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Cingulate cortex: Diverging data from humans and monkeys

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Cognitive neuroscience research relies, in part, on homologies between the brains of human and non-human primates. A quandary therefore arises when presumed anatomical homologues exhibit different functional properties. Such a situation has recently arisen in the case of the anterior cingulate cortex (ACC). In humans, numerous studies suggest a role for ACC in detecting conflicts in information processing. Studies of macaque monkey ACC, in contrast, have failed to find conflict-related responses. We consider several interpretations of this discrepancy, including differences in research methodology and cross-species differences in functional neuroanatomy. New directions for future research are outlined, emphasizing the importance of distinguishing illusory cross-species differences from the true evolutionary differences that make our species unique.

Introduction

Effective action often requires choices between competing alternatives. In many cases, such competition is highly asymmetric and the decision is easy. However, in other cases, everyday behavior can give rise to conflict. An example of a task involving conflict is illustrated in Figure 1a. Extensive theoretical and computational modeling has suggested that monitoring for conflicts – in cases for which several mutually exclusive response options are simultaneously active – could signal the need for increased cognitive control [1–3]. According to this influential view, activity in a conflict monitoring system can trigger adjustments in cognitive control to resolve current conflicts and prevent future ones [4] (Figure 1). Here we consider the neural basis of conflict monitoring, including several novel hypotheses that attempt to reconcile cross-species discrepancies revealed by recent studies of conflict monitoring in monkeys and humans.

It has been suggested that the human dorsal–caudal anterior cingulate cortex (ACC; also referred to as the anterior mid-cingulate cortex [5]; Figure 2a) acts as a conflict monitor [2,3,6] (for alternative views of ACC function see Refs [7,8]). Converging support for this hypothesis comes from functional MRI (fMRI) [9,10], event-related potentials (ERP) [6], local field potentials (LFP) [11], single-unit activity (SUA) [12,13], and lesion studies [14,15] in humans. However, several recent studies have tested for conflict sensitivity in macaque monkey ACC using SUA recordings [16,17], LFP recordings [18], and lesions [19] but found negative results. The conclusion often drawn from the animal research is that results from human studies have been misinterpreted [17,20]. However, a careful examination of the accumulated data reveals frank discrepancy rather than disconfirmation: data for monkeys seem to be simply incommensurable with the human data.

A series of examples reflect this point. For instance, Ito *et al.* found no conflict-related activity within monkey ACC using a saccade countermanding task (in which eye movement plans must be withheld just before execution) [16], whereas Curtis *et al.* [21] found conflict-related activity in single human subjects within ACC for the same task. Emeric *et al.* [18] observed a lack of conflict-related LFP in monkey ACC, whereas such activity has been detected in human ACC with ERP [6] and LFP [11]. Mansouri *et al.* [19] found no effect of monkey ACC lesions on behavioral reactions to conflict, whereas human ACC lesions are associated with changes in such reactions [14,15]. Ito *et al.* [16] and Nakamura *et al.* [17] found no conflict-related SUA in monkey ACC, whereas Davis *et al.* [12,13] did find such SUA in human ACC.

What might explain these discrepancies? In what follows, we summarize what we consider to be the most plausible accounts available. For clarity, we organize these into two major categories. The first involves explanations relating to differences in the methods used to study monkeys and humans. The second looks to the perhaps neglected possibility that fundamental differences might exist between humans and monkeys at the level of functional neuroanatomy.

Differences in methodology

The vast majority of research on human ACC has involved the use of fMRI or ERP, techniques with poor spatial resolution relative to SUA recordings, which is the dominant technique in monkey research. This has led some to suggest that human research has simply mislocalized conflict-related activity [20,22]. More specifically, SUA studies in monkeys have detected apparent conflict-related activity in the pre-supplementary motor area (pre-SMA)

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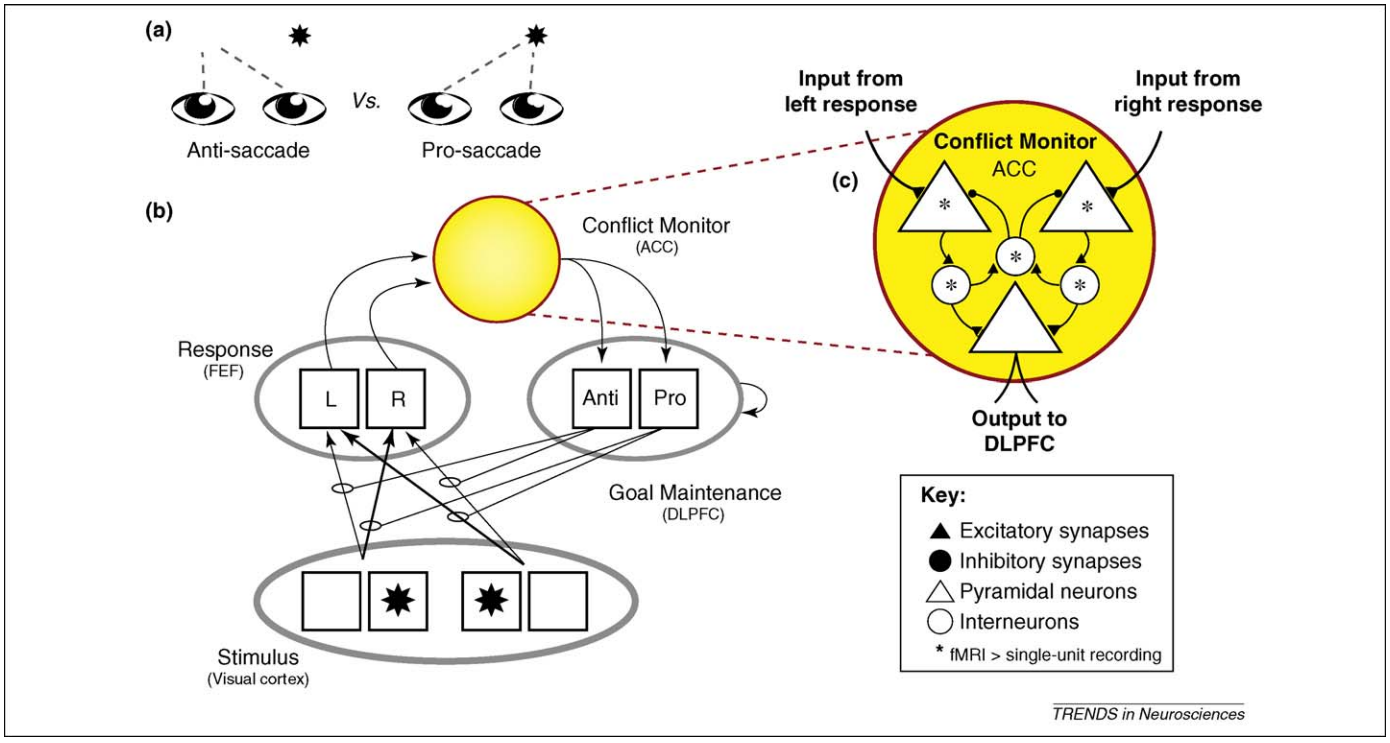

Figure 1. Conflict monitoring in a simple decision task. **(a)** The anti-saccade task. The anti-saccade condition requires an eye movement away from a presented target whereas the pro-saccade condition requires an eye movement toward the target. There is an innate tendency to look toward sudden-onset stimuli, creating more conflict for the anti-saccade condition. Note that a recent fMRI study revealed possible conflict sensitivity in monkey ACC during an anti-saccade task [32]. **(b)** Model illustration of the anti-saccade task based on previous models of conflict monitoring in other task contexts [9]. ACC monitors for conflict between response units and drives activity in DLPFC according to the amount of conflict. DLPFC increases its bias on stimulus–response associations based on its maintained goal/task representation, causing either the left (L) or right (R) eye movement plan in the frontal eye fields (FEF) to win the competition, reducing conflict. This model has been applied to Stroop, Eriksen flanker and other tasks [3]. Note that the response module could be replaced by task-specific activity patterns to be monitored for conflict if variable binding is included in the conflict monitor, as might be the case for non-motor decision conflict monitoring in area 32′ (see the text). **(c)** Hypothetical model of ACC. Because fMRI is biased toward synaptic activity, it is likely to detect the inputs to ACC as well as the interactions between interneurons in the region (indicated by asterisks). By contrast, SUA recording is biased toward pyramidal neuron output and thus might be at a disadvantage in detecting conflict-related activity in ACC. Note that most neural computation takes place in dendrites via synaptic activity [68], suggesting that fMRI might be generally more sensitive to a wider range of neural processing. This diagram incorporates established assumptions regarding pyramidal communication between brain regions, lateral inhibition between pyramidal neurons and populations of excitatory (e.g. spiny stellate) and inhibitory (e.g. basket) interneurons that mediate pyramidal activity.

and supplementary eye fields (SEF), raising the possibility that such activity actually occurs there, rather than in ACC, in humans as well [17,23].

Given the wide variability in localization apparent in fMRI studies of conflict monitoring [8], partly due to variability in the underlying neuroanatomy [24] (Figure 2d), the case for mislocalization to ACC initially seems plausible. However, other data seem to undermine this case. First, even if conflict sensitivity has been mislocalized to ACC in humans, other findings suggest that neurons in monkey pre-SMA and SEF do not actually monitor conflict but might instead simply show modulations in movement-related representations under conditions of conflict [17,23]. Second, in contrast to studies with monkeys, several human studies have found conflict-related activity concurrently in both pre-SMA/SEF and ACC [7,10,25]. Indeed, Curtis *et al.* [21] observed engagement of ACC (and SEF) during performance of a saccade countermanding task that was specifically found not to engage ACC in monkeys. The larger-scale pattern of findings from human research is indicated in Figure 3a–c, which summarizes a large meta-analysis of studies involving the Stroop task [26]. The Stroop effect, the best characterized and most replicated conflict effect [27], involves naming colors of color words while withholding the automatic tendency to read those words (e.g., responding "red" to "BLUE" in a red font). As the figure indicates, the most likely locus of activity across studies of the Stroop effect lies within ACC.

Further evidence against mislocalization is provided by human SUA and LFP studies that revealed conflict-related responses within ACC [11–13], in addition to replicating findings for monkey ACC [28]. It is possible that these human SUA results are unreliable because time constraints during surgery limited the number of conflict-sensitive cells that could be found. Conversely, the fact that *any* conflict-related activity was discovered given these constraints might indicate the robustness of conflict activity in the human ACC. Furthermore, although not all neuropsychological findings are consistent [29], it has been shown in several studies that ACC lesions cause deficits in cognitive control, including disruptions of conflict-related behavioral adjustment [14,15] (Figure 3e). Taken together, the results suggest that conflict-monitoring functions in humans can be reliably localized to ACC.

Therefore, it seems that the limited spatial resolution of human neuroimaging is unlikely to be the cause of discrepancies between the species. It remains possible, however, that methodological features typical of research with monkeys might be the cause. Studies with monkeys, as opposed to humans, have typically recorded SUA, used eye

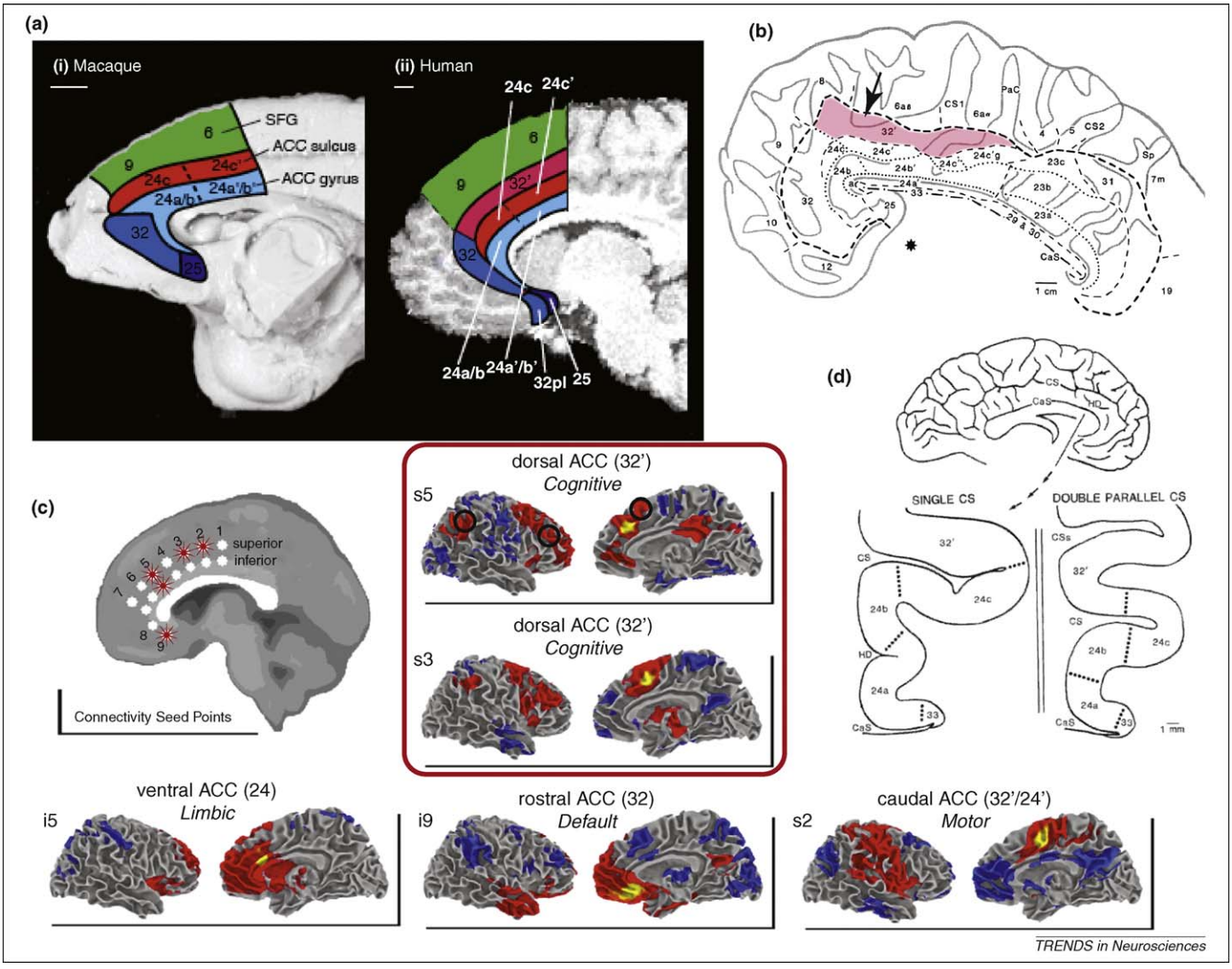

Figure 2. Anatomy of the ACC. **(a)** Macaque (i) and human (ii) primate brains with corresponding anatomical areas. Importantly, a dorsal–caudal extension of area 32, area 32′, is present only in the human brain. Figure adapted from Ref. [20]. **(b)** Flatmap illustration of human anterior cingulate illustrating the location and extent of area 32′. The arrow indicates that area 32′ often extends onto the dorsal medial wall surface. Figure adapted from Ref. [42]. **(c)** Resting-state functional connectivity MRI maps of seed points along human ACC. Area 32′ extends from superior point 3 (s3) to s6 and shows connectivity with cognitive control regions PPC, DLPFC and possibly nearby medial frontal regions. This region is separated connectively from caudal ACC in posterior area 32′/24′ (which seems to be a motor area), ventral ACC in area 24 (which seems to be a limbic area), and rostral ACC in area 32 (which is part of the ''default state'' network; [46]). Figure adapted from Ref. [45]. **(d)** The ACC anatomy is extremely variable between individuals. Some 30–50% of humans have a double cingulate in at least one hemisphere [24,36]. Figure from Ref. [42].

movements as the response modality and used highly overtrained subjects. We consider the implications of each of these features in turn.

The inherent bias toward recording large pyramidal neurons over other types of neurons limits the sensitivity of SUA recording to processes that do not substantially alter spiking of pyramidal neurons [30]. By contrast, the blood oxygen level dependent (BOLD) response, as measured by fMRI, is probably sensitive to a larger variety of neural processing types, including inhibitory competition and local signal accumulation among networks of small interneurons, given that BOLD probably reflects metabolic demand associated with synaptic activity [31]. Importantly, conflict monitoring might rely on local competition among interneurons [3] (Figure 1c). If so, then methods such as fMRI that are sensitive to this activity should be especially effective for detecting conflict responses in ACC. In other words, ACC coding of conflict might be present in both humans and monkeys but might be easier to detect in humans because of the sensitivity of fMRI to a wider variety of neural processes than that of other methods. Consistent with this explanation, a recent fMRI study in monkeys found activity in the ACC [32] that might be due to conflict monitoring (but could alternatively be due to error processing [7]; see the discussion below).

Another limitation of SUA recording is its limited field of view [30], which might reduce the chance of discovering conflict-related neural responses within monkey ACC but only in a circumscribed – and, to date, unsampled – area. The appeal of this explanation is limited by the fact that complementary methods (lesions, LFP) that partially compensate for the limitations of recording SUA have been used in monkey ACC. For instance, Mansouri *et al.* [19] lesioned the entire monkey anterior cingulate sulcus but observed no change in conflict-induced behavioral adjustment, whereas Emeric *et al.* [18] recorded LFP from

monkey ACC and found neural responses to errors and feedback, but not conflict. Therefore, although it remains possible that further investigation will reveal a portion of monkey ACC that responds to conflict, this outcome seems unlikely. Note, however, that possible conflict sensitivity was found with fMRI [32] primarily in the monkey cingulate *gyrus*, whereas the above-mentioned lesion and LFP studies focused on the cingulate *sulcus* (its primary location in humans), leaving open the possibility that even these studies missed the true location of conflict sensitivity in monkey ACC.

Could the discrepancies reflect differences between the tasks typically used for the different species? Monkey studies often use saccadic eye movements, whereas human studies of conflict tend to use button presses. Motor control of the eyes and hands are radically different in several respects, including their degrees of freedom (effectively just two for the eyes and many more for arms and hands), their relative need to take account of gravity and physical obstacles and, neuroanatomically, whether or not the respective cortical systems project directly to motor neurons. It is therefore plausible that the oculomotor and skeletomotor systems might express conflict in very different ways. However, several human fMRI studies using saccadic responses have revealed clear conflict-related ACC activity [21,33,34], as has the recent monkey fMRI study mentioned above [32]. A meta-analysis comparing verbal and manual versions of the Stroop task revealed some differences in the likelihood of activation, but also significant overlap in ACC [26]. These studies suggest that effector differences are unlikely to account for the cross-species discrepancies.

Another methods-based explanation for the discrepancies between human and monkey research relates to training. Human studies typically investigate cognitive task performance after only minimal practice, whereas monkeys are usually studied after months of task-specific training. Such extended training might give rise to differences in task representation or performance monitoring, explaining differences in ACC activity (which has been found to decrease in humans following extended training [35]). One challenge for this explanation is that, despite differences in training duration, human and monkey ACC exhibit similar responses along other dimensions, including responses to errors and action outcomes [28,36]. Nevertheless, a role for training duration in driving the inter-species discrepancies cannot be ruled out on the basis of currently available data.

To conclude this review of methods-based explanations, we suggest that it is unlikely that cross-species discrepancies are due to the distinct spatial sampling limitations of fMRI and SUA recording or to differences in motor responses often used across species. More plausible, and perhaps more intriguing, is the possibility that these discrepancies provide insight into the specific neural processes in conflict monitoring. Specifically, conflict monitoring might occur primarily in populations of ACC interneurons (Figure 1c), which might be more detectable by fMRI (typically used for human studies) than by SUA recording (typically used for monkey studies). Further research is necessary to decisively test this hypothesis.

Differences in functional neuroanatomy

The explanations considered so far implicitly accept the default assumption that monkey ACC is functionally equivalent to human ACC. However, this assumption might be incorrect. Indeed, a close examination of current evidence lends credence to the hypothesis that the conflict-sensitive portion of human ACC has no direct homologue in monkeys.

It is tempting to reject this idea out of hand, given that several parallels have been found between human and monkey ACC, including responses to errors [37], pain [38] and changes in motivation [39]. However, conflict effects in humans are at least partially dissociable from these other effects. In particular, there are subregions of human anterior cingulate (pregenual areas 24 and 32) that, like monkey ACC, show error, pain and reward/punishment sensitivity but not conflict responses [5,37,40,41] (Figure 3f).

The case for species differences becomes more compelling on a close examination of the location of conflict-related responses in humans. As detailed in Figures 2 and 3, the focus of conflict-related activity across studies probably lies within the region labeled area 32′ [42]. This anatomical area has been delineated in carefully executed cytoarchitectonic studies of human cingulate cortex by Vogt *et al.* [42], who distinguished this area from neighboring areas 32, 6, 24, and 24′. These cytoarchitectonic distinctions are mirrored by corresponding regional differences in neurotransmitter receptor architecture and anatomical connectivity [5,43]. Importantly, Vogt *et al.* described area 32′ as a distinctive feature of human ACC, commenting that only the human cingulate contains a region of "cingulofrontal transition cortex" where area 32′ forms a dorsal border for areas 24 and 24′ [42] (Figure 2a,B). For clarity, note that Vogt and colleagues [5,44] considered that area 32′ falls within "anterior midcingulate", reserving the term anterior cingulate for more rostral portions of the cingulate.

In addition to cytoarchitectonic differences, area 32′ also seems to differ from neighboring areas in terms of both connectivity (Figure 2c) [45] and function (Figure 3f) [38,41]. In particular, area 32′ is connected to cortical regions implicated in executive function, including dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) [45]. In contrast, area 24 interacts with limbic regions (e.g. insula, midbrain; Figure 2c) and is implicated in emotional tasks [38,45]. Area 32 is connected to default-mode network regions and is co-active with them during rest [46,47] and is also involved in emotional tasks [38]. Lesions of area 32 do not affect Stroop task performance, whereas lesions in the vicinity of area 32′ do [14] (Figure 2e). Finally, area 24′, unlike area 32′, is connected to M1 [45], is active during motor tasks [48] and is associated with processing of pain [5] and emotion [38].

Overall, area 32′ seems to share a closer functional relationship with pre-SMA (area 6) [8,49] than with subregions of ACC proper. However, even here it is possible to find dissociations in function. In particular, unlike area 32′, pre-SMA is associated with response selection in the absence of conflict [50]. Unlike pre-SMA, area 32′ responds to shifts in motivation [28,37,39], although both regions

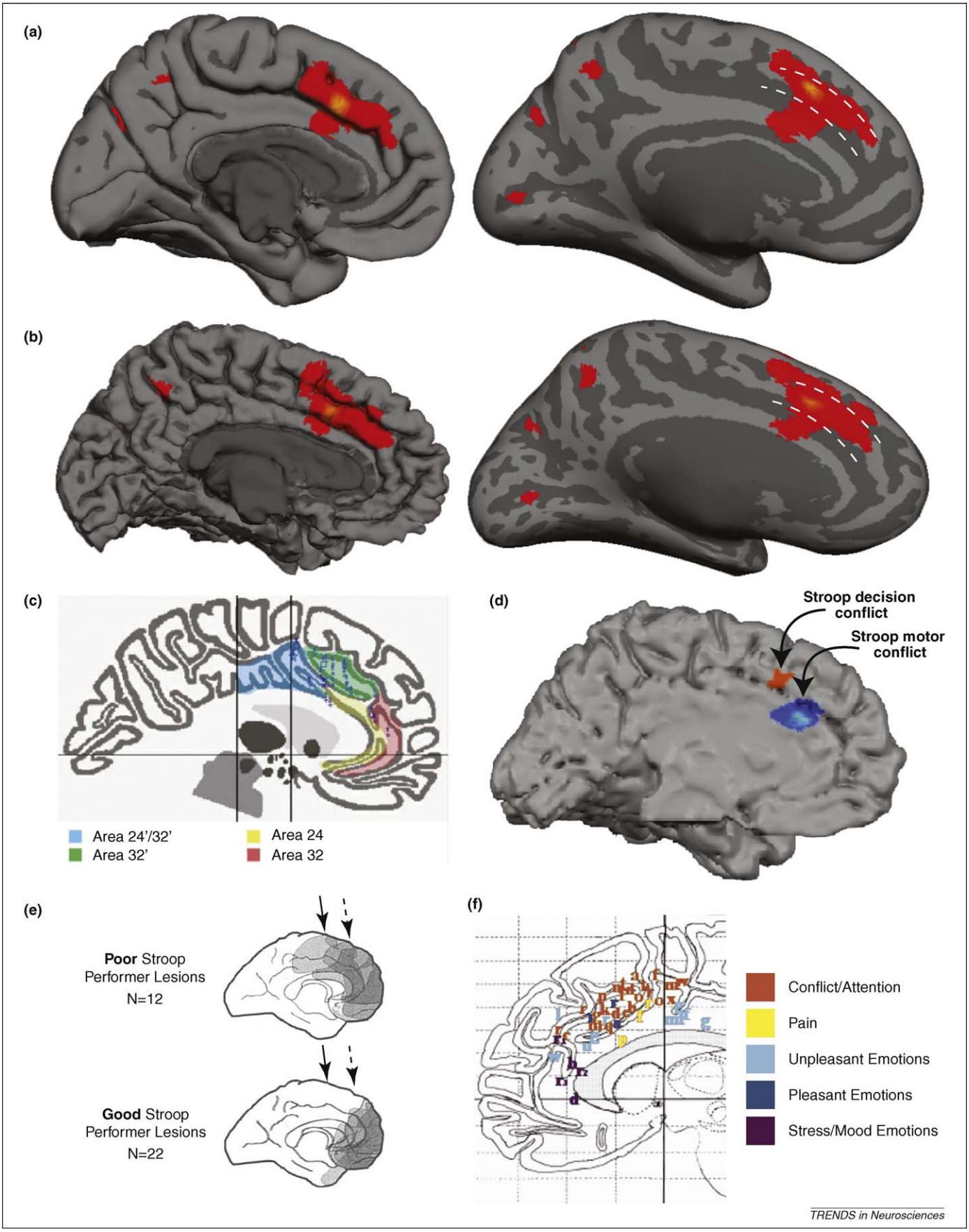

Figure 3. Functional activity during the Stroop task. **(a–c)** Activation likelihood estimation (ALE) meta-analysis results calculated by Laird *et al.* [26] for 19 fMRI and PET studies (27 experiments) involving approximately 250 subjects. **(a)** Focus of the ALE probability map of Laird *et al.* in ACC on the MNI152 template brain (average T1 brain image from 152 normal subjects at the Montreal Neurological Institute, Montreal, QC, Canada). Note that the spatial extent of the map is uncertain because of spatial smoothing (10 mm FWHM). The MNI152 template brain is probably an average of mostly single and some double cingulate sulci. The pial surface is on the left and the

Box 1. Do monkeys perform conflict monitoring?

An important conclusion from human research is that detection of response conflict by ACC triggers compensatory adjustments in cognitive control [3,9]. In line with this idea, Kerns *et al.* [4] found that ACC activation was higher in incongruent (conflict inducing) trials in the Stroop task and that trials associated with particularly high ACC activation tended to be followed by shifts toward more focused or controlled Stroop performance.

Mansouri *et al.* [19] claim to have found a similar dynamic in monkeys, but without a role for ACC. Their animals performed a matching task in which an initial cue stimulus, defined by a particular shape and color, was soon flanked by three probe objects. The task was to identify a target object that matched the cue on the relevant dimension (either color or shape). In high-conflict (H) trials, distractor objects matched the cue on the irrelevant dimension. In low-conflict (L) trials, the distractors did not match the cue on either dimension. The key findings were: (1) faster responses in H trials following other H trials than in H trials following L trials; (2) disappearance of this effect following DLPFC but not ACC lesions; and (3) differential responses in DLPFC neurons during H versus L trials.

Mansouri *et al.* [19] interpreted the last of these finding as indicating that DLPFC neurons were coding for the degree of conflict involved in each trial type. However, there is another possible interpretation. Note that L trials permitted the animal to use a strategy unavailable for H trials. Specifically, in L trials, target selection could rely on visual grouping effects to draw attention toward the global match. It is therefore possible that the DLPFC neurons studied were coding not for conflict but for the *strategy* used in H versus L trials (i.e. feature-based versus grouping-based search). This interpretation might be more parsimonious than the one offered by Mansouri *et al.*, given that DLPFC neurons coding for task rules have been extensively reported [61].

The hypothesis that animals in this study used different strategies in H and L trials would also explain the trial-type sequence effects observed, since transition from an L to a H trial would effectively involve a task switch, with attendant performance costs and sensitivity to DLPFC lesions [62]. This interpretation involves no role for conflict monitoring, suggesting that the reported results do not provide unambiguous evidence of conflict monitoring in monkeys. In the absence of such evidence, the implications of a failure of ACC lesions to affect trial-type sequence effects are unclear. However, it should be noted that other studies beyond the scope of the present review have reported conflict adjustments in monkeys [17,63] (but see Ref. [64]). In any case, we suggest that the question of whether macaque monkeys show conflict sensitivity in ACC, analogous to observations seen in humans, remains open.

exhibit error-related responses [37] (possibly due to limbic or executive functions).

Localization of conflict activity to area 32′ (Figure 3) remains somewhat tentative because it is based on surface anatomy that varies markedly across individuals (but see Ref. [51]). Nonetheless, as Figure 2d illustrates, there are systematic relationships between surface anatomy and the location of area 32′. Specifically, area 32′ tends to lie on the upper bank of the cingulate sulcus when a single cingulate sulcus occurs, but on the gyral surface when a paracingulate sulcus is present [42]. Figure 3a illustrates activity consistent across studies on anatomy averaged across 152 individuals, reflecting a mixture of mostly single and some double cingulates (only 30–50% of individuals have a double cingulate [36]). Figure 3b illustrates these statistics on the anatomy of a single individual with a double cingulate. In both cases the locations of activity across Stroop studies are consistent with area 32′.

The centering of conflict-related activity on human area 32′, an anatomically and functionally distinct region for which there is no known monkey homologue, provides considerable support for the notion that discrepancies between human and monkey research might reflect species rather than methodological differences. This idea suggests that the additional region in humans might provide additional behavioral functions, possibly increasing cognitive flexibility in humans relative to monkeys. If one function of this uniquely human region is conflict monitoring [52], then monkeys should lack behavior that reflects the impact of this monitoring function, such as conflict-induced adjustments in controlled behavior [3,4].

Box 1 considers a challenge to this idea that emerged from a recent study by Mansouri *et al.* [19], which seems to show DLPFC-mediated behavioral adjustments to conflict in monkeys. We suggest that the data from this study are open to an alternative interpretation. However, it is also possible that ventral area 24′, not investigated by Mansouri *et al.*, monitors for *motor* conflict in monkeys and humans, whereas area 32′ provides monitoring of more general *decision* conflict in humans. Motivation for this distinction comes from a recent human fMRI study using the Stroop task, in which response-level conflict engaged area 24′ whereas conflict at the level of color identification (putatively without motor conflict) engaged area 32′ [53] (Figure 3d). This suggests the possibility that both monkeys and humans monitor for motor conflict (area 24′), whereas only humans monitor for non-motor decision conflict (area 32′).

Toward a resolution

The relationship between monkey and human ACC clearly needs elucidation. Monkey fMRI has been useful in clarifying cross-species differences in functional neuroanatomy of other regions such as the intraparietal sulcus

inflated white-matter surface is on the right. The main focus of activity is on the dorsal bank of the cingulate sulcus and just above it (probably area 32′), extending down into the sulcus (areas 32′ and 24/24′) and up onto the medial wall surface (areas 32′ and 6). The dashed white lines indicate the approximate dorsal and ventral borders of area 32′ based on humans having a 60%/40% mix of single and double cingulates [36] and a systematic shifting of area 32′ in these cases (Figure 2d). Note that some atlases fail to illustrate that area 32′ can extend onto the medial wall surface (Figure 2b,d). Also note that further research using histology and/or connectivity is necessary to verify that the location of functional activity is in area 32′. **(b)** Medial wall ALE statistical map for an individual with a double cingulate. Typical neuroimaging results spatially smooth data (by ~10 mm) and average activations across subjects, making localization problematic. Vogt *et al.* [42] showed that area 32′ is centered on the gyrus between the two cingulate sulci in this case (Figure 2d). Some 30–50% of humans have a double cingulate in at least one hemisphere [24,36]. **(c)** Foci of activation across experiments used to create the above surface maps are shown on a double-cingulate Talairach template image. Figure adapted from Ref. [26]. **(d)** Stroop activation dissociating what is probably area 32′ from area 24/24′ by non-motor decision and motor conflict, respectively. Note that studies of motor conflict can show area 32′ activity because many situations with motor conflict also have decision conflict. Figure adapted from Ref. [53]. **(e)** Lesion locations associated with poor (top) and good (bottom) Stroop incongruent trial performance [14]. Only lesions including caudal ACC (indicated by the filled arrow; rostral ACC is indicated by the dashed arrow) were associated with poor Stroop performance. Figure adapted from Ref. [14]. **(f)** Peak activations identified in a meta-analysis of ACC locations of PET and fMRI activations during emotional and cognitive tasks [38]. Peaks tend to be in area 24, rostral area 32, and area 24′ for emotional tasks and in area 32′ for cognitive tasks. The borders between ACC regions are known to vary tremendously between subjects, making any minor functional overlaps in these between-subject maps inconclusive. Figure adapted from Ref. [38].

Box 2. Questions for future research

- What is the functional role of human area 32′? Is this role, like the anatomy of the region, evolutionarily distinct?
- What are the specific functions and inter-subject anatomical variability of nearby ACC and medial frontal regions in humans?
- What neural and metabolic processes take place in ACC during conflict, and how might these processes lead to greater sensitivity to detection by fMRI?
- To what extent does conflict-related fMRI activity in ACC reflect synaptic activity at pyramidal neurons versus interneurons?
- Is monkey area 32 functionally equivalent to human area 32, human area 32′, or some other region? (Note that Brodmann himself did not consider the monkey area he labeled 32 as homologous to his human area 32 [65]).
- How might new, more objective and *in vivo* methods for identifying anatomical areas [66,67] shed light on the neuroanatomical differences that make our species unique?
- To what extent should the macaque monkey model, which is known to differ from humans both behaviorally and by 25 million years of separate evolution [58], be relied on to make inferences about the human brain?

[54]. This technique, with its large field-of-view and sensitivity to a large variety of neural processes, could be used to survey medial frontal cortex, potentially revealing conflict-related activity that was missed by previous neurophysiological studies.

The promise of this approach is suggested by a recent study that yielded evidence of conflict-related activity in monkey ACC [32]. However, differences in the frequency of errors between conditions, as well as a possible selection bias toward high-effort anti-saccade trials due to removal of blocks with many errors, might have confounded the results. Furthermore, no connection was made to previous monkey ACC findings using reward, punishment, pain or explicit error manipulations. Such manipulations would test for dissociations between regions previously identified with SUA recording and the (hypothesized) new region found with fMRI, reconciling this new finding with previous findings in monkey medial frontal cortex.

Upon identification of a region showing conflict-related activity, an important subsequent step would be to record from single neurons and local neural populations within the region. Such coordinated use of fMRI and SUA recording has been useful in identifying monkey homologues for human brain structures such as the fusiform face area [55]. SUA within a conflict-sensitive area identified by fMRI could indicate whether the neurons involved respond specifically to conflict or in a response-specific way, as observed in monkey SEF [17]. It is also possible that little conflict sensitivity will be found in the spiking output of ACC, but that this sensitivity will be clearly evident in local interactive networks of interneurons (Figure 1c), the activity of which is reflected in LFPs or recordings from multi-unit arrays.

If clear conflict-related activity were identified within monkey ACC, it would also be desirable to determine if monkey ACC is tied to subsequent shifts in behavioral performance, as is the case with human ACC [4,9]. If so, lesions to the region should disrupt these sequential adjustment effects.

As discussed above, it remains plausible that there is no monkey equivalent of the human conflict monitoring system. Thus, it is possible that the approach proposed will yield null results. However, even with null results it would be difficult to claim that there is conflict sensitivity in monkey ACC if other functions (motivation, emotion, error, pain, motor processes, etc.) are mapped onto all parts of ACC and no conflict sensitivity is found using a wide field-of-view method (e.g., fMRI) with extensive statistical power. Thus, future experiments using functional neuroimaging in primates will be key in resolving the inter-species discrepancies discussed here, regardless of the outcome of those experiments. See Box 2 for additional unanswered questions pertinent to future research.

Conclusion

The discrepancies between monkey and human ACC research present a riddle. As discussed here, the answer to this riddle might turn out to be quite mundane. It is possible that researchers studying monkeys using SUA recording have not yet hit upon the appropriate region of cingulate cortex or that differences in training regimes explain the difference in findings. However, we have also considered more intriguing possibilities: that conflict monitoring involves neural processes that are likely to be detected by fMRI but missed by SUA recording in monkeys or that crucial differences in species-specific functional neuroanatomy exist.

The literature suggests that there might be *both* methodological and functional neuroanatomical differences. It might be that fMRI better detects conflict monitoring processes in ACC of both species (Figure 1c) [32] *and* that humans have an additional region in ACC for monitoring conflict (Figure 2). These views are reconciled by the possibility that humans have two conflict monitoring regions in ACC, both of which are involved in tasks such as the Stroop task that comprise both motor-level and decision-level conflict [53]. Figure 3d presents evidence that area 24′ (common to both monkeys and humans) is sensitive to motor conflict, whereas area 32′ (unique to humans) is sensitive to non-motor decision conflict. Such sensitivity to non-motor decision conflict in human ACC has been demonstrated by several recent studies [49,52]. We can speculate that area 32′ evolved from nearby areas 32/24/24′, expanding from motor conflict monitoring to much more flexible and generalized decision conflict monitoring in humans. Non-motor decision conflict might facilitate monitoring of decisions not tied to specific motor outputs (such as conflict between conceptual or linguistically encoded decision outcomes), which would provide conflict-driven regulation of cognitive control during a wide variety of difficult decisions (Figure 1b) [56,57]. Of course, further research is necessary to confirm this hypothesis.

The primary impetus for studying ACC function in monkeys has been to use the species as a model for the human case based on the assumption of functional and anatomical homology. Thus, if it is confirmed that species differences explain the contradictions between monkey and human results, this would belie a fundamental presumption of monkey cingulate research. However, such species differences would never have come to light without comparative investigations of humans and monkeys, removing the opportunity to identify cerebral and cognitive

functions that might be unique to each species. These differences could in turn provide insight into the nature of human brain evolution [58–60]. Thus, resolution of the current discrepancies between human and monkey ACC findings represents an important challenge. Addressing this challenge might provide new insight into the cognitive abilities that make our species unique.

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