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Opinion

Monitoring Demands for Executive Control: Shared Functions between Human and Nonhuman Primates

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Fifteen years ago, an influential model proposed that the human dorsal anterior cingulate cortex (dACC) detects conflict and induces adaptive control of behavior. Over the years support for this model has been mixed, in particular due to divergent findings in human versus nonhuman primates. We here review recent findings that suggest greater commonalities across species. These include equivalent behavioral consequences of conflict and similar neuronal signals in the dACC, but also a common failure of dACC lesions to reliably abolish conflict-driven behavior. We conclude that conflict might be one among many drivers of adjustments in executive control and that the ACC might be just one component of overlapping distributed systems involved in context-dependent learning and behavioral control.

Searching for Neural Substrates of Context-Dependent Control of Goal-Directed Behavior

In our daily life we frequently encounter the necessity to decide between competing courses of action. Conflict between potential responses is particularly common and pronounced when current goal-directed processing has to compete with more automatic, habitual responses; for example, while trying to attend to a lecture you may have to override the natural tendency to respond to your buzzing phone. Laboratory studies in humans have shown that while such competition or conflict influences performance negatively in the current trial (where conflict leads to slowed and more error-prone responding), it can improve performance in the subsequent trial when the participants are required to resolve conflict between competing choices again [1–3]. Box 1 details some of the most prominent behavioral tasks and their indices of conflict, including 'conflict cost' (slowed response time on the current trial if the trial is incongruent/high conflict) and 'conflict-induced behavioral adaptation' (faster response time on the current incongruent/high-conflict trial if the previous trial is also incongruent/high conflict). The highly influential conflict-monitoring model [1] of cognitive control [4] proposes that this is the case because conflict serves as a regulatory signal: conflict occurs when rival response options are similarly activated and this will trigger upregulation of top-down control, reinforcing processing of information in line with current task demands. According to this model, then, conflict-induced behavioral modulations are a consequence of trial-by-trial context-dependent tuning of executive control that aim to facilitate conflict resolution [1].

This model both drew support from and promoted an extensive body of work in human neuroimaging showing that conditions involving conflict are associated with heightened activation in a set of brain regions involving primarily the dACC (Box 2) and dorsolateral prefrontal

Trends

There are great similarities between monkeys and humans in conflict-induced behavioral modulations in the context of various cognitive tasks.

In humans and also in monkeys, neuronal activities in the dorsal anterior cingulate cortex (dACC) convey information about the level of conflict between behavioral options.

In monkeys, neuronal activities in the dorsolateral prefrontal cortex (DLPFC) and the orbitofrontal cortex (OFC) represent conflict level independent of the other task-related events.

In humans and also in monkeys, the behavioral effects of conflict experienced in the current trial (conflict cost) remain intact after lesions within the dACC.

In some studies with human patients, but not in monkeys, the behavioral effects of conflict experienced in previous trials (conflict adaptation) are impaired after a dACC lesion.

Conflict adaptation is impaired after lesions within the DLPFC (in monkeys and humans) or within the OFC (in monkeys).

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Box 1. Behavioral Measures and Consequences of Conflict

Depending on the structure of the specific behavioral task, conflict might arise at one or more different levels, including between competing sources of information, between competing behavioral rules, or between competing responses. Conflict might even arise between two tasks if they present different values to the participant in terms of relative cost and benefit, which would demand a strategic decision in choosing a particular task to achieve the goal.

In humans the impact of processing conflict on behavior can be observed in many classic paradigms such as the Stroop task, the Flanker task, the Simon task, and the go/no-go task [3]. For comparable tasks in monkey studies, see Figure 2 in main text. Typically, 'congruent' (or low-conflict) trials, wherein task-relevant and -irrelevant information cue identical responses, are interspaced with 'incongruent' (or high-conflict) trials, wherein task-relevant and -irrelevant information cue incompatible responses. A consistent observation is that participants are less accurate and slower in the incongruent, conflicting conditions, and this is referred to as the 'conflict cost' [1,29]. Importantly, the effects of conflict are not limited to the current trial and can also influence performance in the upcoming trial when the participants are required to resolve the conflict between competing choices again; however, this effect appears as an improved performance in resolving the conflict and is referred to as the 'conflict adaptation effect' [2,29]. One common way to estimate the conflict adaptation effect is to compute the difference in accuracy or response time between incongruent trials that are preceded by congruent trials (the ci condition) and incongruent trials that are preceded by incongruent trials (the ii condition). This conflict adaptation effect is ubiquitous in typical conflict protocols such as the Stroop, Flanker, and Simon tests [1,2,29]. While these sequential effects on behavior have in some instances been attributed exclusively to bottom-up (associative) mechanisms [63], there is now abundant evidence that this effect can still be observed when all bottom-up confounds are controlled for [64]. Thus, while the precise nature of the control mechanisms that mediate the conflict adaptation effect are still being debated, there is currently little doubt that this behavioral phenomenon can be a reflection of some form of trial-by-trial tuning of executive control settings [2,10].

cortex (DLPFC) as well as a range of other co-activated areas including the ventrolateral prefrontal cortex (VLPFC) and the posterior parietal cortex (PPC) along the intraparietal sulcus (for a recent meta-analysis, see [5]). Within this larger network of regions implicated in attentional control [6,7], the conflict-monitoring model posited: (i) a unique function for the dACC in monitoring or detecting conflict; and (ii) that this conflict information is then conveyed to the DLPFC to adaptively adjust the level of executive control [1,2]. The basic idea that 'crosstalk' between processing pathways can lead to conflict (or interference) in information processing, and thus result in slowed and more error-prone responses, is an old one in cognitive psychology and is generally uncontroversial [8,9]. Similarly, the notion that such conflict would – in principle – indicate performance problems and in turn could serve as a useful internal signal for top-down adjustments in processing strategy is well supported, although whether putative conflict-driven adjustments in control offer the best explanation for the data obtained in any particular behavioral study can, of course, be subject to debate [2,10].

What has proven to be a far more controversial aspect of the conflict-monitoring model is the neuroanatomical mapping of the model components. Specifically, whereas most researchers agree on a central role of the DLPFC in goal-relevant top-down control [4], there has been a long-running and heated debate about whether conflict detection represents a primary function of the dACC, is one of several functions of this area, or is not a function of this region at all, such that signals that some investigators interpret as reflecting conflict may instead be reflecting an alternative function [1,3,11–17].

It is generally accepted that evidence from animal models, particularly from nonhuman primates such as macaque monkeys, has proven to be key to advancing our understanding of many aspects of frontal lobe function due to the unique insights these studies can offer with respect to revealing mechanisms operating at the neuronal level (via electrophysiological recordings) and providing evidence about causality and necessity (from the far more circumscribed and reproducible lesions that can be introduced in animals than are ever observable in patient groups). Yet in this field, the animal models have arguably provided the most prominent evidence contradictory to the dACC conflict model. This has been due to repeated failures to find any evidence that monkey dACC neurons represent conflict and a lack of behavioral changes on tasks that elicit

Box 2. Human and Macaque Monkey Anterior Cingulate Regions

Detailed cytoarchitectural comparative mappings of the human (Figure IA) and macaque (Figure IB) cingulate cortex have been provided by Vogt *et al.* [65–67].

Area 24' was initially treated as part of the ACC but as it became clear that it is fundamentally different from area 24 on cytoarchitectural and functional grounds, the term mid-cingulate cortex (MCC) was introduced and the MCC is considered a separate functional unit from the ACC [67,68]. The relative locations of the ACC (yellow shading) and the MCC (light blue, gyral regions; dark blue, sulcal regions) are indicated in the human and macaque flat-map drawings on the left and right in Figure I, respectively. The MCC is further subdivided into the anterior and posterior MCC [67], with the former mostly corresponding to the less anatomically specific but commonly employed phrase [28,69,70] 'dorsal ACC', which we adopt for convenience in this Opinion article. One human cytoarchitectural area, area 32', is noticeably absent in the macaque scheme [66,71,72] and there has been debate about whether this may represent a unique functional area in humans [22,23,73]. This issue is complicated by the fact that the location of area 32' differs depending on the presence of a paracingulate sulcus [65,72]. However, the cortex on the dorsal bank of the macaque cingulate sulcus is not part of the MCC, according to Vogt and colleagues, and there is evidence this region may be a transitional area similar to the human paracingulate gyrus [72]. Moreover, recent studies have demonstrated evidence for a preserved organization of three cingulate motor areas (CMAs) in the human cingulate sulcus (distinct from the SMA and pre-SMA) as in the macaque cingulate sulcus, which partly extend into this dorsal sulcal region [19,74,75]. The most rostral of these CMAs is located in the anterior MCC (aMCC) and is included in the macaque 'anterior cingulate sulcal lesions' (ACCs) reviewed in this Opinion article [21,76], which targeted both banks of the sulcus (the fundus of the sulcus is indicated by an arrow) and extended anteriorly from the aMCC to the anterior tip of the sulcus in the ACC (the intended extent of the monkey ACC lesions is indicated by the broken red line). Resting-state fMRI in humans and monkeys has also revealed similar coupling profiles across species in the dACC and perigenual ACC [69,77]. Figure adapted, with permission, from [65,66].

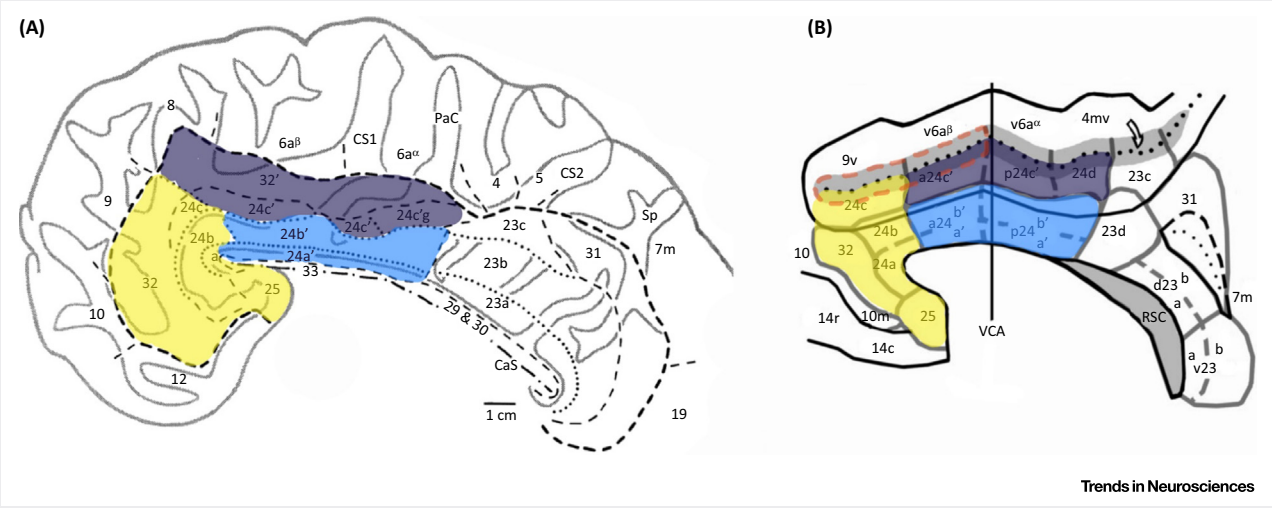

Figure I. Cytoarchitectural Subdivisions of Medial Frontal Cortex in Humans (A) and Monkeys (B).

conflict after dACC lesions (Figure 1) [18–21]. These apparently disparate cross-species findings have even led some authors to propose that nonhuman primates do not process conflict as humans do and/or that the human and monkey dACCs might contribute to cognition in qualitatively different ways [22,23].

In this Opinion article, we argue that more recent findings reveal great similarities between human and monkey data. First, behavioral costs of conflict-inducing conditions, and subsequent adjustments in performance, are seen consistently across the two species. Second, recent results from monkey dACC recordings [24,25] (Figure 2) may now allow apparent cross-species differences in neuronal data to be reconciled. However, we do not interpret these findings as support for a unique and necessary role of the dACC in conflict processing, as, third, our additional review of recent lesion studies speaks against this idea and instead highlights the importance of other frontal territories in supporting adaptive behavior (Figure 1). Considering these recent findings in the context of the broader literature (Box 3), we argue that conflict is likely to be one among many factors relevant for signaling difficulty in response selection in the presence of ambiguous stimuli and choice options, that the dACC is unlikely to serve a single, cardinal function, and that this brain region is just one among many areas partaking in a broader distributed system involved in supporting context-sensitive cognitive control processes.

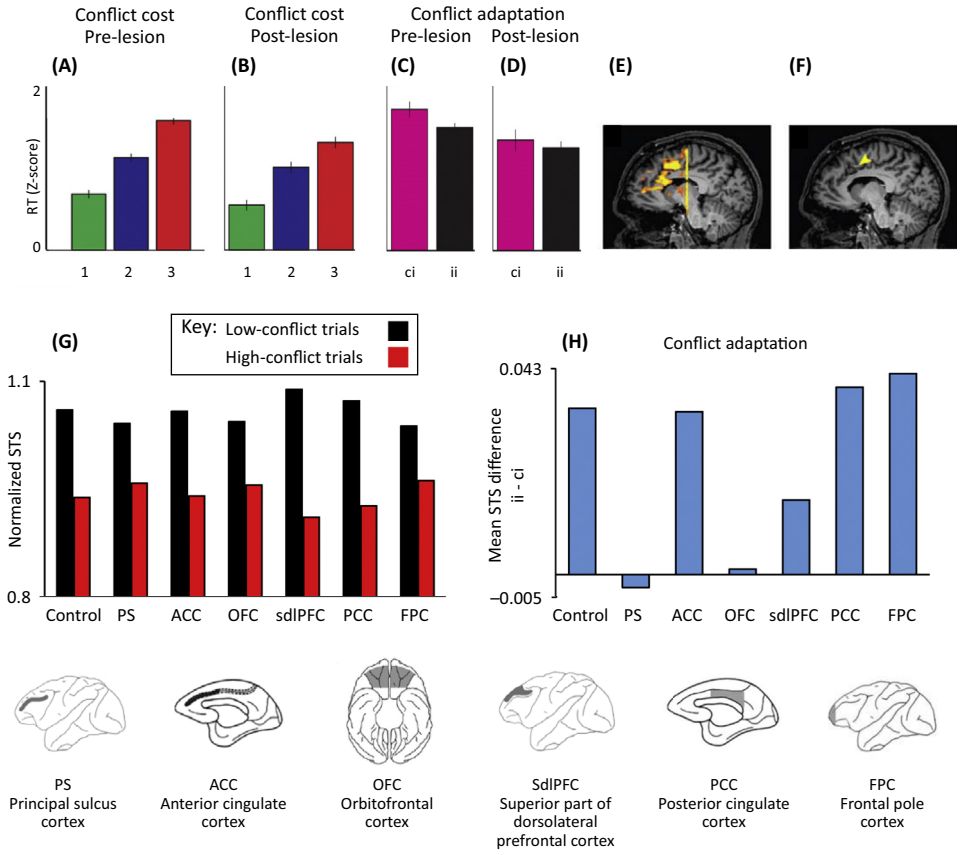

Figure 1. Conflict-Induced Behavioral Adjustments and Lesion Effects in Humans (A–F) and Monkeys (G–H). (A) Response time (RT) of patients is shown at different levels of conflict (conflict level increased from 1 to 3) before an ACC lesion. Conflict cost appeared as longer RTs at higher conflict levels. (B) Conflict cost was not abolished after the ACC lesion. (C) The RT of patients is shown in incongruent-after-congruent (ci) and incongruent-after-incongruent (ii) conditions before the ACC lesion. Conflict adaptation appeared as shorter RTs in ii conditions. (D) Conflict adaptation was significantly attenuated after the ACC lesion. (E) Medial view of the human ACC showing higher activation in the dorsal ACC when the patients faced a high-conflict condition during performance of a conflict task. (F) Medial view of the human ACC in which the arrow indicates the lesion location in patients. The lesion location overlaps with areas that showed conflict-related activation and was then targeted for single-cell recording. (A–F) adapted from [40]. (G) Mean normalized speed of target selection (STS) in low-conflict and high-conflict trials in control and lesion groups. Lesions in different cortical areas did not make any significant change to conflict cost. (H) Mean normalized STS difference between ci and ii trials. The difference in STS between ci and ii trials (conflict adaptation) was significantly decreased after lesions were made in the PS and OFC groups. All lesions were made bilaterally. Control, a group of monkeys without lesions (n = 6); PS, lesions in the cortex covering both banks of the principal sulcus (n = 4); ACC, anterior cingulate cortex (n = 4); sdlPFC, superior part of the dorsolateral prefrontal cortex (n = 3); OFC, orbitofrontal cortex (n = 3); PCC, posterior cingulate cortex (n = 3); FPC, frontal pole cortex (n = 4). The bottom row of images shows reconstructions of the area of lesioned cortex (grey color) on drawings of representative dorsal (PS, sdlPFC, and FPC), ventral (OFC), and medial (ACC and PCC) views of the macaque monkey brain.

Thus, this Opinion article is not aimed at adjudicating between rival views on the details of the dACC's evaluative function (for recent reviews see [14,16,17,26]) or at reviewing additional functions proposed for more rostral subregions of the ACC (for reviews see [27,28]). Rather, we review results from recent neuronal recording and experimental lesion studies that, for the most part, were conducted within the 'conflict-control' framework but clearly speak to putative performance evaluation and adjustment processes in the medial and lateral frontal cortex more generally and whose implications are therefore not limited to (or by) the conflict-control theory.

Box 3. Prominent Alternative Views of dACC Function

The most prominent alternative perspectives to the conflict-monitoring account of dACC function arose from a research literature focused on understanding the neural mechanisms of reward-guided decision-making. Whereas the conflict model has been primarily driven by behavioral and fMRI findings in humans, the reward-guided decision-making literature has been predominantly driven by animal studies, including in nonhuman primates. Many such studies have established the dACC's responsiveness to several key variables involved in reinforcement learning (RL). These include the observation that dACC neurons encode prediction errors [78–80] and reward rates [81]. Moreover, this region has been shown to represent (in human subjects) the volatility (rate of change) of the reward environment [82,83], which is a key factor in driving an optimal learning rate in RL models. Based on these and other findings, it has been proposed that the dACC is involved in computing and comparing 'action values' that signal whether it is most beneficial to maintain or change behavioral strategies [13,14,84–89]. Another strain of RL-focused dACC models has cast this region as specifically predicting and evaluating outcomes [15,80]. For instance, one sophisticated model that attempts to reconcile monkey and human data has proposed that dACC population activity is driven by 'negative surprise' – the omission of an expected outcome [15]. In relating these outcome-learning perspectives to the conflict-monitoring account, it is worth noting some central underlying commonalities. First, it is often overlooked that the conflict-monitoring model itself is an RL-based account, where it is a prediction error in 'control demand' (e.g., being prepared for a congruent Stroop trial but encountering an incongruent one) that drives the up- or downregulation of top-down biasing in anticipation of the next trial [1,90]. Second, all of the models noted here have in common the assumption that the dACC plays a crucial role in evaluating performance or outcomes within a broader 'evaluate-and-adjust' framework where the adjustment in behavioral strategies is typically attributed to the DLPFC. Given these common motifs, a full integration of a conflict (or, more generally, control demand) learning mechanism with the action–outcome learning perspective appears to remain feasible. By the same token, however, the findings that dACC lesions have little impact on the adaptation of behavioral strategies following performance difficulty [21] poses a challenge to all of these models.

Mixed Support for the dACC Conflict Model from Human Neuroimaging and Neuropsychology

Numerous neuroimaging studies in humans have reported enhanced activation in the dACC when participants encounter a high-conflict situation [1,29–31]. Moreover, human imaging studies have shown that the magnitude of dACC activation predicts the degree of behavioral adjustment and the activity level in the DLPFC on the subsequent trial [31] whereas dACC activation in the second trial of the incongruent-followed-by-incongruent (ii) condition was lower than in the congruent-followed-by-incongruent (ci) condition [29,31], suggesting that the conflict level was decreased as control was increased. Finally, accompanying the upregulation of DLPFC activity in ii trials, one can observe enhanced neural processing of task-relevant stimulus features [32]. In addition to these key works, hundreds of human imaging studies where more difficult task conditions were associated with higher dACC activity than easier task conditions have been loosely interpreted within this framework as supporting the dACC conflict-monitoring model. However, a smaller number of studies that very explicitly aimed at determining the dACC's involvement in response conflict monitoring produced results that challenged the conflict-monitoring hypothesis. On the one hand, some imaging studies found no activation in the dACC in relation to conflict level changes [33] or registered activation in more dorsal areas in the medial frontal cortex [i.e., in the pre-supplementary motor area (SMA)] [12,34] in the context of conflict tasks that elicited conflict-related behavioral modulations. On the other hand, other imaging studies showed that while the behavioral effects of conflict remained, the dACC activation gradually faded while the subjects performed more trials of the same task [35]. These findings indicated a possible dissociation between ACC activity and the behavioral effects of conflict.

Additional doubts about a necessary role for the dACC in conflict processing have arisen from mixed results in human lesion studies. Whereas di Pellegrino *et al.* [36] found that patients with dACC lesions have impairments in conflict-related behavioral modulations, Vendrell *et al.*'s [37] earlier study of patients with frontal lesions associated Stroop error rate with the right lateral prefrontal cortex not the dACC. Similarly, Stuss *et al.* [38] reported that the majority of patients with dACC lesions performed the Stroop task within normal limits, in contrast to patients with medial frontal lesions located more superiorly than the dACC, who displayed an exaggerated

Stroop effect. Moreover, Fellows and Farah [39] found that patients with dACC damage showed a normal response to conflict in Stroop and go/no-go tasks. More recently, Sheth *et al.* [40] combined imaging, single-cell recording, and lesion-behavioral studies in humans performing a conflict task. The fMRI study confirmed behavioral effects of conflict (both conflict cost and conflict adaptation) and showed higher activation in the dACC and DLPFC in the high-conflict condition. The activated foci in the dACC were then targeted for single-cell recording (discussed further below) and subsequently for lesion study. Importantly, after selective lesions were made in the same regions within the dACC, the behavioral effect of conflict in the current trial (conflict cost) remained intact but the conflict adaptation effect was significantly impaired. While this finding appears to provide strong support for the necessity of the dACC in human conflict adaptation, van Steenbergen and colleagues [41] have critiqued the lack of a control group in this study and have provided empirical evidence to show that the patient findings could theoretically reflect practice effects whereby the conflict adaptation effect naturally decreases over time.

A recent study [42] directly adopted a conflict task used in previous monkey studies [21] for the study of human patients with lesions that included the dACC and found that an ACC lesion group was indistinguishable from a control group in terms of both conflict cost and conflict adaptation. Moreover, as observed in monkeys [21], another group of patients with DLPFC lesions in the Boschin *et al.* study were impaired on conflict-induced behavioral adaptation. In sum, human lesion studies leave considerable doubts about whether an intact dACC is truly required for conflict-driven adaptations.

Initial Absence of Evidence for a Role of the Monkey dACC in Conflict Processing

Humans are not the only species that face the necessity of making choices and deciding between competing options. Many species, particularly those with developed and complex social and behavioral repertoires like nonhuman primates, face a necessity to resolve the competition between behavioral choices. Imagine a thirsty animal who needs to make a decision between two competing options: approaching a water resource or avoiding it because of the potential and imminent danger of predators. Given these shared cognitive challenges between human and nonhuman primates, one expects to observe common behavioral modulation and neural processing motifs in overcoming them. Accordingly, behavioral indices of conflict cost (i.e., slowed response times under conflict-inducing experimental conditions) and adaptation in behavior following the experience of conflict are robustly observed in the monkey [21,43–46]. However, whether the dACC plays an important role in that behavior has remained controversial.

For example, in a series of studies of the neuronal activity in the monkey supplementary eye field (SEF) and dACC, neuronal activity was recorded in the context of an eye-movement stop-signal task in which conflict emerged between planned/initiated eye movement and the need to redirect the eye movement to a new opposite target location [18,47,48]. It was found that the presence of conflict increased the response time and decreased the accuracy of eye movements. In the SEF but not the dACC, the neuronal firing rate was modulated by the conflict. Nakamura *et al.* [20] recorded neuronal activity in the SEF and dACC in monkeys performing an eye-movement task in which red and green cues instructed leftward and rightward saccades, respectively. Conflict was induced by spatial incompatibility, where the cue was presented either at the location of the target (no conflict) or opposite the location of the target (conflict). In a variant of the task, conflict was also induced by changing the color of the instruction cue, where the foveal cue either remained one color (no conflict) or reversed color after 100 ms (conflict). The monkeys were required to follow the instruction conveyed by the second color. In both tasks conflict reduced accuracy and slowed reaction time (conflict cost).

In the SEF, the neuronal firing rate was higher in the conflict condition. However, this effect took the form of modulation of task-related activity, whereby neuronal signals that encoded the direction of an upcoming saccade were modulated by conflict, rather than a 'pure' representation of a conflict signal *per se*; importantly, no conflict-related modulation was found in the dACC.

The relevance of the search for a pure conflict signal is important for general consideration, as conflict-related behavioral modulations might be a manifestation of aspects of task processing that were modulated by conflict and not necessarily of the detection or evaluation of conflict *per se*. For example, change in conflict level due to crosstalk in stimulus processing streams might increase arousal level or result in a more extended build-up of motor activity before response execution, and these processes might drive neuronal signals in the dACC and elsewhere [49]. An important question is therefore whether conflict as such is an independent task-relevant variable and is represented and maintained in the neural circuitry as a discrete entity in the dACC (or elsewhere) or whether conflict should be thought of as strictly local crosstalk in sensory or motor pathways that might recruit control but does not require a separate representation (see Outstanding Questions).

In another version of the oculomotor stop task, Emeric *et al.* [50] recorded local field potentials (LFPs) in the dorsal bank of the ACC and found that although conflict influenced the monkeys' behavior, the LFP was modulated by error and feedback but not by changes in conflict level. Finally, in a series of studies Mansouri *et al.* [21,45,51,52] trained monkeys to perform a conflict task in which conflict emerged between two behavioral rules (color matching versus shape matching), and the monkeys' behavior exhibited robust conflict cost and conflict adaptation effects. However, this work also found that bilateral lesions to the ACC sulcus (Box 2) affected neither conflict cost nor conflict adaptation (Figure 1). By contrast, lesions to the DLPFC resulted in the abolishment of conflict adaptation effects. As discussed above, similar results have now been reported for the same task in human lesion patients [42]. Taken together, these two studies convincingly demonstrate that the behavioral effects of conflict (i.e., both conflict cost and conflict-induced behavioral adaptation) are remarkably consistent across species when tested with the same paradigm, as are the effects of dACC (and DLPFC) lesions on behavioral performance. These cross-species similarities help refute suggestions [22,23] that conflict-related behavioral modulations in monkeys are instead related to other aspects of the task, such as differences in strategy that the monkeys implement in high- and low-conflict trials; this is also refuted by recent studies using the same task that clearly indicate that monkeys implemented a rule-based strategy in both high- and low-conflict trials [21,51].

Recent Studies Reveal Evidence for Neuronal Representation of Conflict Signals in the Human and Monkey dACC

In contrast to the aforementioned studies showing an absence of neuronal representation of conflict signals in the monkey dACC, support for the ACC conflict-monitoring hypothesis has been forthcoming from electrophysiological investigations in human patients. First, Davis *et al.* [53] recorded neuronal activity in the dACC while presurgical patients performed two variants of the Stroop test (numerical and emotional). They found that, for a significant proportion of recorded dACC cells, the firing rate differed between low- and high-conflict conditions, suggesting that neuronal activity conveyed information about the conflict level (Davis *et al.* did not report whether the neuronal activity was modulated by the conflict level in the preceding trial). Second, a more recent patient study by Sheth and colleagues [40] (Figure 1) also showed that single-neuron activity in the human dACC encoded conflict level independent of other aspects of the task; moreover, the neurons encoded both current and recent conflict and these effects were found at both the single-neuron and population level. These two studies thus argue for neuronal conflict signals in humans, which contrasts sharply with a lack of these signals in the monkey studies described above. Importantly, however, two recent single-cell recording studies

have now also provided evidence for neuronal encoding of conflict information in the monkey ACC (Figure 2). These experiments are not without interpretational difficulties but they are important because they may provide insight into how the aforementioned and currently irreconcilable findings across species may be integrated into a common theoretical framework.

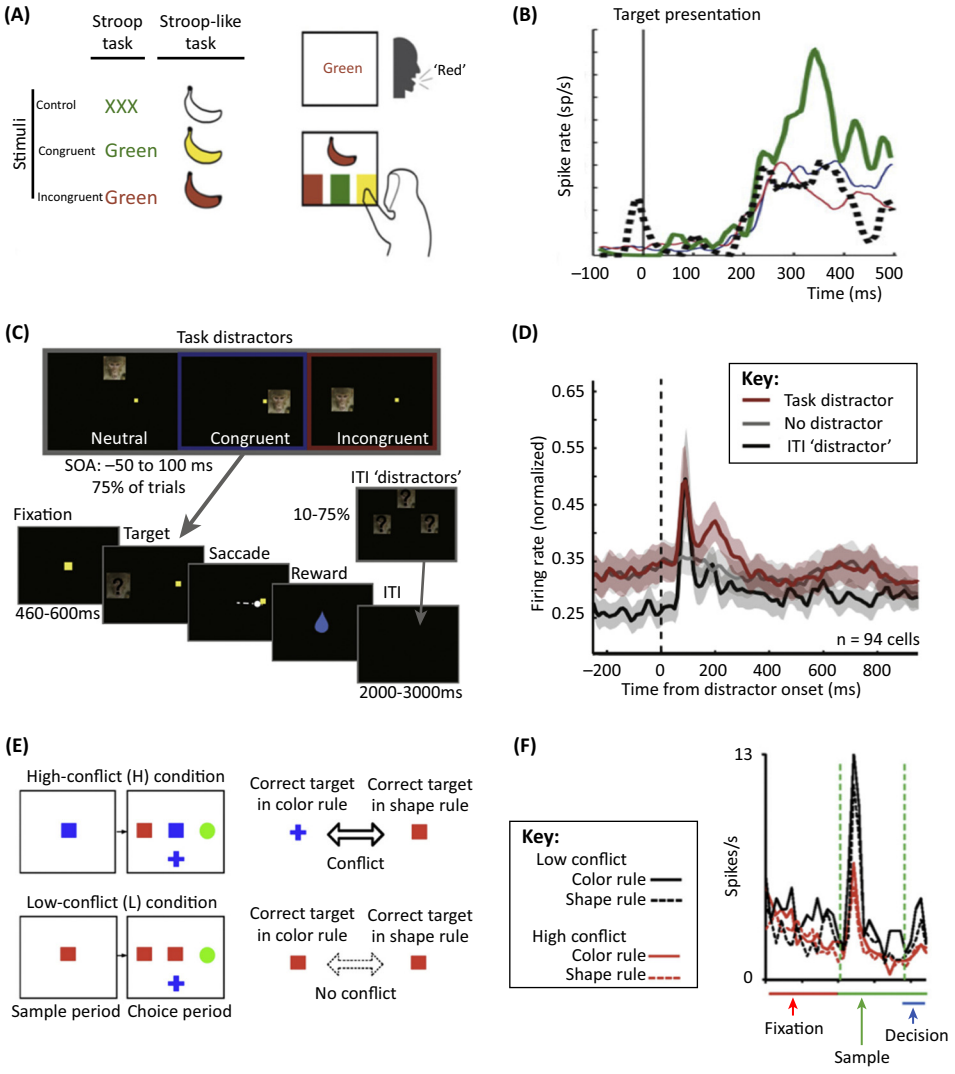

Figure 2. Recently Observed Neuronal Representations in Conflict Tasks in Monkeys. (A) In the classic Stroop task, humans have to name the color of the ink in which a word representing a color is printed without reading it; therefore, in an analogous Stroop-like task for monkeys Michelet *et al.* [25] trained animals to choose the colored target associated with the shape irrespective of its color. (B) Activity of an example single dorsal anterior cingulate cortex (ACC) neuron exhibiting incongruent-related activity (green curve) at an early stage of the task about 300 ms after stimulus onset in the Stroop-like task of Michelet and colleagues. (C) Ebitz and Platt [24] dissociated 'response conflict' (visual distractors briefly flashed during the performance of a simple visually guided saccade task in congruent, incongruent, or neutral position relative to the possible targets) from 'task conflict' (distractors contained social information). (D) ACC neuronal population differentiated between both types of distractor in Ebitz and Platt's study with the primary ACC coding being for the more general task conflict. (E) Mansouri *et al.* [3,21,52] trained animals on a Wisconsin Card Sort Test (WCST) analog with conflict (WCST conflict) in which animals had to learn and remember to apply an uncued abstract rule (color or shape matching) to match a central sample to one of three peripheral choice targets; trials with high and low conflict were randomly intermixed. (F) Activity of an example single orbitofrontal cortex (OFC) neuron representing the experienced conflict level after the sample is presented in Mansouri *et al.*'s study [52]. Adapted from [21,24,25].

First, Michelet *et al.* [25] (Figure 2) trained monkeys to perform a Stroop-like conflict task in which the conflict arose between a color previously learned to be associated with a particular object and the color of that object when presented at test. As in previous monkey studies, they also found significant effects of conflict in the current trial (conflict cost) and in the following trial (conflict adaptation). Activities of a small but significant proportion of dACC cells (in both banks of the ACC sulcus) conveyed information about the conflict level in the current trial. However, contrary to the predictions of the conflict-monitoring theory, these conflict-related activity modulations were not seen in erroneous incongruent trials and information about the conflict level in the previous trial was not represented in the dACC cell activity. Accordingly, although these findings are intriguing it cannot be excluded that these conflict-sensitive dACC neurons may contribute to general focal attention processes as opposed to conflict monitoring *per se* [25].

Second, Ebitz and Platt [24] (Figure 2) trained monkeys to perform a task in which they made goal-directed saccades for a juice reward while periodically confronted with biologically salient distractors and recorded single-cell activity in both banks of the cingulate sulcus in the dACC. Their rationale was to assess conflict at both the level of the task set ('task conflict', here induced by salient distracter stimuli) and the level of physical action ('action conflict'), because paradigms used in humans typically evoke conflict at both levels while studies in monkeys tended to focus on action conflict. The activities of some dACC cells not only signaled errors but also distinguished between these concepts of action conflict and task conflict, primarily encoding the latter. Interestingly, the dACC cell activity conveyed information about current pupil size or upcoming adjustments in pupil size, suggesting a potential mechanism linking dACC activity to modulation of pupil-linked processes such as arousal. One possible account suggested by the authors for the discrepancy between this study and earlier studies that failed to find unequivocal evidence for conflict signals in dACC cell activity is that the source of conflict plays a crucial role in engaging the dACC. Specifically, Ebitz and Platt [24] argue that previous monkey studies may not have elicited task conflict in addition to response conflict in an equivalent manner to that elicited by human conflict tasks such as the Stroop test, wherein distracting irrelevant stimulus information cues a prepotent or habitual task that needs to be suppressed to perform the current task. To the best of our knowledge, human neuroimaging studies have not explicitly attempted to create scenarios where conflict is induced without the possible cuing of an alternative task by irrelevant stimulus features, so there are no extant fMRI data that can speak to this distinction in a clear-cut manner. There are instead numerous human imaging studies that attempted to deconfound stimulus conflict (competition between relevant versus irrelevant stimulus features) and response conflict (competition between an irrelevant stimulus feature and the required response). Results have been ambivalent, however, with some studies reporting dACC activation exclusively for response conflict conditions [54], some exclusively for stimulus conflict [55], and others for both types of conflict [29].

An important implication of these interpretational difficulties is that future studies might operationally define conflict more carefully (as discussed in [24]) to help determine which types of conflict, or which aspects thereof, are encoded in the neuronal activities of different brain regions. For example, in the Wisconsin Card Sort Test (WCST) analog, which was used by Mansouri and colleagues [21] conflict might be elicited between uncued abstract rules, so may be operating at a more cognitive or 'task-set' level, although it might not necessarily be the same kind of conflict as that generated by the kinds of distractors discussed by Ebitz and Platt [24]. We have no doubt that further work in animal models is necessary to test their predictions, to deconfound variables, and/or to better operationalize 'conflict', but we believe these new studies offer crucial impetus for such work to be conducted. Importantly, however, even if the kind of cross-species reconciliation implied by these studies is proved to be robust by future work, we would not argue that this necessarily provides strong support for the dACC conflict-monitoring

model, because neural activity modulation in a brain area during performance of a task does not indicate its indispensable role in the involved cognitive functions. Accordingly, dACC lesions in monkeys do not impair conflict-induced behavioral modulations [21] and there is good evidence emerging that regions beyond the dACC and DLPFC make crucial contributions to conflict processes, thus strongly suggesting that a wider network of interacting brain areas than previously considered needs to be taken into account.

Conflict Signals in Primates: A Network Extending Beyond the ACC

In addition to the dACC studies above, Mansouri *et al.* [21] previously reported that single-cell activity in the monkey DLPFC represented the conflict level (between two opposing abstract rules and the stimulus selection responses they promote) in both the current and the immediately preceding trial. Although human neuroimaging studies have also shown conflict-related activation in other areas such as the VLPFC [5], insular cortex and caudate nucleus [56], and orbitofrontal cortex (OFC) [57–59], the conflict-monitoring model has focused exclusively on the role of the dACC and DLPFC. More recently, Mansouri *et al.* [52] showed that the activity of single cells in the monkey OFC also encoded rule/response conflict independent of the other aspects of the task (Figure 2). However, in contrast to the DLPFC, OFC cells did not encode the history of the conflict in the previous trial. In the case of both the DLPFC and the OFC, bilateral lesions [21,52] impaired conflict adaptation (Figure 1). Therefore, we currently know that the neuronal activity in at least three cortical areas in monkeys (dACC, DLPFC, and OFC) represents rule/response conflict, but only DLPFC cell activity has been observed to encode the history of such conflict. Mansouri *et al.* suggested that a mnemonic process is necessary to maintain conflict information (such as appropriate conflict control settings) between trials and that the DLPFC might support such mnemonic processes to support conflict-related executive control adjustments in the upcoming trials [3,21,60]. A recent imaging study in humans also supports the notion that the DLPFC might be involved in the mnemonic aspect of conflict processing by maintaining information of conflict within and across trials [61].

With respect to conflict cost, however, Mansouri *et al.* [3,21,51,52] have now reported, across an extensive series of studies, that bilateral lesions within the dACC, the DLPFC, the OFC, the posterior cingulate cortex, superior parts of the DLPFC, and the frontal pole cortex all fail to affect this measure (Figure 1). These findings make sense from the perspective that conflict cost (i.e., delayed responses and higher error rates) is a product of crosstalk between parallel stimulus processing streams (e.g., between color and word processing in the Stroop task), which might be evaluated by – and trigger adjustments from – regions in the frontal cortex, but that conflict cost in and of itself is not a product of frontal processing.

There are also differences in the way that conflict signals are encoded in the neuronal activity of different prefrontal and medial frontal regions. In both humans and monkeys, a higher level of conflict leads to a higher firing rate in dACC cells [24,25,40,53]; however, the neuronal representation of conflict in the DLPFC and OFC appears as a firing rate difference between high-conflict and low-conflict conditions so that some neurons increase and some decrease their firing rate in high-conflict conditions [21,52]. These differences might be related to differences in the representation of conflict-associated cognitive states such as ‘cognitive difficulty in resolving the conflict’.

Therefore, models of conflict processes in primates should take into account not only the full range of brain areas now known to be involved in representing conflict signals but also the manner in which they are represented. The early focus on the restricted conflict-monitoring model of dACC function was without doubt highly influential in stimulating research but is increasingly likely to have been too narrow a perspective for a comprehensive description of dACC function and conflict-driven behavioral adaptation. Although more recent theory and

computational modeling has advanced well beyond the traditional notion of the dACC and conflict monitoring, there still exists a temptation to propose a single, cardinal function for the dACC [5]. We would instead take the view that the dACC is likely to contribute to multiple evaluative functions (Box 3) in dynamic interaction with different but partially overlapping brain networks. In delineating these functions, we would like to emphasize in particular the need to reconcile and incorporate evidence from both human and animal models. It remains the case that different conceptions of dACC function are primarily driven by a focus on explaining either human data [16,17] or animal data [14] rather than by their attempted integration.

Concluding Remarks

Understanding how the dACC might contribute to executive control has become a burgeoning field of research but one that has regrettably suffered from a lack of theoretical reconciliation of divergent findings between animal and human investigations. One of the stark cross-species discrepancies we have reviewed has been the absence of evidence for neuronal representations of conflict signals in the monkey dACC, which has motivated some authors to posit clear-cut species dissociations in how the primate brain mediates conflict processing [22,23]. Two recent monkey studies [24,25] and human patient work [40] have directly addressed this issue and provide evidence against cross-species dissociation in the neuronal representation of conflict. At the same time, there is mounting evidence from recent studies in nonhuman primates that reveals striking similarities in conflict-induced behavioral adjustment between monkeys and humans, and we contend that context-dependent executive control adjustment certainly appears to be a cognitive ability shared between humans and other primates that has presumably evolved to optimize the allocation of limited cognitive resources to maintain goal achievement and survival in a complex and changing environment. However, we also argue that a unique and necessary role for the primate dACC in conflict-driven behavioral adaptation is not congruent with lesion data across the two species. Moreover, other studies reviewed above suggest key roles for other regions, including the DLPFC and OFC, in these adaptations. Taking these studies together with a large literature on other outcome evaluation processes and the ACC (Box 3), we consider it unlikely that the dACC will ultimately be best understood as serving a single function [1,16], that this structure is likely to contribute to evaluative functions within a large network of anatomically interconnected areas such that selective dACC damage is not necessarily catastrophic, and that there may also be multiple overlapping networks involving the dACC that operate in a dynamic fashion in a task- or context-selective way.

We have shown here how animal work is already increasing the known components of one network (e.g., OFC) that are necessary for efficient cognitive control beyond those previously recognized [52] and we have reviewed how animal electrophysiology in general is helping provide key insights into how neuronal-level mechanisms differ from region to region [21,24,25,40,52]. One way to determine how the dACC interacts dynamically and causally with different networks of cortical and subcortical regions in the support of adaptive behavior involves recording neuronal activities from multiple areas simultaneously and then observing how interventions (e.g., reversible inactivations, microstimulation) in one area affect interactions between other areas in the network to infer causal influences between brain regions. Another promising new approach to assessing cross-species functional homology comprises the adoption of equivalent neural measurement and perturbation techniques (such as transcranial magnetic stimulation) across species [62]. It will also be essential to strive to integrate the forthcoming next generation of evidence from animal models to inspire, inform, and constrain human research and modeling.

Supplemental Information

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Outstanding Questions

What are the reasons behind different or inconsistent consequences of lesions within the dACC in humans versus monkeys? Are they related to the extent of the lesion or the structure of the cognitive tests?

Why do lesions in the dACC not affect conflict adaptation in monkeys but sometimes impair it in humans? Is this related to differences in the nature of the conflict elicited by the task (e.g., task conflict versus response conflict) or practice level or are there important neuroanatomical and functional differences in the dACC between humans and monkeys?

How is conflict information extracted at the neuronal circuit level and how is it maintained to induce subsequent behavioral adjustments?

Is there a common core function of the dACC that leads to its activation in a wide range of cognitive tasks or is the dACC a multifunctional area that supports different functions in various cognitive domains?

How does the dACC causally interact with other interconnected areas implicated in conflict-induced executive control adjustments (including the DLPFC, OFC, and insular cortex)?

Does the dACC contribute to multiple different, overlapping distributed networks in a dynamic manner depending on task demands or does it operate as part of a single defined network?

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