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A Pause-then-Cancel model of Stopping: Evidence from Basal Ganglia Neurophysiology

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Summary (max 200 words)

Many studies have implicated the basal ganglia in the suppression of action impulses ("stopping"). Here we discuss recent neurophysiological evidence that distinct hypothesized processes involved in action preparation and cancellation can be mapped onto distinct basal ganglia cell types and pathways. We examine how movement-related activity in the striatum is related to a "Go" process and how going may be modulated by brief epochs of beta oscillations. We then describe how, rather than a unitary "Stop" process, there appear to be separate, complementary "Pause" and "Cancel" mechanisms. We discuss the implications of these stopping subprocesses for the interpretation of the stop-signal reaction time – in particular, some activity that seems too slow to causally contribute to stopping when assuming a single Stop processes may actually be fast enough under a Pause-then-Cancel model. Finally, we suggest that combining complementary neural mechanisms that emphasize speed or accuracy respectively may serve more generally to optimize speed-accuracy trade-offs.

Introduction

Inhibition of behaviors that are currently maladaptive is a key feature of normal executive function [1]. The various forms of behavioral inhibition include being more prepared to stop if required ("proactive" inhibition), and terminating movements that have already begun [2-4]. Here we use the term "stopping" to mean suppressing a current impulse to act, in response to a Stop cue ("reactive" inhibition). This suppression of action impulses is specifically compromised in a wide range of conditions, including attention-deficit hyperactivity disorder, obsessive-compulsive disorder, Tourette syndrome, schizophrenia and drug abuse [5].

The basal ganglia have long been implicated in response inhibition [6,7], and the classic layout of distinct functional pathways in the basal ganglia [8] was originally devised to account for neurological disorders involving movements that are either insufficiently, or excessively, suppressed. Even accounts of response inhibition that primarily emphasize cortical or midbrain mechanisms have often postulated a key role for basal ganglia circuits [7,9-11]. Despite this, there have been relatively few studies using the high temporal resolution of electrophysiology to investigate in real time how stopping is achieved within the basal ganglia.

The "stop-signal task" (SST) is a standard test of behavioral inhibition, and the "race model" [12] is the conventional theoretical framework that provides a quantitative account of stop-signal behavior (see detailed reviews elsewhere in this issue). In the race model Go and Stop cues elicit corresponding Go and Stop processes that each race towards completion. If the Go process finishes first, movement is initiated. If the Stop process wins, movement is suppressed. One useful aspect of the SST is that it provides a measure of the speed of stopping (the "stop-signal reaction time"), by inferring how fast the Stop process must be to account for reaction time (RT) distributions. The race model has been extended and refined, e.g. to include an interaction between Go and Stop processes towards the end of their evolution [13,14]. However, a basic property of existing race models is that the Stop process is a single entity. One might therefore expect to find a single distinct neural population whose firing rate time course corresponds to the developing race model Stop process. Based on our recent work in rodents we challenge this idea, and provide an updated

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account of the neural basis of stopping.

A stop-signal task in rats

To study neural manifestations of Go and Stop processes in the basal ganglia, we developed a rat version of the SST [15]. Inspired by seminal SST work in non-human primates employing well-controlled saccadic eye movements [16-19], we used ballistic head/neck movements triggered by auditory cues. At the start of each trial, the rat placed its nose into an illuminated nose-poke port. After a brief, randomized time delay (500-1200ms), one of two auditory Go cues (high or low tone) prompted a corresponding leftward or rightward movement to an adjacent side port. On Stop trials (30% of total) the Go cue was followed by the Stop signal (a white noise burst), indicating that the animal had instead to remain in the center port (for another ~500-900ms). Correct performance in both Go and Stop trials was rewarded with a sugar pellet.

Behavioral performance in this rat SST was qualitatively and quantitatively similar to human and non-human primate stop tasks. In particular Go trials showed a characteristic broad RT distribution, with RTs for Failed Stop trials resembling the early (faster) portion of this distribution [15,20,21]. This is consistent with the race model: Failed Stop trials occur when the Go process is quicker than average (Fast Go), while on Correct Stop trials the Go process is slower than average (Slow Go) and so loses the race.

The combination of neurophysiology and the SST enables a powerful and elegant approach for examining the temporal evolution of behavioral control, by comparing neural activity between trial types. On Correct Stop and Failed Stop trials all the cues presented to the subject are identical, so differences in activity (and behavioral outcome) reflect internal differences - such as trial-by-trial variation in the speed of the Go process. Conversely, to help isolate neural mechanisms involved in stopping one can examine activity differences between Stop and Go trials. This is even more effective if one compares trials for which the Go process is assumed to have a similar initial time course ("latency-matching") – i.e. comparing Failed Stop to Fast Go trials, and Correct Stop to Slow Go trials. Since this comparison effectively subtracts away activity patterns associated with preparation for movement, any remaining activity differences just after Stop cue onset are good candidates for involvement in a stopping mechanism.

To facilitate such comparisons we used a fixed stop-signal delay (the time between Go and Stop cue onset) within each recording session, so that we could readily align neural activity on the Stop cue (or in the case of Go trials, align on the time that the Stop cue would have occurred had it been a Stop trial). Although in other variants of the stop-signal task the stop-signal delay is commonly randomized to discourage "waiting" for the stop signal, we did not find any evidence that the rats used a waiting strategy [15]. The stop-signal delay was adjusted between sessions to obtain a similar number of Correct and Failed Stop trials.

Does the striatum provide the race model Go process?

A core concept in the physiology of the basal ganglia is disinhibition. Basal ganglia output provides a tonic, GABAergic suppression of structures that promote movements, and interruptions in this suppression facilitate those movements. This mechanism was nicely demonstrated for eye movements in non-human primates, for which the substantia nigra pars reticulata (SNr; a basal ganglia output nucleus) inhibits saccade-promoting neurons in the superior colliculus [22-24]. The SNr itself receives GABAergic input from a subset of striatal neurons (the "direct" striatonigral pathway; [23]), and increases in striatal direct pathway activity facilitate movement [25] by interrupting SNr firing [26]. Though best established for orienting-type movements like saccades, such disinhibition of brainstem motor centers seems to be a general mechanism for controlling a range of fundamental behaviors including locomotion [4]. The impact of basal ganglia output on thalamic targets may be more complex [27] and lead to an influence over neocortex that is more subtle than simple increases or decreases in activity [28]. There is also a lingering controversy over whether the basal ganglia help select which action to perform [29] or just invigorate actions chosen and initiated elsewhere [30,31]. Nonetheless there is broad agreement that the striatal direct pathway provides some form of "Go" signal. Within the specific context of theSST, human fMRI studies found evidence for Go-related activation in motor striatum (e.g. [7]) as part of an overall cortical – basal ganglia network involved in movement preparation and execution.

We therefore looked for activity patterns of striatal neurons that could map onto the Go process imagined in the race model [20]. What properties ought such activity patterns to have? They should change after the Go cue that initiates the Go process, but substantially before the onset of actual movement. Furthermore, to be involved in selecting (or at least invigorating) a specific movement, activity should distinguish

between the different movements. Furthermore, following the latency-matching logic, Go-related activity should be very similar when comparing Fast Go and Failed Stop trials (since both involve a faster-than-usual Go process) and very similar when comparing Slow Go and Correct Stop trials (since both involve a slower-than-usual Go process).

As typically observed in other tasks (e.g. [32]) activity of striatal neurons was heterogeneous and sparse. Nonetheless a significant subpopulation distinguished the direction of upcoming movement (ipsi- vs. contralateral) at least ~130ms before movement onset (Figure 1a) and these cells exhibited a sharp firing rate increase during movement initiation (Figure 1b). The time course of this activity was also virtually identical between Fast Go and Failed Stop trials (Figure 1b). These observations support the idea that the striatum conveys the race model Go process that initially evolves independently from a Stop process. Consistent with the disinhibitory character of basal ganglia output, this striatal Go process would enable movements by producing an interruption in SNr firing, that in turn facilitates firing of e.g. superior colliculus neurons [20].

However, the activity of this striatal subpopulation has other noteworthy properties. Although its time course is initially very similar between Slow Go and Correct Stop trials, consistent with conveying a similar slowly-evolving Go process, it then abruptly diverges ~150ms after the Stop signal (compare red, dark blue lines in Fig. 1b). The sudden decrease in striatal firing on Correct Stop trials may be due to inhibitory inputs from the globus pallidus (GP; see below) and might correspond conceptually to a late interaction between Go and Stop processes [13,14].

RT differences between individual Go trials are typically imagined to arise from the Go process building-up at a different rate. A direct correspondence was reported between eye movement RT and a progressive build-up in neuron *firing* rates in a frontal cortical area [16]. By contrast, when aligned on movement onset the striatal neurons showed a similar build-up rate for both Fast and Slow Go trials (Figure 1a). This might reflect the involvement of striatal neurons only in some late subcomponent of Going - for example, once they receive more than a critical level of excitatory drive from cortex [33]. Alternatively striatal networks may have Go-relevant dynamics that are not readily apparent in a crude summation of firing rates [34,35], or that do not manifest as a firing rate "threshold" [36,37].

Beta rhythms and sensorimotor gating

Activity dynamics that are part of, or interact with, a Go process may also be reflected in local field potential oscillations. Beta (~13-30 Hz) oscillations throughout the basal ganglia and thalamocortical networks seem to have a particular, negative relationship to motor output [38,39]. Spontaneous or evoked beta oscillations seem to delay or slow movements (e.g. [15,40,41]), and there appears to be an important link between beta oscillations and dopamine [42-44]. Beta power is exaggerated in Parkinson's disease, consistent with an "antikinetic" state, and dopaminergic drugs (and other therapies) that alleviate Parkinsonian akinesia also reduce beta power [45]. However the role of beta oscillations in sensorimotor processing appears more complex than simply enabling or retarding movements [46,47].

We examined beta oscillations in a set of rat behavioral tasks including the SST [15]. Spontaneous brief epochs of elevated beta (~20Hz) power occur coherently throughout cortical-basal ganglia networks. Elevated beta can also be prompted by both Go and Stop cues, suggesting that these rhythms are not involved solely in either the Go or in the Stop process of the race model. Notably however, the Stop cue provoked a beta increase only on Correct, but not Failed, Stop trials (Figure 1c; see also [48]), even though the sequence of cues presented was identical. We argued that only cues that are actually *used* to direct behavior evoke beta increases.

Speculatively, the elevated beta may indicate a relatively closed "gate" within the basal ganglia, that reduces responsiveness to incoming stimuli. As one possible manifestation of this, Stop cues were ineffective at arresting behavior if they arrived during the time of elevated beta produced by the Go cue [15]. By delaying the evolution of a striatal Go process, the beta network state may normally serve the adaptive function of impeding impulsive responding, but become exaggerated and maladaptive in Parkinson's Disease.

Such ideas remain speculative, in large part because beta oscillations are a broadly-distributed phenomenon whose origins, propagation and functional impact remain less than clear. Furthermore, pronounced changes in beta power appeared only several hundred milliseconds after cue onset, so are unlikely to be directly part of the critical fast development of a Stop process.

Fast progression of Stop cue information through the basal ganglia

We therefore examined the activity of individual basal ganglia neurons during the SST [20], comparing firing rates between latency-matched Go and Stop trials. Prior human imaging work had found evidence that the "hyperdirect" pathway from frontal cortex to the subthalamic nucleus (STN) is an anatomical substrate of the race model Stop process [7] that may suppress movements at the level of basal ganglia output structures such as SNr. Consistent with this, we found neuronal subpopulations in both STN and SNr that showed significant short-latency firing rate increases to the the Stop cue (Figure 2). No such short-latency Stop response was seen in striatum, consistent with the race model idea that Go and Stop processes initially evolve independently.

The STN neurons had a more "sensory" character, responding to the Stop signal quickly (peak ~15ms) and regardless of whether stopping was actually successful or not. By contrast the responses downstream in SNr were a little slower (peak ~35ms) and more "motor"- they strongly correlated with whether the rat would successfully stop in that trial (Figure 2), as if reflecting the *outcome* of a race rather than the Stop process alone. Note that this SNr firing increase only on Correct, rather than Failed, Stop trials is similar to the Stop-cue evoked increase in beta power described above (albeit much faster).

The selective responding of SNr neurons on Correct Stop trials is a form of sensorimotor gating, arising from the relative timing of different inputs [20]. As described earlier, a key late step in the Go process seems to be increases in GABAergic input to SNr from the striatal direct pathway. If this is already underway, then the glutamatergic STN input evoked by the Stop cue is ineffective at driving SNr activity (and behaviorally stopping fails too). In this way, the fundamental idea of a race between Go and Stop processes may map onto a race between distinct anatomical pathways converging on individual SNr neurons.

This is – of course – too simple to serve as a full account of behavioral inhibition, for a variety of reasons. Human studies have often presented the SST as a paradigm of executive function, with a correspondingly prominent role for frontal cortical regions and their hyperdirect projections to STN. Yet in our rat SST it seems unlikely that there is enough time for significant information processing in frontal cortex to occur before the ~15ms latency Stop cue responses we observed in STN (even in primary auditory cortex neurons typically require ~12ms to respond to white noise stimuli; [49]). An alternative potential source of fast auditory STN input is the pedunculopontine tegmental nucleus (PPN; [50], and indeed we have recorded neurons there with Stop cue latencies ~9ms or less [51].

Even more importantly, this fast response is observed not just for the Stop cue, but for the Go cue as well – not a feature one would necessarily expect for a Stop process. In addition, the Stop response is highly transient – for many STN neurons just a single spike – and our modeling suggested that a more sustained change would be necessary to counteract the wave of striatal GABAergic inhibition that normally arrives in SNr just before movement onset.

So, does such speed, transience, and lack of selectivity invalidate the fast PPN-STN-SNr signal as a neural mechanism of stopping? Rather, we proposed that stopping actually involves multiple component subprocesses, with this fast signal serving to briefly delay ("Pause") actions rather than fully cancel them ([20]; see also Figure 3). For example, we note that in variants of the SST where a "Continue" cue is sometimes played instead of a Stop cue, actions proceed but with prolonged RTs [52], consistent with engagement of a Pause mechanism without complete cancellation. In addition, there is substantial evidence that unexpected cues transiently suppress not just the preparation of one particular action, but have a more global impact on even unrelated actions (and thoughts as well; [53]. This is broadly consistent with the idea of a "hold-your-horses" role for STN in reactive behavioral inhibition [54] that buys time for more informed decisions on how to proceed.

Multiple, complementary Stop mechanisms

Which circuits are then responsible for actually cancelling the movement? As noted earlier, we found evidence for a late interaction between Go and Stop processes at the level of the striatum. Specifically, on Correct Stop trials the developing movement-related activity in striatum abruptly dropped away (Figure 1b). We hypothesized that this was due to a strong inhibitory input from the GP. Although the classic

("prototypical") GP neurons project downstream to STN and SNr, the recently characterized "arkypallidal" cells form massive GABAergic projections exclusively back to striatum [55].

To identify the cell type of the GP units recorded in the SST, we first demonstrated that identified arkypallidal, but not prototypical neurons, greatly reduce their firing rate during slow wave sleep. This signature of arkypallidal neurons allowed us to discriminate them in freely-moving rats, by monitoring the same neurons in both the SST and during natural sleep [21].

Consistent with participation in a slower and more selective Stop process, GP Stop response latencies were longer (~60-80ms) and more selective (unlike STN and SNr, the neurons did not also respond to the Go cue). Arkypallidal neurons had significantly stronger and faster Stop responses than prototypical neurons [21], and intriguingly, these responses immediately preceded the inhibition of striatal movement-related activity in Correct Stop trials (Figure 1b). We concluded that arkypallidal neurons have the appropriate timing, selectivity and connectivity to help cancel actions by suppressing the striatal Go process (Figure 3b).

There is an obvious survival advantage in being able to respond quickly to events. Yet the more rapid the response, the less sophisticated the preceding information processing can be. In the case of reactive stopping this presents an inherent trade-off: at one extreme a subject could rapidly interrupt ongoing behavior for any salient sensory change, while at the other extreme the subject could be much more selective about whether to abandon ongoing motor plans, but much slower to do so.

Having separate, complementary Pause and Cancel mechanisms allows the advantages of both speed and selectivity. The less-selective but very fast PPN-STN-SNr response to stimuli blocks movement execution, but only for a brief period, buying time for more detailed assessment of stimulus identity. If this more detailed assessment indicates that stopping is unnecessary, actions can proceed with only a brief delay (10s of milliseconds, compared to the 100s of milliseconds involved in normal movement preparation). In this way, multiple Stop mechanisms allow a more effective speed-accuracy trade-off than would be possible with a single mechanism alone [56].

As a side note, the two stopping subcomponents are quite reminiscent of the distinct phases of dopamine cell responses to unexpected events: the well-known signaling of reward prediction errors is preceded by a faster, transient response that is less selective [57]. This is likely no coincidence, since STN provides a major input to dopamine cells [58].

The slower, more selective Stop responses of arkypallidal neurons presumably reflect more elaborate information processing in structures that provide input to GP. It is not yet known which structures these are since specific inputs to arkypallidal neurons have not yet been mapped. However, GP receives direct inputs from various cortical regions including including supplementary motor areas [59,60] that have been previously related to stopping [61,62].

Implications and Limitations

Our experiments confirmed the basic idea that Go and Stop processes race for completion. However our finding that stopping can be decomposed into complementary subprocesses means that certain assumptions may need to be revisited. In particular, the stop-signal reaction time has been used as a criterion to decide whether neural responses occur early enough to contribute causally to stopping or not (e.g. [63]), but our Pause-then-Cancel model suggests this may be too simple. This is because the stop-signal reaction time should be dominated by the relatively brief time required to engage the Pause mechanism (putting action on temporary hold), even if later mechanisms are essential for complete cancellation. We speculate that these later mechanisms include not only the arkypallidal suppression of striatum described above, but even later phases involved in terminating the cortical and thalamic activity patterns that drive the striatal Go process.

An advantage of the Pause-then-Cancel model is that it makes precise predictions about where and when manipulations should affect RT distributions and stopping performance. For example, we predicted that interfering with the PPN-STN-SNr pathway just at the time of Stop cue onset should decrease stopping performance [51] but particularly affect those trials which are "close calls" - since trials in which the Go process was especially slow should be successful even without the Pause mechanism. The result should be a broadening of the Failed Stop RT distribution. Conversely, interference with arkypallidal neurons should

affect the efficacy of stopping more generally, without as marked an effect on the RT distribution. Testing such predictions presents some technical challenges – for example, we currently lack an effective means of selectively and briefly inhibiting arkypallidal neurons, and while optogenetic manipulations have the required temporal precision, unless illumination is carefully controlled, it can itself engage the fast STN-SNr pathway.

We should re-emphasize that not all aspects of behavioral control can be reduced to performance in the SST [10]. Furthermore, months of SST training may lead rats (and monkeys) to make use of neural pathways that may not exactly map onto those used by minimally-trained humans. Despite these limitations, combining the SST with multi-site basal ganglia neurophysiology has been valuable both for our understanding of basal ganglia operations, and in demonstrating the need to update long-standing psychological models to include multiple component processes of stopping.

Additional Information

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Authors' Contributions
R.S. and J.D.B. wrote the manuscript.

Competing Interests
We have no competing interests.

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Figure captions

Figure 1 Go-related activity in the basal ganglia. (a) Coding of movement direction in striatal units during Go trials, reprinted from [20]. Bars indicate the fraction of units with a significantly higher firing rate in the indicated trial type. Green arrow indicates when the striatal population reached a significant level of direction coding, ~130ms before the onset of movement. (b) Average firing rate of the subset of striatal units that coded for movement direction before movement onset, reprinted from [20]. Different colors indicate mean firing rates in different trial types as indicated. Colored bars at the top mark

significant differences between trial types (cyan: Fast Go vs. Slow Go; blue: Slow Go vs. Correct Stop; purple: Fast Go vs. Failed Stop). (c) Mean spectrogram of the local field potential in GP aligned to the onset of the stop signal (vertical dashed line), reprinted from [15] with permission from Elsevier. Note that there are two transient beta pulses in Correct Stop trials (top panel), but only a single transient beta pulse in Failed Stop trials (bottom panel).

Figure 2 Stop-related activity in the STN (top panels) and SNr (bottom panels; reprinted from [20]). Mean firing rates of Stop cells in Correct and Failed Stop trials and latency-matched control Go trials. Note the sharp increase in firing rate in STN in response to the stop signal in both Correct and Failed Stop trials. In contrast, SNr stop cells respond to the stop signal only in Correct Stop trials, and show instead a movement-related decrease during Failed Stop trials. The grey vertical lines mark stop-signal reaction times in the corresponding recording sessions.

Figure 3 Sketch of the Pause-then-Cancel model (reprinted from [21] with permission from Elsevier). (A) Illustrations of how multiple stop circuits in the brain may be mapped into the race model framework. In Go trials (left) different reaction times are due to variable evolution of the Go process (green lines). All salient sensory events (Go and Stop cues) activate the Pause circuit (orange line) which leads to a transient elevation of the Go threshold (black dotted line). In Failed Stop trials (middle) the Go process reaches the threshold before this Pause mechanism is effectively engaged. In Correct Stop trials (right) the fast transient elevation of the threshold buys additional time for the slower Stop process to win the race. (B) Simplified circuit diagrams. For the Go process the direct pathway from striatum to SNr contributes to the initiation of movement (left). Salient sensory stimuli can evoke the rapid Pause mechanism in PPN, STN and SNr that transiently delays the initiation of movements (middle). This delay is exploited by a slower Cancel mechanism involving GP arkypallidal ("Arky") projections to the striatum. (C) Average firing rate time courses for stop-related neurons during Correct Stop trials. Note the successive "waves" of activity in different basal ganglia subpopulations (STN; SNr; Arky), reflecting different stages of stop cue information processing.