



Conflict in Cingulate Cortex Function between Humans and Macaque Monkeys: More Apparent than Real

Commentary on Cole MW, Yeung N, Freiwald WA, Botvinick M (2009): Cingulate Cortex: Diverging Data from Humans and Monkeys. *Trends Neurosci* 32:566–574

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A recent review in *Trends in Neuroscience* by Cole, Yeung, Freiwald and Botvinick identified a potential fundamental difference in functional properties of the anterior cingulate cortex (ACC) of humans and macaque monkeys [Cole et al., 2009]. The key function in question is monitoring of conflict in response preparation. The conflict hypothesis, defended by the senior authors of the review as a general theory of ACC function, states that when a task calls for multiple competing responses, then executive control is required to resolve the conflict. It is supposed to explain the origin and purpose of event-related potential components such as the error-related negativity (ERN) that occurs after response errors [reviewed by Taylor et al., 2007] and a body of functional brain imaging data. The ERN can be generated by a dipole in the ACC; however, uncertainties in the localization of this dipole as well as other neuroimaging and lesion data demonstrate that more dorsal areas of medial frontal cortex including preSMA also contribute to performance monitoring [e.g. Garavan et al., 2003]. The ERN can also be identified with a reward prediction error originating from the dopamine system [Taylor et al., 2007]. An active literature has developed evaluating

these and other alternative hypotheses using human subjects. The relative merits of these alternative hypotheses are not the focus of this commentary.

Over the last decade this literature derived from human studies has been supplemented by neurophysiological data from macaque monkeys. In monkeys performing an eye movement stop signal task, neurons are found in the supplementary eye field that signal when errors are produced, when reward is delivered and when conflict occurs [Stuphorn et al., 2000]. In contrast, multiple neurophysiological studies of the macaque monkey ACC have reported error and reward signals but an absence of a conflict signal in tasks that should engender such response conflict [Ito et al., 2003; Nakamura et al., 2005; Emeric et al., 2008]. Cole et al. [2009] argue that the lack of a single neuron conflict signal in macaque monkeys in contrast to humans is a manifestation of a fundamental species difference and a greater sensitivity of functional brain imaging methods to weak conflict signals. We will argue that simpler alternative interpretations have not been ruled out.

To account for the apparent incommensurability of results in monkeys and humans, Cole et al. [2009] emphasize spe-

cies differences. We suggest that effector differences should be considered first. The monkey studies that sparked their review were based on data obtained in tasks requiring monkeys to produce or inhibit saccadic eye movements. The human studies used to describe conflict (as well as error and feedback) signals typically employ forelimb movements. Although the motor control of the eyes and of the hands may share common features centrally, they are substantially different peripherally. Eye movements entail fewer degrees of freedom (basically just 2) and need not be concerned about gravity. Natural arm movements entail more degrees of freedom (as many as 7 not counting the fingers) and usually must contend with gravity. Furthermore, and possibly crucially for this review, being an extension of the body, the limbs can get into kinds of trouble that the eyes cannot, e.g. colliding with other objects in the world. Specific neuroanatomical differences should also be highlighted. First, the neurons in the cortex that contribute to eye movement generation do not form synapses on the motor neurons innervating the muscles of the eyes, but the neurons in the cortex that contribute to forelimb movement generation form synapses directly on the motor

neurons innervating the muscles of the limbs. Second, parts of cingulate cortex project to motor cortex and the spinal cord [Dum and Strick 2002], and body movements can be evoked by electrical stimulation of these regions, but such connectivity and excitability for saccades is considerably weaker. Indeed, eye movements are evoked only rarely by stimulation of the ACC of most monkeys. Finally, in many of the studies that report conflict signals with manual movements the alternative responses could be generated together, e.g. press buttons with both hands. In contrast, only one saccadic eye movement can be produced at a time. Why are neuronal responses related to error and reward but not response conflict consistently observed in the ACC? We suggest that conflict signals may not be observed because the oculomotor representation of the macaque ACC does not support enough connections to influence gaze. However, the presence of a conflict signal in supplemen-

tary eye fields can perform the same function for the eyes that such a signal in the ACC can perform for the limbs.

Cole et al. [2009] also suggest that the conflict-sensitive portion of the human ACC has no homologue in macaque monkeys. However, it is not clear that this view is consistent with the most current anatomical descriptions. While the sulcal pattern in humans with the parasplenial lobules is more complex than that in macaques, the cytoarchitecture of the cingulo-frontal transitional cortex identified as area 32 is shared by humans and macaques [Vogt et al., 1995, 2005]. In other words, cortex with cytoarchitecture of area 32 is not absent in macaques, just smaller area. In fact, the caudal part of human area 32c has been identified as a homolog of macaque area 24c, making it part of the cingulate motor areas [Öngür et al., 2003]. The cingulate motor areas in the caudal anterior cingulate are in a unique position to monitor response conflict and exert

control on the skeletal motor system through connections with motor cortical areas and the spinal cord [Dum and Strick 2002]. Meta-analyses of cingulate activation have demonstrated that a somatotopic map corresponding to the cingulate motor areas in monkeys [Picard and Strick, 2001] overlaps with the foci of conflict-related activation across studies within the region labeled area 32' [e.g. Hester et al., 2004].

Although we heartily endorse distinguishing illusory from actual cross-species differences, drawing categorical conclusions from nuanced and often ambiguous data is premature. Fundamentally, it is not clear why the general conflict model should not apply to macaques who exhibit complex, extended responses to ambiguous stimuli with uncertain payoffs. If macaque monkeys are not equipped to monitor conflict, then specifically what should they not be able to do?

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