Dorsal Anterior Cingulate Cortex: A Bottom-Up View

Sarah R. Heilbronner[1] and Benjamin Y. Hayden[2]

[1]Department of Pharmacology and Physiology, University of Rochester Medical Center, Rochester, New York 14642

[2]Department of Brain and Cognitive Sciences and Center for Visual Science, University of Rochester, Rochester, New York 14627; email: benhayden@gmail.com

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Abstract

The dorsal anterior cingulate cortex (dACC) has attracted great interest from neuroscientists because it is associated with so many important cognitive functions. Despite, or perhaps because of, its rich functional repertoire, we lack a single comprehensive view of its function. Most research has approached this puzzle from the top down, using aggregate measures such as neuroimaging. We provide a view from the bottom up, with a focus on single-unit responses and anatomy. We summarize the strengths and weaknesses of the three major approaches to characterizing the dACC: as a monitor, as a controller, and as an economic structure. We argue that neurons in the dACC are specialized for representing contexts, or task-state variables relevant for behavior, and strategies, or aspects of future plans. We propose that dACC neurons link contexts with strategies by integrating diverse task-relevant information to create a rich representation of task space and exert high-level and abstract control over decision and action.

Contents

INTRODUCTION

The function of the dorsal anterior cingulate cortex (dACC) is one of the major puzzles in cognitive and systems neuroscience. Papez (1937) classified the entire cingulum as part of the brain's limbic system, thus linking the dACC with emotional processes. Early human lesion studies certainly supported this view: dACC lesions were shown to produce apathy, emotional instability, and akinetic mutism (reviewed in Paus 2001). However, in the 1990s, with new neuroimaging methods, the dACC became increasingly associated with cognitive functions. In parallel, other lines of research, including neuroanatomical ones, consistently highlighted links between the dACC and motor function. Thus, major approaches to understanding the dACC developed that saw it as an emotional, a cognitive, and a motor structure (for synoptic reviews of these viewpoints and debates about them, see Bush et al. 2000, Devinsky et al. 1995, Matsumoto & Tanaka 2004, Morecraft & Van Hoesen 1998, Paus 2001, Rushworth et al. 2011, Shenhav et al. 2013).

The majority of present-day research on the dACC uses functional magnetic resonance imaging (fMRI) to characterize hemodynamic signals. Ideally, neuroimaging results from humans reflect the aggregated activity of single cells, so results from neuroimaging and single-unit studies should converge to reinforce a single, integrative theory. In practice, however, the portraits of the dACC painted by neuroimaging and single-unit studies, not to mention electroencephalographic and anatomical studies, are different, in both obvious and subtle ways. These different conceptions of dACC reflect differences in what the methods can measure and may also reflect historical differences among scientists using these approaches. We believe that the bottom-up approaches—single-unit and anatomical studies—have not been fully integrated into the larger debates about dACC function. There is now a sizeable corpus of single-unit studies that did not exist at the time of major integrative theoretical reviews by Bush et al. (2000), Morecraft & Van Hoesen (1998), and Paus (2001). Thus, we offer a review of dACC function with a focus on the single unit and anatomical data.

To anticipate our conclusions, a broad survey of this work reveals three major hypotheses about dACC function: that it is involved in monitoring, control, and economic function. We argue, with a bit of speculation, that the bottom-up data point to a way to unify these three viewpoints. Specifically, we propose that single units preferentially represent aspects of context and strategy, and they serve to link one with the other. The broader functions of the dACC then emerge as a consequence of the interactions of these units. We explore each of these ideas in separate sections below. But first, we address some important questions about the anatomy of the dACC.

dACC STRUCTURE

Neuroanatomy of the dACC

The dACC (mainly area 24 in monkeys, and 24 and dorsal 32 in humans, although see the section below titled How Does the dACC Fit into the Cingulum More Broadly?) is located dorsal to the genu of the corpus callosum. It stretches rostrally to the frontopolar cortex and caudally to its border with the posterior cingulate cortex (PCC), roughly at the rostrocaudal position of the central sulcus on the lateral surface (**Figure 1*a***). The cytoarchitecture and connections of the dACC have been reviewed in detail elsewhere (Vogt 2009, Vogt & Gabriel 1993). Its most prominent cytoarchitectonic feature is the lack of a visible layer IV. In other words, it is agranular. This is the case in both humans and nonhuman primates (Petrides & Pandya 1994; Vogt et al. 1987, 1995). Although the distinction between the dACC and the PCC is quite clear cytoarchitectonically (the latter is granular), no sulcal marker in humans or monkeys indicates

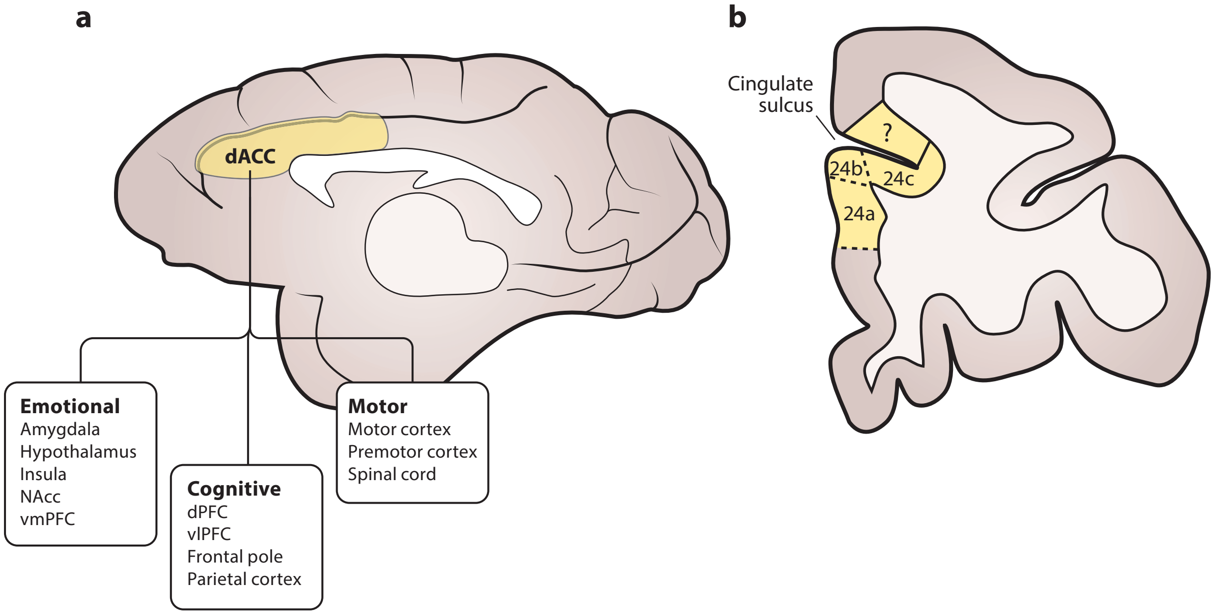

Figure 1

Structure of the nonhuman primate dACC. (*a*) Medial sagittal view of the brain showing the location and extent of the dACC (*yellow*) and some of the key connections discussed in this review. (*b*) Coronal view of the prefrontal cortex showing the subdivisions of the dACC. The gray shaded area is the dorsal bank of the cingulate sulcus, a region of particular controversy. Abbreviations: dACC, dorsal anterior cingulate cortex; dPFC, dorsal prefrontal cortex; NAcc, nucleus accumbens; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

their border. To solve this problem, Vogt (2009) provided neuroimaging templates to estimate the extent of different cingulate subregions in humans.

The connections of the dACC are quite broad (Barbas & Pandya 1989, Morecraft & Van Hoesen 1998, Van Hoesen et al. 1993, Vogt & Pandya 1987) (**Figure 1*a***). They include prominent projections to and from the major brain systems that are associated with emotion [amygdala, hypothalamus, ventromedial prefrontal cortex (vmPFC), insula, ventral striatum], cognition and executive control (dorsal prefrontal cortex, ventrolateral prefrontal cortex, frontal pole, parietal cortex), and motor control (motor cortex, premotor cortex, spinal cord). The cingulate cortex also contains within it three motor areas: the rostral, dorsal, and ventral cingulate motor areas (CMAs). These are located in the cingulate sulcus and project directly to the motor cortex and the spinal cord (Dum & Strick 1991, 1992, 2002; Picard & Strick 1996). The three major sets of connections—emotional, cognitive, and motor—have served as foundations for theories about dACC function (Morecraft & Van Hoesen 1998, Paus 2001, Rushworth et al. 2011). Note that the dACC is also a prominent part of the cortical pain network, leading to the theory that the dACC is critical for monitoring pain (Price 2000). We will not review that topic because it has not been well studied neurophysiologically, but much of what we discuss about monitoring and control may also apply to the pain domain.

Three questions about the neuroanatomy of the dACC are of particular interest to neuroscientists interested in its function. These are explored in the sections below.

How Does the dACC Fit into the Cingulum More Broadly?

One of the most influential parcellations of the cingulate cortex was proposed by Vogt (Vogt et al. 2005, Vogt & Gabriel 1993), who separated it into four subdivisions: the anterior cingulate cortex (ACC; very rostral 24, 32, 25 in nonhuman primates), the midcingulate cortex (MCC; middle and caudal 24), the PCC (23 and 31), and the retrosplenial cortex (29 and 30). The dACC, as the term is generally used now, corresponds to all of Vogt's MCC and a small, dorsal portion of his ACC. This claim is based on the fact that single-unit recording studies in monkeys tend not to differentiate the ACC from the MCC but, instead, cluster dorsally around the genu, avoiding not only the ventral ACC but also the posterior MCC (Procyk et al. 2016). We suggest that future recording studies should include a clear sagittal map of recording sites, allowing for particular attention to be paid to the anterior–posterior position.

Is the Dorsal Bank of the Cingulate Sulcus Really Cingulate?

Almost all dACC neurophysiologists record in the banks of the cingulate sulcus, and most focus on the dorsal bank (**Figure 1*b***). However, there is some doubt about whether the dorsal bank should even be considered cingulate at all. For example, one widely used rhesus monkey atlas refers to this area, moving caudally, as 9/32, 8/32, and 6/32 (Paxinos et al. 2000). Because areas 6, 8, and 9 are not the cingulate cortex, this label suggests that most studies include, or focus on, tissue that is either transitional or ambiguous.

The neuroanatomical literature is divided as to the nature of this well-studied piece of cortex. Petrides & Pandya (1994) claim that the cytoarchitectonic features of the dorsal bank of the cingulate cortex are identical to those seen in pregenual area 32: Layer IV is weak (making this region dysgranular), layer V contains deeply stained pyramidal cells, and so on. These features are fundamentally different from those observed in dorsal areas 9, 8, and 6. Thus, they argue that the dorsal bank is true cingulate and not transition zone. Also based on the cytoarchitectonics, Matelli and colleagues (1991) have argued that most of the dorsal bank is areas 24c and 24d, identical to the ventral bank. By contrast, Vogt et al. (2005) unequivocally claimed that tissue on the dorsal bank is not cingulate at all: It does not share important features with area 24, including the cingulate cortex's relatively small neurons in layer IIIc and high-density neurofilament protein-positive cells in layer V. This view, if true, would invalidate a great deal of dACC neurophysiology.

By Vogt's schema, then, the dorsal CMA is misnamed; it is not a cingulate motor area but, instead, is part of area 6. However, one problem with this classification is that the CMAs have seemingly clear human homologs, and the human versions are clearly localized within cingulate areas. This is possible because investigators agree that in humans the dorsal bank of the cingulate sulcus consists of cingulate area 32 (Vogt et al. 1995). Consistent with this homology-centered viewpoint, Dum & Strick (1991) refer to the dorsal bank as 24c (at least at levels rostral to the arcuate genu, which is where much electrophysiological recording takes place). Their reasoning is based on the continuity of the CMAs around the sulcus. In sum, the neuroanatomical literature provides conflicting information about the dorsal bank of the cingulate cortex, with opinions including areas 24c and 24d, area 32, and noncingulate areas 9, 8, and 6.

Cytoarchitectonics are not the only means of defining anatomical areas (Durstewitz et al. 2010). A review of the connectivity literature shows remarkable similarity between the dorsal and ventral banks of the cingulate sulcus, particularly at rostral levels. For example, both banks receive moderate input from the amygdala (Amaral & Price 1984), project to the vmPFC (Van Hoesen et al. 1993), and send direct projections to the spinal cord (Dum & Strick 1991). Both lack substantial labeling from the perirhinal and parahippocampal cortices (Lavenex et al. 2002). The dorsal and ventral banks also interact strongly with each other (Heilbronner & Haber 2014). At the very least, we suggest that the dorsal bank is anatomically quite similar to the ventral bank, and it may tentatively be classified as cingulate. Nonetheless, direct comparisons will be necessary to resolve the debate.

What Part of the Rodent Brain Is Homologous to the Primate dACC?

Rodents provide an essential platform for basic neuroscience research; however, it is not always clear which areas of the rodent frontal cortex should be thought of as equivalent to the dACC. The entire prefrontal cortex in rodents is agranular, rendering cytoarchitectonic differentiations difficult and making comparison tricky. On the basis of its position, Passingham & Wise (2012) have argued that the rodent area cingulate (Cg) is equivalent to the primate dACC. Others disagree. For example, on the basis of working memory correlates, some have argued that the entire medial prefrontal cortex (mPFC) of rats may be similar to the dorsolateral prefrontal cortex (dlPFC) of monkeys (Cowen & McNaughton 2007, Fuster 1973, Goldman-Rakic 1988, Kesner 2000). Other evidence points to the prelimbic cortex as a dACC correlate. For example, both the dACC in humans and the prelimbic cortex in rodents are necessary for the expression of conditioned fear (Milad et al. 2007). Unfortunately, this question is simply not resolved, so care should be taken when interpreting results from rodents. Thus, although occasional rodent mPFC studies are mentioned in this review, our focus will be on primates: monkeys and humans. We cite a few rodent studies, when relevant, and rely on the authors' own assessments of homologies in these cases.

dACC FUNCTION

We propose that most discoveries about dACC function can be classified into three categories. These major characterizations treat the dACC as a monitor, as a controller, or as an economic structure. None of these views is fully distinct from the others, and all may be simultaneously true. Nonetheless, this tripartite distinction is a useful way of categorizing theories of dACC function.

The dACC as a Monitor

A monitor observes the external and internal environments and forms a summary report that is passed to downstream structures. It is distinguished by its placement outside of, or beside, the basic processes that transform inputs to outputs and generate actions (Norman & Shallice 1986, Schall et al. 2002). Although monitoring signals are often found after decisions and their results (in laboratory tasks, the trial), in some cases monitoring can occur throughout the decision-making process, leading to online changes in performance (Blanchard et al. 2015, Carter et al. 1998, Holroyd & Coles 2002).

Error monitoring. One major early theory of dACC function was that its role was to monitor errors (for a review of the history of this idea, see Holroyd & Coles 2002). This idea is supported by the prominence of error-related negativity in studies of event-related potential (Falkenstein et al. 1990, Gehring & Willoughby 2002, Gehring et al. 1993), a signal that putatively originates in the dACC. This signal has a clear correlate in single neuron activity (Gemba et al. 1986, Ito et al. 2003, Narayanan et al. 2013, Niki & Watanabe 1979, Shen et al. 2015) and in the blood-oxygenation-level-dependent (BOLD) signal as well (e.g., Ullsperger & von Cramon 2001).

There can be no question that the firing rates of dACC neurons are sensitive to error commission. Nevertheless, the strict error hypothesis (meaning that error detection is the exclusive, or even primary, role of the dACC) is generally rejected today (Amiez et al. 2005, Wallis & Rich 2011). The existence of strong control and economic signals in the dACC (see the sections titled The dACC as a Controller and The dACC as an Economic Structure) suggests that errors are one of a broader class of stimuli that drive this region, and that error is a special case of this broader class. One prominent example comes from the observation that contexts in which errors are likely to, but do not actually, occur drive dACC activity (Brown & Braver 2005), as do neutral cues indicating the need to change strategy, regardless of error commission (Amiez et al. 2005).

Conflict monitoring. Conflict monitoring was proposed as a solution to the emergence of data that were inconsistent with the narrow form of the error-monitoring hypothesis (Botvinick et al. 2001, Kerns et al. 2004, Van Veen et al. 2001). In this framework, the dACC tracks the ongoing level of conflict or competition between different possible actions or strategies, and it generates a signal that indicates the need for additional cognitive resources. Evidence supporting the conflict theory of dACC function is plentiful in neuroimaging but scant and inconsistent at the single-unit level. In a well-known study, Nakamura and colleagues (2005) probed the conflict-related activity of dACC neurons in an antisaccade task. They found no modulation of dACC single units by conflict. Several other studies tested conflict coding at the single neuron level and failed to find it (Amiez et al. 2006, Cai & Padoa-Schioppa 2012, Hayden et al. 2011a, Ito et al. 2003, Quilodran et al. 2008). A few recent studies have found modest conflict coding in the dACC, but have neither identified a specific population of conflict-sensitive neurons nor explained why other studies have failed to find such signals (Ebitz & Platt 2015, Michelet et al. 2015, Sheth et al. 2012). The debate has grown strong, and the discrepancy between BOLD measures and single-unit measures has emerged as a great puzzle in the field (Rushworth et al. 2004, Shenhav et al. 2014).

Nakamura et al. (2005) have suggested that the hemodynamic conflict signal reflects activation of a greater number of units rather than an increase in firing rates of conflict-sensitive neurons. Alexander & Brown (2011) have made a conceptually similar argument. Both groups have proposed that conflict signals may be a by-product of dACC function, just as the heat of a car engine is a by-product of combustion, not a signal that regulates driving. This view is consistent with the broader portrait of the dACC as fundamentally a context and action (or strategy) link, and conflict as a factor that modulates the activity of context and action neurons. In any case, the debate is far from resolved.

Reward monitoring. Firing rates of single neurons in the dACC are sensitive to the values of obtained rewards (Amiez et al. 2006), including both gains and losses of secondary rewards (i.e., tokens, Seo & Lee 2009). Neurons also encode rewards that could have been obtained (i.e., fictive or hypothetical rewards, Hayden et al. 2009) and rewards that could have been chosen but were not (Blanchard & Hayden 2014). Reward outcome encoding in the dACC is slower but stronger than in the orbitofrontal cortex (OFC) (Kennerley & Wallis 2009a), and it is stronger than in the dlPFC (Luk & Wallis 2009). Neurons in the dACC encode outcomes from multiple types of chosen offers, and outcome coding reflects reactivation of offer-encoding neurons (Kennerley & Wallis 2009b). The multiple types of reward encoding suggest that the dACC is a domain-general reward monitor, and it is not specialized for specific dimensions along which rewards vary (such as risk or effort) as the OFC is (Kennerley et al. 2011), although it may be specialized for actions that produce the rewards (Horst & Laubach 2012).

Some studies have characterized post-outcome dACC responses as a reward prediction error (RPE), meaning the difference between the expected and obtained reward, a finding consistent with its strong dopaminergic inputs (Kennerley et al. 2011, Matsumoto et al. 2007, Seo & Lee 2007). Other studies have reported a dominance of unsigned (that is, rectified) RPE signals in monkeys and rats (Bryden et al. 2011, Hayden et al. 2011a). Although these two findings may appear contradictory, it is possible they reflect a single signal whose form depends on the task at hand. For example, the dACC may carry a control signal that promotes an adjustment or change in strategy. This control signal would naturally be correlated with reward and would be modulated by surprise (that is, it would correlate with RPE). In some cases, control may reflect signed RPE; in others, it may reflect unsigned RPE. Thus, in other words, the coding of reward may be adaptive rather than labeled line (Duncan 2001).

This adaptive coding possibility is emphasized by the clear context dependence of reward encoding in the dACC. In some studies, higher firing has been observed for smaller rewards (Hayden et al. 2011b, Kennerley et al. 2011, Luk & Wallis 2009, Williams et al. 2004). In others, higher firing has been observed for larger rewards (Hayden et al. 2009, Hillman & Bilkey 2010). In still others, reward encoding has shown a roughly equal mix of positive and negative tunings (Blanchard & Hayden 2014, Hayden et al. 2011a, Kennerley & Wallis 2009b). Moreover, the direction of reward tuning is not always consistent within a study, but it depends on the trial context (Hayden et al. 2011a, Luk & Wallis 2009, Matsumoto et al. 2007, Sallet et al. 2007, Seo & Lee 2007). Similarly, reward-sensitive responses depend on reward history when reward history is critical for performance, but they do not otherwise (Kennerley et al. 2011, Seo & Lee 2007). Overall, it seems clear that dACC neurons do not have as stable a tuning for reward as, say, a middle temporal (MT) neuron may have for motion direction.

Fear and anxiety monitoring. Although much less commonly studied in nonhuman primate models, fear and anxiety learning and expression in rodents and humans have been consistently associated with, respectively, the dACC and putative dACC homologs within the mPFC. Although Bush et al. (2000) distinguish the dACC from the ventral ACC using a cognitive versus emotional distinction, the enormous amount of data implicating the dACC in emotional processes requires a reevaluation of this view. [Etkin et al. (2011) provide a compelling and up-to-date review of this literature.] Etkin et al. (2011) have proposed that the rostral dACC, in particular, is responsible for sophisticated, context-dependent fear appraisal, a view that is congruent with the monitoring hypothesis.

The dACC as a Controller

We monitor our context so that we can control it by changing our behavior. Control, therefore, is a psychological variable referring to the direct regulation of an action, a cognitive process, or even another control process. Distinguishing the monitor and controller hypotheses can be quite difficult in practice because outcomes and adjustments (i.e., control) are so closely aligned. For example, errors tend to cause slower responses in subsequent actions, and detecting the error is the first step in producing the slowing. Evidence for a role of the dACC in control is strong. Both single-unit and BOLD activity are generally greater when control is needed, or is valuable, than when it is not (Johnston et al. 2007, Shenhav et al. 2013). More broadly, conflict (discussed above) is closely linked to the recruitment of control, so the conflict-monitoring hypothesis is often extended to include a role in the recruitment of control (Botvinick et al. 2001). Indeed, a recently proposed comprehensive theory of the dACC replaces conflict with a broader "expected value of control" (Shenhav et al. 2013).

The difficulties of dissociating monitoring and control. One problem that bedevils the study of neural responses is that the variables of interest are often correlated with one another (Maunsell 2004). In the case of the dACC, several monitoring variables predict control. Thus, in one classic study the responses of neurons in the dACC rose across a sequence of three unrewarded trials as a monkey grew to anticipate the rewarded fourth trial (Shidara & Richmond 2002). Even though the reward monitored did not change, the monkey's control (as measured by accuracy) rose along with the firing rate (**Figure 2*a***). Supporting this idea, we have found that neural responses to the same rewards in a foraging task depended on the implications of those outcomes for decisions (Hayden et al. 2011b) (**Figure 2*a***). When task parameters dictated a higher threshold for accepting an offer, firing rates rose more slowly and to a higher firing-rate threshold before they predicted the choice of that offer. It is unclear in these cases whether the neurons were monitoring, controlling, or helping to link these two types of signals.

Motor control and the dACC. The linkage between the dACC and control is emphasized by its close connections with the motor system (Akkal et al. 2002, Morecraft & Van Hoesen 1998, Paus 2001, Shima et al. 1991), including its monitoring of specific elements of compound actions (Hoshi et al. 2005). Neurons in the dACC that are sensitive to both reward and movement direction have been reported in several studies (Cai & Padoa-Schioppa 2012; Isomura et al. 2003; Luk & Wallis 2009; Matsumoto et al. 2003; Nakamura et al. 2005; Procyk et al. 2016; Shima & Tanji 1998; Strait et al. 2015a,b; Williams et al. 2004), including one that showed radial tuning functions (Hayden & Platt 2010). Furthermore, lesions to the dACC impair the ability to form linkages between specific actions and their associated outcomes and also impair the ability to learn the values associated with specific actions (Amiez et al. 2006, Hadland et al. 2003, Kennerley et al. 2006, Rudebeck et al. 2008, Rushworth et al. 2004, Turken & Swick 1999).

Not all evidence is consistent with this viewpoint, however. Several studies have reported no spatial selectivity in the dACC (Hoshi et al. 2005, Ito et al. 2003, Kennerley & Wallis 2009a, Matsumoto et al. 2007, Seo & Lee 2007). Seo & Lee (2007) have proposed that spatial selectivity is contingent on space being relevant for choices. In their study, monkeys played against an intelligent agent that punished any trial-to-trial spatial pattern in their choices; thus, monkeys were incentivized to downregulate spatial regulations, and the dACC did not show spatial tuning. Thus, spatial tuning in the dACC may appear only when space is relevant to the selection of actions. If so, we may say that spatial coding is not necessarily represented in the dACC, but that it is often represented for the reason that space can be important for control.

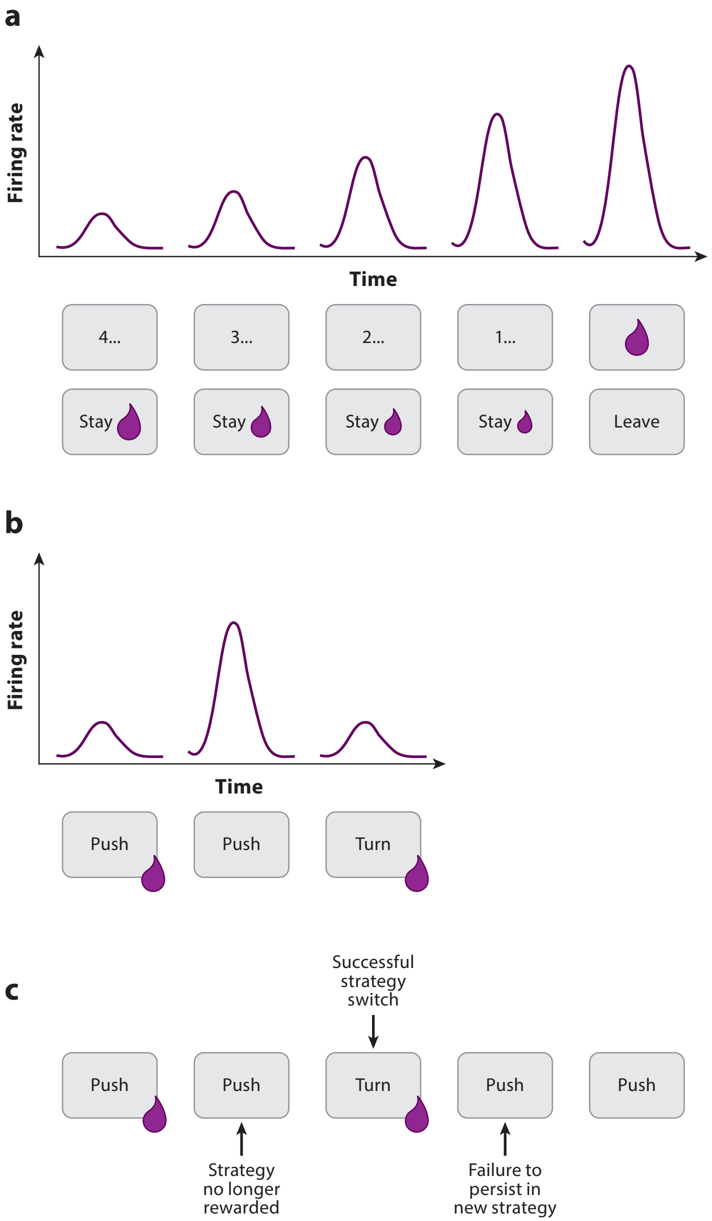

Figure 2

Schematic of the response properties of the dorsal anterior cingulate cortex (dACC). (*a*) In a simple task in which juice rewards (indicated by *purple drops*) occur on occasional but predictable trials, the firing rate gradually rises with the proximity to reward (see Shidara & Richmond 2002). The same pattern is observed in a different task in which rewards occur on each trial but reduce in size until the trial in which the monkey chooses to get no reward and in so doing replenishes the reward on the subsequent trial (see Hayden et al. 2011b). (*b*) In a task in which monkeys have to choose between two alternative strategies (push or turn a joystick) based on previous outcomes (reward or no reward), the firing rates are greatest following trials in which no reward is given (see Shima & Tanji 1998). (*c*) In a similar task, lesions in the dACC produce failures to persist in the new strategy for several more trials following success (see Kennerley et al. 2006).

Control via adjustment. The dACC appears to promote adjustments or changes in action plans or abstract strategies. Shima & Tanji (1998) recorded dACC neurons while monkeys performed a task with two action modes, pushing and turning a handle, one of which was rewarded in each block. The neurons responded most strongly when the reward fell and the appropriate action changed, suggesting that these changes led to the monkey's subsequent behavioral adjustments (**Figure 2*b***). Consistent with this view, lesions to the dACC impaired the abilities to switch, especially in response to a reduction in reward amount (Rushworth et al. 2003, Shima & Tanji 1998, Williams et al. 2004), and to maintain a new strategy following a switch (Chudasama et al. 2013, Kennerley et al. 2006) (**Figure 2*b***). More generally, activity in the dACC has been linked to the receipt of information that leads to changes in beliefs or behavior (Hayden et al. 2011a, Quilodran et al. 2008) and tracks the rate of learning (Behrens et al. 2007, Jocham et al. 2009). The close link between outcomes and strategic adjustments often makes it difficult to disambiguate outcome and control (see above). In one study, we held outcome constant and found that variance in the firing rate predicted adjustment, and when we held adjustment constant we found that variance in the firing rate predicted outcome (Hayden et al. 2009). These results provide preliminary evidence that the dACC may serve as both monitor and controller.

Learning. Learning can be thought of as a form of control that is even more abstract than switching because its consequences are delayed. Learning is closely associated with the dACC in both primates (Alexander & Brown 2011, Kennerley et al. 2011, Rudebeck et al. 2008, Wallis & Rich 2011) and rats (reviewed in Euston et al. 2012). In one influential study of the role of the dACC in learning, the activity of neurons was greater during the explore (i.e., the active learning) phase of a learning task than during the exploit phase of a task (nonsearch, Procyk et al. 2000). Moreover, BOLD activity in the dACC correlates with the learning rate of the decision maker in a volatile environment (Behrens et al. 2007). The idea that the dACC generates a teaching signal is part of a proposal by Botvinick (2007) to resolve the prominent discrepancy between the conflict and choice accounts of dACC function. In his model, the dACC monitors conflict to generate a teaching signal that indirectly improves decision making. This theory remains to be tested at the single-unit level.

Self-control and persistence. Self-control refers to the deliberate regulation of choice in the face of temptation, and it is almost always associated with selecting an option with long-term benefits (Ainslie 1975). Although the bulk of the evidence supports a prominent role for the dlPFC in self-control (Aron et al. 2004, Hare et al. 2009, Knoch & Fehr 2007), the dACC has been associated with successful self-control in an intertemporal choice task (Peters & Buchel 2010), delay tasks (Narayanan & Laubach 2006, Narayanan et al. 2006), response inhibition tasks (Floden & Stuss 2006), and in forced swim tasks (Warden et al. 2012). The dACC is particularly associated with persistence, a key element of self-control (Chudasama et al. 2013, Picton et al. 2007).

Activation of the human dACC produces intense feelings of the will to persevere against any challenges (Parvizi et al. 2013). Perhaps, then, dACC activation serves to motivate choosing the more difficult or demanding pathway when it offers the possibility of a larger reward (Johnston et al. 2007; Rudebeck et al. 2006a,b). Supporting this idea, the dACC is active when tracking progress toward a specific goal (Hayden et al. 2011b, Ma et al. 2014, Shidara & Richmond 2002). One theory is that the dACC carries a value signal that allows decision makers to overcome a tendency to succumb to temptation (Blanchard et al. 2015, Hillman & Bilkey 2010). (For related ideas, see Parent et al. 2015, Passetti et al. 2002, and Rushworth et al. 2003.) Another complementary idea is that the dACC encodes the cost of failing to persist, thereby recruiting self-control (Blanchard & Hayden 2014, Kurzban et al. 2013). In any case, our understanding of the role of the dACC in self-control is limited in part by the lack of a universally accepted animal self-control task, as well as the fact that self-control is a heterogeneous construct (Evenden 1999, Hayden 2016).

Fear and anxiety control. Although the rostral dACC is associated with the appraisal of fear- and anxiety-inducing stimuli, more caudal portions of the dACC may be responsible for regulating the expression of these emotions. For example, caudal dACC BOLD activity is associated with fear-related increases in heart rate and changes in skin conductance (Milad et al. 2007). However, rodent electrical stimulation studies in the mPFC do not consistently and directly induce fear-related behaviors (e.g., Milad & Quirk 2002), but do modulate fear expression. Such studies have not been performed in monkeys; however, results appear consistent with the controller hypothesis.

The dACC as an Economic Structure

A third viewpoint sees the dACC as a structure concerned with reward evaluation and comparison. Because of its neuroeconomic motivations, results emanating from this viewpoint may use different language to discuss similar (or perhaps even identical) phenomena to those described above (Wallis & Rich 2011). The economic viewpoint also overlaps with the much older emotion viewpoint: Reward and emotion may be conceptually distinguishable, but they are often psychologically similar (Bechara et al. 2000).

Value of offers. In addition to monitoring the values of rewards received (see Reward Monitoring, above), the dACC also tracks the values of offers made during a trial, presumably to contribute to choice processes. A good deal of evidence has suggested that the dACC has greater claim on value representation than other putative value areas. In a seminal study, Kennerley et al. (2009) considered the values of options defined in different blocks by three dimensions: payoff, probability, and effort cost. They found that neurons in the dACC represented the values of the offers, as indicated by a common coding for the three value dimensions. This pattern was substantially stronger in the dACC than in the OFC and the dlPFC, suggesting that the dACC is particularly specialized for representing offer value. In contrast, another study reported no representation of the value of offers, just representation of the chosen value, which is an integrated form of value (Cai & Padoa-Schioppa 2012), and a different study reported the encoding of rejected—or unchosen—value (Blanchard & Hayden 2014). A recent study has shown that the dACC (along with the OFC) encoded value, but its format depended on the task in which the animal was engaged (Luk & Wallis 2013). Thus, the dACC may not carry a single, domain-general value signal but, instead, has a transformed task-relevant one. This finding offers the possibility of reconciling the above studies by suggesting that the dACC does not track value per se but, instead, tracks a variable that is correlated with various aspects of value in many cases.

In any case, the prominence of offer value signals in units in the dACC is another area of discrepancy in much of the neuroimaging literature. Abstract value representation is much more often associated with the vmPFC and OFC than the dACC (Bartra et al. 2013, Levy & Glimcher 2012). The reason for this discrepancy remains unclear.

Value of the nondefault option (and foraging value). Choices can often be framed as occurring between a standard (or default) and a nonstandard option. This framing is particularly common in foraging tasks, which have a foreground–background structure (Calhoun & Hayden 2015, Stephens & Anderson 2001). In such cases, some evidence has suggested that the dACC preferentially represents the value of the nondefault option, and the vmPFC represents the value of the default (Blanchard & Hayden 2014, Boorman et al. 2013, Kolling et al. 2012, Strait et al.

2014). Similarly, in a patch-leaving task, phasic dACC activity rises in tandem with the value of abandoning the patch (Hayden et al. 2011b). Across blocks, as travel time and, thus, residence time change, the rate of responding rises in a corresponding manner. These results suggest that the dACC encodes a specific decision variable relating to the value of switching away from the default action. Consistent with this idea, BOLD activity in the vmPFC rises with the chosen minus the unchosen value, but activity in the dACC declines (Boorman et al. 2009, FitzGerald et al. 2009, Lim et al. 2011, Wunderlich et al. 2009). These results suggest that dACC activity is generally greatest in contexts where the nondefault option is preferred; such contexts also often require control or require the selection of new strategies (Shenhav et al. 2013). Consequently, it is difficult to know which function to attribute to the dACC, given the limited data.

Action–outcome associations. A related idea is that dACC neurons are sensitive to associations between actions and outcomes. Neural responses consistent with this idea have been reported in many studies (Amiez et al. 2006, Hayden & Platt 2010, Kennerley et al. 2009, Luk & Wallis 2009, Matsumoto et al. 2003, Quilodran et al. 2008, Shima & Tanji 1998). One possibility is that the dACC may serve as an action–outcome predictor, meaning that it signals the outcomes associated with the specific actions that the decision maker may be considering (Alexander & Brown 2011). One recent study testing this hypothesis examined activity on action–outcome (AO) association trials and stimulus–outcome (SO) association trials (Luk & Wallis 2013). The authors found no encoding of AO associations, but stronger coding of action on AO trials than on SO trials (and the reverse pattern in the OFC). This work argues against the specific hypothesis that the dACC represents AO associations. In either case, it seems reasonable to suppose that the dACC takes advantage of AO associations to drive actions. Nonetheless, the specific contribution of the dACC to AO associations requires further research.

Comparator and chooser. The dACC may serve as the site of comparison and selection in economic choice (Hare et al. 2011, Seo & Lee 2007, Wunderlich et al. 2009). Conventional approaches see economic choice as a serial process, with distinct evaluation and comparison stages; the evaluation stage is often localized to the orbital surface, and the comparison stage may be localized to the dACC. Much evidence links the dACC to comparison, especially in cost–benefit decisions (Croxson et al. 2009, Hillman & Bilkey 2010, Prévost et al. 2010, Walton et al. 2006; reviewed in Rushworth et al. 2011). Lesions to the dACC bias animals away from choices that require more effort but provide a larger reward (Rudebeck et al. 2006a,b). Although correlates of choice are undoubtedly seen in the dACC, a great deal of evidence also favors comparison elsewhere, so there is no reason to believe that the dACC is the unique site of value comparison. [For a sampling of single-unit evidence, see the following: for the OFC, Padoa-Schioppa & Assad (2006); for the vmPFC, Strait et al. (2014); for the ventral striatum, Strait et al. (2015a,b) and Stott & Redish (2014); for the intraparietal sulcus, Platt & Glimcher (1999); for the PCC, McCoy et al. (2003)]. But, perhaps most persuasively, lesions to the dACC do not produce frank deficits in economic choice (Chudasama et al. 2013, Rushworth et al. 2011). Thus, we propose that the dACC is part of a distributed choice process, but it is not the sole or even central site of value comparison.

AN INTEGRATIVE THEORY OF dACC FUNCTION AND QUESTIONS FOR FUTURE STUDY

Several comprehensive theories of dACC function have been proposed. Vogt et al. (1992) argued that the dACC has an executive role but one that is specialized for visceral, skeletal, and endocrine

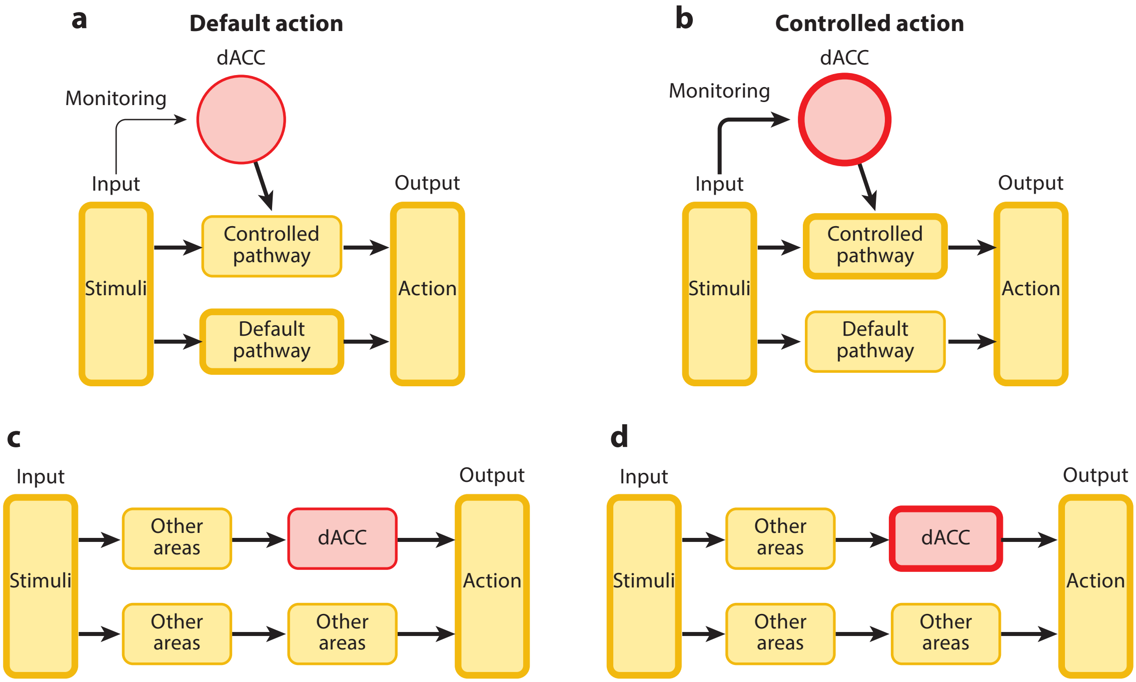

Figure 3

Schematic illustrating two models of the role of the dorsal anterior cingulate cortex (dACC) in control. (*a*,*b*) In some models, the dACC is seen as a controller and, thus, outside the standard input–output transformations that make up decision making, which are presumed to be housed in other brain areas. In such models, (*a*) default (i.e., well-learned or uncontrolled) actions activate the dACC only weakly (indicated by *thin lines*) because the need for control is not detected, but (*b*) controlled actions activate the dACC strongly (indicated by *thick lines*) as the dACC monitors the need for control and summons it. (*c*,*d*) In other models, the dACC serves as one part of the input–output transformation pathway, although it is not necessarily the only way for information to pass toward actions. In such models, (*c*) default actions activate the dACC weakly because input–output transformations are relatively efficient, but (*d*) controlled actions activate the dACC more strongly because input–output transformations require more overall activation.

processes. Morecraft & Van Hoesen (1998), focusing on its anatomy, proposed that the dACC serves as an entry point for limbic information into the motor system. In contrast, Bush et al. (2000) argued that it serves to regulate cognitive and emotional processing. Aside from the inclusion of cognitive variables, the biggest difference among these models is that the Bush group saw the dACC as a modulator of cognitive processes, whereas Morecraft & Van Hoesen saw it as an essential part of those processes, and a relatively late part because it directed motor action.

Continuing these threads, Rushworth and colleagues (2011) have argued that the dACC serves to link actions with outcomes and, thus, to guide actions by offering motor cortex information about the consequences of possible actions. In contrast, Shenhav et al. (2013) have argued that the dACC integrates information relevant for control, and it signals to other regions how that control should be orchestrated (**Figure 3*a*,*b***).

Contexts and Strategies

The general view from the physiological literature is that individual dACC neurons track many task-related variables. We propose that these variables can be categorized into ones that reflect task state and ones that guide (or at least correlate with, if we are being cautious about inferring causality) action. Note that guiding or predicting action can occur in abstract terms, such as change to a new action or increase cognitive control. We use the term context to refer to all variables that are aspects of task state, and we use strategy to refer to any aspect of any action plan, regardless of how abstract it may be.

Of course, the dACC should code variables only if they are relevant to decision making. The phase of the moon, for example, is likely to be irrelevant in almost all contexts, and it should be absent from dACC firing rates in most cases. The absence of coding of task-irrelevant variables is one of the major predictions of our viewpoint. But in the rare cases in which the phase of the moon is important, it should be encoded, and the strength and prevalence of encoding should correspond to its importance. This adaptive coding view may explain several puzzling findings, such as why spatial coding is sometimes observed and why reward coding is inconsistent. It may also help explain the so-called conflict over conflict: The explicit coding of conflict may be useful in some tasks but not in others. Indeed, one key prediction of our model is that some things that activate the dACC in fMRI may not be observable in the activities of individual neurons but, instead, may affect things such as the recruitment of neurons. This idea requires further exploration.

Mapping Contexts to Strategies

We know of no evidence that separate populations of dACC neurons signal context and strategy; instead, it appears that neurons that encode one are more likely to encode the other. For example, spatial representations in the dACC are not housed in a separate set of cells, implying that the coding of nonspatial task variables is embodied in a spatial frame of reference (Hayden & Platt 2010, Hosokawa et al. 2013, Luk & Wallis 2013, Procyk et al. 2016). We propose, therefore, that the dACC embodies a type of storage buffer that tracks task-relevant information to guide appropriate action (**Figure 3*c*,*d***). In other words, it is not outside the input–output transformation process, but is a core part of it. Thus, the reason the dACC monitors so many variables is that it will use the set of information to generate signals that control actions. More specifically, the signals it carries influence actions. This information includes anything that is task relevant, including errors, conflicts, the values of offers, outcomes, and so on. So all of these things should be seen in dACC neurons when they are relevant to actions, whether at present or in the near future (perhaps limited to short-term goals), and not otherwise. It is possible that some or all of the evaluation about what is task relevant and the prioritization of inputs is made in areas prior to the dACC.

We suggest, therefore, that individual neurons can be thought of as elements of a large switchboard that link contexts to strategies, except that the context and strategy of each neuron is itself context dependent (Duncan 2001, Miller & Cohen 2001). These linkages are also, presumably, flexible over longer timescales and adjust in strength due to conventional learning processes. These re-weightings could instantiate learning and could help explain the role of the dACC in learning (Jung et al. 2008, Wang et al. 2012). Our view is similar to and inspired by one proposed by Holroyd & Yeung (2012) and Holroyd & McClure (2015), who used the term option to mean roughly what we mean by strategy. Moreover, we see it as a refinement, motivated by data, of earlier theories of Bush et al. (2000), Morecraft & Van Hoesen (1998), and Paus (2001), rather than as a stark alternative.

The Pre-Premotor Cortex

In this view, the dACC can be thought of as a pre-premotor cortex, as the term conveys the idea that the dACC is part of the motor pathway but an early part of it (the use of the term is not original to us, but we have been unable to identify the first to use it to describe the dACC). Thus, its activation greatly facilitates action, and damage to it requires correspondingly greater activation from other auxiliary inputs to the motor system. This view also conveniently explains the close relationship between dACC activation and self-generated movement (reviewed in Passingham et al. 2010, Paus 2001), including akinetic mutism (e.g., Tow & Whitty 1953). It also explains the increase in activity during active versus passive contexts (Forstmann et al. 2006, Raichle et al. 1994, Walton et al. 2006) and, speculatively, may help explain evidence linking dACC activity to free will (Brass & Haggard 2007, Fried et al. 2011). Of course, one limitation of our pre-premotor perspective is that it cannot account for the functions of the cells within the cingulate motor areas with direct spinal projections.

A Map of Task Space

If each individual neuron represents a small fragment of a larger task space (which may also be called the task set), then the dACC as a whole represents its entirety (Lapish et al. 2008, Luk & Wallis 2013, Ma et al. 2014). Some evidence directly supports the idea that the dACC embodies a map of task space: In a spatial task, rodent mPFC ensembles represent space abstractly and dynamically, and do so more strongly than the hippocampus does (Hyman et al. 2012). Similarly, in monkeys dACC neurons primarily track specific actions associated with decisions and decision type (Hosokawa et al. 2013, Luk & Wallis 2013). Qualitatively similar responses are seen in the OFC, and both areas may represent aspects of a larger task-state circuit (see also Wilson et al. 2014). Indeed, it is possible that the idea of task-state representation may apply to the PFC as a whole (and not just the dACC and OFC), and it may include other areas, such as the striatum and amygdala.

FUTURE ISSUES

Beyond the relatively narrow confines of dACC function, we think the following are some of the most important questions and issues for future research into the dACC.

1. Clever task designs should be able to test the hypothesis that variables are encoded in the dACC only when they are relevant for actions during the current trial and in the near future. Such designs may also be able to define more precisely the time windows for which the dACC does and does not track such variables and determine whether there are any action-relevant variables that cannot be encoded by dACC neurons.
2. Our field of view is quite narrow; we need to expand it to include the other cingulate regions: the subgenual, pregenual, posterior, and retrosplenial cingulate cortices. Is it possible to identify a single general role for the cingulate cortex across multiple areas, or is the cingulate designation just an anatomist's term for a group of areas that have little in common functionally?
3. How much variation in function exists within the dACC itself? Do the dorsal and ventral banks play fundamentally different roles? And how different are the CMAs from the rest of the dACC? How about the seldom-examined cingulate gyrus (Chang et al. 2013; Rudebeck et al. 2006a,b)?
4. Several of the results reported here have been replicated in other brain areas, such as the dlPFC, the supplementary eye fields, and the OFC. At the same time, neuroimaging studies often focus on regions of interest or on areas that have the strongest effects rather than all areas that show effects of interest. To what extent is dACC function unique within the frontal lobe?

5. What role does the dACC play in regulating learning?
6. We need to know much more about primate–rodent homologies to make more direct comparisons across studies and to ensure the value of newer, rodent-specific methods.
7. One limitation of our model is that it does not attempt to wrestle with the extensive neuroimaging data on dACC aggregate function. We will need to link primate and human studies by learning more about the activation-flow coupling function.
8. The dACC is prominently involved in several psychiatric disorders; how does its dysfunction contribute to disease, and how can we target the dACC to hasten cures?

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