Anterior cingulate cortex and the control of dynamic behavior in primates

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Abstract

Controllers of continuous behavior in dynamic volatile contexts must mediate action selection and learning across many time scales, differentially, in response to the level of uncertainty and volatility. This review argues that the anterior cingulate cortex (ACC) is particularly well suited for this function. First, the ACC is interconnected with prefrontal, parietal, and subcortical regions involved in valuation and action selection. Second, the ACC integrates and signals diverse behaviorally relevant information across multiple time scales, and these signals encapsulate decision- and learning- processes – encoding high dimensional information about value and uncertainty of future outcomes and of subsequent behaviors. Third, the ACC signals behaviorally relevant information flexibly – representing information about current and future states in a valence, context, task, and action specific manner. Fourth, the ACC dynamically controls information seeking behaviors to resolve uncertainty about future outcomes. We review electrophysiology and circuit disruption studies in primates to further this point, discuss its relationship with novel therapeutics for neuropsychiatric disorders in humans, and conclude by relating ongoing efforts in primates to work in rodent medial frontal cortical regions.

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Monosov and colleagues review how dynamic and risky decisions, foraging and information seeking are controlled by value, valence, and context sensitive neurons in the anterior cingulate cortex

Introduction

Controllers of continuous behavior must mediate action selection and learning across many time scales, differentially, in response to changes in external and internal states, such as for example the levels of environmental volatility and uncertainty, changing the agents’ beliefs in a dynamic manner. In this REVIEW, we argue that the anterior cingulate cortex (ACC) is particularly well suited for this function. First, the ACC is prominently interconnected with most prefrontal, parietal, and subcortical regions involved in valuation and action selection. Second, the ACC integrates and signals diverse behaviorally relevant information across multiple timescales, and encapsulates decision-making and learning, by encoding high dimensional information about value and uncertainty before, during, and after decisions. Third, the ACC signals behaviorally relevant information flexibly – representing information about current and future states in a valence, context, task, and action specific manner.

Hierarchical models that assign cognitive functions to relatively localized pools of neurons in the cerebral cortex have been a crucial tool in systems neuroscience, greatly increasing our mechanistic understanding of perceptual decision-making, visual categorization, and economic choice [1–6] and have extended our knowledge of high dimensional sensory representations in the brain [7,8] and of reinforcement learning [9–11]. However, it has been challenging to conceptually fit ACC into these frameworks. We propose that (i) the role of ACC in the decision-making circuitry, and more broadly in behavioral control mechanisms, may depend on the details of the tasks the brain is solving, particularly on whether measurements of uncertainty or volatility are important for guiding ongoing behaviors, and that (ii) the ACC may contain distinct circuits serving distinct aspects of behavioral control, but that these circuits may not be anatomically segregated.

In recent years there have been several review articles about the ACC that concentrated on the results across brain imaging studies that average the activity of thousands of single neurons (for example see [12, 13]). Several reviews also outlined the diversity of function among single ACC neurons [14, 15]. This REVIEW adds by outlining electrophysiology and circuit disruption studies in primates in service of a coherent theory of the role of ACC in behavioral control, and relates this theory to the development of novel therapeutics for neuropsychiatric disorders in humans.

The anatomy of the primate ACC and the regional scope of this Review

The ACC is composed of multiple regions that support a wide range of functions in emotion, motivation, higher cognition, and motor control (Figure 1). The ACC lies on the medial surface of the brain, extending from the level of premotor cortex, curving rostrally with the genu of the corpus callosum and then caudally, ventral to the callosum. It is divided cytoarchitectonically into areas 25, 32 and 24 [16–20]. Area 25 is a relatively small region located caudally, ventral to the callosum. In the human brain, areas 24 and 32 extend...
throughout this territory, with area 32 dorsal to area 24 caudally and extending rostral and ventral to it as it tucks beneath the genu. In the Macaque brain, area 32 is more limited and primarily occupies the most rostral position. Overall, the ACC can be divided functionally along its dorsal-ventral and rostral-caudal axes. There are three major divisions of the ACC in non-human primates [21]: the sACC (area 25), the pregenual ACC (pACC, some area 32 and rostral part of area 24) and the midcingulate (caudal part of area 24).

The pACC together with the rostral part of the midcingulate are also referred to as the dACC. In human neuroimaging studies, the pACC is often referred to as the rostral ACC (rACC). To avoid confusion, we use rACC to refer to pACC, and dACC to refer to the ACC caudal to the genu of the corpus callosum [22,23].

Area 25 (sACC) receives inputs from medial orbitofrontal cortex, area 14, the hippocampus, and the amygdala [22,23]. Its functions remain fairly mysterious because only a small number of studies have particularly concentrated on this region. Some evidence is emerging that it is involved in visceral and emotional functions, such as in the control of mood or internal state [24–30].

The rACC is connected with both the sACC and dACC. Its connections include a combination of inputs from OFC areas 11 and 13, and from dorsolateral areas 9, 46, and 9/46, and ventrolateral area 47, thus placing the rACC in a pivotal position to mediate many cognitive, behavioral, and emotional functions. Unlike the dACC, it has minimal connections to posterior cingulate areas [21,22,31]. Caudally, the dACC is relatively more strongly connected with motor control areas, including frontal eye fields (FEF) and premotor areas [22,23,32]. It has been proposed that the dACC has a relatively important role in the development of motor planning and action execution [32,33].

There are no clearly defined borders between the sACC, rACC and dACC based on their anatomical connections [21,31]. Rather, these areas exhibit a gradient in connectivity from the most rostral and ventral areas (32 and rostral 24) to the caudal and dorsal areas (central and caudal 24). However, interestingly, amygdala projections continue to terminate in patches throughout the ACC, including the dACC [34].

Most of the single neuron electrophysiology studies that the REVIEW reviews were conducted in rACC and anterior regions of dACC, particularly in the ACC sulcus. The REVIEW refers to this region from hereon as the ACC, making more precise anatomical distinctions when possible.

**ACC signals control-variables related to value and uncertainty during decision-making**

A major effort in systems neuroscience has been to understand how the prefrontal cortex contributes to decisions based on abstract representations of action values and rules. Such decisions present themselves in a variety of forms. Some notable interrelated examples are (1) deciding when to stay in a particular environment to obtain reward and exploit its riches, and when to leave and go elsewhere to explore new rewards and novel opportunities, (2) deciding among diverse options, offers, or rewards to choose the one that is best or most...
rewarding based on its attributes and the current internal and external state of the agent, and
(3) deciding when a volatile environment has changed.

We first review the role of ACC in the deliberation phase of these decisions. In this section,
we begin with value-based decisions among offers, and then move to a discussion of
decisions closely related to foraging and exploration in volatile contexts.

In an early study of ACC in a choice task, single ACC neurons were recorded while
monkeys evaluated two offers associated with three decision variables: different probability
and quantity of reward, and cost or effort [35]. The authors found that before the monkeys
reported their choices, ACC neurons encoded one, two, or all three of these decision
variables.

It could be argued that ACC neurons that encoded the values of all three attributes signaled
subjective value – that is a theoretical construct roughly equivalent with a highly abstract
representation of the utility of a given option, weighting all its behaviorally-relevant
attributes or features. To test this further, Cai and Padoa-Schioppa (2012) studied the activity
of the dorsal and ventral bank of the ACC sulcus as monkeys chose between different fruit
juices in variable quantities [36]. Before the monkeys overtly indicated their choices, dorsal
bank ACC neurons encoded the subjective reward value of the juice offer that the monkeys
will choose on that trial. The authors also noted that in their task, the ACC did not contain
neuronal pools that encoded the values of the individual offers that would theoretically be
required to make a comparative decision.

It is worthwhile to point out that the value of the chosen option and the total value of the
available offers, a variable closely tied to the value of foraging, particularly for choosing
when to stay or leave in an environment or patch [37–39], are highly correlated in many
economic choice tasks [36]. And, though the authors did find that in their task across the
entire population, ACC activity was better explained by chosen value, their analyses did not
indicate that ACC does not contain total value coding neurons. Indeed, a key input to the
ACC, namely the basal forebrain is sensitive to total value [40] and encodes other foraging
or exploration related variables such as behavioral/motivational salience, uncertainty, and
novelty [41]. Finally, both of the previous studies of ACC did not distinguish the encoding
of chosen value from outcome prediction related signals, such as those resembling or
derived from different forms of prediction errors related to the presentation of the choice
offers.

Differentially, one study argued that single ACC neurons did encode the subjective values of
individual offers in a sequential decision-making task in which the offers were presented
asynchronously [42]. However, their analyses could not distinguish representations of
unexpected changes in state value (e.g., prediction errors) from representations of offer
values. Hence, an alternative way of interpreting their results is that each offer in a
sequential decision making task constitutes a new value state and if it is better or worse than
the preceding one then there will be a positive or negative prediction errors [11] which are
known to be important determinants of ACC activity [43,44]. This consideration reconciles
their results with previous work.
To further study how ACC neurons encoded predictions or values of rewards during choice, Kennerly and Wallis (2011) analyzed ACC neurons’ value signals during the choice- and the choice outcome- phases of their multi-attribute decision-making task [45]. They found that many ACC neurons encoded decision-related attributes of the chosen option during both the decision and outcome epochs with similar sign and across similar decision attributes (but also see [46] for important interpretational caveats). For example, the ACC neurons that were selectively excited by increases in value during choice, were most likely to display excitation that scaled with unexpectedly positive outcomes (Figure 1A, but see Figure 1B and subsequent discussions about valence specificity and prediction error coding).

An important point worth noting here is that none of these results indicate that ACC is not involved in choice. As information about offers appears sequentially/asynchronously or if the task is dynamic, prediction error-related computations are likely to influence decisions and beliefs on a short and long-time scale (e.g. over subsequent trials).

Relatedly, in one very interesting study monkeys were allowed to gather information about choice options before finalizing their decisions with gaze shifts [47] (Figure 1C). The authors found that some ACC neurons dynamically tracked the relationship among the attended-information (particularly, the attended offer attributes) and the monkeys’ favored option. Particularly, they found that the ACC contains a belief confirmation signal that closely relates (and may be derived from) prediction errors that theoretically should be important for the commitment to a decision in a dynamic or volatile environment.

In sum, the studies reviewed thus far suggest that ACC neurons signal several key variables closely tied to the reward value related predictions during many epochs of decision making.

**ACC signals control-variables in a valence and context selective manner**

Upon first order inspection the data thus far seems at odds with several prominent views of ACC. The first one that ACC encodes the negative value of noxious or aversive events and is somewhat dedicated to processing pain [48–53]. The second one that ACC deploys attention to monitor task-performance, to detect errors [54–63]. This theory predicts that many ACC neurons ought to be activated by salient, engaging, and cognitively demanding situations, irrespective of their subjective value or valence.

Consistent with the first theory, Iwata and colleagues discovered that some ACC neurons are excited by noxious stimuli [50]. Do these aversive neurons also display inhibition to reward? In other words, do they encode rewards and aversive noxious events on a common currency (subjective value) scale, such as for example the lateral habenula [64]? Or are they excited by both, encoding their salience or motivational intensity of rewards and punishments? To address this, a recent study recorded the activity of single neurons during two distinct contexts: one in which conditioned stimuli predicted certain and uncertain rewards, and one in which they predicted certain and uncertain aversive outcomes (air puffs) [65]. The subjective aversiveness of the air puffs was verified with an outcome-avoidance procedure. Before the outcomes were delivered, many ACC neurons signaled value or uncertainty of predictions about either rewards or punishments (Figure 1B). These neurons were mostly intermingled and anatomically non-separable. However, punishment uncertainty neurons did
seem to be most common in the anterior ventral lateral region of ACC sulcus right around the genu [65].

The same study also found that a minority of ACC neurons signaled information about rewards and punishments by displaying excitation to both, rather than excitation to one and inhibition to the other. Finally, valence-specific neurons predicted the nearing of their preferred valence over long time scales (across blocks). For example, during the aversive block, reward value sensitive neurons increased their background activity slowly as the reward block neared [65].

These simple observations have several important implications. First, ACC value-related signals do not represent all motivational outcomes on a common currency scale (also see [66]).

Second, the ACC contains explicit representation of uncertainty. Third, the unweighted average signal of all the neurons in ACC could resemble a motivational salience signal mirroring many human fMRI studies.

In sum, the ACC may contain intermingled circuits that contribute to control of a wide-range of reward and punishment related behaviors and internal states. From these observations, we conjecture that valence specific and non-specific ACC neurons project to distinct and to overlapping brain regions – hence their value- and uncertainty- related representations can be readout flexibly, to mediate salience or value computations, or to mediate valence-specific action planning, such as to trigger fight or flight responses [67]. Ongoing efforts in our laboratory, for example, are aimed at discovering circuits that particularly receive punishment uncertainty signals that we discovered in the ACC. The goal there being to understand how the ACC may regulate behavior in aversive and/or anxiety-promoting states.

**ACC signals control-variables for foraging**

Many of our daily decisions resemble foraging because we must integrate information over many timescales and update our beliefs about the value of an environment or set of decisions, to choose when to stay and when to leave, and/or when to switch behavioral and learning strategies [37,38,68,69]. Measuring uncertainty and volatility is crucial in these dynamic foraging decisions [68]. Next, we review how ACC serves these functions.

Amiez et al recorded single ACC neurons while animals chose among two probabilistically rewarded targets whose expected values changed over time. They found that many ACC neurons signaled task-value before the decision-report and before the “optimal” (highest value) option was discovered [70]. In the authors’ foraging task, this type of value signal is important for choosing whether to stay-or-leave [38] and for regulating information gathering [68,71–74] to update beliefs and adjust learning (meta)parameters. The same authors found that immediately following ACC inactivation, monkeys’ adaptive exploration-related behavior was disrupted [70]. Additional evidence for the theory that ACC may be ideally suited to regulate foraging comes from the observation that ACC choice and value related signals are highly sensitive to the history of reinforcements over long time scales [43]. ACC neurons track gains and losses of rewards signaled by visual cues or tokens as
animals progressively forage to increase their future payoffs [75]. Importantly, as the value-
functions of probabilistic offers changed, ACC neurons correspondingly changed their
activity, with some ACC neurons dynamically encoding the difference in the offers’ value
functions.

Platt and Hayden (2011) trained animals on a task that aimed to simulate foraging in distinct
patches [76]. The monkeys tracked rewards over multiple time scales to decide when to
“move on” and leave a patch. Some ACC neurons accumulated information about rewards
over many trials, and their activations predicted stay or leave decisions before the choice was
made.

Importantly, during foraging, ACC neurons dynamically track not only value but also
uncertainty. For example, Khamassi and colleagues observed that as monkeys performed an
explore-exploit foraging task, a sizable proportion of single ACC neurons activity was
related to animals’ outcome uncertainty, and this signal systematically increased towards the
time of the decision outcome, beginning before the monkeys’ choice [77] (also see Figure
2D, and subsequent section on post-decision feedback).

In sum, these data may suggest that the ACC may play an important role in foraging and
choice in volatile context and integrates outcome history over long time scales to guide
behavioral adaptation.

The ACC guides action selection dynamically to reduce uncertainty in instrumental and
non-instrumental information seeking

Agents negotiate uncertainty around them by seeking information to update their beliefs. We
recently outlined two types of information seeking behaviors: instrumental and non-
instrumental [71]. During instrumental information seeking, an agent aims to obtain
information that has an instrumental value, for example to update future actions and learn
their values, and gain more reward. It is well exemplified by the many decision-related
behaviors under uncertainty and volatility discussed in previous sections.

Instrumental information seeking can also be studied by offering subjects the ability to
check their own performance and learn about their future rewards [71,78]. Utilizing this
approach, a recent paper discovered that ACC contains neurons that seem to be somewhat
specific to decisions to check one’s performance [78] (Figure 2D). And, a very recent study
found that exploration maybe proportional to the time horizon of a given task, and is related
to ACC activations [79]. This is important because uncertainty is important to resolve
particularly when there is a long versus short time horizon over which the knowledge gained
can be subsequently exploited. That is, if an agent will be performing a task for a long time,
resolving uncertainty is particularly important to harness its rewards and instrumental
information seeking maybe enhanced by the ACC.

Non-instrumental information seeking does not directly impact future decisions or future
rewards [71], at least not in a straightforward sense. This type of information seeking is
observed in many species and is common in our everyday decision making, because (i
dynamic updating of beliefs may help agents when contexts change suddenly, for example
when environmental volatility fluctuates and detecting it requires persistent monitoring of events and outcomes, (ii) when foraging under predation or in social settings, knowing future outcomes early is crucial for complex behavioral adaptations and in these and other situations heightened uncertainty intolerance may be adaptive, and (iii) treating information as valuable may have become an evolutionarily favorable feature of behavior [68], for example because belief formation in itself may have value or utility (see i) [68,71,80].

While the role of the ACC in instrumental information seeking has been more commonly studied, until recently nothing was known about whether and how it participates in non-instrumental information seeking.

To guide non-instrumental information seeking, ACC would need to detect uncertain outcomes, predict the time of uncertainty resolution, and use this prediction to mediate action selection, dynamically to motivate behavior aimed at obtaining uncertainty-resolving information. We recently designed an information viewing paradigm in which monkeys express a strong trial-by-trial anticipation to resolve their reward uncertainty through their uninstructed and unrewarded gaze behavior, but cannot use the information that they obtain to change the timing, size, frequency, or magnitude of their rewards [81] (Figure 2E). Reward uncertainty was resolved by visual cues, and monkeys anticipated their presentation by persistently gazing at the location where the uncertainty resolving cues would soon appear. Importantly, some ACC neurons, and many neurons in regions of basal ganglia to which the ACC projects [81,82], preferentially detected uncertain reward predictions and ramped to the predicted time of uncertainty resolution. Moreover, we found that ACC-basal ganglia uncertainty signals dynamically promoted information seeking because fluctuations in uncertainty-sensitive signals predicted the monkeys gaze shifts to view informative cues on a moment-by-moment basis. In the process of guiding non-instrumental information seeking, the ACC could play a particularly central role at a pre-motor stage because among the interconnected ACC-basal ganglia network, the ACC was the earliest predictor of active information seeking behavior [81].

As a final note of caution, the results that ACC dynamically guides instrumental and non-instrumental information seeking should not yet be interpreted as direct evidence for the control of a curiosity-phenotype by ACC. Curiosity is a constellation of behavioral patterns, among which a heightened level of information seeking about future uncertain rewards, states, or actions is observed [68,71,74,83–86]. But, for example, heightened information seeking is also expressed in OCD and anxiety patients who often display a reduction in other curiosity-related intrinsic motivations such as novelty seeking, and/or in curiosity-related traits, such as impulsivity [87]. At this stage, how the ACC participates in the control and coordination of curiosity remains an open question that requires more investigation. One hint may be obtained by studying how the ACC mediates or interacts with the oculomotor system. Gaze is the primary instrument of information gathering for primates. And, accordingly, brain regions that control gaze, such as area LIP, reflect the diversity of attitudes and motivations that comprise curiosity to control gaze [88,89]. Therefore, understanding how ACC neurons that mediate information seeking interact with LIP and with other oculomotor-related regions, such as the frontal eye fields and the superior...
colliculus, will be an important step towards understanding the role of ACC in the diversity of curiosity related behaviors.

Post-decision feedback and outcome signals in the ACC predict subsequent states and actions

Shima and Tanji (1998) found that ACC neurons’ outcome signals predicted stay-or-switch decisions in an action-outcome association task in which the values of actions changed without warning [90]. Temporary inactivation of the ACC interfered with adaptive switching of actions. From this study, an important question arose: do ACC feedback signals resemble quantitative reward prediction errors – that is the difference between received and predicted reward values? Or, do they have different or additional algorithmic features and contribute differentially to learning and behavior? Here, we present evidence for the latter view.

Kawai et al (2015) contrasted the ACC and the lateral habenula, a key controller of dopamine prediction errors [91,92], in a probabilistic reversal learning task in which the animals had to integrate past outcomes to decide when they should switch their choices from one target to the other. ACC neurons were highly sensitive to several past trials’ outcomes (Figure 3A). And, ACC outcome-related neurons’ activity predicted the animals’ subsequent changes in behavior. In contrast, the lateral habenula tracked mostly single trial’s outcomes by encoding outcome-related reward prediction errors (but also see [93]). Their findings are consistent and extend previous results [43,76] that showed that ACC tracked the history of reinforcements to mediate behavior.

Not only do ACC post outcome feedback signals contain historical information, but they are also sensitive to the parameters of subsequent behavioral adjustments because they are sensitive to whether the animal can utilize them to update action values [44].

Relatedly, in human patients undergoing cingulotomy [94] (and see [95]), dACC neurons were particularly activated by cues that indicated that subsequent movements would need to be altered.

Another important explicit difference between ACC outcome/feedback signals and “classically” defined reward prediction errors is there sensitivity to hierarchical structure of decision-making paradigms, a feature that in theory would be crucial for accurate belief state updating and credit assignment in complex naturalistic environments. Particularly, beyond history dependent multi-time scale representation of decision outcomes, single neurons in the ACC are also sensitive to the sources of decision uncertainty. Sarafyazd and Jazayeri (2019) trained monkeys on a task in which the variability in outcomes was related to several sources of uncertainty: one due to volatility or changes in task rules, and one due to errors or noise in perceptual decision making [96]. The authors found that the ACC contained neurons whose outcome signals were selective for outcome related prediction errors that were due to changes in rules, indicating that the ACC could signal hierarchical feedback signals for belief updating [47,97].
These observations indicate that the ACC post outcome feedback signals are distinct from the reward prediction errors observed in many dopamine and in almost all lateral habenula neurons.

How might such complex feedback signals in ACC participate in dynamic tasks, like foraging, is still a question of many recent and ongoing studies. Quilodran and colleagues assessed the role of ACC in action evaluation during a foraging-like search task [98]. There, some ACC neurons’ activity during the initial exploration, before the best option was discovered, responded to feedback, but once the monkeys discovered the highest-valued option and began exploiting their knowledge, the same neurons’ activity shifted to responding to trial initiation (Figure 2D – left). Consistent with the sensitivity of ACC neurons to the goals and context of foraging, in a dynamic pursuit task, some ACC neurons multiplexed a diversity of behavioral control variables with the future position of the prey [99].

To summarize, ACC outcome or feedback signals are related to the specifics of contexts, actions, and tasks, and adjust behavior based on the uncertainty, value, and history of the environment or context [45,46,65,75,91,98]. ACC feedback signals contain information about previous history of trials and actions and about future predictions. And, these signals are distinct from reward prediction errors in classical reinforcement learning algorithms.

Behavioral changes following lesions of the ACC support its role in behavioral control in uncertain environments

Some of the oldest studies of ACC lesions in monkeys, observed that ACC damage changed monkeys social and exploratory behaviors [14]. And, precise anatomical work indicates, that ACC lesions do not impact many aspects of cognition, learning, decision making, and behavioral control. For example, many memory related functions are not impacted by ACC lesions [100,101]. Performance in value-based decision-making tasks that are not dependent on belief updating and internal measurements of uncertainty or volatility are also spared [102]. Moreover, in tasks in which the action outcome mappings are stable, ACC lesions produce little or no behavioral changes [103]. Finally, in task switching with stable rules that animals learn to optimize reward rate, ACC lesions produce little or no behavioral effects [104].

In our view, this is consistent with single unit physiology studies in macaques: in stable tasks, in which uncertainty or volatility are low, the ACC does signal expected outcome or feedback related variables, but may not play as active of a role in guiding decisions or choices. Also, ACC encodes decision variables throughout all epochs of many tasks over different time scales. This historical representation of value before, during, and after decisions is key for behavioral control under volatility and uncertainty, but may not be important when uncertainty is low, and no learning or adaptation is required.

Kennerley et al (2006) trained monkeys on several tasks in which the monkeys freely choose among two actions to get reward [102]. In the first experiment, the two actions’ values were not independent. One of the actions was rewarded for 25 trials, and once the monkey experienced a reward omission, the appropriate strategy was to switch to the other action to
get reward. This experiment strongly resembled the paradigm of Shima and Tanji (1998) in which monkeys ought to perform a simple win-stay or loose switch strategy. Like Shima and Tanji (1998), Kennerley et al (2006) also found deficits, but using a more sophisticated set of analyses, discovered that they were mostly due to changes in weighting of reward history (and not specific to negative or positive feedback or sign of prediction errors, and not due to the detection or monitoring of errors). Next, the experimenters tested monkey’s ability to perform a similar task, but one in which the two action values changed independently. Also, here, the outcomes were probabilistic instead of deterministic. This more uncertain and volatile task resembles naturalistic foraging in which the weighting and integration of feedback over many time scales is crucial for performance. In this experiment, following ACC lesions, monkeys were severely impaired and unable to perform the task adaptively. A final control experiment, indicated that the same ACC lesions did not disrupt economic or value-based decision making in stable environments.

In sum, permanent lesion study by Kennerley et al [102], temporary inactivation studies by Amiez et al [70], and many single unit neurophysiology studies in monkeys together point towards a key role of ACC in controlling action in uncertain and volatile environments, and particularly in foraging, where switching from patch-to-patch is often required to gain the best rewards. In fact, a recent study tested the relationship of this capacity and ACC activity. They found that ACC disruptions render macaques less able to utilize or know the value of alternative options they might switch too [105]. Particularly, after ACC disruption their switching behavior is less guided by the values of alternatives.

Intrinsic properties ACC neurons may support their role in multiple time-scale history-dependent control

The capacity of ACC to encode control-variables closely related to value and uncertainty dynamically throughout all “epochs” of behavior, on different, and particularly on long timescales, may be related to intrinsic properties of neurons in the ACC as well as to their wide-ranging connectivity. While intrinsic properties of neurons in auditory cortex may be optimized such that they can encode rapid fluctuations in the auditory landscape, without strong history dependence, neurons in the prefrontal cortex may be optimized to encode information on a longer time scale, to mediate decision making in a dynamic or volatile context in a historical manner [106]. This notion is supported by empirical data. Indeed, sensory cortices display shorter time constants and amazingly, among all the prefrontal cortical areas, ACC displays the longest [4,106–108].

A recent study found that in cortex (Figure 3B), there may be multiple, parallel hierarchies of timescales that were largely independent from each other and that were not clearly related to task selectivity of single neurons [106]: two related to prior choice and reward outcomes, one related to ongoing fluctuations in activity, and one related to response to task epochs. Moreover, the same study found a direct relationship of choice- and reward-memory timescales to behavioral adjustments in a dynamic decision task. Across all these hypothetically distinct time scales, the ACC seemed to display longest time constants [4, 106–108].
Differentially, other studies using different analyses showed that intrinsic time scales could predict task selectivity [109]. And, for example, short spiking time scales within ACC may contribute to feedback processing, whereas long time scales contribute to processing changes in reward over many trials [108]. However, a key consistent finding across all of them remains: the ACC contains particularly long-time constants.

From these studies one could conjecture that diverse long timescales in ACC may arise due different sources. For example, intrinsic time scales may arise due to short-term plasticity and neurotransmission (e.g., particularly GABA-B and NMDA). While, timescales related to prior trials (Figure 3), maybe due to anatomical connectivity and behaviorally relevant, or task triggered, circuit reverberation [106].

A final point on synaptic plasticity in ACC is that to support its role in guiding dynamic behavior in volatile environments, it may also have unique mechanisms for metaplasticity that could contribute to the agent’s capacity to estimate volatility [110, 111]. This hypothesis could help to explain the deficits observed by Kennerley et al (2006) [102]. Also, we have recently conjectured that this metaplastic process could be related to uncertainty and surprise signals in the basal forebrain [68]. Future studies are required to assess the validity of these proposals.

Much work remains necessary to understand how multiple timescales mediate behavior. Recent neuroimaging studies have made progress in this direction and also showed that the ACC contains signals of estimated reward trends over long timescales [112, 113]. Their work points to the idea that multiple timescales are crucial for foraging behaviors in which one must decide when to stay versus when to switch, and particularly adapt one’s learning rate to the uncertainty or volatility of the environment. But future studies are needed to test this hypothesis further in animals and humans, and to further develop a computational understanding of how artificial learning agents can benefit from multiple timescale representation [68].

Summary hypothesis

The ACC contains groups of neurons that track the predicted value of cues or offer attributes, and distinct forms of uncertainty (e.g., reward and aversive-outcome uncertainty) before, during, and after a variety of decisions (Figure 4 – dark green represents ACC at the bottom and top of the figure). In general, ACC neurons signal information over long and short scales, and are highly sensitive to decision structure/hierarchy, internal state, behavioral context, and valence of actions and outcomes. Anatomically intermingled ACC neurons may mediate particular actions or behaviors through distinct circuits and serve distinct computations (Figure 4 – middle). Whether and how the ACC mediates behavior, and which behaviors it drives, depends on (i) whether the environment is stable, or volatile and uncertain, and (ii) whether behavioral adjustments relative to the history of choices, actions, and outcomes are necessary or adaptive.

Clinical relevance

Human ACC lesions do not produce consistent deficits in the performance of a variety of critical behaviors related to language, visual integration, many forms of decision making,
memory, and motor control [114–119]. However, consistent with studies in non-human primates, lesions of human r/dACC impair task performance in tasks in which action values change as a function of time [94]. For example, Di Pellegrino and colleagues (2007) showed that patients with rACC lesions failed to use previous information to modulate current responses [120]. Also, Camille and colleagues (2011) showed that in an action-value learning task, patients with large r/dACC lesions were more likely to shift their response differentially from controls [118].

In line with the role of ACC in behavior in volatile and uncertain contexts, the r/dACC is thought to play a central role in obsessive-compulsive disorder (OCD) [121] and in other anxiety disorders that broadly are associated with intolerance for uncertainty and with deficits in dynamic and/or risky decision making [122, 123]. When the intolerance for uncertainty was tested in OCD patients divided into two groups, checkers and non-checker, checkers manifested higher uncertainty intolerance than then non-checkers group [124] suggesting a heightened eagerness in some OCD patients to seek information to reduce uncertainty. This effect is not necessarily related to a misunderstanding of value-related information (e.g., offer attributes) or due to probability distortions because OCD patients show similar response patterns as controls to risky choices when the outcome probabilities are specified, but avoid more ambiguous choices [125, 126]. To understand how ACC circuitry becomes dysregulated in OCD patients (through life experiences, trauma, and/or genetic disposition) studies of plastic and metaplastic processes in ACC will play a particularly illuminative role.

Hence, our theory that ACC dynamically controls information seeking and mediates behavioral adaption under uncertainty on multiple time scales, and that these functions are supported not only by ACC neurons’ activity but also by their synaptic properties, may have deep implications for the clinic.

First, this is the case with the emergence of neural interface technologies for neuromodulation. Current successful neuromodulation strategies are open-loop focal stimulators [127] for the treatment of Parkinson’s disease, and experimentally for the treatment of unipolar depression [128]. But, given the high degree of intermingling of functionally diverse neuronal populations (with broadly distributed connections) within the ACC, novel technical methodologies for neural interfacing may be required to achieve successfully treatment in the clinic. For example, a closed loop system with the capacity (i) to flexibly excite versus inhibit ACC circuits in response to feedback from other brain regions (ii) in response to changes in the patient’s contextual and behavioral state (e.g., in response to the patient’s digital ecosystem) may be necessary. Furthermore, neuromodulation may need to be performed with an electrode-interface that could consider the organizational heterogeneity of ACC, perhaps via more anatomically precise electrode arrays. Current clinical neuromodulation systems have macroscale electrodes that record and stimulate the neural parenchyma on the scale of 1-2 mm, but this may not be sufficient. Finally, given the high dimensional nature of neuronal computations in ACC, neuromodulation ought to consider non-linear relationships between stimulation and the physiologic and the behavioral inputs/outputs that control them. Thus, above and beyond
basic preclinical research of the circuitry of the primate ACC, the development of novel artificial-learning algorithms will be required for successful modulation.

Second, for psychiatry, it is important to appreciate that disorders of information seeking and uncertainty processing are not only a symptom of OCD and anxiety. Information seeking is now chronic, and thanks to smart phones and other technology, we are often confident that we can (or have reduced) our uncertainties in seconds or minutes (though note, that the information obtained from rapid digital queries is often sampled from the tails of possibility distributions, and may not actually represent the most likely answers to our queries, or be accurate, further promoting our future uncertainty). In any case, our lifestyles may be re-scultping our information- and uncertainty/risk- attitudes, perhaps through the ACC. We hypothesize that in information rich environments, such as ours, on occasions when uncertainty is irreducible at our preferred time scale, we may experience a maladaptive ramping-up of our desire for information, and because the information is sometimes unavailable, many of us can experience maladaptive anxiety- or depression- related internal states.

**Relationship to work in rodents**

Recent work in rodents has highlighted regions of rodent medial frontal cortex or “prefrontal” cortex (mPFC) as being similar to the primate ACC. Important insights from this work must be considered. First, like primate ACC, rodent mPFC neurons seem to carry signals that may be required for foraging stay-or-leave decisions and for behavioral control in dynamic environments [129–133]. Particularly, some mPFC neurons may be sensitive to uncertainty or volatility [131], and rodent mPFC helps to shape prediction errors in tasks or contexts in which hidden state inference is beneficial [134]. Second, lesions of this region in rodents results in deficits in foraging and exploration related behaviors under uncertainty and volatility [132, 135]. Third, rodent studies mirror our findings of valence specificity in mPFC [136]. Finally, consistent with our proposal in Figure 4, the Stuber laboratory recently provided evidence that neurons with distinct value or outcome coding strategies project to distinct subcortical targets [137] (also see [138]). Given such mounting data, additional experiments are now required to assess the functional similarities and differences across species at the neuronal level.

**Limitations and concluding remarks**

The REVIEW did not delve into data from all anatomical regions of the ACC, in particular Area 25, or sACC, was not the subject of our discussions. While it is a target for the treatment of unipolar depression in humans [29], little is known about its functions. Monosov and Hikosaka (2012) recorded sACC neurons and found that some of them weakly modulate their activity with the overall probability of punishments, and that the same neurons often also respond to unexpected reward omissions and to most punishment deliveries [25]. This result differentiated it from neighboring area 14C which robustly encoded reward-related variables in a blocked appetitive / aversive procedure. Bouret and Richmond (2010) recorded in anterior sACC, mostly in area 32, and found that sACC neurons tracked internal states, such as satiety, but did not dynamically track the values of...
visual reward-value cues on a trial-by-trial basis [26]. Lesions of sACC in monkeys changed their autonomic responses [27]. One speculation is that timescales, and relationship with internal state, change systematically as a function anterior-posterior location in ACC. In that model, sACC would be in a key position to regulate “mood”, in other words to regulate the overall state of action (e.g. to depress or suppress the probability of action and movement over long periods of time, for example if there is a lull in rewards).

Also, the REVIEW did not entertain the distinction between representations of action value and object or cue value in ACC. There is significant evidence that the ACC may prominently impact action valuation. And, that neuromodulators, in particular the basal forebrain, that carry signals about behavioral importance [41] and about the total value of choices or contexts [40], may directly impact how ACC impacts action related processes [139,140], particularly during foraging and/or while under uncertainty.

The REVIEW points out that the ACC contains highly intermingled pools of neurons with distinct behavioral adaptation - (or control objective -) functions (Figure 4). Future experiments must assess if these neurons have distinct anatomical connectivity. Therefore, novel pathway and cell-type specific tools will be required to better understand their precise role in cognition and to apply this knowledge in the clinic. This will be particularly valuable for assessing how value- and uncertainty- related representations in ACC are read out (Figure 4). We suggest that such valence specificity can mediate salience or value computations, depending on how signals from ACC are utilized by downstream regions (Figure 4 – middle row), or to rapidly mediate valence-specific action planning (Figure 4 – second to bottom. For example, we found that some neurons in the internal capsule bordering regions of the striatum, that receive particularly dense inputs from the ACC, are sensitive to reward, but not punishment, uncertainty [141]; and that this ACC-striatum pathway directly drives information seeking to resolve reward uncertainty [81]. But in contrast, the distinct projection patterns of ACC punishment uncertainty neurons that we uncovered in anterior ventral regions of the bank of the ACC [65] remains unknown. To understand their functional role, and of other valence and context specific signals in ACC, the push towards temporally precise and cell type specific functional circuit mapping approaches in primates must now be made.

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Figure 1. Primate anterior cingulate cortex.
Sagittal model of rhesus macaque brain. Locations of different cingulate regions are shown.
sACC – subcallosal anterior cingulate cortex. rACC – rostral anterior cingulate cortex.
dACC – dorsal anterior cingulate cortex. pACC – posterior cingulate cortex. AC – anterior commissure. CC – corpus callosum.
Figure 2. Distinct value-, uncertainty-, and choice-related variables in the anterior cingulate cortex.

(A) Example anterior cingulate cortex neuron from Ref 45. In a two forced choice multi-attribute choice task, this ACC neuron scaled its activation with chosen value before the choice was made (left) and with the prediction error associated reward delivery (middle). The same neuron did not encode prediction errors when reward was omitted (right). The experimenters found a diversity of prediction-related computations in ACC during all epochs of their task. (B) Data from Ref 65. Single ACC neurons (rows) display a diversity in their valence sensitivity, and their uncertainty and value coding. The neuron matrix in this plot was organized by an unsupervised hierarchical clustering algorithm for facilitate visual inspection of cluster/clump-like organization. Color scale: 0.5 indicates no significant
coding, values greater than 0.5 indicate significant selective excitation, values less than 0.5 indicate significant selective inhibition. Very few neurons encode punishment value and reward value on a common currency scale (with opposite signs). Note that only prediction signals are shown here. However, in the same study, similar pattern of results was observed in ACC outcome responses: many single neurons signaled information about predictions and their outcomes with significant valence specificity. (C) ACC neuronal activity from Ref 47. As animals took more- or less- time to inspect attributes of offers, ACC activity scaled with belief confirmation in their choices. This inspection may be a form of non-instrumental information seeking because the animals sacrificed time (reward rate) for additional confirmatory-information. (D) Examples of foraging-related and instrumental-information seeking related activities in the ACC. Data are from Ref 77 on the left, and Ref 78 on the right. As animals forage, ACC signals outcome related information after the feedback. After finding the best option, the animal exploits the knowledge, and the activity of the same ACC neurons shifts to the time of trial initiation (left). In a decision task, some ACC neurons discriminate the decision to check one’s own performance versus continue to work (right). Performance information is instrumental and can be used to update performance. Checking signals are particularly prominent in ACC versus latera prefrontal cortex (LPFC). (E) Data are from Ref 81. Monkeys’ uninstructed gaze (left) behavior in an information observation task reveals motivation to seek advance information about uncertain rewards. This information seeking is non-instrumental because it cannot be used to modify reward rate. On Info trials (red), a peripheral visual stimulus predicted uncertain rewards. One second after, it was replaced by uncertainty-resolving cue stimuli (red arrow). Monkeys’ gaze on Info trials was attracted to the location of the uncertain prediction in anticipation of receiving informative cues that resolved their uncertainty. After uncertainty resolution in Info trials, gaze is split to trials in which reward will be delivered (dark red) and reward was not delivered (pink). On Noinfo trials (blue), another visual cue also predicted uncertain rewards. Here, the subsequent cue stimuli, shown 1 second after, were not informative and the monkeys resolved their uncertainty at the time of the trial outcome (blue arrow). In Noinfo trials, gaze was particularly attracted to uncertain visual stimuli in anticipation of uncertainty resolution by outcome delivery. Probability of gazing at the stimulus ramped up in anticipation of the uncertain outcome until it became greater than other conditions (50% > 100%; compare blue with dark red). (E-middle) ACC neural activity anticipates uncertainty resolution. Same format as left. (E-right) ACC activity predicts information seeking gaze behavior. Mean time course of gaze shift-related normalized ACC activity aligned on gaze shifts onto the uncertainty resolving informative stimulus (green) and off the stimulus (purple). ACC uncertainty-related activity was significantly enhanced before gaze shifts on the stimulus.
Figure 3. Historical encoding and multiple timescales in ACC activity

(A) Data are from Ref 91. In a dynamic decision making task in which monkeys had to switch their actions by integrating the history of several past trials (left), some ACC neurons encoded information about outcome omissions across many previous trials. This was in contrast, with the lateral habenula neurons (LHb) – an established source of reward prediction errors. LHb neurons were sensitive to mostly the current trial’s outcome prediction error. Also, as in Refs 45 and 65, this study found a diversity of prediction-related signals that were context- and outcome-specific (data not shown). (B) Data from Ref 106. Cartoon depiction of the estimation of multiple hierarchies of time scales in cortical activity (left) during dynamic decision making. Results are on the right. Intrinsic timescale – activity in a given time epoch is related to previous epochs in the same trial. Seasonal timescale – activity in a given time epoch is related to activity in the same epoch in a previous trial. Reward and choice time scales – activities during reward and choice in the current trials are related to activities in the same epochs in a previous trial. Hierarchies are shown across several cortical brain areas. ACC appears at the top of these hierarchies.
Figure 4. ACC mediates behavior before, during, and after decisions by encoding control variables in a context and valence sensitive manner.

A hypothetical black box model of behavioral control by ACC. Valence specific signals from the ACC (top, dark green box) can be combined for subjective/integrated value computations (red box) and or for salience/attention related computations (light green boxes). Pluses and minuses denote inhibitory versus excitatory influence on abstract representations. In some contexts, ACC valence specific signals may directly mediate valence-selective action planning (third box from the top), such as during fight or flight responses when many aversive or noxious events are expected. After decisions and actions (bottom, dark green box), partially distinct ACC neurons may encode predictions for future behavioral adjustments. Here, a useful question to ponder is: why would uncertainty directly impact action planning? We found that reward uncertainty selective neurons in the ACC mediate information seeking gaze shifts to resolve reward uncertainty (Figure 2). This
exemplifies that not all actions or behaviors are value or absolute-value driven. Hence, uncertainty signals may impact action selection directly (but note that nothing yet is known about punishment uncertainty selective neurons in ACC, therefore their influence on neural computations here is particular conjectured). Understanding the outputs of ACC with anatomical and molecular precision is now required to further empirically test these hypotheses (see Limitations and Concluding Remarks).