Journal Club

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Disentangling the role of posterior parietal cortex in response inhibition

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Review of Osada T et al.

Introduction

The functioning of the prefrontal cortex (PFC) is thought to underlie our ability to modulate thoughts, behaviors, and emotions according to our goals or plans. A critical feature of such regulation is the capability to inhibit actions when they are no longer appropriate; for example, stopping yourself from picking up a cup of tea when you realize it is hot. In laboratory experiments, inhibitory control is usually operationalized as the inhibition of an impending motor response, typically in reaction to an external signal (Aron et al., 2014). A common laboratory test is the stop-signal task (Verbruggen and Logan, 2009), in which people make key presses in response to "Go" signals. In a minority of trials, a "Stop" signal is given after the Go signal and participants must attempt to inhibit their impending response. Unlike the latency of Go responses, the latency of stopping cannot be directly observed as successful inhibition results in the absence of a key press. However, this latency can be estimated by varying the interval between the Go and Stop signals, and titrating it until the probability of successfully stopping is ~0.5. At this interval, it is assumed that the "race" to completion between the putative Go and Stop processes, initiated by the Go/Stop signals and ending in the generation/inhibition of a response, is on average a tie (Verbruggen and Logan, 2009). This implies that on average the two processes end at a similar time. It then follows that one can estimate the time taken to inhibit a response (stop signal reaction time, SSRT) by subtracting the time of the Stop signal (start of the Stop process) from the average duration of the Go process (from the Go signal to the time of the response, go reaction time).

Functional magnetic resonance imaging (fMRI) research has shown that PFC regions, including the right inferior frontal cortex (rIFC), are more strongly activated during Stop versus Go trials (Garavan et al., 1999; Aron and Poldrack, 2006). This has prompted much research attempting to establish a role for PFC in stopping and has implicated a putative fronto-basal-ganglia–thalamocortical network in such reactive response inhibition (Aron et al., 2014). Although those early fMRI studies also showed that parietal cortex (e.g., angular gyrus and temporoparietal junction, TPJ) was strongly activated during response inhibition, the possibility of these areas playing a role in stopping has been largely overlooked.

In a recent article in the *Journal of Neuroscience*, Osada and colleagues examined this possibility (Osada et al., 2019). They used transcranial magnetic stimulation (TMS) to transiently disrupt processing in posterior parietal cortex (PPC) while participants performed the stop-signal task. A benefit of this approach is its capacity to reveal the relevance of certain brain structures in a temporally precise way. To determine candidate PPC regions for stimulation, the authors first used fMRI to identify areas activated during the task. They observed significant activation of rIFC, presupplementary motor area (pre-SMA), TPJ, and intraparietal sulcus (IPS). Then they used resting-state activity patterns to parcellate PPC into smaller areas that are functionally connected to frontal areas involved in response inhibition (rIFC, pre-SMA; Aron et al., 2014). This procedure identified IPS as a suitable stimulation site. TPJ served as a control site to test the spatial specificity of the TMS effects because it was active during the task but not functionally connected with pre-SMA or rIFC. Single TMS pulses were delivered over the IPS or TPJ at a wide range of times within the SSRT, which was ~220 ms, to examine the temporal specificity. The results from two experiments in separate groups of participants showed that TMS over the IPS prolonged SSRT compared with trials without TMS, but only when delivered ~25 ms before the end of SSRT. Importantly, TMS over TPJ did not affect SSRT

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at any stimulation timings. These results are consistent with the idea that IPS is involved in inhibitory control and, intriguingly, reveal that the IPS is critically active toward the end of the Stop process (i.e., the last 10% of the SSRT).

It is worth noting that studies like this, using external stimulation methods to probe causal brain–behavior relationships, always come with the caveat that effects of stimulation might be indirect. Therefore, IPS might not have been directly involved in stopping. Instead, TMS might have activated outputs from IPS to functionally connected, stopping-relevant (rIFC, pre-SMA) or action-relevant (premotor and primary motor cortex) brain regions and disrupted their processing at a critical time. That IPS was active during the task speaks against this. However, to fully rule out this interpretation, it might have been useful to include another TMS control site, one that is functionally connected to IFC and pre-SMA, but not active during the stop-signal task.

Nevertheless, taking the current results at face value, one might ask what function IPS serves during response inhibition, particularly given that its involvement occurs so late in the Stop process. The authors surmise that TMS to the IPS might affect decision-making related to stopping of the response. The decision here would presumably be whether to "trigger" the Stop process when one detects the Stop signal. However, such a role seems at odds with current understanding of the Stop process. First, a salient Stop signal was used during the task, which makes detection misses unlikely. Second, participants were explicitly aware of the meaning of the Stop signal, so any decision-making step would likely be small. This is consistent with modeling of the Stop process, which shows that it rarely fails to be triggered (<10% of Stop trials; Matzke et al., 2017).

A more fundamental issue is that previous studies suggest the effects of stopping on the motor system can be read out much earlier than the critical window of IPS involvement, implying that the Stop process is active in advance of any putative IPS-related decision to stop. For example, the excitability of motor output pathways, assessed via TMS, is suppressed in successful Stop trials >50 ms before the end of the SSRT (Coxon et al., 2006). More importantly, recent work has hinted that the voluntary commands to agonist muscles are themselves suppressed well before the end of SSRT (Raud and Huster, 2017). In that study, EMG activity recorded from the agonist muscles in successful Stop trials initially rose just as it did when responding in Go trials, but then declined suddenly. This decline in motor output occurred ~150 ms after the Stop signal and ~50 ms before the end of SSRT, which incidentally is close to the onset of motor system suppression noted above (Coxon et al., 2006). On this basis, we speculate that the true latency of stopping in these tasks is ~25% shorter than SSRT, an idea consistent with recent findings that standard modeling of the race process results in an overestimation of SSRT by tens of milliseconds (Skippen et al., 2019). One explanation might be that SSRT is artificially prolonged by electromechanical delays associated with a key press. This delay period might reflect a so-called "ballistic" stage of action that, once started, cannot be inhibited and thus must run to completion (de Jong et al., 1990). If this were true, then a drastic reinterpretation of the results of Osada et al. (2019) might be required because the TMS would have been delivered after the apparent "point of no return" (de Jong et al., 1990).

Another way of interpreting the results of Osada et al. (2019) is that PPC participates in the inhibition of motor responses, but is not part of the "executive" fronto-basal-ganglia–thalamocortical network for inhibitory control. A large body of evidence has implicated PPC in roles related to planning and online control of movements (Andersen and Cui, 2009). Furthermore, a recent study by Desmurget et al. (2018) demonstrated that intracortical stimulation of human IPS leads to a spatially selective inhibition of voluntary movements. The spatial selectivity of this inhibition potentially dissociates it from the "global" suppressive effects of reactive response inhibition on the motor system (Wessel and Aron, 2017). In this view, PPC might be involved in forms of motor inhibition that ensure movements are correctly executed (e.g., preventing early release of movements and ensuring their timely termination), but is not involved in inhibition of impending actions in reaction to an external signal. This could be why activation of IPS was not correlated with SSRT (Osada et al., 2019). Instead, disruption of IPS just before the movement, when the cortical activity is close to the movement threshold, might lead to a slight premature release of the movement. Note that Go reaction times were apparently unaffected by TMS over IPS (Osada et al., 2019), but there was a suggestion of a difference between TMS and no TMS in the combined dataset ($p = 0.06$). In Stop trials, this premature release of movement would reduce the likelihood of stopping at a given interval between the Go and Stop signals, thereby increasing SSRT. This would imply that there are two separate (but potentially interacting) mechanisms for inhibiting actions that serve distinct purposes: a parietal one regulating the current action plan and a prefrontal one serving to inhibit action plans when they are no longer appropriate.

The recent work of Osada et al. (2019) raises fascinating questions and puzzles regarding the timing of the Stop process and the contribution of different cortical nodes to response inhibition. We look forward to future studies seeking to resolve the spatial and temporal dynamics of response inhibition through combined EMG- and behavior-derived estimates of stopping latency, along with improved behavioral modeling, functional imaging, and brain stimulation methods.

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