Inoue, Y., and Mihara, T. (1998). Epilepsia *39* (*Suppl 5*), 7–10.

Lee, K.H., Meador, K.J., Park, Y.D., King, D.W., Murro, A.M., Pillai, J.J., and Kaminski, R.J. (2002). Neurology *59*, 841–846.

Lieb, J.P., Dasheiff, R.M., and Engel, J., Jr. (1991). Epilepsia *32*, 822–837.

Motelow, J.E., Li, W., Zhan, Q., Mishra, A.M., Sachdev, R.N.S., Liu, G., Gummadavelli, A., Zayyad, Z., Lee, H.S., Chu, V., et al. (2015). Neuron *85*, this issue, 561–572.

Marrosu, F., Portas, C., Mascia, M.S., Casu, M.A., Fa, M., Giagheddu, M., Perato, A., and Gessa, G.L. (1995). Brain Res. *671*, 329–332.

Norden, A.D., and Blumenfeld, H. (2002). Epilepsy Behav. *3*, 219–231.

Steriade, M., McCormick, D.A., and Sejnowski, T.J. (1993). Science *262*, 679–685.

Tae, W.S., Joo, E.Y., Kim, J.H., Han, S.J., Suh, Y.L., Kim, B.T., Hong, S.C., and Hong, S.B. (2005). Neuroimage *24*, 101–110.

Uncovering a Missing Link in Anterior Cingulate Research

Amitai Shenhav[1] **and Matthew Botvinick**[1,2,*]
[1]Princeton Neuroscience Institute
[2]Department of Psychology
Princeton University, Princeton, NJ 08540, USA
*Correspondence: matthewb@princeton.edu
http://dx.doi.org/10.1016/j.neuron.2015.01.020

Research on human anterior cingulate cortex has long indicated a role in detecting conflict. However, efforts to find parallel effects in non-human primates were surprisingly unsuccessful. Here, Ebitz and Platt (2015) break the resulting impasse by uncovering what appear to be conflict-related signals in monkey cingulate cortex.

In order to get anything done, especially in the present technological age, it is necessary to resist distraction. If you want to buy a book online, you must struggle against having your attention hijacked by those disturbingly relevant sidebar ads. If you sit down with the resolve to finally write that paper, you may end up spending a significant portion of your time restraining the impulse to just quickly peek at your email or social media feed. Given the ubiquity of such distraction and its impact on our ability to sustain goal-directed behavior, it has been a major aim of cognitive neuroscience to understand how the brain regulates conflicts between goals and distractors.

Human neuroimaging research has consistently implicated the dorsal anterior cingulate cortex (dACC) in situations that involve conflict between a goal-directed response and a distracting alternative. For instance, if one is shown the stimulus GREEN in a red font and is asked to name the display color, this triggers greater dACC activity than when the word presented does not itself name a color (e.g., GRAIN) (Cole et al., 2009; Shackman et al., 2011). Moreover, such activity has been shown to predict subsequent increases in cognitive control, manifesting as an intensified focus on the task (in the foregoing example, an increased attention to stimulus color over word identity). Such findings led to the theory that the dACC may monitor for conflict, alongside other signals, in order to guide adaptive adjustments in control (Botvinick et al., 2001).

Over the years, a number of challenges have been raised to the notion of conflict monitoring in dACC. A majority of these have eventually been disconfirmed or else accommodated within a broader framework that still involves conflict (Botvinick, 2007; Shenhav et al., 2013). However, one formidable difficulty was raised by single-unit recording studies in monkeys, which at least initially failed to detect conflict-related signals in dACC (see Cole et al., 2009). At first, it seemed possible that the conflict responses observed in humans using fMRI and EEG might not reflect actual single-neuron spiking activity, but instead something more epiphenomenal. But no: Sheth and colleagues (2012) found conflict-related activity in the same region of human dACC using both fMRI and single-unit recordings and further showed that lesioning this region impaired conflict-related control adjustments. In view of such results, it seemed that human and monkey research might simply be incommensurable, perhaps reflecting fundamental differences in cingulate function between species.

However, recent findings have significantly altered the lay of the land. First, a study by Amemori and Graybiel (2012) offered hints of preserved conflict signaling in monkeys, showing that conflict between similarly valued choices (decision conflict) was encoded in a medial frontal region anterior to dACC. And now, as reported in the present issue, a study by Ebitz and Platt (2015) provides evidence for conflict signaling within monkey dACC itself, in a situation involving interference between goals and distractors.

Apparent Conflict Signals in Monkey dACC

In the experiment by Ebitz and Platt, monkeys performed a task that required them to saccade to a visual target on the left or right side of a computer display. On most trials, this target was accompanied by a second stimulus that was task irrelevant but salient, namely an intact or scrambled picture of a monkey face. Critically, this distractor could appear in any of three locations: immediately adjacent to the target (congruent distractor); on the opposite side of the display, adjacent to the alternative target location (incongruent); or at an upper central location where no targets ever appeared (neutral).

These different kinds of distractors allowed the authors to explore two kinds of conflict that have been previously studied in the human neuroimaging literature. "Action conflict" differentiates incongruent from congruent distractors. Distractors on incongruent trials cued responses inconsistent with the goal-relevant response, creating conflict between competing saccade plans, reflected in a slower response time. Congruent distractors, by contrast, cued saccades toward the target, speeding goal-relevant responses. As opposed to action conflict, "task conflict" separates both incongruent and congruent distractor trials from trials in which the distractor was neutral or absent, reflecting the fact that in these former cases participants experience interference between their goal of detecting the target and the exogenously triggered "task" of fixating the distractor item. This triggering effect, and thus task conflict, is presumed to be stronger on congruent and incongruent trials than on neutral trials, because in the former cases the distractor appears near locations that are task relevant and thus more avidly attended.

Ebitz and Platt recorded from dACC while subjects performed their task and found that a majority of neurons encoded the presence of distractors. Many of these neurons also responded to identical distractors that were shown during the inter-trial interval, when no target was present, but fired more to the distractors that appeared during the task. Critically, distractor-responsive neurons fired more overall when the distractor was congruent or incongruent rather than when it appeared in a neutral location, consistent with the signaling of task conflict.

A Link to Variations in Pupil Size and Task Preparation

By tracking the size of the monkeys' pupils throughout the task, the authors were able to show that conflict-related responses in dACC were related to trial-to-trial adjustments in cognitive control. They found that the size of a monkey's pupils at the start of each trial predicted how distractible the monkey would be on that trial. Smaller baseline pupil size predicted reduced influence of distractors on the monkey's behavior, i.e., less response slowing on incongruent trials and less speeding on congruent trials. Baseline pupil size also appeared to vary from trial to trial according to the recent history of task conflict. Specifically, pupils were smaller following a trial that involved either a congruent or an incongruent distractor. In other words, increased task conflict on one trial predicted smaller baseline pupil size on the following trial, which in turn was associated with decreased distractibility.

These findings were paralleled by patterns of activity in dACC. The authors found distractor-sensitive dACC neurons whose activity also predicted the magnitude of adjustments in baseline pupil size on the following trial, and they showed that activity in these cells mediated the influence of distractors on subsequent pupil constriction. Overlapping populations of neurons in dACC revealed analogous effects when the monkeys committed an error, both in terms of signaling the errors and predicting pupil adjustments that resulted.

Implications for Conflict-Related Accounts of dACC

Given the long-standing disconnect between monkey and human studies on dACC, the findings from Ebitz and Platt align surprisingly well with current theories of human dACC function. Although details vary, most contemporary theories portray the dACC as monitoring task exigencies in order to guide adaptive changes in cognitive processing and/or behavior (Cavanagh and Frank, 2014; Holroyd and Yeung, 2012; Rushworth et al., 2012; Shackman et al., 2011; Shenhav et al., 2013). For instance, we have recently proposed that dACC regulates cognitive control function based on a cost-benefit analysis, which takes into account both the current demand for control—signaled by conflict, errors, surprise, and other quantities—and any reward or penalties riding on task performance (Shenhav et al., 2013). Under this theory, one key output channel for the dACC is via the locus coeruleus, a neuromodulatory structure that influences both task focus and pupil size (Aston-Jones and Cohen, 2005). Clearly, the results from Ebitz and Platt fit very tidily with such an account.

Ironically, the challenge is not so much to square the findings from Ebitz and Platt with human research, but to understand how they can be reconciled with previous studies in monkeys. As noted earlier, such studies have notoriously failed to detect conflict-related signals in dACC (Cole et al., 2009). What might explain the dramatically different outcome of the Ebitz and Platt study? The authors themselves offer two possible explanations. First, they suggest that previous studies may have failed to identify conflict signals because they focused exclusively on action conflict rather than testing for effects of task conflict. This proposal receives some indirect support from the human fMRI literature, where task-level conflict effects (i.e., congruent greater than neutral) have been described since some of the earliest studies (Botvinick et al., 2001; Carter et al., 1995). Furthermore, at least two studies have observed effects of task conflict and action conflict in different (indeed, non-overlapping) sectors of the dACC (Desmet et al., 2011; Milham and Banich, 2005). If such an anatomical dissociation also exists in monkeys, it might further explain why Ebitz and Platt succeeded where previous studies have failed.

Nevertheless, some details of the Ebitz and Platt study create slight complications for a strong interpretation based on the notion that monkey dACC is exclusively sensitive to task conflict. First, certain findings suggest that congruent trials in their task may have induced not only greater task conflict than neutral trials, but also greater action conflict. The authors report that distractors on congruent trials often triggered errant saccades, which presumably often targeted the distractor. And correct responses on congruent trials were often displaced toward the distractor. These observations suggest that congruent trials might have triggered action conflict, by setting up a competition between responses aimed at target and distractor.

If this is the case, then the contrast between congruent (and incongruent) trials and neutral trials would not uniquely isolate task conflict, but would capture action conflict as well. A further complication arises from the fact that Ebitz and Platt did in fact observe neurons whose activity correlated with action conflict, as this was operationalized in their study. Some of these neurons were more active on incongruent than congruent trials, while others showed the reverse pattern, but at an informational level, of course, these patterns are equivalent.

The second potential explanation that Ebitz and Platt offer for the negative results of earlier monkey studies is that the behavioral tasks in those studies may not have induced sufficient conflict to trigger the kind of pupil-linked shifts in arousal and task focus that were observed in the new study. If dACC activity is inextricably linked with such psychophysiological shifts, the earlier failure to detect the sought-for signals would then be no surprise. While this proposal is technically defensible—earlier work did not examine changes in pupil size—it should be noted that some previous monkey studies did assert evidence for conflict-induced shifts in cognitive control (e.g., Emeric et al., 2008; Mansouri et al., 2007). Explaining the absence of conflict signals in those studies would thus require a fairly nuanced and restrictive characterization of the missing ingredient.

Whatever the appropriate interpretation for the disconnect from earlier studies, the findings from Ebitz and Platt do clearly indicate that monkey dACC neurons respond to task-relevant distractors and that these distractor-related signals (in conjunction with error-related signals) influence subsequent control states. It may still be possible that dACC responded to these control-relevant distractors for some reason other than that they generated conflict, for instance, that they induced a representation of a specific reward or punishment value. Indeed, such alternatives continue to be explored for putative conflict-related findings in human neuroimaging studies, and it will be the task of future research to generate and test these alternative accounts in monkey dACC, as has been done over the past two decades of human research. The dACC's role in mediating pupillary adjustments will also need to be further substantiated through the use of causal methods (e.g., lesion or inactivation). Direct investigation of the proposed role of locus coeruleus in the circuit governing pupil-linked shifts in control would also help flesh out the story. Finally, given that the authors interpret these pupillary effects in terms of shifts in arousal, future studies would further benefit from combining these pupillary measures with complementary measures of such autonomic changes.

Despite the questions they raise, the findings from Ebitz and Platt already do something very important, which is to place the human and monkey literature on more similar footing, both in terms of empirical observations and the theoretical paradigms that naturally apply. We do not expect all of the residual empirical and theoretical conflicts to be resolved in the near future, but are hopeful that the current study sets these two bodies of research on course to at least see eye-to-eye on the final outcome.

REFERENCES

Amemori, K., and Graybiel, A.M. (2012). Nat. Neurosci. *15*, 776–785.

Aston-Jones, G., and Cohen, J.D. (2005). Annu. Rev. Neurosci. *28*, 403–450.

Botvinick, M.M. (2007). Cogn. Affect. Behav. Neurosci. *7*, 356–366.

Botvinick, M.M., Braver, T.S., Barch, D.M., Carter, C.S., and Cohen, J.D. (2001). Psychol. Rev. *108*, 624–652.

Carter, C.S., Mintun, M., and Cohen, J.D. (1995). Neuroimage *2*, 264–272.

Cavanagh, J.F., and Frank, M.J. (2014). Trends Cogn. Sci. *18*, 414–421.

Cole, M.W., Yeung, N., Freiwald, W.A., and Botvinick, M. (2009). Trends Neurosci. *32*, 566–574.

Desmet, C., Fias, W., Hartstra, E., and Brass, M. (2011). J. Neurosci. *31*, 1366–1374.

Ebitz, R.B., and Platt, M.L. (2015). Neuron *85*, this issue, 628–640.

Emeric, E.E., Brown, J.W., Leslie, M., Pouget, P., Stuphorn, V., and Schall, J.D. (2008). J. Neurophysiol. *99*, 759–772.

Holroyd, C.B., and Yeung, N. (2012). Trends Cogn. Sci. *16*, 122–128.

Mansouri, F.A., Buckley, M.J., and Tanaka, K. (2007). Science *318*, 987–990.

Milham, M.P., and Banich, M.T. (2005). Hum. Brain Mapp. *25*, 328–335.

Rushworth, M.F.S., Kolling, N., Sallet, J., and Mars, R.B. (2012). Curr. Opin. Neurobiol. *22*, 946–955.

Shackman, A.J., Salomons, T.V., Slagter, H.A., Fox, A.S., Winter, J.J., and Davidson, R.J. (2011). Nat. Rev. Neurosci. *12*, 154–167.

Shenhav, A., Botvinick, M.M., and Cohen, J.D. (2013). Neuron *79*, 217–240.

Sheth, S.A., Mian, M.K., Patel, S.R., Asaad, W.F., Williams, Z.M., Dougherty, D.D., Bush, G., and Eskandar, E.N. (2012). Nature *488*, 218–221.