness depends on the flexible updating of stopping goals to incorporate information from discrete as well as diffuse features of the environment. Diffuse features may include the environmental setting as a whole (the "context"), for example, when an individual has been instructed to inhibit responding under certain circumstances, or to ignore distracting stimuli. Alternatively, the diffuse context may refer to trial-by-trial learning, during which negative feedback signals influence behavior on subsequent trials. Cues that initiate proactive inhibitory control may also be discrete stimuli, such as those indicating the probability that stopping will need to occur, as well as negative occasion setters (cue indicates that the response to another stimulus should be withheld; see below).
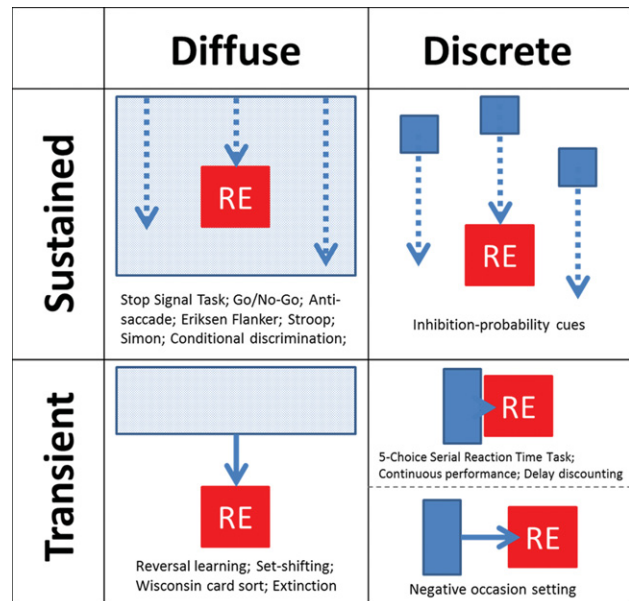

Figure 1. The generation of a proactive inhibitory control signal is influenced by temporal dynamics. All inhibition tasks include a "reactive epoch" (RE), that is usually stimulus-associated, and during which the outcome is either to emit or omit a response. Proactive control processes can be initiated in response to diffuse (shaded boxes) or discrete (solid boxes) cues in the environment. In addition, informative cues may be present in a sustained or transient manner. Sustained cues may not directly predict an impending RE (dashed lines), whereas transient cues are in direct temporal proximity to an impending RE (solid lines). These axes have been used to categorize a number of commonly used inhibition tasks with regard to the manner in which inhibitory control is implemented.

The second axis is differentiated by the temporal proximity of the inhibitory control signal to the implementation of motoric inhibition (see also Braver 2012). Proactive inhibitory control can be sustained over a much longer period than the RE, as is the case when diffuse or discrete cues may not directly predict an impending RE. Alternatively, proactive inhibitory control may be initiated by a transient event, such as the preceding trial or a negative occasion setter, directly associated with an impending RE. A somewhat different form of inhibition can also occur in this manner during "delay" tasks, in which the RE occurs between an inhibitory cue and a response-triggering cue. In these tasks, the delay, but not complete omission of responding, is required. Variation on these axes may influence the success of reactive inhibitory control. As a general note, there is some overlap between these categories. For example, the stop-signal in the SST is a discrete cue; however, it occurs too late to induce proactive control. Nonetheless, this framework may prove useful for appropriately selecting tasks that tap proactive versus reactive inhibition as described below.

Learning processes associated with proactive inhibition

Successful inhibitory control depends in large part on detecting and using the environmental cues that indicate that a response should be inhibited (Chatham et al. 2012; Wardak et al. 2012; Aron et al. 2014; Verbruggen et al. 2014b). Critical to this process is identifying and *learning* the meaning of such cues, while also learning to ignore irrelevant stimuli. Furthermore, the acquired information must also be represented mnemonically such that

it can be utilized to shape responding when inhibitory cues are encountered again (Munakata et al. 2011; Majid et al. 2013; Verbruggen et al. 2014a). Learning and memory processes may be especially important for proactive inhibition, which often requires maintaining the representation of an environmental cue that signals that a future response should be withheld. Similarly, proactive inhibition requires the maintenance of task goals as well as a top-down bias to facilitate the processing of upcoming cognitively demanding events (Chikazoe et al. 2009b).

One means to isolate proactive from reactive inhibitory processes may thus be to use behavioral procedures that focus on learning the meaning of inhibitory signals, while also exploiting the temporal dynamics that are unique to proactive inhibition. This would be most apparent when responding is suppressed under conditions that would normally elicit a response. This is modeled in the serial feature negative discrimination (SFND) paradigm that produces negative occasion setting (Fig. 2; Holland et al. 1999). An "occasion setter" is a cue that provides information that resolves the ambiguity of another stimulus and modulates behavior that is directed to it (Pavlov 1927; Skinner 1938; Holland 1992; Bouton 2006). In the case of a negative occasion setter, the cue indicates that the response to an upcoming stimulus should be withheld. This paradigm models inhibition in situations in which the meaning of a stimulus (response or do not respond) is ambiguous, and can change on a moment-to-moment (i.e., trial by trial) basis. In this way, learning about negative occasion setters has direct bearing on adaptive behavior because they indicate the conditions under which a response will not be associated with an anticipated outcome and should be inhibited.

Although this form of inhibitory control has received scant attention in the literature, it may be a particularly useful avenue for studying proactive inhibitory control processes. In a typical SFND procedure (Fig. 2), trials in which a "target" stimulus is presented by itself are followed immediately by reinforcement. On other trials, a "feature" stimulus is presented just before the target, and no reinforcement occurs on those trials. Thus, the feature stimulus acts to "set the occasion," or the context, for the meaning of the target stimulus and indicates that a response should be withheld during the subsequent presentation of the target (Holland and Morell 1996; Bouton and Nelson 1998; Bueno and Holland 2008). Importantly, the feature stimulus is an explicit cue, indicating that inhibition is necessary, but is separated in time from the target stimulus, which is the point during the trial where inhibitory control must be implemented for the trial to be considered successful. This allows for a greater extent of temporal isolation between proactive and reactive control processes than standard inhibitory paradigms like SST.

Currently, the experimental procedure for testing inhibitory control in this way has been used primarily in rodent models.
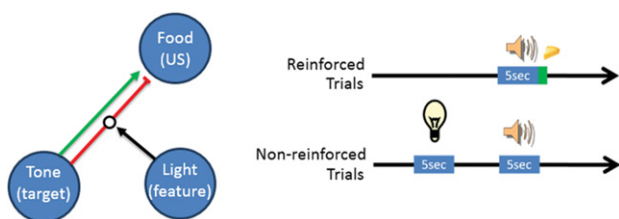

Figure 2. Configuration of cues and schematic diagram of a typical serial feature negative discrimination paradigm. Red and green lines indicate inhibitory and excitatory relationships, respectively. The feature cue acts as a signal that prepares the subject to disambiguate the meaning of the target cue. When the feature is present, responding during the target should be omitted. When the feature is absent, responding during the target cue is appropriate.

Similar temporal separation between the activation of proactive processes and the response epoch are present in modified stop tasks that include a cue indicating the probability that a stop-signal will occur (Zandbelt et al. 2013b; Vink et al. 2015). However, in these tasks the stop-signal still occurs *after* a go-signal and thus, at least to some extent, inhibitory control will manifest to abort an ongoing response. Conversely, a negative occasion setter indicates that a cue interpreted as a go-signal on some trial types should now be interpreted as an inhibitory cue, and a response should not be initiated in the first place. Further development of inhibition paradigms that incorporate this type of trial structure in both human and animal studies will likely be of valuable use for future research.

The SFND procedure also facilitates studying learning processes. Early in training, rats gradually learn to respond when the target is presented. However, successful discrimination between the trial types is indicated by responding more when the target is presented by itself and withhold responding to the target when it is preceded by the feature (Holland et al. 1999; MacLeod and Bucci 2010; Meyer and Bucci 2014). Comparing the neurobiological processes that are active during the presentation of the target across training may be very useful for informing the learning processes that contribute to inhibitory control. Flexibly updating the meaning of cues is crucial for regulating behavior that is contingent upon those cues. In addition, both reversal and extinction processes involve updating the representations of cues in the environment, and responses directed toward these cues (for reviews of these topics see Delamater and Westbrook 2014; Hamilton and Brigman 2015). These procedures may also be useful for studying the underlying behavioral and systems level learning processes that contribute to the implementation of inhibitory control.

Finally, the SFND procedure provides a means of elucidating the neurobiological factors that contribute to omitting a response and how these factors differ from those required for preparing to suppress a response. The dlPFC, which has been implicated in both reactive and proactive inhibition of a prepotent response (van Belle et al. 2014), may also be involved in the proactive process of response omission due to its role in monitoring environmental cues in order to generate appropriate response strategies (Ragozzino 2007; Hikosaka and Isoda 2010). Moreover, the rodent homolog of dlPFC (prelimbic cortex) is required for successful inhibitory control in the SFND paradigm (MacLeod and Bucci 2010). Also of interest is OFC, based on evidence that this region is particularly important for mediating cue representations under circumstances of ambiguity (Schoenbaum et al. 2009; Gremel and Costa 2013). This is of particular relevance for negative occasion setting, where behavior directed toward the same stimulus must either be emitted or withheld, depending on the presence of environment signals. Moreover, subcortical regions such as NAC that contribute to the motivational aspects of a stopping goal (outlined above) may also prove to be of importance in preparing to omit a response. Indeed, contemporary research has conceptualized a framework wherein prefrontal and subcortical regions work in concert toward mediating goal-directed behavior, including situations where inhibition is the most appropriate course of action (Casey et al. 2008; Somerville and Casey 2010; Heatherton and Wagner 2011). Consistent with this concept, we have recently shown that a dynamic interplay between neural activity in OFC and NAC is essential for proactive inhibition as measured in a negative occasion setting procedure (Meyer and Bucci, in press).

Implications for psychopathology

Inhibitory control difficulties are apparent in a number of neuropsychological disorders such as ADHD (Schachar et al. 1995, 2007;

Oosterlaan and Sergeant 1998; Rubia et al. 1998, 2005, 2007, 2009a; Aron and Poldrack 2005; Bekker et al. 2005; Lijffijt et al. 2005; de zeeuw et al. 2008; Durston et al. 2009; Bari and Robbins 2013b), OCD (Lipszyc and Schachar 2010), schizophrenia (Kiehl et al. 2000; Raemaekers et al. 2002; Vink et al. 2005b; Enticott et al. 2008; Hughes et al. 2012), conduct disorder (Oosterlaan et al. 1998; Rubia et al. 2009b), Tourette syndrome (Goudriaan et al. 2005; Ray Li et al. 2006), substance use disorders (Fillmore and Rush 2002; Fillmore et al. 2006; Garavan et al. 2008; Chambers et al. 2009; Liao et al. 2014), and pathological gambling (Grant et al. 2011). Such difficulties are also present in neurodegenerative disorders such as Huntington's disease (Majid et al. 2013) and Parkinson's disease (Gauggel et al. 2004; Mirabella et al. 2012), as well as in normal cognitive aging (Kramer et al. 1994; Coxon et al. 2012; Smittenaar et al. 2015). Disruptions to inhibitory control may reflect problems in learning to use environmental cues to activate and maintain information about which actions are most appropriate in a given context rather than problems in downstream implementation of inhibition (Munakata et al. 2011). If stopping goals cannot be maintained, proactive inhibitory control processes will be difficult to initiate (Aron et al. 2014). Thus, these populations may show differential reliance on reactive versus proactive control (Zandbelt et al. 2011; Braver 2012). A more nuanced and fine-grained analysis of cognitive control function in these different groups may provide more effective therapeutic interventions. Furthermore, the appropriate targets for cognitive intervention may have somewhat similar characteristics and should be geared toward supporting prefrontal maintenance of the appropriate contextual information (Munakata et al. 2011; Chatham et al. 2012).

Conclusions

Behavioral paradigms that model how a subject prepares to stop an upcoming response tendency have significant relevance for real-world demands because inhibition manifests according to the goals of the subject rather than purely in reaction to an external signal (Aron 2011). However, there is currently a troubling lack of insight into how goals are established and translated into regulation of the inhibitory signal. Learning to inhibit behavior involves a number of neurocognitive processes, which are implemented in the brain by complementary circuits. The research reviewed in this article highlights the need for precise operational definitions of the underlying cognitive processes that contribute to inhibitory control. Inhibitory control can be viewed as one output component from the much larger process of actively maintaining abstract goal-related information (Miller and Cohen 2001; Munakata et al. 2011). Thus, future research may benefit from considering the interactions between the systems underlying this process, when attempting to isolate the neural correlates of inhibitory control.

Although the exact details of the circuitry underlying inhibitory control are still in debate, an emerging theme is that reactive and proactive inhibition function in a complementary manner to permit efficient and flexible control of behavior in response to details of the surrounding environment. Furthermore, even if different inhibitory phenomena do not share one common neural substrate, they likely have mechanistic similarities. As such, the mechanistic details of response inhibition may also underlie control across functional domains, including non-motor processes such as emotional and motivational impulses, as well as attention directed to distracting and irrelevant stimuli. Thus, mapping the neural architecture of cognitive control through studies of reactive and proactive inhibition may be very useful in determining the parallel neurobiology of a range of control scenarios.

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