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The Pause-then-Cancel model of human action-stopping: Theoretical considerations and empirical evidence

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ABSTRACT

The ability to stop already-initiated actions is a key cognitive control ability. Recent work on human action-stopping has been dominated by two controversial debates. First, the contributions (and neural signatures) of attentional orienting and motor inhibition after stop-signals are near-impossible to disentangle. Second, the timing of purportedly inhibitory (neuro)physiological activity after stop-signals has called into question which neural signatures reflect processes that actually contribute to action-stopping. Here, we propose that a two-stage model of action-stopping – proposed by Schmidt and Berke (2017) based on subcortical rodent recordings – may resolve these controversies. Translating this model to humans, we first argue that attentional orienting and motor inhibition are inseparable because orienting to salient events like stop-signals automatically invokes broad motor inhibition, reflecting a fast-acting, ubiquitous Pause process. We then argue that inhibitory signatures after stop-signals differ in latency because they map onto two sequential stages: the salience-related Pause and a slower, stop-specific Cancel process. We formulate the model, discuss recent supporting evidence in humans, and interpret existing data within its context.

1. The study of action-stopping

1.1. Action-stopping and its significance

Motor inhibition allows animals to stop an action even after it has already been initiated, for example, when withholding a reaching movement after spotting a lurking predator. In the face of changing environments or unexpected events, individuals that possess the ability to stop ongoing actions may continue the pursuit of short- or long-term goals while behaving flexibly and keeping themselves safe from bodily harm.

In humans, the ability to implement action-stopping is subject to variation across individuals (Forstmann et al., 2008) and the lifespan (Coxon et al., 2012). Moreover, certain neurological and psychiatric disorders are associated with deficits in motor inhibition, leading to difficulties with behavioral action-stopping (Obeso et al., 2011; Penades et al., 2007; Nigg, 2001; Morein-Zamir and Robbins, 2015; Lavagnino et al., 2016). Therefore, there is a vested public health interest in understanding the neural process(es) underlying motor inhibition as they support the ability to stop initiated actions. Additionally, prominent work across many recording and imaging modalities (cf. Chapter 2) has suggested that the neural circuitry that exerts inhibition over movement also implements control over other types of neural representations, such as those underlying working memory or attentional focus (Ravizza and Ivry, 2001; Frank et al., 2001; Johnson and Anderson, 2004; Aron et al., 2007; McNab and Klingberg, 2008; van Schouwenburg et al., 2010; Chiu and Egner, 2015; Anderson et al., 2016; Wessel et al., 2016; Wessel and Aron, 2017; Soh and Wessel, 2020; Tempel et al., 2020). Therefore, by expanding our understanding of the circuits that serve motor inhibition, we may learn more about how inhibitory control broadly facilitates flexible behavior and cognition. Notably, many excellent reviews already exist on the subject of action-stopping and motor inhibition (Ridderinkhof and Van Der Molen, 1997; Aron, 2007; Chambers et al., 2009; Munakata et al., 2011; Jahanshahi et al., 2015; Schall et al., 2017), and the potential extension to non-motor processes has also been reviewed elsewhere (Wessel and Aron, 2017). However, recent years have seen lively and controversial debates surrounding the very basics of human action-stopping in the human brain, which still remain unresolved.

In this theoretical paper, we discuss the neuroscience of action-stopping in humans and attempt to reconcile these open questions by proposing a new model of motor inhibition in humans, based on an

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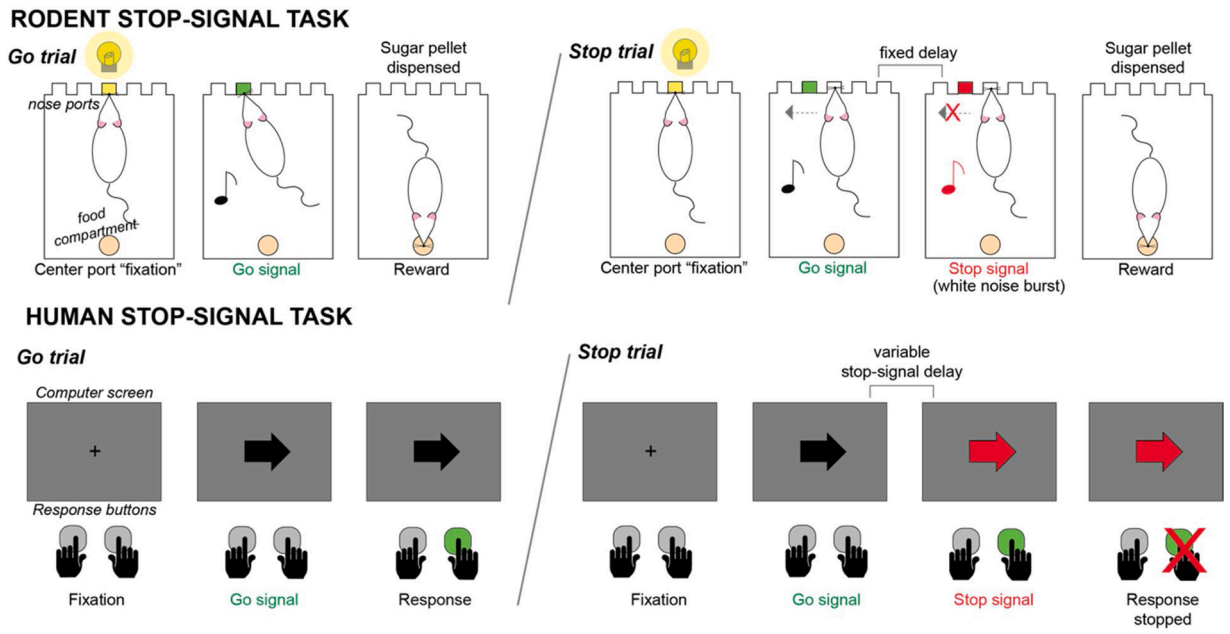

Fig. 1. Examples of a rodent and human stop-signal task (SST). The rat is put in a test chamber with nose ports on one end and a food dispenser at the other. The beginning of a trial is cued by cage lights turning on, at which point the rat puts its nose in the central port to indicate readiness. On each trial, the rat hears an auditory cue that indicates the direction of the "go" response. On a go-only trial, the rat moves its nose to the indicated nose port following the required fixation time. On stop trials, a stop-signal consists of a subsequent burst of white noise. If the rat does not perform a trial accurately, the lights come back on and no sugar pellet is dispensed. If the trial is performed accurately, the rat receives a sugar pellet. Human participants perform a visual version of the SST on a computer. Go and stop signals consist of black and red arrows presented on the computer monitor and the participant uses buttons on a keyboard to respond.

existing model derived from recent experimental findings in rodents – the "Pause-then-Cancel" (PTC) model of motor inhibition (Schmidt and Berke, 2017).

1.2. The use of the stop-signal paradigm in action-stopping research

The study of action-stopping employs paradigms that cue participants to withhold or cancel prepotent actions – such as the Go/No-Go task (Donders, 1969), the stop-signal task (Logan and Cowan, 1984), or the anti-saccade task (Hallet and Adams, 1980). In this theoretical paper, we focus largely on work using the stop-signal task (SST), which is considered the gold-standard among those tasks (Verbruggen et al., 2019). However, we will provide arguments that the theoretical framework we present later in this theoretical paper (see Chapter 5) applies to motor inhibition in other paradigms as well – including, but not limited to, the Go/No-Go and anti-saccade tasks.

In the SST, participants respond to imperative stimuli (go signals) on every trial, but must attempt to withhold the response when presented with a second stimulus (the stop signal), which is shown following a variable delay on a subset of trials (typically ¼ or 1/3). (See Fig. 1 for examples of this task in rodents and in humans.) Though no response is made on successful stop trials, the latent timing of the stop process can be estimated from known characteristics of the correct go and failed stop reaction time distributions, using a popular computational model. This measure of the latent stopping process is called stop-signal reaction time (SSRT; Logan et al., 1984; Logan, 1994; Verbruggen and Logan, 2009). The calculation of this quantity is made possible through a horse race conceptualization of the processes involved in this task: on each stop-trial, the go-signal triggers a prokinetic go-process that works towards executing the cued response, whereas the subsequent stop-signal triggers an anti-kinetic stop-process that aims to cancel it (Logan and Cowan, 1984; Schall and Godlove, 2012; Verbruggen and Logan, 2009; Kok et al., 2004; Matzke et al., 2013). Historically, this "stop process" deployed during the SST has been conceptualized as a unitary process. According to the popular horse race model of motor inhibition put forth by Logan and Cowan (1984), a single stopping process is initiated following the stop-signal and races the go process, with both racing until a threshold is reached. The outcome of this race determines whether the action is either successfully stopped or not. Though this model fits behavioral data gleaned from the SST, researchers have long struggled to reconcile central assumptions of the model, such as the independence of the go and stop processes, with neural recordings.

In contrast to single-stage horse race models, Schmidt and Berke (2017) recently proposed a *two-stage* model of action-stopping (based on their work recording from the rodent basal ganglia) – the Pause-then-Cancel (PTC) model. This model posits that action-stopping results from the combination of two anti-kinetic, inhibitory processes, which are underpinned by two complementary basal ganglia pathways. They proposed that the first stage of the two-stage inhibition sequence is constituted by a short-latency "Pause" process, which – akin to the "hold-your-horses" concept of Frank (Frank, 2006) – actively delays the go process (notably, this is a departure from the original independent horse race model of Logan and colleagues). This initial Pause stage is accompanied by a second stage, constituted by a slower "Cancel" process, which shuts off ongoing invigoration of the go response. Both processes work together to effect stopping: the Pause process hampers the Go process, thereby purchasing time for the Cancel process to shut off ongoing drive to the Go response before the movement is executed. As we will argue here for humans (and as Schmidt and Berke have done for rodents), the PTC model may more accurately reflect the pathways underlying go and stop processes in the brain (reviewed in Chapter 2) compared to single-stage models of motor inhibition. Furthermore, mapping this model to the human brain may in fact resolve several controversial debates that the field of human action-stopping has grappled with over the past two decades (cf. Chapter 3).

1.3. Aims of the current theoretical paper

In this theoretical paper, we attempt to adapt the framework of the PTC model from the rodent domain into the human domain and integrate recent findings from the human literature on action-stopping into this framework. Specifically, we aim to:

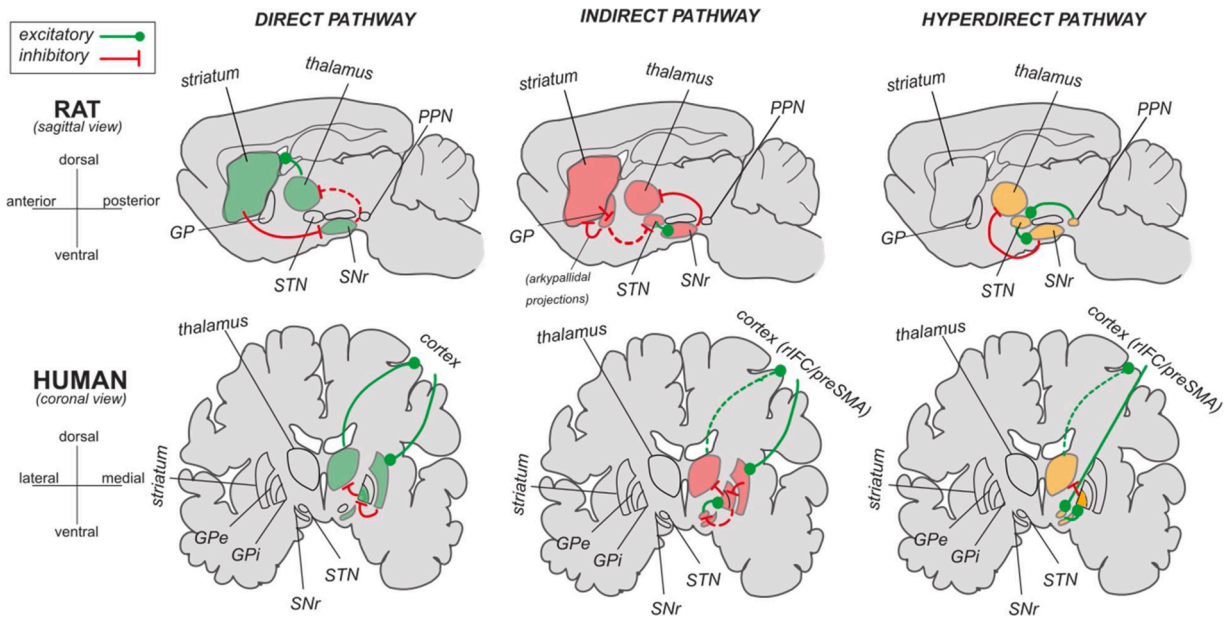

Fig. 2. The direct, hyperdirect, and indirect pathways in rats (as described in Schmidt and Berke, 2017) and in humans. Excitatory (glutamatergic) connections are represented in green, inhibitory (GABAergic) connections are represented in red, and dotted lines represent a reduction in signaling. In Schmidt and Berke's (2017) PTC model, the pedunculo-pontine tegmental nucleus (PPN) is proposed to initiate the signaling cascade involved in the Pause phase. However, human action-stopping literature focuses on the role of cortical regions such as the right inferior frontal cortex (rIFC) and pre-supplementary motor area (pre-SMA) in recruiting cortico-basal ganglia pathway mechanisms (see Chapter 2.1.3). The relative focus on cortical versus subcortical regions in the respective literatures is a reflection of the species' neuroanatomy and the degree of training and automaticity that is involved in performing the action-stopping behavior in the SST.

- Translate the anatomical pathways associated with action-stopping in humans onto the anatomical pathways described in the rodent PTC model.
- Map the neural and physiological signatures associated with action-stopping in humans to the two stages of the rodent PTC model.
- Propose how the Pause and Cancel processes may generalize to control contexts besides outright action-stopping.

Through these aims, we also hope to resolve two ongoing, controversial issues in the human literature on action-stopping, which we highlight in Chapter 3: First, the fact that many purported neurophysiological signatures of motor inhibition occur at different times after a stop-signal. Second, the question of which neural processes reflect the attentional detection of the need to stop, and which ones reflect motor inhibition itself.

2. The neuroscience of action-stopping

Before discussing in detail how the PTC model may be integrated with existing literature on action-stopping in humans, we will briefly review the (cortico-)basal ganglia pathways which purportedly underlie movement and motor inhibition in both species. For more exhaustive reviews, the reader is directed to existing literature (e.g., Aron, 2011; Jahanshahi et al., 2015; Kenemans, 2015). This will provide a foundation for subsequent chapters, which will deal specifically with our proposed human version of the PTC model.

2.1. Neuroanatomy of action-stopping

2.1.1. Pathways that underlie motor inhibition in rodents and humans

According to dominant neuroanatomical models, movement execution and motor inhibition are implemented by three complementary basal ganglia pathways (**see** Fig. 2). In their 2017 review, Schmidt and Berke describe these three pathways as they have been elucidated by neurophysiological research in rodents. Importantly, these three basal ganglia pathways are generally ascribed the same function by the literature on human movement and action-stopping (though some exceptions are noted in Chapter 2.1.3). The rodent PTC model makes specific predictions about how and when these pathways are recruited during motor inhibition. Before outlining these predictions in detail in Chapter 2.1.2, we summarize these pathways and their purported function here.

The direct pathway. The basal ganglia exert tonic, GABAergic inhibition of the motor cortex and other movement-related areas, preventing movement at rest (Graybiel, 2000; Hikosaka, 2007). For movement to occur, the cortico-basal ganglia direct pathway *net-disinhibits* brain areas responsible for movement execution, such as primary motor cortex or the frontal eye fields (Chevalier and Deniau, 1990). This is accomplished by GABAergic drive from the striatum to the substantia nigra pars reticulata (SNr), which results in reduced inhibition from SNr to motor regions (Hikosaka and Wurtz, 1985; Basso and Sommer, 2011). During movement initiation in the SST (and other tasks) in rats, this sequence of events can be directly observed – neuronal activity patterns in striatal subpopulations distinguish between contra- and ipsilateral movements at least 130 ms prior to movement initiation (Schmidt et al., 2013).

The indirect pathway. The indirect pathway is a purported multisynaptic, net-inhibitory pathway within the basal ganglia. Inputs from cortical or other brain regions are routed first through the striatum (specifically, the putamen) before signaling reaches the globus pallidus (GP), the subthalamic nucleus (STN), and the substantia nigra pars reticulata (SNr). In rodents, the GP contains inhibitory neurons that project to STN and SNr, but, as Schmidt and Berke (2017) describe, it also contains arkypallidal neurons (a population corresponding to the external segment of GP in humans) that project to the striatum, ostensibly allowing it to inhibit and thereby cancel direct pathway drive for movement at the source.[1] Though the GP is separated into internal and

[1] Though Schmidt and Berke (2017) propose that GP arkypallidal neurons inhibit prokinetic striatal neurons during stopping, we note that there is also a subpopulation of anti-kinetic (D2) neurons in striatum by which this cancellation of direct pathway drive might alternatively be accomplished (Eagle et al., 2011; Robertson et al., 2015).

external segments in humans, this is considered to be the same route by which the indirect pathway exerts anti-kinetic, inhibitory effects in humans as well.

The hyperdirect pathway. The hyperdirect pathway is a purported monosynaptic input pathway to the basal ganglia that bypasses typical input nuclei of the indirect pathway (outlined above) to directly innervate the STN (Parent and Hazrati, 1993; Nambu et al., 2002; Brunenberg et al., 2012; Chen et al., 2020). This is followed by glutamatergic innervation of SNr by the STN. In both humans and rodents, this pathway has inhibitory effects on motor output and is often described as a rapid 'gating' mechanism in the broader literature, as it results in a heightened threshold of GABAergic input to SNr required for movement to proceed (Wiecki and Frank, 2013).

2.1.2. Predictions of the Pause-then-Cancel model

Schmidt and Berke's rodent PTC model makes several explicit predictions about how the abovementioned basal ganglia pathways govern motor inhibition during action-stopping. Action-stopping is proposed to involve the recruitment of *both* inhibitory pathways: the hyperdirect basal ganglia pathway, which implements the Pause process, and the indirect pathway, which carries out the Cancel process. How each of these processes are proposed to contribute to motor inhibition according to the PTC model is described in the following.

The Pause process. The Pause process, accomplished by way of the hyperdirect pathway, is proposed to instantiate a "hold-your-horses" state (Frank, 2006), wherein the movement process is temporarily inhibited by an output gate that raises the threshold required for movement if the SNr has not yet received GABAergic input from the striatum (which would allow movement to occur). In line with these predictions, during the SST, responses from neurons in the rat STN can be observed as early as 15 ms following a cue to stop, but notably, on both successful and failed stop trials (Schmidt et al., 2013). This suggests that this STN-mediated gating is implemented following all stop signals but does not necessarily result in successful stopping. On the other hand, firing in SNr follows shortly after at 35 ms and differentiates between successful and failed stopping: SNr neurons exhibit a rapid post-stop-signal increase in activity specifically during successful stops but not during failed stops (Schmidt et al., 2013). Schmidt and Berke theorized that the hyperdirect pathway *pauses* the go process, thereby purchasing additional time for the purported subsequent Cancel process to become effective in shutting off the innervation of the response. This is advantageous because inhibitory influences of the indirect pathway take considerably longer to implement than the hyperdirect pathway, due to an increased number of synapses and involved nuclei. A notable detail in their model is the proposition that the Go signal is also followed by an invocation of the Pause process – and indeed, that the Pause process' invocation may extend to any task-relevant stimulus that is due to be utilized in the service of motor control. As will be seen in subsequent chapters, this latter assertion is also key in the current adaptation of the PTC model to the human domain.

The Cancel process. In the PTC model, though the Pause process is theorized to delay movement execution by raising the threshold for execution, it does not on its own stop the movement outright. Complete cancellation of a motor program purportedly depends on the Cancel process, which Schmidt and Berke proposed is implemented by the indirect basal ganglia pathway. When the STN excites the SNr during Pause, it also excites the globus pallidus (GP), and thereby its inhibitory arkypallidal projections to the striatum. Ultimately, this results in inhibition of the striatum, which contains the populations of neurons ramping to response threshold during the go process. In support of this, Schmidt and colleagues observed that the latency of neuronal responses in the rodent GP are longer (60−80 ms) and more selective than those associated with the Pause process – neurons respond during stop but not go trials and are shortly followed by reduced activity of movement-related neurons in the striatum (Schmidt et al., 2013). Therefore, the Cancel process via the indirect pathway is ultimately responsible for successful stopping by removing direct pathway drive to the specific movement that is being inhibited.

2.1.3. Key differences between rodent and human action-stopping literature

While the PTC model of action-stopping has been explicated in rodents, movement execution and motor inhibition in humans are purportedly underpinned by the same three neuroanatomic basal ganglia pathways as in rodents (e.g., Jahanshahi et al., 2015), as reviewed in Chapter 2.1.1. Still, two notable differences exist in these literatures. The first difference is functional and pertains to the proposed contributions of hyperdirect and indirect pathways. In humans, these pathways are generally ascribed roles in implementing different modes of motor inhibition – 1) a nonselective and reactive inhibition that is activated following stimuli which cue stopping and 2) selective inhibition made possible by proactive control, which relies on foreknowledge of when to stop an action or which action to stop (cf. Braver, 2012; Aron, 2011). The second difference is anatomical, and pertains to the proposed role of neocortical regions, which – due to phylogenetic differences in cerebral development – naturally play a larger purported role in human models of motor control.

The indirect pathway's proposed role in humans. In contrast to the rodent PTC model, existing theories of motor inhibition in humans tend not to focus on a potential role of the indirect pathway in reactive motor inhibition – i.e., the inhibition that takes place following and *in reaction to* the stop-signal. Instead, it is purported that the broad effects of the abovementioned hyperdirect pathway underpin the implementation of reactive inhibitory control – i.e., the type of inhibition deployed after an actual stop signal (Band and van Boxtel, 1999; Aron and Poldrack, 2006; Xu et al., 2008; Geday et al., 2009). The indirect pathway and striatum, on the other hand, have been described as underlying slower-latency proactive and selective stopping, especially when individuals have foreknowledge that stopping will be required (Aron, 2011).

There is some research in humans, however, that has indeed asserted the PTC model's proposal that both pathways are activated in parallel during reactive action-stopping. Computational models of the basal ganglia, supported by experimental data, suggest that the hyperdirect pathway may raise the threshold for responding by way of the STN, but that the indirect pathway is required for complete action cancellation (Wiecki and Frank, 2013). The model put forth by Wiecki and Frank differs from Schmidt and Berke's model in that it assumes D2 neurons within the striatum inhibit prokinetic neuronal populations during inhibitory control, whereas Schmidt and Berke propose the activation of an arkypallidal population in GP serves that purpose. However, similar to the rodent PTC model, it does not completely and explicitly account for the well-established roles of multiple areas of cortex (discussed in the Chapter below) during stopping or neurophysiological signatures during different phases of inhibition, which is the goal of the current theoretical review.

Cortical contributions to action-stopping. In the PTC model described by Schmidt and Berke, inputs from cortical regions during action-stopping are not considered, which is likely a consequence of the fact that the PTC is a rodent-based model. In contrast to rodents, the contributions of cortical regions to action-stopping in humans have been extensively investigated.

One specific difference between the rodent model and the human literature is the proposed origin of the hyperdirect pathway, which Schmidt and Berke (2017) suggest involves the pedunculopontine tegmental nucleus (PPN), based on assumptions that cortical regions could not perform local computations and signal the STN fast enough to account for early (15 ms) firing in STN. However, Chen and colleagues (2020) recently demonstrated that a hyperdirect pathway exists from human prefrontal cortex (PFC) to STN, and that antidromic stimulation in STN leads to recordable firing in cortex as soon as 1−2 ms later (see also Kelley et al., 2018). This is particularly important given the fact that the specific PFC region identified by Chen et al. – the right inferior frontal cortex – is prominently involved in human models of

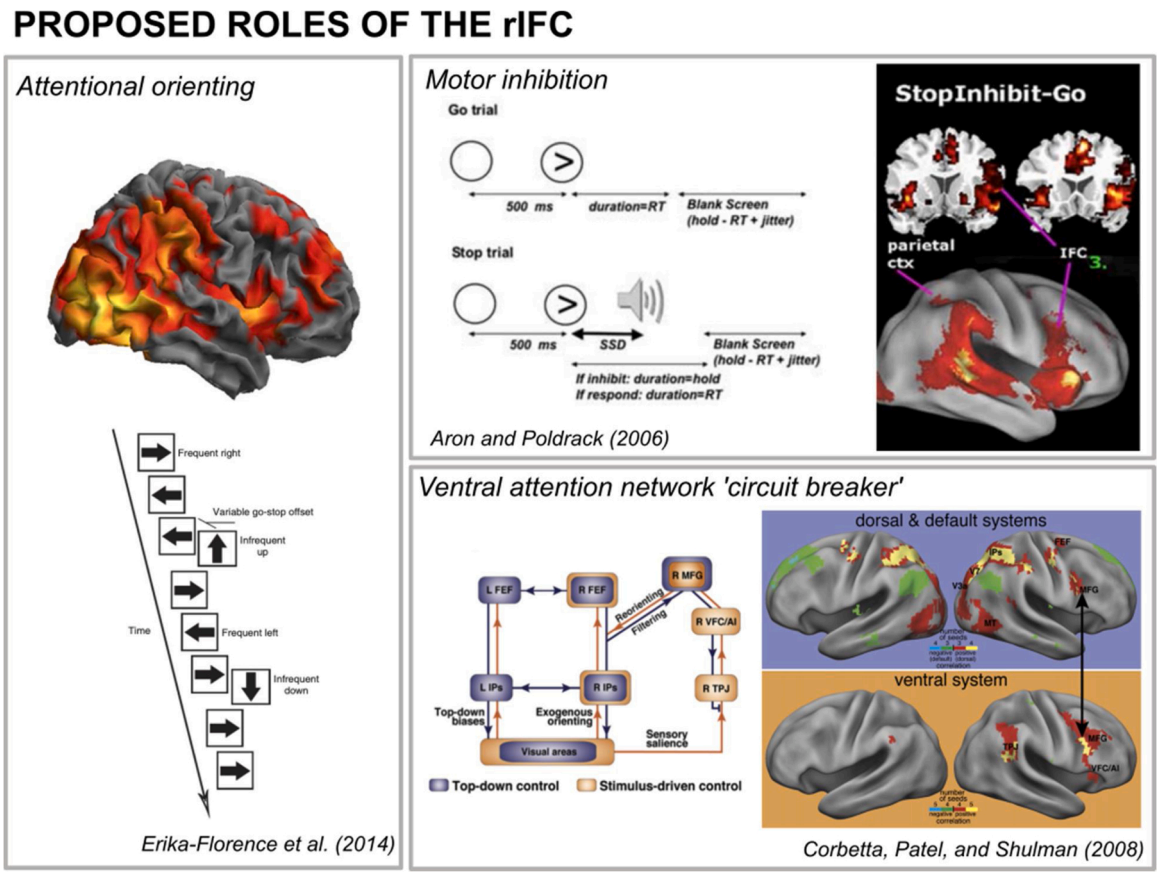

Fig. 3. Proposed functions of rIFC during cognitive control. The rIFC is responsive to infrequent stimuli, even without overt or explicit motor inhibition requirements. Erika-Florence et al. (2014) demonstrated rIFC BOLD signal in response to infrequent events alone, collapsed across task blocks in which infrequent events cued different requirements (ignore, count, stop, etc.). In contrast, the motor inhibition-specific account of rIFC function proposes that the rIFC implements motor braking following the stop-signal. Aron and Poldrack (2006) demonstrated that BOLD signal is increased in rIFC for Successful Stop > Go during the SST. In their 2008 review paper, Corbetta and colleagues proposed a role of the ventrolateral prefrontal cortex for regulating bottom-up attention. They classified it as a Ventral Attention Network region well-situated to communicate with the Dorsal Attention Network, thereby triggering switches between bottom-up and top-down attention modes (with rIFC functioning as a 'circuit breaker' for the Dorsal Attention Network in case the Ventral Attention Network detects a salient event).

action-stopping (see below). It is therefore feasible that a hyperdirect pathway in humans may begin in the prefrontal cortex with conduction speeds fast enough to produce early STN firing.[2]

Indeed, the hyperdirect pathway's broad inhibitory effects during motor inhibition are central to existing network models of action-stopping in humans. A fronto-basal ganglia network (Wessel and Aron, 2017; Chambers et al., 2009; Aron et al., 2007) in the human brain has been described to underlie rapid action-stopping in the SST; when a signal to stop is detected, regions of the PFC recruit the STN via the hyperdirect pathway, the STN excites the internal segment of the globus pallidus (GPi), and a proposed net-inhibition of the thalamus results, cancelling the motor programs maintained in thalamo-cortical loops. However, the exact cortical region from which the hyperdirect pathway in this model originates is still debated. The roles of regions in the medial and lateral prefrontal cortex in triggering motor inhibition and executing action-stopping have been studied using multimodal approaches (including EEG, fMRI, local field recordings, TMS, and the lesion method). Disruption of two cortical regions in particular – the pre-supplementary motor area (pre-SMA; BA 24/32; Floden and Stuss, 2006; Chen et al., 2009; Cai et al., 2012a; Obeso et al., 2013) and the right inferior frontal cortex (rIFC; specifically BA 44/45; Aron et al., 2003, 2004) – leads to deficits in motor inhibition. The exact, respective roles of these two cortical regions in action-stopping are controversially discussed.

rIFC. The rIFC is known to be a key node in stimulus-driven attentional orienting networks (Corbetta and Shulman, 2002), but it has also been proposed to act as a braking mechanism during movement via its recruitment of the STN (see reviews by Aron et al., 2004, 2014). Early fMRI work exploring the rIFC's role in stopping found right-sided lateralization of activation during motor inhibition (though see also Swick et al., 2008 and Erika-Florence et al., 2014), specifically in the middle and inferior frontal gyri, insula, inferior parietal lobule, and angular gyrus (Garavan et al., 1999). A subsequent lesion study revealed a correlation between lengthened SSRT and the extent of damage to the rIFC, which was stronger than correlations of SSRT to damage in any other PFC region (Aron et al., 2003). Much work in the following years has supported these findings, demonstrating that the rIFC is activated during action-stopping and that action-stopping deficits are associated with permanent or temporary disruption of rIFC (Wager et al., 2005; Hampshire et al., 2010; Chikazoe, 2010; Bari and Robbins, 2013). The rIFC's role in action-stopping purportedly is to recruit the STN via the hyperdirect pathway from rIFC to basal ganglia (Chen et al., 2020). However, two questions remain regarding the rIFC's specific role in action-stopping: 1) whether the rIFC is responsible for implementing inhibition, or whether it has a more domain-general, inhibition-independent function, such as the attentional detection of the stop-signal, and 2) whether the rIFC is the critical region for triggering

[2] Moreover, the extremely low-latency STN firing in Schmidt and Berke's data is likely also partially attributable to the degree of overtraining that takes place to enable rodents to reliably perform a version of the SST.

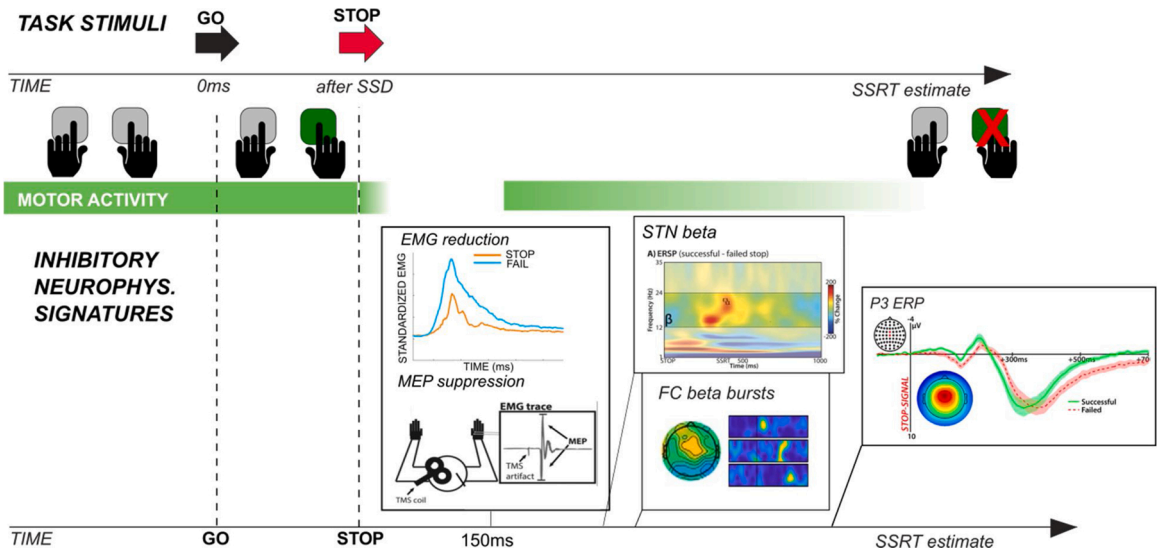

Fig. 4. Timeline of inhibitory electrophysiological signatures observed in humans during the SST. Reduction in EMG activity at the responding muscle and a global reduction in cortico-spinal excitability (indexed with TMS and MEPs) can be observed 150-180 ms following the stop-signal (diagram from Wessel et al., 2016). Similarly, STN beta and beta bursts at frontocentral regions of the scalp emerge about 100 ms prior to SSRT (figures from Wessel et al., 2016 and Wessel, 2020, respectively). The P3 onsets shortly before SSRT (figure from Dutra et al., 2018).

action-stopping, rather than another region, such as the pre-SMA (see Fig. 3). The PTC framework can be used to make specific predictions in this regard, which we detail in Chapter 5.

pre-SMA. Similar to the rIFC, the exact function of pre-SMA during action-stopping is still debated. Suggested functions of the pre-SMA include triggering internally generated movement, motor learning, and cognitive control (for a review of pre-SMA structure and function see Nachev et al., 2008). However, it is widely agreed upon that the pre-SMA is heavily involved in linking action to rules and conditions in a task setting, especially when conflict is present (Bunge et al., 2003; Rushworth et al., 2004, 2008). Studies utilizing fMRI approaches have demonstrated activation of the pre-SMA during action-stopping (Garavan et al., 1999; Sharp et al., 2010; Rae et al., 2014; Li et al., 2006). Remarkably, pre-SMA is activated differentially for conditions in which stopping is required, and not just when attending to a salient stimulus – which is not the case for rIFC (Sharp et al., 2010). This has motivated the arguments that rIFC supports attentional orienting to stop-signals, while the pre-SMA accomplishes active inhibition of ongoing responses (Sharp et al., 2010), and that while the rIFC is sensitive to stop-signal presentation and may recruit pre-SMA, the pre-SMA is the location of active motor inhibition (Duann et al., 2009). Research that has causally tested the relationship between pre-SMA and action-stopping likewise supports claims that the pre-SMA has a pivotal role to play during stopping. Patients with lesions of the mesial frontal lobe have marked deficits when performing the SST (Floden and Stuss, 2006), virtual lesion approaches that administer disruptive repetitive TMS to pre-SMA ostensibly produce delays in stopping actions (Chen et al., 2009; Cai et al., 2012a; Obeso et al., 2013), and direct electrical stimulation of pre-SMA is related to speech arrest during speaking (Fried et al., 1991).

The study of pre-SMA's relationship to action-stopping is marred by several known complications. First, there is some degree of variance in location of activated medial prefrontal cortical regions that have been termed "pre-SMA". For example, Chikazoe et al. (2010) review findings of fMRI BOLD activations during the SST, a Go/No-Go task, and an antisaccade task. While the medial PFC region activated during inhibitory conditions in the Go/No-Go task is located within pre-SMA, activated regions during the SST and antisaccade tasks are notably more ventral, verging on the mid-cingulate cortex. Second, there is a large degree of individual variation in cingulate morphology (Fornito et al., 2004; Huster et al., 2007), which further complicates exact localization of activation without conducting single-subject analyses. Third, anatomical landmarks and divisions based on underlying cytoarchitecture in the medial PFC do not overlap exactly. These factors exacerbate attempts to conclusively discern the role of pre-SMA (or other mPFC substructures) in action-stopping. Moreover, they complicate 'causal' studies of these relationships due to the wide range of approaches utilized to localize pre-SMA during disruptive TMS. For example, Cai et al. (2012a) and Obeso et al. (2013) both utilized neuronavigational approaches informed by structural MRI scans, but Cai et al. stimulated a target coordinate (MNI x = 10, y = 6, z = 72) more dorsal and caudal than Obeso et al. (MNI x = 10, y = 20, z = 44). As a result of these factors, the causal links between pre-SMA and stopping remain somewhat unclear.

Some researchers have attempted to tease apart specific roles of the rIFC and pre-SMA in action-stopping by stimulating or imaging both regions (Duann et al., 2009; Tabu et al., 2011; Swann et al., 2012; Rae et al., 2015; Lee et al., 2016), but a consensus has yet to be reached. Perhaps most importantly, a common theme in the summarized work is that these two regions are anatomically well-situated to communicate both with each other (via the frontal aslant tract; Kinoshita et al., 2015) and with the basal ganglia, and are part of a network of regions recruited during motor control contexts (Aron et al., 2007). Any attempt to translate the PTC model to the human action-stopping literature must therefore account for the respective roles of rIFC and pre-SMA in the two-stage model. We attempt such a mapping between the PTC model and rIFC / pre-SMA in Chapter 4 below.

2.1.4. *Summary*

In this Chapter, we summarized the basal ganglia pathways that underlie motor control and inhibition, proposed explanations for extant differences in the rodent versus human literature, and introduced cortical regions thought to contribute to stopping in humans. In Chapter 4, we will provide a detailed discussion of how the PTC model translates to humans, proposing roles for cortical regions such as rIFC and pre-SMA in the translated PTC model. However, before mapping the PTC to pathways and regions in the human brain, we review another aspect of the literature which requires addressing in a human PTC model – the proposed neurophysiological signatures of motor inhibition.

2.2. Neurophysiology of motor inhibition

The neurophysiological concomitants of motor inhibition are no less controversially discussed than its underlying neuroanatomical structures. Understanding the neurophysiological markers of inhibition is particularly important because it is widely understood (and indeed, a direct implication of horse race models) that the relative *timing* of activity within the neural networks determines whether a response can be successfully stopped or not, rather than their activation alone. Hence, while the neuroanatomical networks underlying motor inhibition in humans have been primarily investigated using fMRI, the exact implementation of inhibitory processing can be most accurately investigated using an array of neurophysiological methods that possess the necessary time resolution. These include electromyography (EMG), motor evoked potentials (MEPs), electroencephalography (EEG), and intracranial recordings of local field potentials (LFPs). Used in tandem with the stop-signal task, work using these methods has revealed several potential signatures of motor inhibition that relate systematically to inhibitory task requirements or to SSRT.

We will now describe these approaches and the purported neurophysiological signatures of motor inhibition that they have yielded. This is done with two motivations in mind. First, we aim to illustrate that there is variability in their timing with respect to the stop-signal and SSRT (see Fig. 4), which informs their interpretation and has been subject to much recent debate (Jana et al., 2020; Huster et al., 2020; Skippen et al., 2020; Wessel, 2020; Tatz et al., 2021). Second, we later aim to align each signature with specific processes in our human version of the PTC model in Chapter 4, thereby offering an explanation for the differential timing of these signatures.

2.2.1. Electromyographic recordings

In the SST, the ultimate outcome of a trial is the absence or presence of a behavioral response – i.e., moving a muscle to perform a movement (typically, pressing a button) or not. However, it is possible to obtain finer-grained information about the final stage of motor output during a single trial by examining electromyographic activity at the level of the responding muscle. For example, even if an outright response is not made, subthreshold increases in muscle activity following the go signal can serve as a measure of how far the go process had proceeded before a stop was implemented. This approach was used in formative work by De Jong and colleagues (1990) to demonstrate that there is no "point of no return" in manual responses; that is, even when the go process is so far along that muscle activity is observed at the level of the peripheral responding muscle, successful stopping is still possible.

More recently, it has been suggested that a partial EMG signal at the responding muscle during successful stop trials may be used to directly measure the latency of the stop process, rather than using indirect estimations in the form of SSRT. Unlike SSRT, this would even allow for estimation of stopping speed at the single-trial level. The first utilization of this approach was provided in landmark work by Raud and Huster (2017), who, on trials on which the overt response was successfully stopped, but which nevertheless showed measurable amounts of EMG activity at the associated muscle, observed a reduction of this subthreshold EMG activity at ~150 ms following a stop signal – i.e., nearly 50 ms before the SSRT measured in their participants. This finding suggests that stopping at the level of the muscle in fact occurs much earlier than is estimated by SSRT. This finding was later replicated by Jana et al. (2020), who proposed that therefore, stop-related reductions in EMG can potentially serve as a trial-to-trial outward index of the stop process.

2.2.2. Single-pulse transcranial magnetic stimulation (TMS) and motor-evoked potentials

Single-pulse TMS applied to the corticomotor representations of specific muscles can be used to elicit motor-evoked potentials (MEPs) – significant voltage deflections in the EMG trace. The amplitude of this motor-evoked potential is considered a proxy measure for the net cortico-spinal excitability (CSE; For more on this approach and its use during the SST, see Day et al., 1989; Rothwell et al., 1991; Rothwell, 1997; Rothwell et al., 1999; Rossini et al., 2015; Duque et al., 2017). The primary mechanism by which MEPs are evoked is considered to be the TMS-induced evocation of volleys in descending cortico-spinal fibers, which innervate the spinal motor neurons synapsing on muscles on the contralateral side of the body. However, it is well-acknowledged that TMS may also activate other populations of neurons which influence the same cortico-spinal fibers, such as intracortical neurons, cortico-cortical projections, or thalamo-cortical fibers (Duque et al., 2017).

Just as the EMG reduction described in the previous chapter, CSE reduction is observed approximately 150 ms following the stop-signal on successful stop trials (Badry et al., 2009). Notably, this MEP amplitude suppression, which reflects a reduction of MEP amplitude below even baseline measurements, is global and nonselective – in other words, it is observed even in task-unrelated muscles. This broad CSE effect was first reported by Badry and colleagues (2009), who observed MEP reduction in a task-unrelated leg muscle during a manual task. Subsequently, Cai et al. (2012b) observed MEP reduction in a task-irrelevant hand muscle when participants were cued to stop vocal responses, and Wessel et al. (2013) observed CSE suppression in a task-unrelated hand muscle when participants were instructed to stop eye movements. Together, these (and other) TMS studies have consistently shown that CSE is broadly suppressed below baseline around ~150 ms following stop-signals. (For visual stop-signals; auditory stop-signals notably lead to shorter SSRT and may hence show earlier signs of CSE / EMG suppression).

2.2.3. Beta activity in the local field potential

While EMG and MEPs offer insights into the dynamics of motor inhibition at the skeleto-motor system and the motor effectors themselves, neurophysiological recordings from the central nervous system have revealed several potential signatures of both subcortical and cortical processes that may index aspects of the stopping process. In the spectral domain, increases in amplitude in the beta frequency band (15–29 Hz) have been observed over frontocentral and right ventrolateral cortex following the stop signal in scalp recordings (Swann et al., 2011; Wagner et al., 2018; Wessel 2020). Intracranially, similar task-evoked changes in beta have been recorded in the vicinity of rIFC and pre-SMA (Swann et al., 2009, 2012; Ghahremani et al., 2018). Subcortically, beta amplitude increases are seen in basal ganglia regions such as the STN (Ray et al., 2012; Wessel et al., 2016) and the motor thalamus (Diesburg et al., 2021). Furthermore, beta band activity in the STN relates directly to cortical beta during motor inhibition: Stimulation of the STN changes beta profiles observed in cortex following stop signals (Swann et al., 2011), STN beta Granger-predicts beta in the motor cortex when inhibition is used to resolve motoric conflict (Wessel et al., 2019), and single-trial beta band amplitudes in the STN predict the degree of CSE suppression observed after a stop-signal (Wessel et al., 2016). In the STN, this signature's correspondence to stopping success is mixed, with some studies demonstrating heightened beta during successful stops specifically (Alegre et al., 2013; Benis et al., 2014; Wessel et al., 2016; Ray et al., 2012), and some studies demonstrating similarly heightened beta for both failed and successful stops compared to go trials (Bastin et al., 2014).

Much of what is understood about how beta activity relates to movement and action-stopping has been elucidated through observations of averaged beta power. However, recent investigations have revealed that individual-trial beta activity, including in subcortical areas, is not a sustained signature – instead, it is transient and burst-like (Sherman et al., 2016; Shin et al., 2017). Beta bursts in cortical regions have an inhibitory effect on perception and movement; stimuli preceded shortly by a beta burst in somatosensory cortex are less likely to be detected (Shin et al., 2017) and responses made shortly following a beta burst in motor cortex have longer reaction times than responses that aren't preceded by a burst (Little et al., 2019). Biophysical models have suggested that these bursts relate to the simultaneous arrival of proximal

and distal excitatory drive to synapses of cortical pyramidal neurons (Sherman et al., 2016).

Several recent studies in particular have demonstrated that beta burst dynamics on the single trial level underlie the abovementioned canonical stop-related changes in averaged cortical beta. Utilizing EEG recordings and stop-signal task data from over 200 individuals, Wessel (2020) observed increases in burst rates over frontocentral scalp sites during successful stopping, which were immediately followed by increased beta bursting over bilateral sensorimotor cortex. Moreover, Jana and colleagues (2020) found that beta bursts over frontal cortex were followed within 20 ms by broad skeleto-motor suppression and within 40 ms by outright stopping detectable at the motor effector, and Enz and colleagues (2021) demonstrated that greater scalp-level beta burst volumes (burst duration × frequency span × amplitude) are predictive of fast, successful stops. A fourth study has similarly demonstrated the beta burst dynamics related to action-stopping in the human subcortex: successful stop trials showed increased beta burst rates in both STN and motor thalamus, and – just like the scalp-recorded fronto-central beta bursts in Wessel (2020), STN bursts were immediately followed by increases in sensorimotor beta bursting (Diesburg et al., 2021). In sum, local field potential recordings, measured both intracranially and on the scalp, consistently support the notion that beta band activity across the nodes of the purported inhibitory cortico-basal ganglia circuitry may be an index of motor inhibition during action-stopping. The exact timing of these effects is not as consistent as for the EMG/CSE findings in previous sections, largely because the intracranial recordings in particular are typically taken from abnormal brains of epilepsy or movement disorder patients. However, the scalp studies of Wessel (2020); Jana et al. (2020), and Enz et al. (2021) indicate that elevated beta activity may be present even prior to the ~150 ms time point at which EMG/CSE suppression have been observed.

2.2.4. The frontocentral P3 ERP

Investigations of event-related potentials (ERP) derived from scalp-EEG in early SST studies led researchers to suggest that the frontocentral P3 ERP reflects deployment of the inhibitory process during action-stopping (De Jong et al. 1990). The P3 onsets earlier for successful compared to failed stop trials (Kok et al., 2004), which is in line with a key prediction of the race model – i.e., that an earlier onset of the stop process (as ostensibly reflected in the P3) would incur a higher probability of successfully stopping. Furthermore, P3 onset latency in stop trials correlates with SSRT, regardless of the modality of response (Anguera and Gazzaley, 2012; Wessel and Aron, 2015; Huster et al., 2020). More broadly, the frontocentral P3 appears to have a close trial-to-trial relationship with motor activity. Wessel (2018) demonstrated that higher degrees of prepotent motor activity on individual NoGo-trials (measured using the lateralized readiness potential) were accompanied by greater P3 amplitudes. Moreover, Nguyen et al. (2019) observed that P3 amplitude scaled with force measurements during failed stopping, so that smaller P3s were associated with greater force (i.e., a less inhibited incorrect response). The P3′s links to the motor system have been further corroborated in a study by Hynd et al. (2020), which demonstrated that P3 onset latency relates to inhibitory GABA activity in motor cortex: subjects with higher levels of inhibitory $GABA_a$ activity (measured using short-interval intracortical inhibition, SICI) showed larger and earlier P3 ERPs following stop signals.[3]

Though the P3 onsets prior to SSRT (depending on the quantification; Wessel and Aron, 2015; Huster et al., 2020), the fact that the P3 does not peak until *after* SSRT has led some to propose that the process underlying this signal is not crucial to inhibitory success – in other words, that the P3 does not reflect the stop process (Dimoska et al. 2003; Huster et al., 2013; Naito and Matsumura, 1994). An observation used to support this argument is that other ERPs which occur before the P3, such as the frontocentral N2, peak before and correlate with SSRT estimates, and therefore may serve as better candidate signatures of the stopping process (Huster et al., 2020; Skippen et al., 2020). On the other hand, Anguera and Gazzaley's 2012 results contradict those findings, by showing a correlation between P3 peak and SSRT, but not between N2 peak and SSRT. Because of this ongoing debate, the relationships between the N2, P3, and the stop process remain controversial.

2.2.5. Other signatures

We note two additional inhibitory signatures which are not observed in the SST itself, but which have been proposed concomitants of motor inhibition in non-human animals. During a version of the anti-saccade task, firing rates of neurons in the frontal eye fields accumulate to a threshold for movement when a saccade is made. Firing rates in the same neurons decrease following a stop-signal when a saccade is successfully avoided (Hanes et al., 1998). Though saccades, unlike limb movements, are ballistic (De Jong et al., 1990), the activity of these neurons in the frontal eye fields during countermanding parallels the pattern of activity of neurons in the rat striatum during stopping (Schmidt et al., 2013). Both populations of neurons represent the accumulation of prokinetic activity to a threshold at which movement is generated. If a stop-signal is presented and the trial is a successful stop trial, that accumulation becomes a decrease in firing instead, and a movement is not made.

Another group of researchers found that dopamine neurons in the substantia nigra and striatum were activated during saccade cancellation, and that disrupting these neuron populations led to deficits in saccade inhibition (Ogasawara et al., 2018). The activity of the dopaminergic system, which operates on the order of seconds and not milliseconds, might be too slow to contribute to rapid motor inhibition, but this finding may indicate that dopamine neurons in the basal ganglia have an important role to play in the retuning of motor programs following motor inhibition.

2.2.6. Summary

The neurophysiological signatures of motor inhibition described in this Chapter fall into two ostensible groupings, based their temporal relationship to the stop-signal and SSRT. EMG reductions at the responding muscle, suppression of motor-evoked potentials, and beta burst activity (both over frontal cortex and in subcortex) occur at early latencies after stop-signals – i.e., comparatively long before SSRT (roughly ~140–150 ms after visual stop-signals). A second group of later signals include stop-associated differences in the firing of movement-related neurons in the frontal eye field (though this is observed in saccade countermanding and not the SST), firing of striatal dopamine neurons, and the frontocentral P3, all of which *onset* shortly before SSRT (depending on quantification), but *peak* after it. This discrepancy in the timing of these signatures has led investigators to propose that some of these signatures may not represent stopping per se, and specifically that the later signatures are indeed too late to contribute to reactive stopping. We will discuss this controversy in detail in the following Chapter, and in Chapter 5 we discuss how viewing these signatures through the lens of a two-stage and not a unitary model of stopping may help resolve this debate.

3. Current controversies in human motor inhibition research

Now that we have reviewed the current state of the field in regards to the neuroanatomy and neurophysiology of action-stopping, we will focus on the ongoing debates in the field. Currently, there are two dominant controversies within the field of human action-stopping, which we have alluded to at several points in the first two chapters. Here, we now expand on them in more detail, before proposing how a translation of the PTC model to human neuroscience could potentially address both of them (in Chapter 5).

[3] Though Hynd et al. did not find a relationship between SICI and SSRT, Chowdhury and colleagues have repeatedly demonstrated correlations between these two measurements in the SST (Chowdhury et al., 2019a, 2019b, 2020).

The first controversy relates to the fact that it is near-impossible to disentangle attentional orienting from motor inhibition, both experimentally and, consequently, with respect to neurophysiology and neuroanatomy. The second controversy pertains to the observation that the neurophysiological signatures of motor inhibition occur at markedly different time points following the stop-signal, raising the question of whether they reflect the same unitary motor inhibition process. These two well-acknowledged problems continue to hamper efforts towards an agreed-upon model of human action-stopping. In this chapter, we describe the literature outlining these problems in detail, followed by a proposition to reconcile both debates by proposing a human adaptation of the PTC model.

3.1. Attentional processes confound measures of inhibition in the SST

In the classic design of the SST, stop-signals are infrequent – that is, they occur on a minority of trials (generally 25–33 %). Rare stop-signals are intentional (and indeed recommended) because they promote a prepotent go response tendency (Verbruggen et al., 2019). However, due to this design feature of the SST, attentional orienting and motor inhibition demands are inherently confounded. In essence, any stop-signal will trigger both processes: attentional orienting to a task-related, infrequent event (the stop-signal), followed by the actual inhibition of action. Finding ways to separate these signatures has proved a thorny problem for researchers and has also raised questions about which purported signatures of motor inhibition are specific to instructed action-stopping and which signatures are more generally related to attentional orienting to infrequent, task-relevant stimuli.

3.1.1. Attentional orienting in the stop-signal task

In a 2004 study by Ramataur and colleagues, the authors observed that the amplitude and latency of the frontocentral P3 scales with stop signal probability; as the stop signal became less frequent, the P3 was enlarged and started at shorter latencies. These results were largely interpreted as proof of the P3′s relationship to inhibition, which was originally proposed by De Jong et al. (1990). The researchers suggested that as the stop-signal becomes more infrequent, more inhibition is required to stop increasingly prepotent motor responses. However, Dimoska and Johnstone (2008) raised concerns about the interpretation of these ERP differences, which they concluded are due to confounds from attentional orienting effects to increasingly infrequent stimuli and not a difference in inhibitory processes. This conclusion was based on the observation that infrequency-related P3 amplitude effects were observed in conditions where participants were instructed to ignore the second stimulus as well as conditions in which the second stimulus cued the need to stop.

In Waller et al. (2019), we attempted to separate the respective contributions of attentional orienting and motor inhibition to the P3 ERP using an independent components analysis (ICA). We designed a control task that was visually identical to the stop-signal task, but which did not cue action-stopping; participants made a second response to a second, infrequent signal instead of inhibiting their actions. We found that the P3 following infrequent signals in the control task occupied the same independent component as the P3 after stop-signals, suggesting the two ERPs may stem from the same underlying neural generator.

Of note, there is an epistemological limitation to any attempt to prove that one "neural signature" reflects the *same* mechanistic process in separate contexts (like attentional orienting and motor inhibition). Since overlap in one domain (e.g., the ERP generated on the scalp, or the BOLD response generated in a voxel) could always be due to unobservable differences in another domain (e.g., the actual underlying patches of cortex, or the individual neurons therein), the closest one can come towards 'proving' equivalency of processing is the collection of converging evidence from several domains. This, combined with the theoretical dictum of favoring parsimony, is the essence of any such argument. Indeed, beyond the overlap in the independent component underlying either P3 response in Waller et al. (2019), we also observed an incidental, non-instructed slowing of responses on trials that contained the infrequent signal. Moreover, the degree of this slowing scaled with P3 amplitude. Based on these results, we suggested preliminarily that attentional orienting alone may involve a deployment of motor inhibition, and that the P3 is a generic marker of motor inhibition across contexts. Furthermore, converging subsequent evidence then came from the CSE domain, in which we observed a reduction of MEP amplitudes following infrequent events that were presented at times that match the typical stop-signal, but did not instruct stopping (cf., Iacullo et al., 2020; Tatz et al., 2021; see below for more detail). The abovementioned fundamental epistemological limitations to the equivalency-hypothesis notwithstanding, this provided evidence from neurophysiology (P3), behavior (RT), and motor system excitability (CSE) to suggest that infrequent event detection involves some degree of inhibition, even absent any action-stopping demands. This innate entanglement further complicates any attempt to find unique signatures of inhibition or attentional detection of the stop-signal during action-stopping.

Likewise, in the fMRI field, separating the relative contributions of attention and inhibition has complicated efforts to delineate the neuroanatomical extents of cortical networks that contribute to action-stopping specifically. This problem is aggravated in the fMRI domain due to the inherent low time resolution of the method. Still, much fMRI work has been conducted to attempt to solve this issue, especially vis-á-vis the role of the rIFC. In 2010, Hampshire and colleagues published a study in which they tested whether the rIFC's (specifically the right inferior frontal gyrus) activity in the SST is due to motor inhibition requirements, or simply due to attentional orienting (because of stimulus infrequency). They demonstrated that, in fact, rIFC was recruited in a variety of SST-like situations where a second, infrequent stimulus was present but did not cue inhibition, including when the infrequent stimulus did not cue a motor response at all (required counting). They concluded that there was "*no evidence to support the hypothesis that the RIFG plays a unique or specialised role in inhibition*", and rather that their "*findings accord best with a role for the RIFG in reconfiguring a representation of the currently attended input*" (direct quotes, Hampshire et al., 2010). This and subsequent work (such as Chatham et al., 2012) led to the proposition that "*there are no inhibitory modules within the frontal lobes and that behaviouralinhibition is an emergent property of spatially distributed functional networks*" (quote from Erika-Florence et al., 2014). We interpret these studies as the primary challenge for the proposed strictly-inhibitory role of rIFC.

Elicitation of inhibition during attentional orienting tasks. As mentioned briefly above, recent evidence has shown that classic experimental designs purporting to measure attentional orienting also canonically invoke motor inhibition. In our opinion, it is now established that unexpected perceptual events, even when presented outside of a stopping context, produce inhibition (Wessel & Aron, 2013; see also: Dutra et al., 2018; Novembre et al., 2018, 2019). The links between the P3 and attentional orienting to infrequent stimuli absent the requirement of inhibition (oddballs) have been previously established (Verleger et al., 1994; Friedman et al., 2001; Debener et al., 2005; Polich, 2007; Elchlepp et al., 2016). However, studies which elicit the 'oddball-P3′ also tend to produce uninstructed behavioral slowing during response conditions cued by infrequent events. For example, Elchlepp and colleagues (2016) found that infrequent stimuli cuing 'Ignore' instead of 'Stop' or 'Respond again' elicited a P3 and were associated with RT slowing. These RT effects alone cannot be taken as proof of the presence of motor inhibition, as they may merely result from the reorienting of attention after an oddball stimulus. Similarly, a conclusion of inhibitory processes active in a given task situation based on the presence of a neural signature without reference to behavioral or peripheral signatures of stopping would constitute reverse inference. Nonetheless, when combined with convergent physiological evidence, as from Iacullo et al. (2020), of suppression of the motor system, these RT effects point towards the presence of motor inhibition processes inherent in attentional orienting

processes. Other groups have found similar evidence. Novembre and colleagues have demonstrated that similar reductions in overall motor system activity as measured in isometric force are observed ~100−150 ms following infrequent, surprising events (Novembre et al., 2018 and 2019). Critically, this reduction in ongoing force is observed following events that do not cue inhibitory control at any point during the task context, and is followed by response execution. Therefore, the presence of observable reductions in excitability of the motor system speaks against accounts that RT slowing following infrequent events simply reflects orienting time, or that the P3 reflects attentional orienting alone with no motor inhibition.

If there truly is motor inhibition whenever attentional orienting is required, this has significant implications for the field of human action-stopping as a whole, given the wide use of attentional orienting "control tasks" which attempt to isolate and subtract contributions of attentional orienting from functional signatures of motor inhibition in the SST (Schmajuk et al., 2006; Dimoska and Johnstone, 2008; Hampshire et al., 2010; Boehler et al., 2010; Tabu et al., 2011; Dodds et al., 2011; Chatham et al., 2012; Erika-Florence et al., 2014; Bissett and Logan, 2014; Elchlepp et al., 2015; Lawrence et al., 2015; Verbruggen et al., 2010; Waller et al., 2019). The abovementioned findings suggest that when activity related to "attentional orienting" in the control task is subtracted from stop-signal-associated data, at least some aspects of motor inhibition will be removed from the neural data as well, and it is unclear what subprocesses of motor inhibition (or other cognitive processes) are left behind and analyzed. Given the prevalence of this approach, it is safe to assume that much of the human action-stopping literature is affected by this problem.

As the evidence above illustrates, purported signatures of motor inhibition such as MEP suppression and the frontocentral P3 are context non-specific – that is, they are observed both during instructed action-stopping and during attentional orienting to infrequent stimuli. In Chapter 5, we will thoroughly discuss how we believe the Pause-then-Cancel model accounts for the wide variety of contexts in which these signatures may be observed.

3.2. Latency differences between purported signatures of inhibition and SSRT

A second current controversy in the field of human action-stopping arises from the differences in timing between proposed signatures of motor inhibition and SSRT as a behavioral measurement of action-stopping. As described in Chapter 2, these signatures fall into two de-facto groupings, relative to when they occur with respect to the stop-signal:

1 *Early signatures (which begin and peak before SSRT).* Suppression of CSE (Badry et al., 2009), reduction of EMG at the target muscle (Raud and Huster, 2017), and beta bursting on the scalp (Wessel, 2020) are early-latency signatures of motor inhibition observed during the SST. These signatures are observed starting around 140−150 ms following visual stop signals.
2 *Late signatures (which onset shortly before SSRT).* The P3 ERP (Wessel et al., 2015), ramping activity in pro-kinetic neuronal populations in regions like the FEF and striatum (Hanes et al., 1998; Schmidt and Berke, 2017), and activation of the dopaminergic system (Ogasawara et al., 2018) are all purported signatures of motor inhibition which onset right around the immediate pre-SSRT period, starting ~200 ms following visual stop-signals in the case of the P3.

As is evident, there are two time periods during which purported measurements of inhibition occur: either right before SSRT, or well before it. In Chapter 5, we will further address how a human PTC model may prove helpful in relating these signatures from the SST to underlying motor and cognitive processes, and how SSRT fits within a two-stage PTC model of action-stopping.

4. Translating the Pause-then-Cancel model to humans

4.1. Some notes on a rodent SST

Before we outline our translation of the PTC model to the human brain, we note some important differences regarding the nature of rodent and human neuroscience research. Schmidt and Berke's delineation of the PTC model in the rodent brain entails neuroanatomical and behavioral work with great potential to inform our understanding of homologous pathways which underlie action-stopping in humans. However, there are some well-acknowledged shortcomings to performing cognitive neuroscience in non-human animal models – namely, the overtraining required to enable non-human animals to perform the task to criteria and the differences in neocortical complexity across species.

Rodents cannot perform the SST the way that human participants do, which Schmidt and Berke acknowledge in their review of the PTC model (2017). Rodents may certainly learn through extensive training to complete a stop-signal task (Leventhal et al., 2012; Eagle et al., 2008; Bari and Robbins, 2011; Homberg, 2013); rats in Schmidt and colleagues' 2013 study responded to go signals accurately approximately 70 % of the time, successfully stopped 50 % of the time (when the stop-signal delay was held constant at a fixed delay – a suboptimal design choice in humans, who quickly learn to withhold motor initiation until the end of the fixed stop-signal delay), and demonstrated faster failed stop reaction times than correct go reaction times. The latter finding in particular is in line with predictions of the independent race model (Logan and Cowan, 1984), suggesting that these animals are indeed engaging in reactive stopping. However, these metrics were recorded following a two- to three-month training period (Schmidt et al., 2013), while human participants generally learn, practice, and perform the SST within a few minutes. Neuroplastic changes that occur in over-trained rodents could potentially lead to the very-low latency STN firing observed by Schmidt and Berke (2017). Furthermore, while rats did not show explicit signs of slowing in preparation to stop, extensive training with a fixed stop-signal delay could potentially lead to rats learning how and when to anticipate stop signals, similar to humans. Stop-signal task studies in humans typically use either adaptive stop-signal delay durations, or use a range of fixed-delay periods, which improve SSRT estimates and prevent learned prediction of stop-signal timing (Verbruggen et al., 2019), which can lead to delayed motor initiation and an associated elimination of the motor prepotency necessary to require inhibitory control during stopping.

In addition, because rodent neocortical development is far inferior to humans (e.g., Clowry et al., 2010), there is a possibility that the STN in rodents might receive fewer or less complex top-down inputs from frontal regions to the basal ganglia. In addition, humans are known to make use of complex strategies which reflect a relative trade-off between proactive and reactive strategies (and are even given carefully worded SST instructions to avoid unwanted strategies in their behavioral performance; Verbruggen et al., 2019). Despite these limitations, we believe that the PTC model and the foundational findings it is based upon (Schmidt et al., 2013) can be translated into the human domain. However, these differences should be kept in mind when directly comparing rodent to human behavioral performance on the SST. And, importantly, these differences may help explain extant differences between rodent and human literature, such as the lack of focus on cortical inputs in the rodent PTC model.

4.2. The Pause-then-Cancel model in humans

Here, we propose a two-stage, Pause-then-Cancel model of action-stopping in humans. This model maps the Pause and Cancel processes identified in rodents onto homologous pathways in the human brain. In addition, we propose roles for higher-order cortical areas which have known contributions to action-stopping in humans (viz., rIFC and pre-SMA). Finally, we speculate on the potential alignment between the

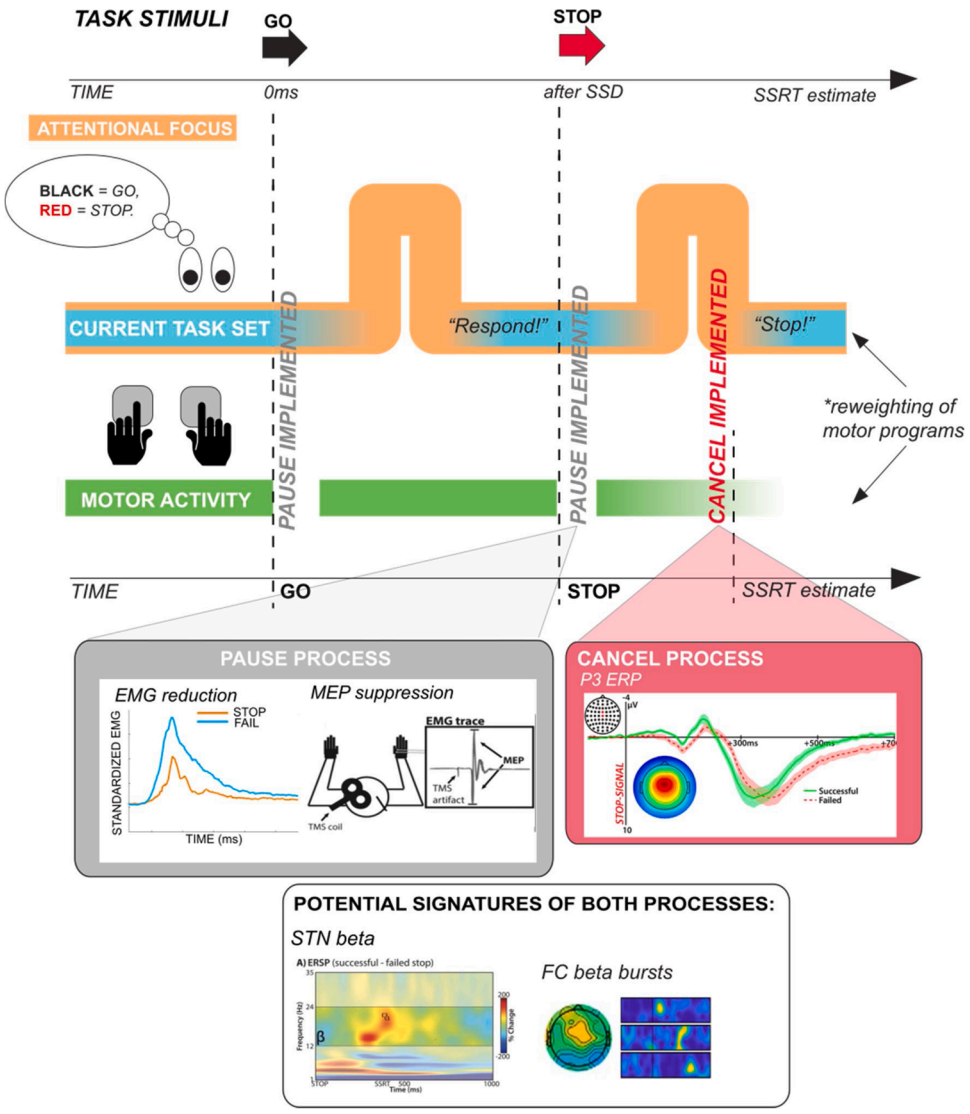

Fig. 5. A proposed timeline of the recruitment of Pause and Cancel processes following go and stop signals in the SST. The Pause process is elicited following every event that elicits attentional reorienting – that is, each task-relevant stimulus. During the Pause phase, motor inhibition is exerted globally (as can be indexed in RT slowing, EMG traces, and in the suppression of MEPs). Following stop signals, this Pause-facilitated inhibition of EMG activity is measured as the latency of behavioral stopping. The Cancel process is prepared each time Pause is implemented, but only deployed when outright stopping is appropriate in the task context. During the Cancel phase, ramping-down of pro-kinetic neural activity is proposed to occur, followed by a retuning of motor programs (as indexed by P3).

known neurophysiological signatures of motor inhibition in humans and the two stages of the Pause-then-Cancel model.

4.2.1. The Pause process

We propose that, in humans as in rodents, the Pause process is underpinned by the monosynaptic hyperdirect pathway of the basal ganglia, by which the STN is recruited rapidly following stop-signals to net-inhibit thalamocortical drive, thereby temporarily suspending motor output. Local field potential recordings of the human STN reveal beta power increases specific to stop trials (Ray et al., 2012; Wessel et al., 2016). These observations align with single-unit recordings from STN in rodents, in which firing rates varied by trial type (go versus stop) but did not differentiate stopping success (Schmidt et al., 2013). Furthermore, research has linked activity in the STN to early global, nonselective suppression of CSE. When we (Wessel et al., 2016) collected LFP recordings from externalized STN DBS leads while using TMS to elicit MEPs, we found a trial-by-trial relationship between STN beta increases and MEP amplitude decreases during stopping. Though this single study is correlative, we propose that MEP suppression in this case is an expression of the temporary suspension of motor output during the Pause process.

It is notable that BOLD-fMRI studies with sufficiently strong field strengths and sufficiently short echo times (Miletić et al., 2020; de Hollander et al., 2017) have shown that STN BOLD activity is increased on failed compared to successful stop trials. While at superficial consideration, these results seem at odds with the current theory, we actually believe them to align well. According to the PTC theory, any salient stimulus (including both go- and stop-signals) will recruit the Pause phase, and hence, STN. As other work using depth electrode recordings has shown (Brown et al., 2006; Kühn et al., 2008; Siegert et al., 2014; Cavanagh et al., 2014), this also goes for action errors, which lead to STN activity following incorrect responses. Hence, we propose that go- as well as stop-signals will all lead to STN activation following go/stop-signal presentation. Failed stop-trials will then engage additional response-locked STN activity due to error processing. BOLD will not be able to distinguish these temporal dynamics due to its lack of time resolution. However, this theory is eminently testable using depth-electrode data.

In presenting their PTC model, Schmidt and Berke (2017) suggested the pedunculopontine tegmental nucleus (PPN), and not a cortical region, is responsible for initiating the Pause process following a signal to stop. This conclusion was based on the observation that neurons in the primary auditory cortex typically take at least 12 ms to respond to stimuli, while neurons in the PPN fire within 9 ms of a stop signal. Based on these characteristics, they concluded the auditory cortex could not have signaled the STN in time to account for STN firing following the stop-signal, at around 15 ms. Instead, we suggest that in humans, where behavior in a task like the SST is not as overtrained as in non-human

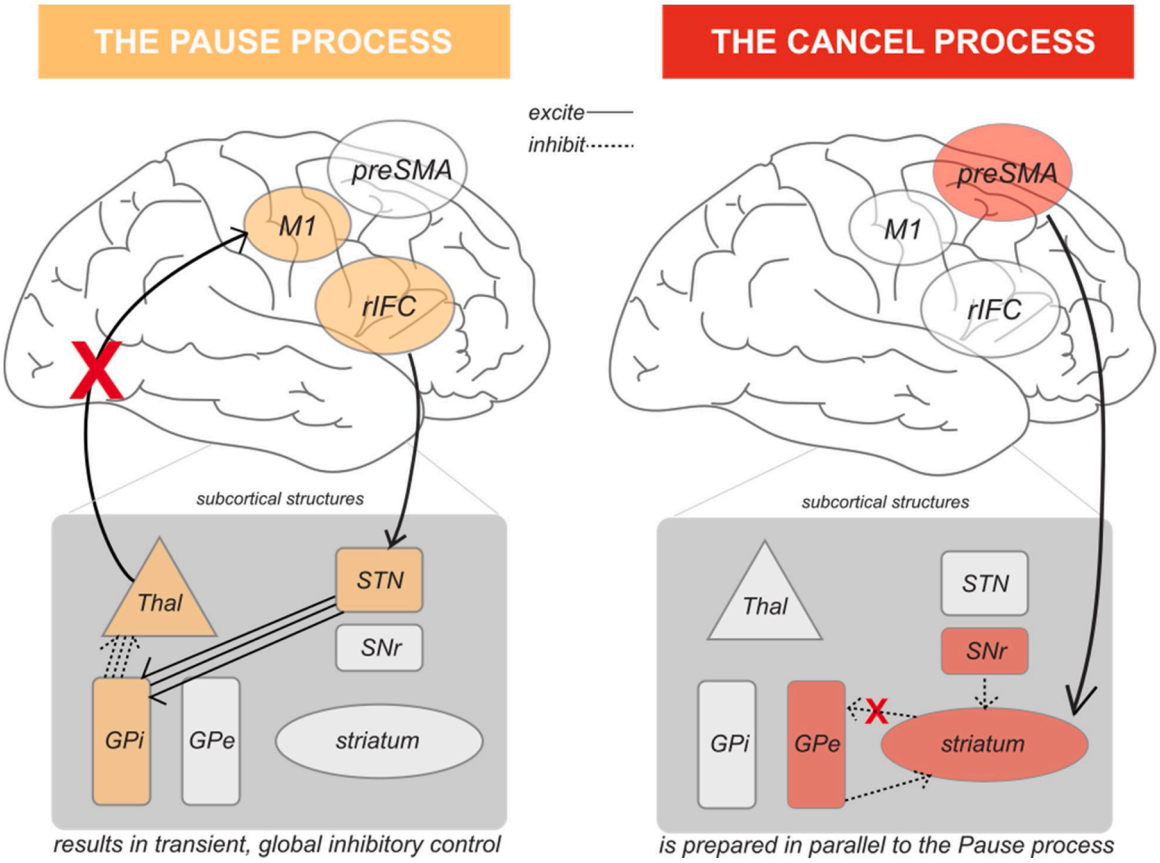

Fig. 6. The cortical and subcortical regions of the human brain proposed to underlie the Pause and Cancel processes. The Pause process involves the recruitment of the hyperdirect pathway, by way of the rIFC. Net-inhibition of the thalamus and thalamocortical loops is proposed to lead to nonselective motor inhibition. During the Cancel phase (which is implemented in parallel to Pause during action-stopping), antikinetic neuronal populations in the indirect pathway lead to the inhibition of prokinetic neurons in the striatum, thus removing the drive to movement implemented by the direct pathway. During movement cancellation, recruitment of the pre-SMA signals the re-weighting of task motor programs. Not shown: the perceptual detection of the initial stop-signal, performed by the respective sensory cortex, which then ostensibly signals to the two cortical origins of the Pause and Cancel processes.

animals, the rIFC is responsible for triggering the Pause process following detection of a go- or stop-signal in sensory cortex. (See Fig. 5 for a timeline of how we propose Pause and Cancel are implemented following go and stop signals.) Activity of the rIFC is observed during action-stopping (Aron et al., 2004, 2014; Aron et al., 2015), as well as salience-detection and attentional reorienting following task-relevant stimuli (Corbetta and Shulman, 2002; Corbetta et al., 2008), meaning that it is functionally well-suited to the role of beginning the inhibitory cascade following a salient event. Furthermore, intracranial recordings recently confirmed the existence of a monosynaptic hyperdirect pathway from rIFC to STN in humans, with axon conductance speeds on the order of milliseconds (Chen et al., 2020), meaning this region is also well-situated neuroanatomically to signal the STN fast enough for involvement in the earliest stages of reactive stopping. (See Fig. 6 for a diagram of the cortical regions which are proposed to map onto the Pause and Cancel processes.)

We furthermore posit that the Pause process is part of a universal orienting response common to all task-relevant events – i.e., a Pause is observed in, but not exclusive to, the stop-signal task (and therein, following *both* the go- and stop-signals) and other paradigms that involve infrequent or otherwise salient events. Indeed, the rIFC is composed of subregions that respond both to inhibitory and attentional demands, suggesting that this region is responsive to salience regardless of task context (read more about this in Chapter 5.1.1). Moreover, a recent study revealed that early latency reductions in CSE and EMG are observed both following stop signals *and* following infrequent 'Ignore' signals, moreover to the same degree and with identical latencies. We consider this to be evidence that these proposed 'early latency' signatures are not specific to the instructed stopping context but generalize to any condition in which attentional orienting is required (Tatz et al., 2021). We therefore suggest that the Pause mechanism is activated in non-inhibitory tasks following salient, task-relevant stimuli, such as oddball stimuli in an oddball paradigm or stimuli that elicit attentional-reorienting (e.g., Posner and Cohen, 1984). Its invocation after stop-signals is therefore a non-specific consequence of the salience of those signals.

4.2.2. *The Cancel process*

We propose that the Cancel process, which removes the ongoing invigoration of the Go response maintained within the prokinetic direct pathway, is carried out via the indirect basal ganglia pathway in humans. This implies that the indirect pathway is involved in reactive stopping, which represents a departure from some of the human action-stopping literature, in which the indirect pathway is ascribed a more prominent role in selective and proactive motor inhibition (e.g., Aron, 2011; Majid et al., 2013).

We further propose that the Cancel process more broadly consists of a revision of the motor program by way of the pre-SMA. During the stop-signal task, it specifically involves removing the drive to movement generated by the striatum. Though its exact role during action-stopping is disputed, there is no doubt that the pre-SMA has a critical role to play at some point during the inhibitory process. As outlined in Chapter 2.1.3 above, the pre-SMA is preferentially activated during stop trials (Garavan et al., 1999; Sharp et al., 2010; Rae et al., 2014; Li et al., 2006) and

damage to or disruption of this region ostensibly leads to deficits in stopping (Floden and Stuss, 2006; Chen et al., 2009; Cai et al., 2012a; Obeso et al., 2013). Given the general consensus on the pre-SMA's role in linking motor responses to task rules and conditions (Nachev et al., 2008), it is likely that the pre-SMA is one of the final brain regions recruited during the later stages of inhibition that involve adjustment of (or in the case of the SST, complete cancellation of) motor programs. Notably, its activation following stop-signals specifically, and not infrequent, salient stimuli that do not cue stopping (Sharp et al., 2010), distinguish the pre-SMA's role from the role of the rIFC and the orienting-associated Pause process.

Due to demonstrated links between the frontocentral P3 ERP and the pre-SMA (Huster et al., 2010), we propose that the P3 ERP indexes the motor retuning accomplished by the pre-SMA during the Cancel process. As with the Pause process, we suggest that the Cancel mechanism may generalize to task contexts outside the SST and other action-stopping paradigms. For example, in the case of the SST, the indirect pathway and pre-SMA accomplish the full cancellation of the motor program. However, outside of the SST context, when complete cancellation is not desirable or appropriate, the indirect pathway and pre-SMA might instead be recruited to differing degrees to implement strategic, fine-grained adjustment of motor representations. For example, even outside of the SST context, the P3 is highly sensitive to task contingencies and motor demands. Infrequent or unexpected events that do not cue participants to slow or stop a response still elicit a P3 (Verleger et al., 1994; Cycowicz and Friedman, 2004; Polich, 2007; Wronka et al., 2008; Waller et al., 2019), though events that require a non-motor operation (counting instead of responding) from the participant elicit smaller P3′s than those stimuli which cue a response (Verleger et al., 2016). There have already been reviews published outlining the possibility that the P3 indexes context-updating outside of the context of the SST (cf. Barceló, 2020), and it is possible that 'retooling' of task representations or broader task contingencies occurs outside of the adaptation of motor programs. For now, we will refrain from speculating about those processes here. Simply put, we propose that the frontocentral P3 observed during the SST most likely represents the pre-SMA-driven retuning of motor programs during the Cancel phase. Specifically, we suggest that the instantiation of this adaptive mechanism in the SST is the removal of ongoing prokinetic drive via the striatum.

Moving forward, we strongly recommend that any investigation of the P3 in this account consider that ERP amplitude differences associated with task modalities could be driven by changes in the underlying neural generators, and thus constitute activation of *distinct* processes. Indeed, we do not claim that the presence of a P3-type waveform alone constitutes the presence of a Cancel process. We predict that advanced EEG approaches (such as ICA and MVPA), converging evidence in other modalities (fMRI, TMS, EMG, ECog), and relationships between neural signatures and behavior will be key in evaluating the theory we present here.

In the following Chapter, we will outline the implications of this purported PTC model of human action-stopping, especially with regards to the controversies detailed in Chapter 3.

5. Implications of a human Pause-then-Cancel model

5.1. Resolution of outstanding controversies

We propose that the application of the PTC model to humans stands to reconcile two specific outstanding controversies in the field, which have received much recent attention and were detailed in Chapter 3.

5.1.1. Attentional orienting and motor inhibition

As part of the human PTC model, we suggest that attentional orienting and motor inhibition are confounded in the human action-stopping literature because any type of salient event will trigger the Pause process – including the broad, low-latency inhibition of the motor system that constitutes said process. This also explains why both the stop-signal task and purportedly non-inhibitory tasks that involve attentional orienting activate the rIFC (Corbetta and Shulman, 2002; Sharp et al., 2010; Erika-Florence et al., 2014) – because the rIFC triggers the Pause process via the hyperdirect pathway to the basal ganglia (Chen et al., 2020) in all cases. In other words, we propose that the Pause process, *and the inhibitory effects it entails*, is a universal, stereotypic, and ubiquitous part of the orienting response to any salient, task-relevant event.

5.1.2. Latencies of inhibitory signatures

In the following, we explicate how and why we hypothesize that each of the neurophysiological signatures highlighted in Chapter 2.2 map onto either the Pause or Cancel process.

Proposed signatures of the Pause process. We propose that the suppression of CSE and EMG activity that occurs within 150 ms of (visual) stop signals reflects the Pause process. The motor inhibition occurring during the Pause process of action-stopping is conceptualized as a "hold your horses" (Frank, 2006) type of response – rapid, transient, and broad in its effect. Similarly, CSE suppression in the SST occurs rapidly following stop signals, at around 150 ms, is transient, and is observed even in task-unrelated muscles (Stinear et al., 2009; Badry et al., 2009; Cai et al., 2012b; Wessel et al., 2013; Duque et al., 2017). This reduction in CSE has been linked to activity in the STN (Wessel et al., 2016), providing evidence that these observations at the muscle level may be results of STN activity. Moreover, reduction in MEP amplitude has been observed in task motor effectors immediately following cues to respond, before movement initiation and a corresponding increase in MEP amplitude (Duque et al., 2014; Klein et al., 2016; Duque et al., 2017). This aligns with accounts predicting the presence of the Pause process following any salient task stimulus, not just following stimuli which cue stopping.

Proposed signatures of the Cancel process. We propose that longer-latency signatures observed after CSE and EMG reduction reflect the Cancel process of stopping, wherein the drive to movement is removed and motor programs strategically re-weighted. In the rodent brain, the Cancel process distinguishes successful from failed stops, unlike the purported Pause process (Schmidt et al., 2013). Because the frontocentral P3 peaks around 300 ms following the stop signal and onsets significantly earlier during successful compared to failed stop trials (Kok et al., 2004; Wessel and Aron, 2015), we propose that the P3 reflects the Cancel and not the Pause process of action-stopping.

Potential signatures of both processes. Because of the link between averaged beta power in STN and nonselective CSE reduction (Wessel et al., 2016), it seems likely that STN beta is a signature of the Pause process. However, we acknowledge it is possible that beta may in fact be a signature of both the Pause and Cancel processes because it relates to both early, nonselective CSE suppression and deployment of selective inhibition (Lavallee et al., 2014). Furthermore, increases in average beta during stop trials have been observed in regions associated with both processes – STN (Wessel et al., 2016; Bartoli et al., 2018; Ghahremani et al., 2018; Wessel et al., 2019), rIFC (Swann et al., 2009), and pre-SMA (Swann et al., 2012), and at their potential projection sites on the scalp (Wagner et al., 2016; Castiglione and Aron, 2020; Wessel, 2020; Soh et al., 2021). Moreover, recent work has demonstrated prominent increases in beta burst rates during stopping in both STN and motor thalamus at later latencies following SSRT (Diesburg et al., 2021). Hence, beta power may be a signature of inhibitory network-wide communication in both of the cortico-basal-ganglia pathways which underlie action-stopping, especially given that stimulation in the STN changes the scalp profile of average beta band activity (Swann et al., 2011).

Other purported signatures of inhibition outside of the SST. In Chapter 3 we described two additional signatures associated with action-stopping outside the SST context. These signatures of saccade countermanding, decreases in firing of prokinetic neurons in FEF and activation of striatal

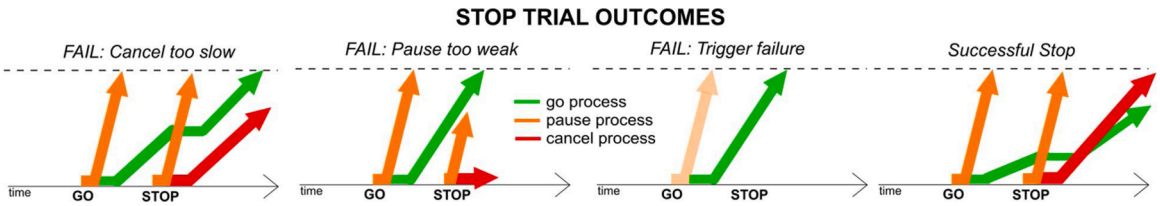

Fig. 7. Examples of Go, Pause, and Cancel process activity for different stop trial outcomes. A stop trial might result in a failed stop if the Pause or Cancel processes occur too late to pause or stop the Go process, or if inhibitory processes fail to initiate (trigger failure). (However, it is unclear whether trigger failures should affect only stop-related inhibitory processes, or also the go-associated Pause phase.) A stop trial will result in a successful stop if the Cancel process finishes before the Go process reaches the threshold for movement. In this case, the Pause process might buy time for the Cancel process to finish.

dopamine neurons, seem to align most closely with the Cancel process. In fact, the decrease in firing of prokinetic FEF neurons during countermanding closely mirrors the reduction of firing of prokinetic striatal neurons during the Cancel process as described by Schmidt and Berke (2017). While we mentioned previously that the activation of the dopamine system might be too slow to contribute to deployment of motor inhibition on the same trial, dopamine might play a role in the adjustment of global task contingencies and thereby affect performance on subsequent trials.

5.2. Implications for the horse race model and SSRT

As noted in the previous section, a translation of the PTC model to humans may stand to resolve outstanding controversies in the human stopping literature and provide those who study it with a framework to help navigate these issues. However, the application of this model to human action-stopping represents a departure from the way that stopping is classically modeled – as a unitary process. The PTC model shares several assumptions with race models of inhibition (especially the interactive race model; Boucher et al., 2007) and is itself a race model by definition. However, it is distinct from classic horse race models in two ways. First, it assumes stopping is a two-stage and not a unitary process. Second, it implies important distinctions between inhibition and a classically defined stopping process.

At the conceptual level, the PTC model assumes the go and stop processes interact at two different time points during the race. The Pause process interferes with the go process immediately following the go and stop signals when the threshold for movement is raised. In this way, the Pause mechanism gates the go process by temporarily raising the threshold for responding, and thereby biasing the race in favor of the stop process. Later, the Cancel process directly interacts with the go process when direct pathway drive to movement is ultimately eliminated, resulting in a decay of prokinetic drive away from the threshold for a response (similar to the decline in firing of saccade neurons in FEF following a stop signal on successful stop trials; Schall and Godlove, 2012).

An interesting question is whether the Pause-facilitated gating implements an output gate (on movement) or an input gate (on incoming sensorimotor information) in the basal ganglia. Our interpretation is that the Pause process described by Schmidt and Berke, which "*blocks movement execution…for a brief period*", implements an output gate on movement. However, in their conceptualization this gating is directly related to changes in the *threshold* required for movement to occur, because the Pause circuit "*leads to a transient elevation of the Go threshold*". Interestingly, they also touch on input gating within the same paper when discussing recorded beta signatures. They state that "*elevated beta may indicate a relatively closed 'gate' within the basal ganglia that reduces responsiveness to incoming stimuli*". This elevated beta was observed following both Go and Stop cues, and they noted that stopping was more likely to be ineffective if Stop cues arrived during the time of elevated beta produced by Go cues (direct quotes in this paragraph from Schmidt and Berke, 2017). We suggest these observations align with our account that beta may be a signature of the Pause process because both are or should be observed following any salient stimulus. Future work might further parse whether and how the Pause phase specifically instantiates 1) an output gate, 2) an input gate, or 3) some combination of the two.

This PTC model implies important distinctions between neural inhibition and the overall "stop" process (as put forth in the race model), which we propose to be comprised of two processes (Pause and Cancel). This also implies that the deployment of neural motor inhibition processes does not guarantee the achievement of behavioral stopping. The PTC model also holds that when the stop processes *are* successfully initiated, there may be more than one reason why a stop is unsuccessful: either the Pause mechanism was unsuccessful or occurred too late or the Go process was too far along for an initiated Cancel mechanism to affect the response (see Fig. 7). A third condition may result in a failed stop when the stop processes fail to initiate at all, that is, when a trigger failure occurs (Matzke et al., 2017a, 2017b). Therefore, in the context of the SST, the deployment of motor inhibition in the form of the Pause process does not always equate to stopping (which was pointed out by Schmidt and Berke, 2017).

The reason that this distinction is important is because the PTC model implies yet another critical distinction between inhibition at the *neural* level and stopping at the *behavioral* level. In the SST, completion of the Pause process (which involves reduction of EMG and CSE) very likely coincides with measured stopping at the behavioral level. However, if there is a short delay between go and stop signals and the stop-associated Pause process occurs before movement begins, it is possible that inhibitory processes may be completed before a response is ever initiated, and therefore no Cancel process is necessary. This particular case may be evidenced by reduction in CSE following the stop signal (Badry et al., 2009), but no subsequent increase and decrease of EMG activity in the task effector (Raud and Huster, 2017; Jana et al., 2020). On the other hand, if a response is partially underway, is interrupted by the Pause process, and eliminated during the Cancel process, both CSE and EMG reduction might be observed. As we have already pointed out, muscle activity during stopping (as measured by reduction in EMG at the task effector; Raud and Huster, 2017; Jana et al., 2020) does not match with SSRT estimations, and because EMG / CSE reduction seems to align more closely to the Pause process (cf. Tatz et al., 2021), we suggest it is unlikely SSRT can distinguish between completion of the Pause versus Cancel process, or both. Therefore, in this two-stage model, SSRT is not an optimal measure of either behavioral stopping or of underlying inhibitory processes, and ultimately, it is an open question which underlying processes (with respect to Pause versus Cancel) SSRT may be capturing, or what pre-Pause perceptual and detection processes may be inadvertently included in the estimate.

We note that this account adds to recent work highlighting the inherent flaws in SSRT as a measure (Matzke et al., 2017a,b; Huster et al., 2020; Bissett et al., 2021). However, in the absence of responding-muscle EMG (Raud and Huster, 2017; Jana et al., 2020), SSRT remains the only behavioral measurement of the speed of stopping. We suggest SSRT should be considered with caution when used as the *only* measurement of stopping – i.e., in the absence of neurophysiological measurements. Furthermore, because SSRT is directly related to

Box 1
Based on our translation of the PTC to corresponding fronto-basal ganglia pathways and common neurophysiological measures in human motor inhibition, we have generated some predictions to aid with empirical testing of this model framework.

Prediction 1: Successful stopping in the SST does not require a Pause before Cancel process. According to the PTC model, the Pause process does not determine stopping success (Schmidt and Berke, 2017), though the Pause process is advantageous for stopping success when a go process is relatively far along. We propose that successful stopping and the activation of the Cancel process does not require the prior activation of the Pause mechanism following the stop signal. In fact, recent work demonstrated that participants can perform a task with a stop signal on *every* trial, producing approximately 50 % successful stops (Dykstra et al., 2020). Despite frequent stop-signals, the P3, our purported measure of the Cancel process, was still elicited and onset earlier for successful than for failed stops. This prediction could be tested further by using single-pulse TMS to evaluate the presence or absence of global CSE suppression during such a frequent-stop SST. If observed, absence of CSE reduction in task-unrelated muscles might thereby indicate the absence of a Pause mechanism during contexts where stop-signals are frequent or less salient, or when participants have foreknowledge about needing to stop.

Prediction 2: The timing of the Pause process can be measured directly using physiological signatures. As we have proposed, the Pause process may relate to the onset of early nonselective inhibition of the motor system, as indexed by EMG and MEPs. If this is the case, the latency of the completion of the Pause process can be measured directly from partial EMG traces. It is less clear how one might go about estimating the latency of the Cancel process, however. We propose that identifying and tracking scalp- or peripheral-level correlates of the remaining drive to movement post-Pause (which the Cancel process inhibits) may allow for estimation of the length of Cancel. Potential noninvasive approaches might include quantification of the scalp-EEG readiness potential (also known as the Bereitschaftspotential), tracking residual EMG activity following initial Pause-related reductions, or utilizing whole-scalp classification approaches like multivariate pattern analysis.

Prediction 3: Signatures of the Cancel process scale with the amount of change needed to motor representations. The P3, a proposed signature of the Cancel process, increases in amplitude as stop signals become less frequent (Ramautar et al., 2004). Similarly, P3 amplitude scales with the motor demands in oddball paradigms – the need to respond to an infrequent stimulus produces a larger P3 than simply counting or ignoring infrequent stimuli (Verleger et al., 2016). It is likely, therefore, that the Cancel process is implemented in differing degrees depending on the complexity of motor retuning required in the current task context. One way to test this would be by using a stop-then-change paradigm. We predict that the requirement to stop during an SST and then perform a separate response or change task sets should produce a larger P3 than a simple stop would.

RT (Huster et al., 2020), it might be preferable to directly relate neural signatures of inhibition with neural signatures of going (Wessel, 2018; Nguyen et al., 2019) or to signatures of physiological inhibition (Chowdhury et al., 2019a, 2019b, 2020; Hynd et al., 2021).

If this two-stage account of stopping is accurate, researchers should take these limitations of SSRT as a measure of stopping into account when designing SST studies and interpreting results. They should also carefully evaluate what portion of the motor inhibition response they are most interested in studying when designing tasks – the Pause process, the Cancel process, or the compound behavior (outright stopping). Studies of the hyperdirect pathway facilitated Pause process should account for the pre-Pause perceptual processes and the co-occurrence of reorienting and inhibition inherent in the Pause mechanism. Researchers interested particularly in the indirect pathway-related Cancel process should consider how to design tasks that reduce the likelihood of the Pause process being implemented; using an SST with frequent stop-signals might accomplish this (Dykstra et al., 2020), but could possibly affect the strategies participants use to complete the task. Because the Pause and Cancel processes are recruited in parallel (but with different speeds), we currently assume the activation of the Cancel process depends in part on the salience-detection processes inherent in the Pause process. However, distilling neurophysiological signatures of the respective stages of a PTC model may yield new insights about estimating the timing of inhibition during the SST, and should inform the development of computational models of the PTC framework that can be directly compared with other classic models of manual stopping (Logan et al., 1984; Band et al., 2003; Boucher et al., 2007; Wiecki and Frank, 2013) and with emerging multi-stage models of saccade countermanding (Bompas et al., 2020).

6. Predictions of a human PTC model

Box 1.

7. Conclusion

In the current theoretical paper, we propose a two-stage model of human action-stopping, based on recent theoretical and empirical work in non-human animals by Schmidt and Berke. We believe that this model is able to account for a wide array of findings in action-stopping literatures across species and methodologies. The model also accommodates all known neurophysiological signatures of action-stopping and has the potential to resolve two key ongoing debates in the stopping literature: disentangling attentional detection from motor inhibition and resolving the disparate timing of the purported signatures of inhibition. As such, it provides a falsifiable empirical framework and alternative to predominant models that frame the process underlying action-stopping as a unitary process. We hope that tests of the predictions and implications of this model can spur new ideas within the domain of action-stopping research in humans.

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