



Anterior cingulate cortex and adaptive control of brain and behavior

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Abstract

Research examining the functional underpinnings of anterior cingulate cortex (ACC) and its relationship to cognitive control have been described as “perennially controversial” and a “Rorschach Test” for modern neuroscience. Although there is near universal agreement that ACC is important for the adaptation of behavior, debate, despite decades of work, stems from the exact manner in which ACC goes about doing this. This chapter provides a brief overview of the various past and present theoretical arguments and research surrounding ACC function, and highlights an emerging literature of single unit ACC recordings from several species that support these theories. We will finish the chapter by focusing on our work examining the firing of single neurons in rat dorsal medial striatum (DMS) and ACC, and examining DMS’s dependency on ACC to accurately signal adaptive behavioral output. Ultimately, we will conclude that ACC carries a myriad of signals (error detection, reinforcement/feedback, value, response conflict, etc.) necessary for the modulation of attention and task-relevant/irrelevant signals so that difficult decisions can be made and action plans adapted when necessary.



1. Introduction

Understanding the factors and strategies that govern adaptive decision-making and cognitive control has provided a near endless supply of research directions for past, present and future work in cognitive neuroscience. At its core, this research is defined by an attempt to understand which brain circuits facilitate our ability to change and adapt behavior, and how. Decision-making is one of the most pervasive aspects of human life, everything we do from when we choose to wake up to when we choose to go to sleep is in some way a decision. Decisions, much like behavior, exist on a continuum from automatic to effortful. Deciding to brush one's teeth is (hopefully) an example of a relatively automatic decision, whereas choosing a college major or where to go to college in the first place is likely more effortful. Automatic and effortful decisions blend seamlessly into our day to day, often without impeding our actual ability to carry on with daily life tasks (i.e., work, chores, socializing). Consequently, much research has been devoted to understanding how we are able to navigate the world so successfully despite a constant barrage of decisions and distractions.

As an example, consider something relatively trivial that many of us do every day, navigating a car/bike/or walking with a GPS. The logistics of operating our preferred form of transportation notwithstanding, using a GPS is fairly straightforward; you key in an address, a handful of routes populate, you usually choose the fastest one, and then "voila!" you are on your way. Already in this example we have made several decisions, first the decision to go somewhere, second to consult our GPS, and third, to decide which route to take. Often we do not even think of these steps or process them as decisions because generally speaking, they are all relatively automatic, taking just a few seconds, if that, to make.

However, as we begin moving toward our intended goal sometimes, seemingly out of the blue, our decisions must adapt to new information, as for example, when our GPS informs us that an alternative route exists. If we are aware of the fact that traffic on the current route is getting bad, or we cannot stand the idea of potentially encountering traffic, we may quickly make the adaptive low effort decision to choose the newly offered route. However, if the predicted ETA associated with choosing the alternative route is no better than the ETA associated with staying on the current route, or if the alternative routes takes us on roads with lots of potholes or requires paying a toll, then adapting behavior becomes more difficult

because there is competition between multiple factors. In other words, in the absence of clear cost or benefit to either route, conflict between staying or changing course arises and will drive (pun intended) the recruitment of additional cognitive resources so that a decision can be made.

In many ways, the decision of whether to invest time or energy into overwriting a previous decision or quickly countermanning a previous plan of action when necessary parallels what is asked of subjects performing numerous cognitive control tasks that probe cognitive function. The stop-signal task for instance, asks participants to make a relatively automatic (GO) response (i.e., press a lever after hearing tone A), on a majority of trials, only to then randomly interleave a different trial type, STOP trials, on a lower percentage of trials. On STOP trials, a participant must withhold a response in the presence of a second cue (i.e., do not press a lever after hearing tone A when light is on). This task along with others, such as the Stroop Task, The Flanker Task, and Foraging Tasks, has formed the bedrock of research into cognitive control. This chapter catalogs the history of the debate over the contribution of ACC to the adaptation of behavior, and highlights recent novel work exploring the role of this brain region using single unit recordings in a variety of behavioral paradigms demonstrating that ACC signals that contribute to attention, error processing, value and effort computations, and response conflict.



2. The evolution of the conflict monitoring hypothesis

2.1 Conflict-monitoring

While the exact function of ACC continues to be debated, early network theories of cognition and control suggested ACC contributed to executive function (Mesulam, 1981; Papez, 1937; Posner & Dehaene, 1994; Posner, Petersen, Fox, & Raichle, 1988). In his theory of emotion, Papez theorized that ACC, in part due to its connections with the hypothalamus, was a “receptive region for the experiencing of emotion” (Papez, 1937). Papez speculated that the emotive process radiated from ACC to other brain regions, providing a kind of emotional context that in turn would influence or bias planned behavior (Papez, 1937). As functional theories of ACC moved away from emotion, per se, and more toward cognition, Mesulam hypothesized that ACC contained a map of motivational valence that helped direct attention and biased motor planning accordingly (Mesulam, 1981). Attentional network theorists refined this view, suggesting that ACC was critical for the selection of task or goal-relevant actions and later that

ACC was responsible for attentional awareness and implementation of control (Posner et al., 1988; Posner & Dehaene, 1994). Other evidence supporting ACC's involvement in control came from patient studies in which cingulotomies produced marked deficits in "attentional abilities" (Janer & Pardo, 1991; Turken & Swick, 1999).

The 1990s ushered in the use of neuroimaging techniques that in turn helped support and refine theories of ACC function. Using the Stroop Task, Pardo and others showed strong activation of ACC when subjects were asked to respond to the ink color in which a conflicting color name was presented (Bench et al., 1993; Carter, Mintun, & Cohen, 1995; Pardo, Pardo, Janer, & Raichle, 1990). Similarly, evidence suggested that ACC was activated more when detecting multiple color forms or motion targets was necessary in comparison to passive viewing (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991), suggesting that ACC is preferentially activated by incongruence, as well as when action is required. Other work revealed that ACC was activated more strongly when the number of targets increased (Posner et al., 1988), but that this activation decreased when subjects were allowed to practice with the stimulus set (Raichle et al., 1994).

With evidence implicating ACC in functions pertaining to the ability to resolve conflicting information between relevant inputs and incongruent distractors growing, a new theoretical perspective emerged (Botvinick, Braver, Barch, Carter, & Cohen, 2001). This perspective, aptly named the "conflict-monitoring hypothesis," postulated that one role of ACC might be in the detection of instances where a subject's intended action, and the action dictated by environment were at odds (i.e., response conflict). In these instances, once detected, a "conflict-signal" would develop to help bias attention, motor planning and action selection in downstream brain regions to drive behavior toward the correct response. The theory attempted to account for a variety of different behavioral results that implicated a role for ACC in tasks requiring response override (Bench et al., 1993; Bush et al., 1998; Carter et al., 1995; Casey et al., 1997; George et al., 1994; MacLeod, 1991; Pardo et al., 1990; Paus, Petrides, Evans, & Meyer, 1993; Stroop, 1935; Taylor, Kornblum, Minoshima, Oliver, & Koeppel, 1994), tasks that studied underdetermined responding (Andreasen et al., 1995; Barch et al., 2001; Buckner et al., 1995; Deiber et al., 1991; Friston, Frith, Liddle, & Frackowiak, 1993; Frith, Friston, Liddle, & Frackowiak, 1991a, 1991b; Jueptner, Frith, Brooks, Frackowiak, & Passingham, 1997; Petersen, Fox, Posner, Mintun, & Raichle, 1988, 1989; Playford et al., 1992;

Raichle et al., 1994; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Yetkin et al., 1995), and tasks that involved error commission (sCarter et al., 1998; Dehaene, Posner, & Tucker, 1994; Falkenstein, Hohnsbein, & Hoormann, 1995; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993; Gratton, Coles, Sirevaag, Eriksen, & Donchin, 1988; Scheffers, Coles, Bernstein, Gehring, & Donchin, 1996), as well as studies that did not fully fit within the other three categories (Baker et al., 1996; Corbetta et al., 1991; D'Esposito et al., 1995; Grasby et al., 1993). The work created a computational framework where ACC, focused on conflict monitoring, could account for the behavioral results of almost all of these findings.

Importantly, this work did not maintain that the sole function of ACC was conflict-monitoring, rather that this was just one of several functions likely served by ACC (Botvinick, 2007; Botvinick et al., 2001; Botvinick, Cohen, & Carter, 2004). Instead, this account merely ascribed a "special status" to response conflict (Botvinick et al., 2004), suggesting that many of the behavioral phenomenon associated with ACC in the past could be accounted for using this framework. Specifically, this model held that ACC was engaged most strongly during conflicts at the level of response selectively, and that trial history or sequence effects cannot be attributed entirely to attention, perceptual, or motor priming. Indeed the computational foundation of theory shows reactive adjustments in control on trial to trial basis can be accounted for by conflict signals (Botvinick et al., 2001, 2004). This was supported by work showing that increased ACC activity on incongruent trials of the Stroop task was associated with relatively low interference on subsequent trials (Kerns et al., 2004), suggesting that ACC is responsible for shifts in cognitive control on subsequent trials.

2.2 Merging conflict-monitoring with expected outcomes

While the original crafting of the conflict-monitoring hypothesis offered a theory that accounted for many of the behavioral and neuroimaging findings related to ACC, it did not account for everything, and with an increased focus on the role of ACC, and cognitive control more generally, challenges to the conflict-monitoring hypothesis began to appear. Research emerged suggesting that ACC responds preferentially to aversive outcomes or reductions in reward (Gehring & Willoughby, 2002), suggesting a potential role for ACC in guiding action selection based on past outcomes (Hadland, Rushworth, Gaffan, & Passingham, 2003; Holroyd & Coles, 2002;

Matsumoto, Suzuki, & Tanaka, 2003; Rushworth, Walton, Kennerley, & Bannerman, 2004). Moreover, studies in rats and monkeys found that ACC lesions did not disrupt task switching (which requires conflict detection), but did impair evaluation of effort necessary to obtain reward (Dias & Aggleton, 2000; Rushworth, Hadland, Gaffan, & Passingham, 2003; Walton, Bannerman, Alterescu, & Rushworth, 2003).

At the same time, research looking at the involvement of ACC in action outcome encoding revealed that the firing of monkey ACC neurons reflected the relationship between cue and reward (Matsumoto et al., 2003), and that lesions disrupted the reward guided selection of actions (Hadland et al., 2003). Moreover, evidence from a sequence learning task suggested that populations of cells in ACC were critical for mapping action outcome relationships necessary for successful sequence learning (Procyk, Tanaka, & Joseph, 2000). Similar results were described in rats, where ACC was shown to represent errors and preparatory attention within the same behavioral sequence (Totah, Kim, Homayoun, & Moghaddam, 2009). Collectively, these findings led to the development of an alternative hypothesis that suggests the function of ACC was more directly concerned with action outcome learning, and the guiding of decision-making based on the expected value of reward, rather than conflict monitoring per se (Rushworth et al., 2004).

It is worth noting at this point that just as the conflict-monitoring hypothesis was unable to account for several new results, these alternative accounts, in turn, were also unable to fully account for some of the findings supported by conflict-monitoring. Occasionally, these alternative hypotheses even required aspects of conflict monitoring in order to appropriately model their results (Frank, Woroach, & Curran, 2005; Holroyd & Coles, 2002). As evidence for both theories continued to accrue, a reframing of the original conflict-monitoring hypothesis was proposed, one that attempted to account for both the conflict-monitoring findings and the outcome evaluation/decision-making theories (Botvinick, 2007). This hybrid model, framed as an extension of the initial conflict-monitoring hypothesis, suggests that conflict acts as a teaching signal, which in turn, drives a form of avoidance learning to bias behavioral decision making toward “cognitively efficient” strategies (Botvinick, 2007). In other words, instead of an occurrence of conflict triggering ACC, and thus shifting control to protect against future conflict, this new view suggests that the experience of conflict instead drives the avoidance of tasks or strategies that have given rise to conflict in the past (Botvinick, 2007). In this way, the experience of conflict is encoded as a negative reinforcing event

that biases future behavior away from experiencing conflict again. In line with this theory, work investigating effort in rodents has suggested that lesions to ACC modulate the willingness of rats to engage in physically effortful tasks based on the value of reward (Walton et al., 2003; Walton, Bannerman, & Rushworth, 2002; Walton, Kennerley, Bannerman, Phillips, & Rushworth, 2006), and evidence from monkeys performing a foraging task suggest that ACC lesions diminish willingness to sustain actions that lead to reward (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006).

2.3 Foraging

The emphasis on effort in addition to a desire to explore the evolution of cognitive control within a more ethologically relevant perspective led to an increased interest in exploring the role of ACC in the context of foraging behavior (Kolling et al., 2016; Kolling, Behrens, Mars, & Rushworth, 2012; Shenhav, Cohen, & Botvinick, 2016). In many ways, like the GPS example at the beginning of this chapter, a foraging context emphasizes the fact that adaptive decision-making does not occur in isolation. Decision-making is a tool often employed in the service of achieving an overarching goal and/or action, such as successfully navigating to one's desired destination. Already, data has suggested that within the foraging context, the ACC of monkeys contributes to both reward and error processing, and damage to ACC diminishes the willingness to sustain rewarded actions (Kennerley et al., 2006). In an attempt to more directly incorporate these findings, the conflict-monitoring hypothesis was extensively reframed into what is now known as the expected value of control (EVC) hypothesis (Shenhav, Cohen, et al., 2016; Shenhav, Straccia, Cohen, & Botvinick, 2014).

The EVC theory subsumes previous conflict-monitoring accounts as well as offers a broader explanation for ACC functioning in general (Shenhav, Cohen, et al., 2016). Critically, EVC predicts that control signals vary along two dimensions: (1) identity, a judgment about what the appropriate action/response may be and (2) intensity, a determination of how achieving the appropriate response should be executed (Shenhav, Cohen, et al., 2016). In this view, conflict, encoded as the need to put forth effort, drives the biasing of behavior in the appropriate direction, and specifically within the context of foraging, choice difficulty (i.e., when to continue harvesting versus when to move on from a patch) is reflected as a proxy for effort/conflict. Two fMRI studies showed that when decision difficulty was highest,

ACC activity also peaked (Shenhav et al., 2014; Shenhav, Straccia, Botvinick, & Cohen, 2016). Researchers separated choice difficulty from reward value by noting that within a foraging context, when the value of staying versus leaving is equal, the decision on whether to stay or leave is more difficult, and control is required. However, when the value to stay or go, respectively, is high, then the decision is obvious, and ACC should not be involved. In line with this prediction, ACC activity was increased only when decision difficulty was also high, and not when the value of staying or going was obvious (Shenhav et al., 2014, Shenhav, Straccia, et al., 2016). While in this view, the meaning of conflict, at least as originally presented, has certainly been expanded, the advantage to EVC is that it offers a comprehensive explanation of conflict both on its own and within a foraging context, while also providing a clearer rendering of the functional role of ACC.

Unsurprisingly, the EVC theory has not been universally accepted, as the question of whether reward value or the need to put forth control rages. Consider the GPS example again. As described earlier, the difficult decision arises when you are asked to decide between staying on the same route where traffic has slowed versus taking a new route that offers a similar ETA. With the EVC theory in mind, this decision is difficult because the overall outcome (i.e., ETA) is essentially the same, suggesting a need for ACC engagement in order to exert control and drive behavior appropriately. In a foraging context, this example would be similar to the reaching the optimal point at which an animal must decide to leave one patch in order to find another. The original patch still has food to harvest, but staying too long may deplete the resources to the point that the benefits of staying and eating no longer outweigh the costs associated with going without food or resources while traveling to find a new patch. At the same time, the GPS and foraging decision could also be viewed as relatively easy. At this point in time along the decision timeline, both ETA or resource supply are equal so the law of least work might predict that an animal would stay until accruing some deficit rather than engage in the hassle of preemptively acting.

This is where an alternative account of ACC function has risen from the original effort and expected outcome work. This alternative account suggests that ACC is primarily concerned with search value (i.e., the average value of the environment) which predicts whether to continue searching or to stay put. If the average value associated with a particular action (i.e., staying in on the originally chosen GPS route or staying in the same patch) begins to decrease, an animal would then be motivated to move on (i.e., choose the alternative route or find a new patch), but if the value is relatively

high or the values of going and staying are relatively equal (i.e., ETA's for both routes are the same, or there is still resource to harvest) then an animal's motivation for search would be minimal. Consistent with this theory, a recent human fMRI study showed that ACC is strongly activated by the quality, quantity and interaction of quality and quantity features of an offer, and that tracking of subjective values correlates with choice (de Berker, Kurth-Nelson, Rutledge, Bestmann, & Dolan, 2019).



3. What does ACC signal? Insights from behavioral neurophysiology

As it stands now, EVC and search value hypotheses, as well as their respective predecessors, offer explicit predictions about ACC function. One favors functions related to conflict or choice difficulty while the other suggests that ACC estimates average value of stimuli and actions in the environment. Despite the constant reframing of the conflict-monitoring hypothesis, two critical questions that have lingered over decades of cognitive and computational research has been: What information do single neurons in ACC carry? Do single ACC neurons detect conflict like BOLD signals do or does ACC influence behavior via signals more closely aligned with reinforcement/feedback and value/effort estimates? While the single neuron data showing that ACC does signal expected value is abundant (Amiez, Joseph, & Procyk, 2006; Blanchard & Hayden, 2014; Cai & Padoa-Schioppa, 2012; Hayden, Heilbronner, Pearson, & Platt, 2011; Hayden, Pearson, & Platt, 2011; Ito, Stuphorn, Brown, & Schall, 2003; Kawai, Yamada, Sato, Takada, & Matsumoto, 2015; Kennerley, Behrens, & Wallis, 2011; Kennerley, Dahmubed, Lara, & Wallis, 2009; Luk & Wallis, 2013; Nakamura, Roesch, & Olson, 2005), until recently, there has been surprisingly few single unit studies that support that ACC contributes to conflict-like mechanisms and adaptive adjustments in behavioral control outside the realm of value, reward, or effort encoding.

Early single unit work in this field focused on neural correlates of error detection (Amiez et al., 2006; Ito et al., 2003; Quilodran, Rothe, & Procyk, 2008; Rushworth & Behren, 2008); Totah et al., 2009) and aspects of behavioral feedback related to reward and attention (Kennerley et al., 2006; Oliveira, McDonald, & Goodman, 2007; Rothé, Quilodran, Sallet, & Procyk, 2011). For example, Hayden and colleagues showed that activity in monkey ACC was high when rewards were delivered and omitted unexpectedly in a task in which rewards were delivered at predetermined

probabilities (Hayden, Heilbronner, et al., 2011). Importantly, changes in ACC firing occurred regardless of valence at the single cell level suggesting that primate ACC encodes unsigned reward prediction errors consistent with theories put forth by Pearce and Hall (Hayden, Heilbronner, et al., 2011). Consistent with these findings, we have also shown that neurons in rat ACC fire similarly to appetitive reward and aversive shock suggesting that activity in ACC better reflects attention as opposed to signed value per se (Schneider, Sciarillo, Nudelman, Cheer, & Roesch, 2020). Further, we have shown that activity in ACC is elevated on behavioral trials after reward contingences changed unexpectedly for both up- and down-shifts in value, suggesting that ACC appears to not only be involved in detecting errors but in utilizing that information to drive Pearce and Hall-like attention and learning on subsequent trials (Bryden, Johnson, Tobia, Kashtelyan, & Roesch, 2011; Vázquez, Pribut, Burton, Tennyson, & Roesch, 2020).

From this work it has been clear that firing in ACC correlates well with commission and omission errors, attention, and value in the service of adaptive decision-making but for a long time it was unclear if single neuron activity or even ensemble activity over multiple neurons correlated well with conflict between competing responses as is it does in so many fMRI studies that originally fueled early theories of ACC function. Below, we describe cross species data that have shed light on this issue.

3.1 Humans

Surprisingly, much of the single-unit support for conflict-related encoding ACC has come from humans. Although human ACC recordings originally suggested attentional modulation of ACC neurons (Davis, Hutchison, Lozano, Tasker, & Dostrovsky, 2000), subsequent research using a high-conflict version of a Stroop-like task revealed elevated activity on high-conflict trials (Davis et al., 2005). These results were further supported by more recent work using a multi-source inference task suggesting that human ACC neurons are continually modulated by expected cognitive demand (Sheth et al., 2012). In this task, subjects were asked identify the position of the unique number in an array of three numbers. Researchers varied the positioning of the unique number (i.e., left, middle, or right), which relative to the distractors, modulated cognitive demand accordingly (Sheth et al., 2012). Critically, ACC neurons mirrored conflict-adaptation hypotheses, or the Gratton effect, described previously by an fMRI study (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Sheth et al., 2012).

Subsequent work utilized targeted dimensionality reduction characterized activity across the population of ACC neurons as reflecting the amplification of task-relevant information during conflict as opposed to a general conflict signal or an epiphenomenal signal arising from the co-activation of competing inputs (Ebitz et al., 2020).

3.2 Non-human primates

Evidence for conflict monitoring by ACC at the single neuron level has been notably harder to come by in non-human primates. In monkeys performing a saccade-based countermanding task, single units in ACC showed selectivity for reinforcement and error detection, but no conflict-like signals were observed (Ito et al., 2003). This is in contrast to a previous result showing that single neurons in supplementary eye field (SEF) did show conflict-specific responses (Stuphorn, Taylor, & Schall, 2000), leading some to speculate whether species difference in brain homology between monkeys and humans may account for these discrepancies (Botvinick et al., 2004; Cole, Yeung, Freiwald, & Botvinick, 2009; Ito et al., 2003; Rushworth et al., 2004). A second study, utilizing two behavioral tasks, a spatial incompatibility task and a reversal task, recorded from SEF and ACC in monkeys and found little to no evidence for conflict-monitoring signals in either brain region. Instead, researchers showed possible evidence for representation of both competing responses that theoretically could give rise increased BOLD signals observed in human fMRI studies, but were unable to identify a single population of cells independently encoding conflict, as predicted by the original framework of the conflict-monitoring hypothesis (Botvinick et al., 2001; Nakamura et al., 2005). Notably, recent work in rats expands on this idea suggesting that feedback-related negativity in ACC neurons is generated across neurons in a similar fashion (Hyman, Holroyd, & Seamans, 2017).

The first signs that the firing of single ACC neurons could represent conflict and associated arousal came from a study that examined cue directed saccade behavior in the presence or absence of social and nonsocial distractors (Ebitz & Platt, 2015). Social distractors significantly slowed reaction times more than non-social distractors, and when they were incongruent with the saccade target (Ebitz & Platt, 2015). Neurons in ACC were modulated both by social context and task-relevant distractors (i.e., distractors presented during the response window versus those presented during the ITI) (Ebitz & Platt, 2015). Further, firing of ACC neurons predicted

conflict-related changes in pupil diameter, a measure of arousal, attentiveness and task engagement (Ebitz & Platt, 2015). Collectively, these findings suggest that firing in monkey ACC is modulated by conflicting distractors, however, since congruency affected firing in both directions a clear population level “response conflict-signal” was not evident (Ebitz & Platt, 2015).

3.3 Rats

To address this issue in rats, our lab developed a novel-variant of the stop-signal task to be used for behavioral neurophysiological studies in rats (Brockett, Tennyson, deBettencourt, Gaye, & Roesch, 2020; Bryden et al., 2019). As illustrated in Fig. 1A, rats were trained to place their nose in a central port, at which point a light cue on either the left or right side was flashed for 100ms. On 80% of the trials (i.e., GO trials) this cue predicted which of two fluid wells the rat must respond to in order to receive a reward. On the remaining 20% of trials (i.e., STOP-change trials) within 100ms of the first cue (i.e., GO cue) and second cue (i.e., STOP cue) was illuminated instructing the rat to cancel its initial response in the direction of the first cue, in favor of a response in the direction of the second cue in order to obtain reward. Critically, unlike traditional stop-signal tasks in which the appropriate response on STOP-trials is the refrain from any action, correct responding on this “stop-change task” requires the rat to cancel one action in favor of another.

During performance of this task, “response conflict” arises on STOP-change trials from neural signals that promote opposite actions (i.e., the response signaled by the first cue and the response signaled by the second cue). This is demonstrated behaviorally in that rats were slow and performed worse on STOP trials, and in that rats were extremely fast on STOP errors, moving quickly in the wrong direction. More interestingly, we were able to observe response conflict at the neural level by recording from motor-related neurons in dorsal medial striatum (DMS), an area whose firing is positively correlated with movement speed. This is illustrated in Fig. 1 which plots the average populations firing over 122 neurons in rats performing our STOP-change task. On GO trials (blue), activity strongly represents firing of the upcoming movement (Fig. 1B). This is a clean un-conflicted signal from start to finish, with significant differences between response directions (blue tick marks) emerging shortly after the presentation of the first cue and ending shortly after the completion of the response (arrow embedded in tick marks). On STOP-change trials (Fig. 1C), accurate response signals were slow to emerge in line with slower movement speeds and less accurate behavior

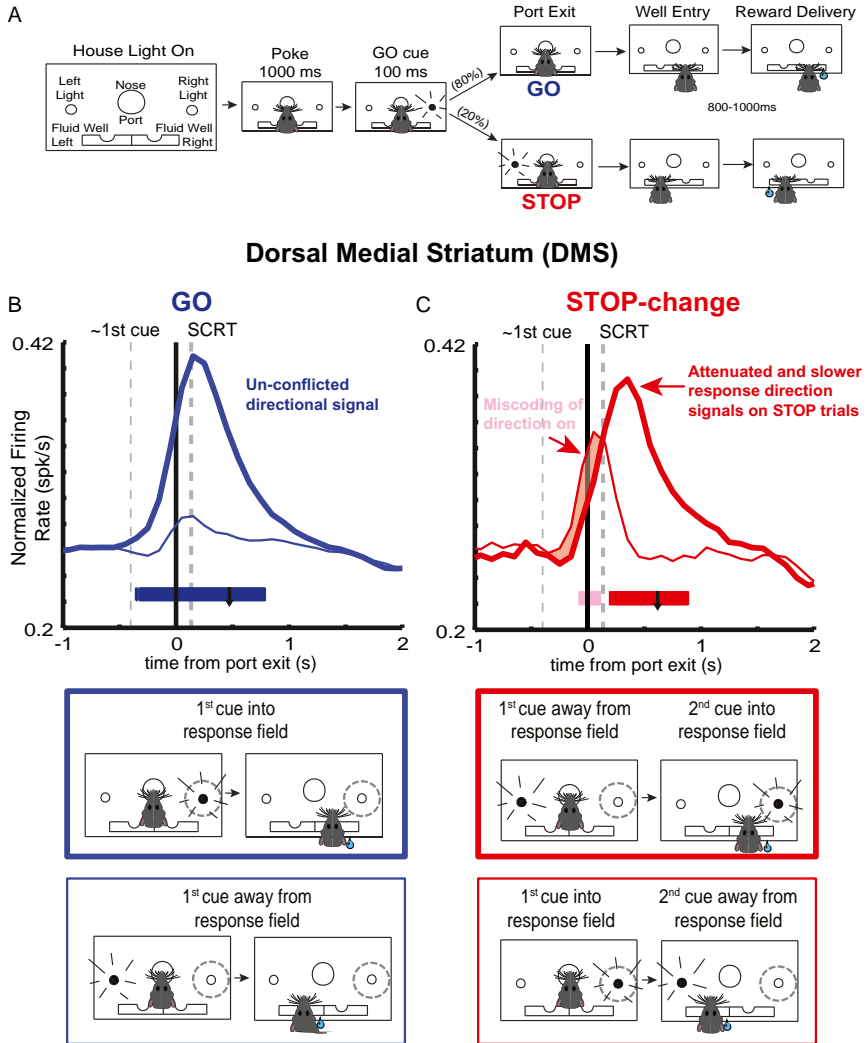


Fig. 1 Miscoding and slow development of accurate directional response signals in DMS during performance of a STOP-change task. (A) Illustration of the stop-change task (Brockett et al., 2020; Bryden, Burton, Kashtelyan, Barnett, & Roesch, 2012). Rats were instructed to hold their nose in the center port for 1 s, at which point a GO cue would be presented to either the left or right of the rat. On 80% of trials the GO cue instructed the rat as to which of the two fluid wells to move to in order to receive reward. On the remaining 20% of trials, STOP trials, after the initial GO cue, a STOP cue was presented on the opposite side, instructing the rat to inhibit its initial response in the direction of the GO cue, in favor of responding in the direction of the STOP cue. (B) Population firing of DMS neurons on GO trials aligned to center port exit. Thick and thin blue lines reflect

(Continued)

on STOP-change trials. Specifically, on trials where the first and second cues are into and then away from the response field, respectively, activity increased initially but then rapidly shuts down (thin line), whereas when the first and second cue is away from and then into the response field, respectively, activity was slow to rise (thick red line). The shaded red area in this plot reflects time when there was response conflict (i.e., competition between left and right responses). Importantly, accurate response tuning in DMS resolves early enough to enact behavioral change within a single trial as measured by the Stop Change Reaction Time (i.e., STOP minus GO reaction times; SCRT). Notably the resolution of the two conflicted signal (Fig. 1C; thick vs thin red lines; tick marks indicate significant differences) in DMS corresponded amazingly well to the SCRT, and when errors were made, activity failed to reconcile prior to the SCRT, reflecting the location of the incorrect movement (Brockett et al., 2020; Bryden et al., 2012).

When thinking about response conflict in the context of single neurons, average population level firing—as shown in Fig. 1—consists of single neurons whose firing failed, weakly, or accurately represented the correct response direction on STOP trial. Extreme examples of this continuum (i.e., fails to represent vs. accurately represents the correct response) are illustrated in Fig. 2. Both units show directional tuning on GO trials in that firing is significantly stronger for movement made in one direction versus the other. For these examples, activity was stronger for rightward GO movements, thus “right” is considered to be “into” the cell’s response field (i.e., gray dashed circle in inset) or the cell’s “preferred” response direction.

Now, let’s consider how these same neurons fire on STOP-change trials. For Unit 1, illustrated in Fig. 1A, firing strongly reflected the action signaled

Fig. 1—Cont’d firing in the preferred and non-preferred directions, respectively. Illustrations of directionality are shown below. The time necessary to inhibit a response (stop-change reaction time; SCRT) is defined as the difference between STOP trial movement time and GO trial movement time and is depicted by the dashed line. (C) Population firing of DMS neurons on STOP-change trials aligned to center port exit. Thick and thin red lines reflect firing when responses were made into the preferred (i.e., into the response field) and non-preferred directions (i.e., away from the response field), respectively. *Figures adapted from Bryden, D.W., Burton, A.C., Kashtelyan, V., Barnett, & B.R., Roesch, M.R. (2012). Response inhibition signals and miscoding of direction in dorsomedial striatum. Frontiers in Integrative Neuroscience, 6, 69 and Brockett, A.T., Tennyson, S.S., deBettencourt, C.A., Gaye, F., & Roesch, M.R. (2020). Anterior cingulate cortex is necessary for adaptation of action plans. Proceedings of the National Academy of Sciences, 117, 6196–6204.*

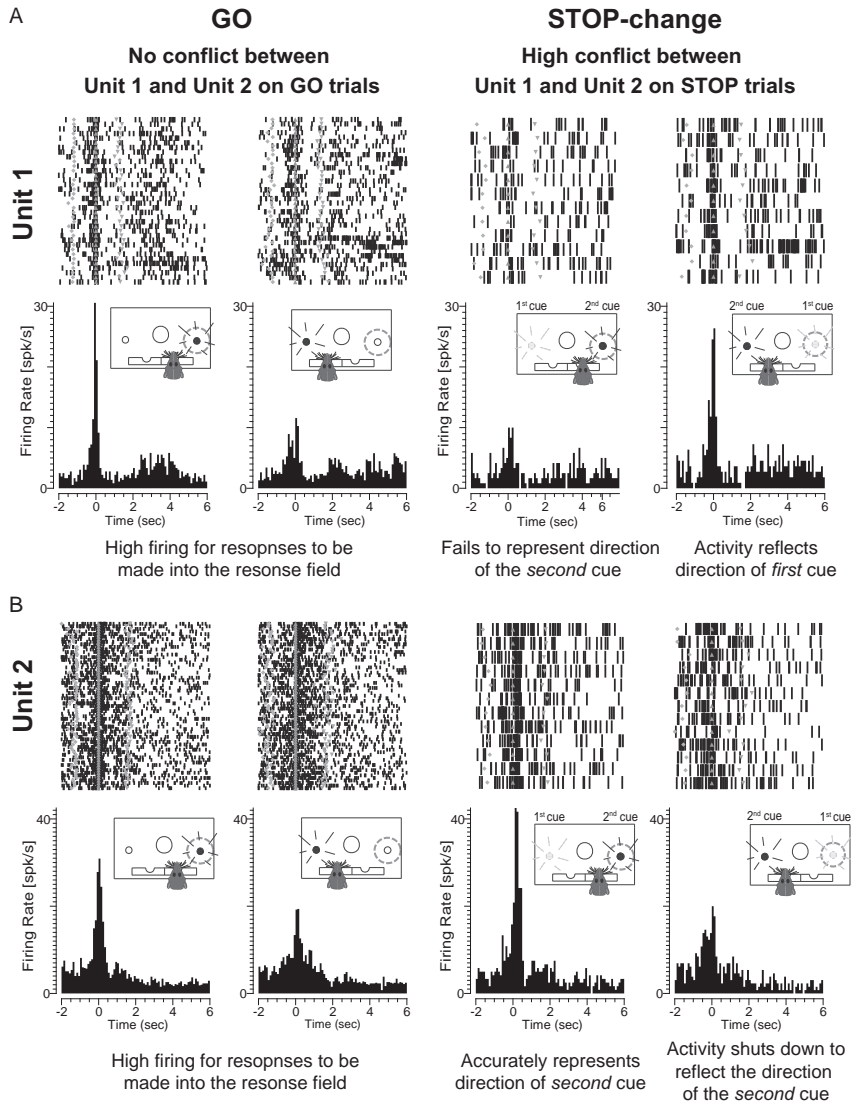


Fig. 2 Raster plots showing firing for individual neurons from DMS. Firing of example units on correct GO and STOP-change trials. High firing is observed on GO trials reflecting the direction the rat intends to move in. The direction associated with higher firing is referred to as the “preferred” direction or “into the response field”. a. Unit 1 fails to represent the direction of the correct response, instead firing represents the direction of the first cue. (B) In contrast, when looking at Unit 2, firing in the direction of the 2nd cue emerges on the STOP-change trials and firing in the direction of the first cue is correctly shut down. *Figures adapted from Bryden, D.W., Burton, A.C., Kashtelyan, V., Barnett, & B.R., Roesch, M.R. (2012). Response inhibition signals and miscoding of direction in dorsomedial striatum. Frontiers in Integrative Neuroscience, 6, 69.*

by the first cue, and never accurately represents the correct response direction. One can imagine that having too many of these units active during a STOP-change trial would result in movement into the wrong direction. Although neurons like this are present in normal rats at significant levels, the majority of neuronal firing looks like Unit 2. For this neuron, the firing reflects the correct response direction on STOP-change trials (i.e., the direction of the second cue light). In examining these two units, one can see how response conflict can arise in the brain with different units simultaneously signaling opposite directions on STOP-change trials (high conflict), but not during performance of GO trials (no conflict). With these results we firmly established, both from a neural standpoint and a behavioral one that the two responses (left versus right) are in conflict with each other when rats perform our behavioral paradigm. The question that remained is whether or not ACC is able to (i.e., signal conflict) and is necessary to resolve this conflict (i.e., response conflict cannot be resolved without ACC).

To address this question we recorded from ACC in rats performing the identical task (Bryden et al., 2019). We found that neurons in ACC increased firing on STOP trials compared to GO trials in a directional fashion (see Fig. 3). Firing emerged just after the presentation of the STOP cue and well before the stop-change reaction time (Fig. 3B; SCRT), as well as before the resolution of directional signals in DMS. Further, we found that firing correlated with both movement time and accuracy, suggesting that when ACC was engaged, rats tended to slow down and perform better. Lastly, consistent with human imaging studies (Botvinick et al., 1999; Bryden et al., 2019), we found that ACC firing was strongest on high conflict trials (STOP trials that follow GO trials; i.e., incongruent that follow congruent trials) compared to lower conflict trials (STOP trials that follow STOP trials; i.e., incongruent followed by another incongruent trial; Fig. 3C).

These results demonstrate that firing in ACC can contribute to within trial adaptation of behavior and downstream motor units. This was true averaged across the entire population of recorded ACC neurons (Fig. 3B) and significant in the majority of task-related single units (Fig. 4A; Trial-type circle). Notably, this signal is unique to ACC in that counts of neurons carrying such a signal is absent from other brain regions that we have recorded from (Fig. 4B–D), including DMS (Bryden et al., 2012), lateral orbitofrontal cortex (Bryden & Roesch, 2015), and medial prefrontal cortex (Bryden et al., 2016). Also important to note is that neurons that were modulated by conflict, also tended to be directionally selective (Fig. 2A; green).

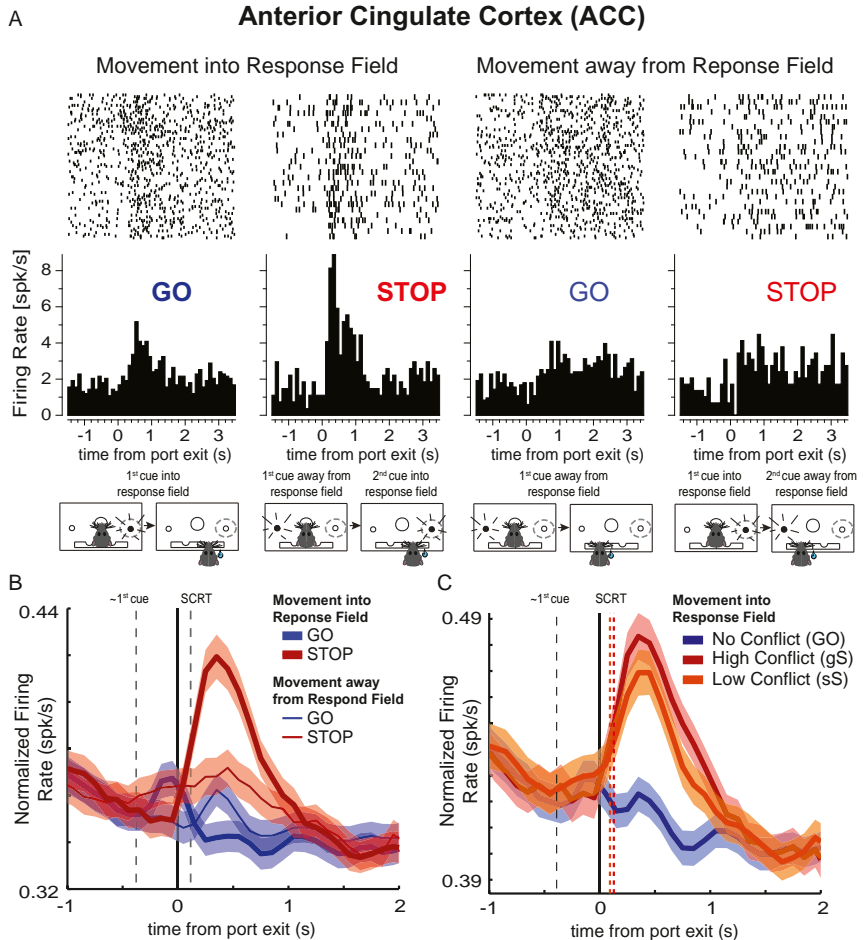
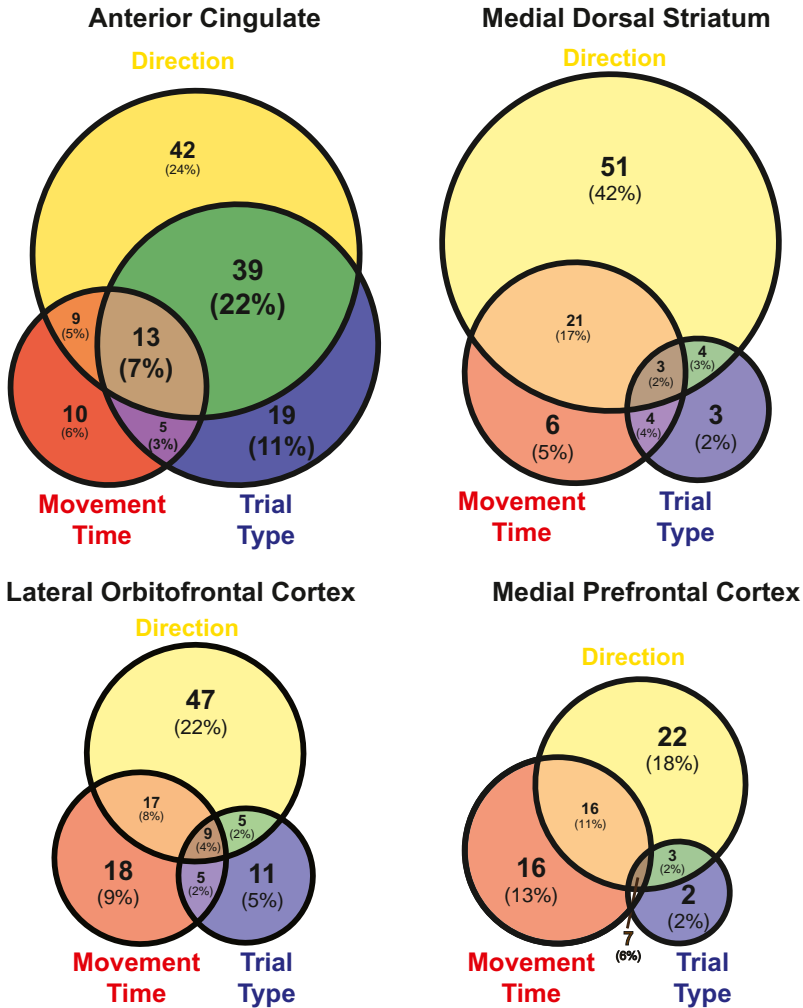


Fig. 3 ACC fires more strongly on STOP-change trials. (A) Raster plots of an example unit showing higher firing on STOP-change trials when the movement was made into the unit's response field. (B) Population histograms mirror single unit examples showing selectively higher firing on STOP-change trials when the direction of the movement was made into the response field (i.e., preferred direction). (C) ACC firing is modulated by the degree of conflict, showing higher firing on 'high conflict' trials (red) (i.e., trials where a STOP-change trial is preceded by a GO trial) relative to low conflict trials (orange) (i.e., trials where a STOP-change trial is preceded by another STOP-change trial). Note that both high and low conflict trials are higher than GO trials (blue). *Figures adapted from Bryden, D.W., Brockett, A.T., Blume, E., Heatley, K., Zhao, A., Roesch, M.R. (2019). Single neurons in anterior cingulate cortex signal the need to change action during performance of a stop-change task that induces response competition. Cerebral Cortex (New York, N.Y.: 1991), 29, 1020–1031.*



β-valence	Direction		Movement Time		Trial Type	
	+	-	+	-	+	-
mDS	59*	20	6	28*	9	5
IOFC	30	48	20	29	19	11
mPFC	21	24	9	28*	8	5
ACC	46	57	22	15	67*	9

Fig. 4 Neurons in ACC are highly selective for direction and trial-type on the stop-change task (e.g., Fig. 3A). (A–D). Multiple regression on firing during the response epoch (port exit to fluid well entry) for neurons in ACC (A), medial dorsal striatum (B), lateral orbitofrontal cortex (C), and medial prefrontal cortex (a.k.a. prelimbic region) (D).

Thus, single ACC neurons are not globally representing the presence of conflict, but signaling the need for conflict resolution in a specific response direction. This finding harkens back to the human single neuron data demonstrating that conflict signals in ACC may serve to amplify relevant task features to adapt behavior accordingly (Ebitz et al., 2020).

To determine if these unique conflict-like signals in rat ACC were indeed necessary for the adaptation of behavior and in downstream motor-related signals, we performed a second study where we lesioned ACC unilaterally in rats performing the identical STOP-change task while simultaneously recording from DMS in the same hemisphere. In line with the hypothesis that ACC is necessary to resolve response conflict, ACC lesions increased STOP errors and lengthened the time necessary for rats to inhibit and redirect behavior on successful STOP-change trials (Brockett et al., 2020). These deficits in behavior suggest that the brain and therefore the rat is less able to reconcile the conflict between the two competing response directions. Indeed, average response selectivity across the population of DMS neurons did not significantly discriminate between the two directions and the frequency of single neurons that accurately (i.e., like the single neuron in Fig. 2B) signaled the appropriate action were fewer after ACC lesions. Thus, without ACC, DMS failed to signal the correct action on STOP-change trials. Further, when rats made errors, activity strongly represented the location of the first cue as in example unit 1 (Fig. 2A). This over representation on the incorrect response on

(D). Circle size represents the relative proportions of neurons showing significant partial r^2 values for the labeled task parameters (direction (yellow), movement time (red), trial-type (blue)). Positive β -values indicate greater firing for the contralateral direction (direction), greater firing for slower movement time (movement time), and greater firing for STOP over GO trials (Trial-Type). Asterisks indicated significantly more β -values for one valence within a parameter (binomial sign test; $P < 0.05$). Only in ACC, were proportions of neurons that increased firing on STOP in the significant majority (67 vs 9 neurons). Figures adapted from Bryden, D.W., Burton, A.C., Kashatelyan, V., Barnett, B.R., Roesch, M.R. (2012). Response inhibition signals and miscoding of direction in dorsomedial striatum. *Frontiers in Integrative Neuroscience*, 6, 69; Bryden, D.W., Burton, A.C., Barnett, B.R., Cohen, V.J., Hearn, T.N., Jones, E.A. et al. (2016) Prenatal nicotine exposure impairs executive control signals in medial prefrontal cortex. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, 41, 716–725; Bryden, D.W., Brockett, A.T., Blume, E., Heatley, K., Zhao, A., Roesch, M.R. (2019). Single neurons in anterior cingulate cortex signal the need to change action during performance of a stop-change task that induces response competition. *Cerebral Cortex (New York, N.Y.)*, 29, 1020–1031; and Bryden, D.W., Roesch, M.R. (2015). Executive control signals in orbitofrontal cortex during response inhibition. *Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, 35, 3903–3914.

STOP-change trials is illustrated across the entire population of recorded DMS neurons in Fig. 5C. Average firing quickly rose to the first cue light that was presented in the preferred direction (i.e., into the response field) and did not shut down until after the SCRT (i.e., after it was too late). In addition to

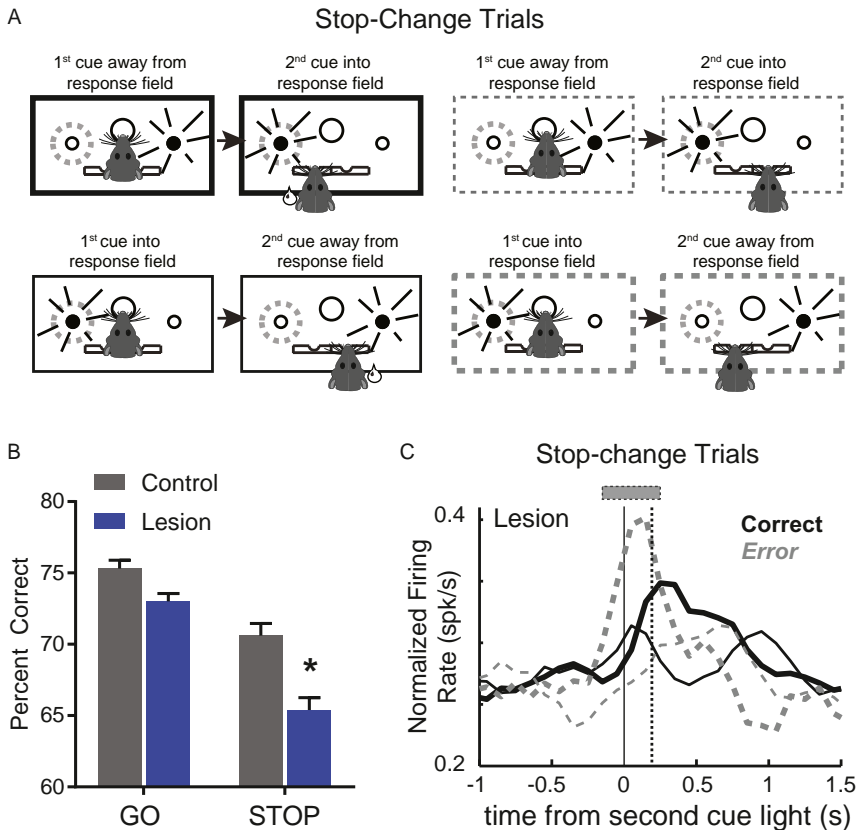


Fig. 5 Unilateral ACC lesions disrupt STOP trial performance and firing in DMS. (A) Illustrations of responding into (thick) and away from (thin) a neuron's response field on correct (solid) and errant (dashed) STOP-change trials. (B) Rats with unilateral ACC lesions perform significantly worse on STOP-change trials compared to control rats. (C) Population histogram for lesioned rats ($n = 53$) aligned to the onset of the STOP cue. Solid lines represent firing on STOP-Change trials where the rat made a correct response and dashed line represent firing on STOP-Change trials when the rat committed an error. Thick and thin line represent firing into (thick) and away from *thin) a neuron's preferred direction. Tick marks (gray bar) represent significance when comparing thick to thin lines within trial type. *Figures adapted from Brockett, A.T., Tennyson, S.S., deBettencourt, C.A., Gaye, F., & Roesch, M.R. (2020). Anterior cingulate cortex is necessary for adaptation of action plans. Proceedings of the National Academy of Sciences, 117, 6196–6204.*

ACC being necessary to be able for directional signals in DMS to adapt mid-trial, ACC was also necessary for modulation of firing on subsequent trials during conflict adaptation that deemphasized processing of the first cue, while strengthening directional selectivity associated with the second cue (Brockett et al., 2020).

Overall these results demonstrate that ACC—which predominately fired more strongly under high-conflict trials—is necessary for the reduction and amplification of the inappropriate and appropriate response signals in DMS, respectively, consistent with the impaired ability of rats to perform STOP-change trials after ACC lesions.



4. Conclusion

The debate over ACC function has been tenuous, but at the same time, has motivated decades of elegant work, elevating the status of research involving cognitive control to arguably the pinnacle of cognitive neuroscience thus far. The debate and subsequent attempts to support or overthrow the current schools of thought also highlights the importance of theory driven research. This work has incorporated the full spectrum of neuroscience and computational techniques spanning all major methods and models of neuroscience research to show that ACC is fundamentally important for guiding and adapting behavior. While the debate is far from over, single unit recording work is beginning to uncover the neural signals that contribute to these functions. It is becoming clear across the field of behavioral neurophysiology that firing of single neurons and ensembles of neurons represent multiplexed information across multiple domains. ACC seems to be no exception, carrying signals related to error detection, reinforcement/feedback, attention, value, and conflict to name a few. Ultimately, ACC seems to use this myriad of signals to modulate attention and task-relevant/irrelevant signals in downstream structures so that decisions can be made and action adapted when plans change.

Conflict of interest

The authors declare no biomedical financial interests or potential conflicts of interest.

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