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The midcingulate cortex and temporal integration

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Abstract

The ability to integrate information across time at multiple timescales is a vital element of adaptive behaviour, because it provides the capacity to link events separated in time, extract useful information from previous events and actions, and to construct plans for behaviour over time. Here we make the argument that this information integration capacity is a central function of the midcingulate cortex (MCC), by reviewing the anatomical, intrinsic network, neurophysiological, and behavioural properties of MCC. The MCC is the region of the medial wall situated dorsal to the corpus callosum and sometimes referred to as dACC. It is positioned within the densely connected core network of the primate brain, with a rich diversity of cognitive, somatomotor and autonomic connections. The MCC shows strong local network inhibition which appears to control the metastability of the region – an established feature of many cortical networks in which the neural dynamics move through a series of quasi-stationary states. We propose that the strong local inhibition in MCC leads to particularly long dynamic state durations, and so less frequent transitions. Apparently as a result of these anatomical features and synaptic and ionic determinants, the MCC cells display the longest neuronal timescales amongst a range of recorded cortical areas. We conclude that the anatomical position, intrinsic properties, and local network interactions of MCC make it a uniquely positioned cortical area to perform the integration of diverse information over time that is necessary for behavioural adaptation.

Keywords

Cingulate; Timescales; Anterior Cingulate; Midcingulate; Adaptation; Performance monitoring; Inhibition; Metastability

On time and behaviour

Integrating information across time at multiple timescales is a key feature of higher order cognition. Information integration across time permits us to link events and actions separated in time; to draw out useful evidence from a history of behavioural and environmental reactions; and to construct serial, time-extended plans that provide both retrospective and prospective contexts to behaviour. This capacity is thus linked to the fact that the environment itself is structured along multiple timescales. This capacity appears phenomenologically in the structure of behaviours of animal species that have advanced adaptive abilities and problem-solving skills. Primates, for instance, can plan extended routes to seek resources; and they can decide, reorganize, and use detours in the face of intervening events and knowledge acquired from past events (Janmaat et al., 2006; Noser and Byrne, 2007). Certain primates and birds also use the history of interactions with objects to build tools (Gruber et al., 2016). In laboratory settings the ability of monkey species to extract adaptive performance rules over a long task history is well established (Harlow, 1949). These capacities can be considered together as capacities of behavioural adaptation. In its essence, the adaptation of behaviour requires integration of multiple information sources over multiple time scales, to integrate action, outcomes, and episodic information. Adapting to real life situations is mostly non-markovian because the history of behavioural interaction is crucial.

In a highly dynamical system like the brain, performing functions and calculations at multiple concurrent timescales requires specialized algorithms and machinery. This is therefore a difficult task requiring a complex neurobiological implementation, but in highly adaptive species the development of such capacities is clearly worthwhile (Pearson et al., 2014). Several lines of research suggest that certain frontal areas have specific roles in the elaboration of behaviours over long timescales (Passingham and Wise, 2012). In this chapter we collect evidence from multiple domains suggesting that the midcingulate cortex (MCC) of primates contributes to the integration of information over long timescales. We propose that the physiological properties of the MCC network provide the dynamical properties necessary for this temporal integration, and that in turn these properties permit the multiple functions that have been ascribed to MCC, i.e. learning, feedback adaptation, and regulation of exploratory behaviour.

The first lines of evidence for a role of frontal medial cortex regions in temporal integration come from studies focused on adaptive behaviour. Indeed, efficient adaptation relies on extracting knowledge, structures as well as changes, from a series of interactions with the environment. In experimental setups this corresponds learning from outcomes and feedback after a series of choices. In human and non-human primates a large-scale network encompassing frontal and posterior associative cortical areas contribute to adaptive behaviours (Duncan, 2010; Mitchell et al., 2016; Premereur et al., 2018).

Moreover, fMRI consistently reveals activations in one region in the medial wall in relation to outcome monitoring and the apparent regulation of cognitive control (Passingham, 1996; Jueptner et al., 1997; Bush et al., 2002; Kouneiher et al., 2009; Amiez et al., 2012). The region, often named dACC in the primate literature, corresponds to the anatomically defined midcingulate cortex (MCC, see figure). Studies sometimes show extensions of activation into preSMA or SMA and in more or less anterior parts of the MCC, and the dissociation of these activations remains an important task for the field (Amiez et al., 2013). MCC activation is observed when subjects actively seek information and/or rewards, for example when they are exploring or foraging. The MCC seems sensitive to the volatility of the environment, for example to the temporal stability of outcomes, as well as to the propensity of subjects to make choices based on information integrated over multiple trials (Behrens et al., 2007; Meder et al., 2017). The activation of this region in particular during exploratory decisions reveals its particular role in encoding values and prospective information relevant to adaptation (Kolling et al., 2012; 2016b). Studies suggest, then, that evaluation and temporal integration of information in or through the MCC might serve to guide and sustain selected behaviours in the face of current and changing features of the environment (Kolling et al., 2016b).

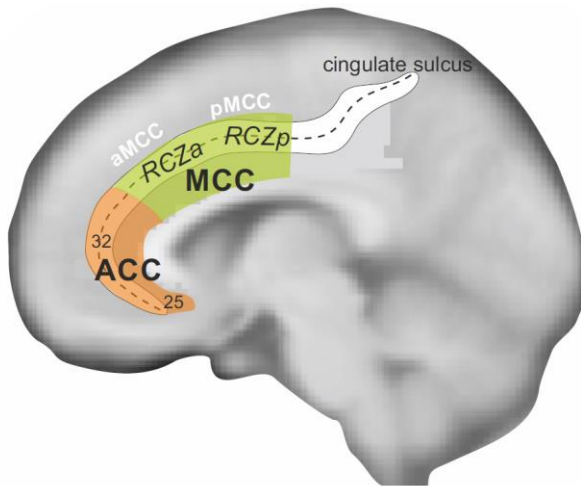


Figure 1. Schematic representation of the cingulate regions MCC and ACC in human (left) and monkey (right). In both species the MCC contains cingulate motor areas, CMAR, CMA and CMV in monkeys, and RCZa and RCZp in humans.

Testing in patients for clinical investigations has provided compelling data on the behavioural effect but also on the subjective feeling induced by electrical

microstimulation of the MCC (Talairach et al., 1973; Parvizi et al., 2013; Caruana et al., 2018). This stimulation regularly leads localized effects on natural goal-directed behaviours like exploratory scanning of the environment with the eyes or the head, tactile search, kneading or palpation directed toward the body or towards nearby objects (Talairach et al., 1973; Caruana et al., 2018). Patients also report general feelings of an urge to act. These results could be interpreted as reflecting MCC contribution to generate the incentive for behaviours directed towards information search. The effects of microstimulation on search-oriented behaviours concern mostly the anterior part of the MCC, the equivalent of CMAR in monkeys.

Studies in human subjects reveal a wide array of correlative roles for the MCC, but there is amongst these a clear case for a role for the MCC in the temporal integration of diverse signals necessary for adaptive behaviour. Our proposition here is that the best way to understand this role, and the way in which seemingly diverse responses emerge from the same region, is to consider in detail the mechanisms within MCC and its position within the anatomical hierarchy. The rest of this chapter therefore considers the evidence, largely from animal studies, for mechanisms of temporal integration in MCC.

The neurobiological source of temporal integration in MCC

Multiple neuroanatomical and physiological features suggest that the MCC holds a special position within the executive and more global networks, and that it is well placed and constructed to integrate diverse information in the temporal domain.

Anatomical specificities of the MCC.

In most monkey recording studies referred to in this chapter, the regions of interest have been the cortex lying within the cingulate sulcus, most often the dorsal bank, and at rostro-caudal levels anterior to the genu of the arcuate sulcus (Procyk et al., 2016). We refer to this region as MCC. The entire MCC region is subject to debate in part because of the multiple versions of labelling used to describe its subdivisions. Regions' names as well as cytoarchitectonic labels are used in different ways across multiple papers, reviews, and even brain atlases. Major labelling issues are the definitions of 'ACC' or '24c', which have evolved. Here we provide a definition of the term MCC we use.

The MCC is an anatomical entity defined by B Vogt and colleagues, based on connectivity, cytoarchitectonics, and receptor mappings. It is

evidenced in humans and monkeys, with putative equivalents in rodents, and it appears to have a separate functional identity (Vogt et al., 1995; Vogt and Paxinos, 2012; Vogt, 2016).

Cytoarchitecture. In humans, the MCC includes the functional subdivision frequently referred to as dACC. It is positioned dorsal to the corpus callosum and, in humans, posterior to the level of the genu of the corpus callosum. MCC cytoarchitecture can be contrasted to the cytoarchitecture of the ACC (anterior cingulate cortex) which is rostral to MCC, and to the cytoarchitecture of the PCC (posterior cingulate cortex). MCC is composed of agranular cortex, which like ACC lacks a granular layer IV (Palomero-Gallagher et al., 2009). In Vogt's nomenclature, MCC includes cytoarchitectonic areas a24c',b', and a', areas p24c',b' and a' as well as area 24d. The posterior part of MCC, containing area 24d, has the largest pyramidal cells which contribute to cingulate spinal projections and form the caudal cingulate motor areas in monkeys. Debates regarding comparative assessments in monkeys and humans relate to the dorsal and anterior parts of the MCC. Anteriorly, the limit with ACC is not clearly identified and could contain an intermediate (rACC) region. The dorsal limit of the sulcus, in terms of architecture and function is also debated (Sallet et al., 2011). Histological work from multiple groups show that indeed the dorsal limit position might vary along the rostral-caudal axis and potentially vary with species and individuals. More precise work is required to solve these issues. In this chapter we include the dorsal bank of the cingulate sulcus because the cytoarchitecture, the connectivity patterns and the extension of cingulate motor areas (see below) suggest an anatomo-functional link to the rest of MCC (Petrides and Pandya, 1994; Sallet et al., 2011; Procyk et al., 2016).

Receptor mapping. In humans and non-human primates, the MCC region and its subdivisions are also characterized by specific patterns of receptor distributions. We cite here two remarkable features. The anterior MCC contains higher levels of dopamine receptor D1 binding in the superficial layers, whereas area 24d has virtually none in superficial and deep layers. Also of note is the relative level of GABAergic receptor mappings: anterior MCC contains relatively lower levels of GABA-B receptors and slightly higher levels of GABA-A, compared to posterior MCC. The distribution of GABA receptors differs also clearly between anterior MCC and ACC (Bozkurt et al., 2005; Palomero-Gallagher et al., 2008; 2009).

MCC in the anatomical hierarchy.

The MCC also sits at a remarkable anatomical position, first within the large-scale network formed by cortical

areas, second within the somato-motor systems, and third in relation to the autonomic system. The large-scale cortical network is, in primates, a system with heterogeneous densities of inter-area connectivity (Markov et al., 2013). It forms a so-called bow-tie organization including a core network with high density (>90%) of connections between areas, linked to side systems by low density connectivity patterns (Markov et al., 2013). The structure has some similarities with the early model of global workspace architecture that contained a central general workspace network connected to hierarchically distant modules processing specific information (Dehaene et al., 1998). Within the core network lies the MCC and its interconnections with the lateral prefrontal cortex, as well as other cortical regions that were shown to form the Multiple-demand network (Duncan, 2013). As we shall see, MCC's position within this architecture, combined with more local intrinsic properties, appears crucial for its functional identity.

The MCC displays other anatomical features that, we think, must be considered to comprehend its functional specificity and contributions to cognition. First the MCC has anatomical links with the sensorimotor system, and contains, in monkeys and humans, two sensorimotor maps named CMAr and CMAc in monkeys (M3 and M4 in Morecraft et al., 1996) and RCZa and RCZp in humans (Picard and Strick, 1996; Amiez and Petrides, 2014). These maps are somatotopically organized and are connected to corresponding fields in supplementary premotor, lateral premotor, motor and spinal regions, with a rostro-caudal gradient displaying more primary and spinal connections posteriorly and more premotor and prefrontal connections anteriorly (Dum and Strick, 1991; He et al., 1995; Dum and Strick, 2002; Loh et al., 2018). Face, eye, upper and lower limbs seem to be represented, with one face representation positioned at the most anterior limit of the MCC. The most rostral and dorsal MCC region has been shown active in multiple studies involving behavioural adaptation in one way or another. The region mentioned in the human brain imaging literature is often referred to as dACC or dmPFC, with terms associated to significantly variable locations of activation within the human brain. In fact, the anterior and posterior subdivisions of the MCC (aMCC and pMCC) seem to be activated differently during cognitive tasks and more precise descriptions of brain activations, potentially on a subject by subject basis, are required to really grasp the functional specificity within this region (Amiez et al., 2013). We have suggested recently that the somatotopic organization of MCC reflects fields devoted to the detection and evaluation of domain-specific feedback relevant for adaptations (Procyk et al., 2016; Loh et al., 2020). Because of the specificity of connectivity

patterns of MCC maps it is possible that they contribute to different functional uses of feedback, i.e. contributing to trigger different adaptive cognitive or behavioural reactions.

Finally, the MCC is, within the medial frontal cortex of primates, one main source and target of connections with the autonomic system. Recent investigations have shown that, contrary to rodents, the primate medial frontal cortex is 3 to 4 synapses away from an organ like the adrenal medulla (Dum et al., 2016; 2019). Neurons trans-synaptically labelled after injection in the adrenal medulla are notably located within the somato-motor fields of the CMAr and CMAc. A review of human brain activations testing covariations of brain activity with autonomic measures showed that the MCC might have subdivisions related to the sympathetic and parasympathetic systems respectively (Amiez and Procyk, 2019).

In sum, the most rostral subdivisions of MCC that contain somatomotor fields also have connections with the lateral prefrontal cortex and with the sympathetic system. Such overlap of cognitive, somatomotor and autonomic connectivity is, we propose, a crucial property of the MCC. This connectivity and position within the cortical core bring rich and diverse inputs to the MCC, permitting it to perform functions that extend beyond any specific modality of information type, in particular favouring an integrative function. Our argument here is that a particularly important part of this role is the integration across time that can be carried out with this diversity of information. Central to this claim is the idea that the intrinsic properties of the cortical cells themselves, the construction of the local circuits, and in particular the nature of local inhibition, allow MCC to perform temporal integration over longer timescales than other cortical regions, and to do so with diverse information provided by its position in the cortical hierarchy.

Intrinsic cortical features of MCC.

The cell physiological properties of MCC can provide clues to its dynamical specificities and position in the temporal hierarchy. Specific physiological data in monkeys for a region at the border between ACC and MCC show that the nature of local inhibition might be an important feature in MCC (Medalla et al., 2017). Spontaneous inhibitory postsynaptic currents are more frequent, long and large in cingulate layer III neurons compared to other prefrontal regions (Medalla et al., 2017). Data from human MCC shows that GABA-B receptors are dense, especially in its posterior part, pMCC (Zilles and Palomero-Gallagher, 2017). Robust inhibition and long inhibitory time constants should

contribute to the extension of the time window for signal summation and thus extend local temporal receptive fields. In artificial hierarchical networks, environmental uncertainty can be dynamically captured by variations of the E/I tone (Pettine et al., 2020). In humans, dynamical integration of environmental uncertainty is circumscribed to the MCC (Behrens et al., 2007). A recent study also linked subjects' ability to integrate information in time and their glutamate and GABA concentrations in the MCC (Scholl et al., 2017). In general terms, inhibition is a strong determinant of network activity (Mongillo et al., 2018). The diversity of synaptic inhibition can flexibly structure network dynamics by gating pyramidal inputs depending on the current task demand (Womelsdorf et al., 2014; Tremblay et al., 2016; Wang, 2020). For example, MCC inhibitory activity has been proposed as a mechanism for transient network disengagement in response to errors (Rothé et al., 2011; Shen et al., 2015). Inhibitory controlled circuits are more robust to excitatory volatility (Mongillo et al., 2018). This robustness might be particularly important for areas receiving converging multimodal inputs, and that need to integrate that information across time. Indeed, there is a macroscopic gradient of synaptic inhibition from sensory cortices to associative areas (Wang, 2020). MCC slow inhibitory decay times generate low frequency rhythmic oscillatory activity (Kopell et al., 2010; Medalla et al., 2017) supporting communication between distant cortical areas (Hahn et al., 2014). MCC excitatory and inhibitory spike trains synchronize to different frequency bands (Voloh and Womelsdorf, 2018). Such cell type specific oscillations could be a means for flexible long-range tuning of coherent network activities according to the current demand. A recent study reported that MCC stimulation elicits recurrent activity in the LPFC (Nácher et al., 2019), an activity pattern that has been associated with working memory temporal maintenance (Mongillo et al., 2018; Wasmuht et al., 2018). In this framework, MCC activity and in particular inhibition would contribute to network synchronisation and structuration of local and distant cortical areas.

We propose therefore that MCC inhibitory tone determines the activity of local units and leads to more stable or slowly evolving network dynamics favouring multimodal associations in the temporal domain. And these properties appear to be particularly exaggerated within MCC relative to other areas of association cortex, placing MCC not just at the heart of the dense core of associative cortical areas (Markov et al., 2013), but also as new analyses and modelling suggest, at the pinnacle of a hierarchy of cortical timescales.

Based on anatomical data and large-scale network modelling, XJ Wang and colleagues have recently shown that the anatomical organization and hierarchies within the large-scale cortical network was accompanied by temporal hierarchies (Murray et al., 2014; Chaudhuri et al., 2015). Individual neuron spiking shows some level of autocorrelation that reflects its propensity to keep a firing mode. The autocorrelation decay, referred to as spiking timescale (Murray et al., 2014), measured at the population level in different areas increases from posterior, sensory, areas to anterior frontal regions, forming a temporal hierarchy. Within the set of areas investigated in this study MCC displayed the longest timescale (about 300ms), compared to LPFC (190ms) or area MT (65 ms) (Murray et al., 2014; Cavanagh et al., 2018). Medial frontal regions also show longer timescales in rats (Murakami et al., 2017). Such differences in timescale might provide areas with different information processing capability, and in particular the capacity to integrate information over long temporal scales, like rewards or feedback encountered across trials of a cognitive task (Bernacchia et al., 2011). Indeed very recent work proposes that cortical dynamics are modulated by a range of timescales, potentially generated by independent mechanisms, some of which directly link to relevant task parameters, whilst others like the general intrinsic timescale remain independent (Spitmaan et al., 2020). Large scale modelling leads to the proposition that the specific timescale of cortical areas emerges both from the large-scale pattern of inter-areal connectivity and from intrinsic properties of areas, including local recurrent excitatory connectivity which was found to increase in density in parallel to the temporal hierarchy (Chaudhuri et al., 2015). Other important features that appear to change across the cortical hierarchy and may relate to these changes in timescale include the ratio $T1w/T2w$ in structural MRI scans, and the level of tonic inhibition (Wang, 2020). We explore indeed the interplay between the macroscopic gradient of synaptic inhibition and timescale hierarchy (possibly via disinhibition; Wang, 2020) in the final section.

The outcome of this work is that the MCC is situated at the core of a cortical network, with the longest neuronal timescale of recorded cortical areas, relatively strong local network inhibition, and a rich diversity of cognitive, somatomotor and autonomic connections. We argue that these are the building blocks for a system whose neurophysiological role will be to integrate diverse signals over time, a role particularly relevant in the context of behavioural adaptation. In the following sections we discuss the neurophysiological correlates of behaviour in MCC and relate them to the properties described above. We propose that the diversity of neural responses in MCC

makes particular sense in the light of this overarching function of temporal integration for adaptation

Neurophysiological and causal correlates of temporal integration in MCC

Neurophysiological studies in rodent and non-human primate models provide details of the neural processes implemented by MCC and reveal neural correlates of the history of outcomes and values in a task, as well as the switching between behavioural states. These point to a role for MCC neurons in functions dedicated to gathering information over time for subsequent regulation of behaviour, a role that a limited number of intervention studies appear to confirm. Similar properties have been observed in the rat medial frontal cortex and while the anatomical correspondence in the rat brain is still in discussion, we will refer here to relevant data from medial frontal cortex (MFC) areas IL, PL and AC (Vogt and Paxinos, 2012; Mars et al., 2018; Schaeffer et al., 2020).

History of outcomes and values.

MCC and MFC single unit activity encodes for reward based action selection in simple tasks in rats, monkeys and humans (Shima and Tanji, 1998; Williams et al., 2004; Sul et al., 2010), but also for the enactment of serial actions where each action is coded relative to future outcomes (Procyk et al., 2000; Procyk and Joseph, 2001; Shidara and Richmond, 2002). Intervention studies in the MCC are rare, but those that exist confirm that MCC is directly contributing to the regulation of decisions based on rewards (Shima and Tanji, 1998; Amiez et al., 2006; Kennerley et al., 2006). Shima and Tanji (1998), for example, showed that neurons in the cingulate motor areas within MCC signalled a reduction of reward that indicated that a change in action should be subsequently chosen, but only when the action was indeed successfully changed. Such activity is necessarily a response to a recent reward history over several trials, rather than a single outcome. The alteration of this MCC activity by local muscimol injection leads to a deterioration in the adaptation of action selection based on the diminishing reward size (Shima and Tanji, 1998). These responses in MCC are therefore driven by more information than the immediate action to be committed - they include information about the temporal context of that action. This temporal context is of course mostly of use to ensure that the action is well adapted, and importantly MCC activity also encodes feedback of actions or choices that is relevant to adaptation, i.e. in situations where action and feedback are the focus of attention and where it can reduce uncertainty.

It is long established that cells in MCC respond to both rewards and errors (Amiez et al., 2005), and that responses to these events are modulated by their predictability and potentially their behavioural relevance (Quilodran et al., 2008). In addition, MCC neurons represent the expected magnitude or the probability of an upcoming reward on trial-and-error learning tasks (Kennerley et al., 2011). So whilst initial reports made a straight link between immediate reward and cell activity, it is now clear that the recent history of reward alters the firing of these cells (Seo and Lee, 2007; Kawai et al., 2015), and that this effect will occur with varying timescales across neurons (Bernacchia et al., 2011). For example, Kawai et al (2015) showed that MCC cells, and in particular putative inhibitory neurons (Kawai et al., 2019), not only maintained the information about the last outcome but also stored outcome experiences from several past trials. MCC cells in this protocol also signalled a subsequent shift in strategy, activity that is discussed in more detail below.

The ability of MCC activity to reflect outcome history has an impact on behaviour. Monkeys with bilateral MCC sulcus lesions have difficulties in integrating and building reward-action history in an uncertain context and in adapting choice behaviour (Kennerley et al., 2006). Effectively the lesion appears to reduce the span over which recent outcomes are used to adjust decisions. MCC appears to have a central role in updating action values based on the outcome history, helping to improve behavioural performance towards a specific goal (Kennerley et al., 2006; Seo et al., 2007). In general therefore these deficits seem to involve a loss of exploratory behaviours – the observed effects appear to combine altered valuation of outcomes and a reduced capacity to integrate the implications of those outcomes over time, the consequence on adaptive behaviour being quite consistent.

Rodent pharmacological inactivation and chemogenetic perturbation also show that medial frontal regions in rats have a causal role in integrating outcome history and in regulating explore/exploit behaviours (Tervo et al., 2020). Indeed, the distributed ensemble dynamics might be tuned by monoaminergic afferents. Noradrenergic (NA) inputs are proposed to contribute to abrupt network reconfiguration and to promote transitions between exploitation and exploration (Bouret and Sara, 2005), and we discuss these state transitions in more detail below. NA inputs to the MCC would allow the dynamical modulation of learning rates (Silvetti et al., 2018). Consistent with those views, selective NA input enhancement in the rat MCC artificially increases behavioural stochasticity and leads to an increase in response variability. In turn, NA input suppression

restores the ability to weight previously received feedback for choice regulation (Tervo et al., 2014).

In addition rare studies can provide information on the effect of cingulotomy in human patients, supporting a role for ongoing behavioural adaptation based on context from prior trials, both in the context of decisions to act (Williams et al., 2004) and in more cognitive contexts where previous trials might provide interfering information (Sheth et al., 2012). Wider lesions to the cingulate region have been reported to lead to global reductions of action and speech, often characterized as akinetic mutism (Németh et al., 1988; Devinsky et al., 1995). Such deficits have been proposed consistent with much of the above evidence if we consider the role of the MCC as acting to motivate time-extended behaviours, rather than driving trial-by-trial adaptations (Holroyd and Yeung, 2012).

Recent work proposes how the MCC goes about using outcome history to drive upcoming behaviour: it is proposed that MCC neurons encode expected outcomes as a latent state representation of actual outcomes (Hyman et al., 2017). The interaction between expected and actual outcome representations on trials where they do not match may drive a dynamical shift that we often record as an error signal. MCC cells certainly do show error signals - they respond to errors in the form of absent rewards (Niki and Watanabe, 1979). Again this error activity is modulated in a manner that reflects the temporal context, for example how much or how close a reward was before the error (Amiez et al., 2005), and indeed cells in MCC also encode both the overall task value in terms of reward, as well as the actual reward obtained (Amiez et al., 2006; Sallet et al., 2007). This activity has a causal impact on behaviour as alteration of local MCC activity by local muscimol injection leads to a loss of efficiency in exploration for more rewarded stimuli in a choice task (Amiez et al., 2006).

These comparative feedback responses translate to the population level, where error- and feedback-related potentials (such as the error-related negativity [ERN] and feedback potentials [FRPs]) have been widely shown to differentiate outcome valences when recorded over the medial part of the frontal lobe in electroencephalography (EEG) (Gehring et al., 1993; Falkenstein et al., 2001; Miltner et al., 2001), electrocorticography (EcoG, (Wilson et al., 2016)), and the local field potential (LFP) (Gemba et al., 1986). Of course these are not standalone signals, rather they appear to provide information about the value of the feedback in terms of behavioural adaptation, be it for directly driving adaptation on subsequent trials (Shima and Tanji, 1998; Quilodran et al., 2008; Khamassi et al., 2015; Monosov, 2017), or for motivating more extended behaviours beyond simple trial-to-trial adaptation (Walsh and Anderson, 2011; Holroyd and Yeung, 2012). It is this

concept of time-extended behaviours that is of particular relevance here, therefore, and it is this time-extended information that is necessary to signal the necessity to change state or strategy in a task.

Neural and behavioural state switches.

Monkey MCC and rat MFC show phasic neural changes at behaviourally relevant events together with global neural state changes between different behavioural states or strategies separated by switches, like exploratory behaviour and repetitive behaviour (Karlsson et al., 2012; Enel et al., 2016). For example MCC neurons signal behavioural shifts on subsequent trials (Kawai et al., 2015), whilst neural signals anticipating and signalling patch leaving or strategy switching in sequential foraging tasks are observed in phasic unitary and high-gamma activities in both primates and rodents (Quilodran et al., 2008; Rothé et al., 2011; Karlsson et al., 2012). Powell and Redish (2016) showed that on tasks where a reward criterion change was imposed, rats showed state transitions of MFC activity after they had learned about that contingency change, but before their behaviour changed. In contrast, when rats were permitted to change strategies themselves (i.e. without imposed criterion changes), similar state transitions occurred before changes in behaviour, therefore in a manner predictive of this un-imposed strategy switch (Powell and Redish, 2016). This implies that the MFC is signalling the need for a change in strategy, rather than passively reflecting such a change.

Across a range of studies, a picture emerges where the neural dynamics of MCC correlate with the state of uncertainty inherent to exploratory situations and the control or monitoring of information seeking behaviour (Stoll et al., 2016; White et al., 2019). In addition, MCC activity has strong correlation with valuation processes - a multiplicity of signals reflect dynamical information accumulation in the MCC (Kennerley et al., 2011; Hunt et al., 2018). These signals are absent from OFC and LPFC activities. This integrated information is therefore used to make the decision to maintain or change the current course of action (Quilodran et al., 2008; Mansouri et al., 2009; Khamassi et al., 2015; Stoll et al., 2016).

Hayden et al 2011 found that neural activity during foraging scaled with the value of leaving the current exploited option and reflected an integrate-to-threshold process built across trials and leading to patch leaving (Hayden et al., 2011). Accumulation processes are observed in other frontal areas such as the FEF but they are continuous and ramp within trials, i.e. over a short timescale (Hanes and Schall, 1996). It is tempting to think that the specific neural dynamics observed during exploration or foraging provide the MCC with neural state

properties that favour integration of information across time, i.e. over long timescales.

The way these correlated activity states are expressed over time is an important feature of encoding in MCC and across the frontal cortex. It may be that the capacity to shift neural state is an intrinsic feature of these cortical architectures, perhaps independent of external stimuli or constraints, which is then tuned to the needs of any ongoing task. An interesting and open question in the field is therefore how these properties are harnessed for the functional uses we ascribe to them, and a starting point is to consider how general this dynamic shifting of neural state is in MCC.

For example, we described above that information about feedback is encoded in the MCC, but this encoding occurs dynamically within the time course of a trial, starting just before outcome delivery until the next decision is made (Stoll et al., 2016; Hunt et al., 2018). The term dynamic here refers to the idea that information encoding changes over time, such that a decoder that can decode some behavioural variable from neural data at one period in time is no longer able to decode the same information later in time, while the variable is still encoded by the neural activity. In this sense the encoding is dynamic. The question of whether representations in MCC are dynamic or stable over time depends on the timescale in question, but it is increasingly clear that frontal cortical regions inherently combine elements of stable and dynamic coding. For example values in MCC are represented by mixed activity regimes composed of a stable subspace and a dynamic ensemble (Enel et al., 2020). This configuration grants the system a level of flexibility - a substrate of sustained information which can be combined with time-sensitive representations. The combination of both representations is likely crucial for the organization of behaviours in time and resembles the properties of delay activity much discussed regarding lateral prefrontal cortex (Cavanagh et al., 2018; Miller et al., 2018).

It is becoming increasingly clear that there is a distinct organization in this combination of stable and dynamic coding regimes. For example, Stoll et al (2016) used cross-temporal decoding of MCC activity to show semi-stable codes of feedback and decisions that carry over inter trial periods during foraging tasks. This appears to be particularly the case when, as in this study, decisions rely on the history of previous choices. MCC activity in this case can be considered as a set of trajectories organized in a sequence of discrete quasi-stationary states. This organization of activities in time is referred to as metastability (Durstewitz et al., 2010; La Camera et al., 2019). States can be organized around key perceptual

and motor events or structured by ensemble activity regimes independently from external cues.

Metastability has been observed in other cortical areas and is proposed to form a neuronal substrate for specific internal representations of the environment (Rich and Wallis, 2016; La Camera et al., 2019). State stability is believed to reflect internal representations and the deployment of selective attention required for the current task demand (Engel et al., 2016). Transitions are more frequent when representations of internal rules are susceptible to change and are marked by an abrupt shift of dynamics in distributed neuronal ensemble (Durstewitz et al., 2010).

How might these metastable states be used to promote the functions of MCC? There are likely to be several answers to this question, again depending on the temporal scale of investigation. Value signalling in the MCC reflects temporal integration of experienced rewards (Amiez et al., 2006; Hunt et al., 2018) while also monitoring counterfactual options (Hayden et al., 2009; Kolling et al., 2016a), and network transitions occur in periods when internal states are being updated and actively monitored. So, state transitions may well represent shifts in belief based on the same weighting of prior evidence and current outcomes. For example such state transitions would be signalling a shift to a more exploratory strategy of choice (Karlsson et al., 2012). Indeed, in foraging tasks, MCC trajectories describe two pseudo attractor spaces reflecting the structure of the task that alternates between phases of behavioural exploration and exploitation. Here state-space transitions are triggered by the monitoring of specific events such as feedback that reflect the need to adapt strategy (Quilodran et al., 2008; Enel et al., 2016).

Inhibitory control of MCC metastable states

Our most recent work provides direct evidence on how local intrinsic properties and timescales of MCC cells cause metastability, suggesting how such dynamical properties contribute to the role of MCC in adaptive behaviour (Fontanier et al., 2020). We studied the temporal signatures, specifically the auto correlogram time constant and latency, of single neurons in monkey MCC and lateral prefrontal cortex (LPFC), recorded during a decision-making task. As suggested by Murray and colleagues (Murray et al., 2014), cells demonstrated a longer intrinsic timescale in the MCC than LPFC. We then showed that the temporal signatures were highly structured, showing anatomical organization within the MCC, and specific cell-type differences in the auto

correlogram features between fast and regular spiking neurons.

Importantly the timescales of certain neurons showed functional adaptation to the timescale of behaviourally relevant information in the task at hand. In MCC and for regular spiking neurons only, we observed that on average timescales of the neurons lengthened when the monkeys were engaged in the task, compared to when they were pausing from the task. In addition, we showed that both the neuron-type and the timescale of that neuron within that type were determinant of the contribution of that neuron to encoding important behavioural features of the task, like reward feedback provided after choices (particularly putative interneurons for negative feedback), or value related information used across multiple trials (Fontanier et al 2020).

We then used these data to inform research using biophysically constrained network models to link back to the inhibitory properties discussed above. This work revealed that specific cellular conductances in the modelled cells (specifically intrinsic after-hyperpolarization (AHP) potassium and synaptic inhibitory GABA-B conductances) were critical determinants of the specificity of dynamics of MCC and LPFC. These features were sufficient to provide a causal account for temporal signatures. Intriguingly, these conductances drove the cells to the recorded timescales by organizing activity into metastable states, with inhibition controlling state stability and transitions. Our model predicted therefore that the state duration in this metastable system would scale non-linearly with the timescales of different cortical regions, and we provided strong evidence to support this prediction from the monkey neurophysiological data, even reaching behavioural timescales. Our proposition on the basis of this work, therefore, is that inhibitory-controlled metastability constitutes the central dynamical process of MCC network function, locally specifying the temporal organization underlying cognitive processes operated by frontal areas.

Conclusion

The MCC, the region of the medial wall situated dorsal to the corpus callosum and sometimes referred to as dACC, is positioned within the densely connected core network of the primate brain, and has a rich diversity of cognitive, somatomotor and autonomic connections. The MCC shows strong local network inhibition in particular driven by GABA-B activity. This inhibition appears to control the metastability of the region – an established feature of many cortical networks in which the neural dynamics move through a series of quasi-stationary states with jump-like modulations between them. In

particular it is proposed that the strong local inhibition in MCC leads to particularly long dynamic state durations, and so less frequent transitions, with the duration of these states even approaching the timescale of behavioural phenomena. Apparently as a result of these anatomical features and synaptic and ionic determinants, the MCC cells display the longest neuronal timescales amongst a range of recorded cortical areas.

We have argued that the anatomical position, intrinsic properties, and local network interactions of MCC make it a uniquely positioned cortical area to perform the integration of diverse information over time that is necessary for behavioural adaptation. The functional role of the MCC is therefore defined by these properties and we consider it a single central function. The MCC will perform this integrative function on different information types that arrive, given its rich connectivity. Performing the same integrative function on different incoming types of information will lead to a diversity of behavioural correlates. Whilst one reading of the literature might be that these diverse behavioural correlates mean that MCC has many different cognitive functions, we underline that the evidence presented above suggests that the operation performed by MCC itself is a single underlying function common to different cognitive labels.

This proposal leaves of course many important questions to be addressed. The neurobiological source of these temporal features, and the contribution of the place

within the cortical hierarchy remain to be further examined. We also need to better understand the extent to which the variations in metastability and timescale are causal of the functions of MCC and other regions, or whether in fact those features result from adaptation to the context. Are these intrinsic properties that are applied to different functional uses, or are these properties tuned to fit the task in hand? Studies during task acquisition will be crucial here. Regions like the MCC do not, of course, act independently but as part of a densely connected network, for example showing interaction with LPFC. As such there remain questions to be answered about how regions with differing timescales and differing dynamic regimes can interact in a manner that permits computations that are relevant for cognition.

The purpose of this chapter was to elaborate a synthesis of data from multiple levels of investigation, in order to seek a coherent multi-scale view of the function of the midcingulate cortex. While many pieces of information are still required from anatomical, biophysical, neurophysiological and behavioural experiments, the recent data suggest that the synaptic and cellular properties, the local network configuration as well as the embedding of MCC in specific large scale functional networks provide this region with capabilities relevant to the regulation and adaptation of behaviour over long time scales.

References

- Amiez C, Joseph J-P, Procyk E (2005) Anterior cingulate error-related activity is modulated by predicted reward. *The European Journal of Neuroscience* 21:3447–3452.
- Amiez C, Joseph J-P, Procyk E (2006) Reward encoding in the monkey anterior cingulate cortex. *Cereb Cortex* 16:1040–1055.
- Amiez C, Neveu R, Warrot D, Petrides M, Knoblauch K, Procyk E (2013) The Location of Feedback-Related Activity in the Midcingulate Cortex Is Predicted by Local Morphology. *Journal of Neuroscience* 33:2217–2228.
- Amiez C, Petrides M (2014) Neuroimaging Evidence of the Anatomic-Functional Organization of the Human Cingulate Motor Areas. *Cerebral Cortex* 24:563–578.
- Amiez C, Procyk E (2019) Midcingulate somatomotor and autonomic functions. In: *Handbook of Clinical Neurology*, 1st ed. (Vogt BA, ed), pp 53–71. Elsevier B.V.
- Amiez C, Sallet J, Procyk E, Petrides M (2012) Modulation of feedback related activity in the rostral anterior cingulate cortex during trial and error exploration. *NeuroImage* 63:1078–1090.
- Behrens TEJ, Woolrich MW, Walton ME, Rushworth MFS (2007) Learning the value of information in an uncertain world. *Nat Neurosci* 10:1214–1221.
- Bernacchia A, Seo H, Lee D, Wang X-J (2011) A reservoir of time constants for memory traces in cortical neurons. *Nat Neurosci* 14:366–372.
- Bouret S, Sara SJ (2005) Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. *Trends Neurosci* 28:574–582.
- Bozkurt A, Zilles K, Schleicher A, Kamper L, Arigita ES, Uylings HBM, Kötter R (2005) Distributions of transmitter receptors in the macaque cingulate cortex. *NeuroImage* 25:219–229.
- Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, Rosen BR (2002) Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proc Natl Acad Sci USA* 99:523–528.
- Caruana F, Gerbella M, Avanzini P, Gozzo F, Pelliccia V, Mai R, Abdollahi RO, Cardinale F, Sartori I, Russo Lo G, Rizzolatti G (2018) Motor and emotional behaviours

- elicited by electrical stimulation of the human cingulate cortex. *Brain* 24:563–17.
- Cavanagh SE, Towers JP, Wallis JD, Hunt LT, Kennerley SW (2018) Reconciling persistent and dynamic hypotheses of working memory coding in prefrontal cortex. *Nature Communications* 9:1–16.
- Chaudhuri R, Knoblauch K, Gariel M-A, Kennedy H, Wang X-J (2015) A Large-Scale Circuit Mechanism for Hierarchical Dynamical Processing in the Primate Cortex. *Neuron* 88:419–431.
- Dehaene S, Kerszberg M, Changeux JP (1998) A neuronal model of a global workspace in effortful cognitive tasks. *Proc Natl Acad Sci USA* 95:14529–14534.
- Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulate cortex to behaviour. *Brain* 118 (Pt 1):279–306.
- Dum RP, Levinthal DJ, Strick PL (2016) Motor, cognitive, and affective areas of the cerebral cortex influence the adrenal medulla. *Proceedings of the National Academy of Sciences*:201605044.
- Dum RP, Levinthal DJ, Strick PL (2019) The mind-body problem: Circuits that link the cerebral cortex to the adrenal medulla. *Proceedings of the National Academy of Sciences* 116:26321–26328.
- Dum RP, Strick PL (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci* 11:667–689.
- Dum RP, Strick PL (2002) Motor areas in the frontal lobe of the primate. *Physiol Behav* 77:677–682.
- Duncan J (2010) The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn Sci (Regul Ed)* 14:172–179.
- Duncan J (2013) The Structure of Cognition:Attentional Episodes in Mind and Brain. *Neuron* 80:35–50.
- Durstewitz D, Vitoz NM, Floresco SB, Seamans JK (2010) Abrupt transitions between prefrontal neural ensemble states accompany behavioral transitions during rule learning. *Neuron* 66:438–448.
- Enel P, Procyk E, Quilodran R, Dominey PF (2016) Reservoir Computing Properties of Neural Dynamics in Prefrontal Cortex O'Reilly JX, ed. *PLoS Comput Biol* 12:e1004967.
- Enel P, Wallis JD, Rich EL (2020) Stable and dynamic representations of value in the prefrontal cortex. *Elife* 9:1040.
- Engel TA, Steinmetz NA, Gieselmann MA, Thiele A, Moore T, Boahen K (2016) Selective modulation of cortical state during spatial attention. *Science* 354:1140–1144.
- Falkenstein M, Hielscher H, Dziobek I, Schwarzenau P, Hoormann J, Sunderman B, Hohsbein J (2001) Action monitoring, error detection, and the basal ganglia: an ERP study. *Neuroreport* 12:157–161.
- Fontanier V, Sarazin M, Stoll FM, Delord B, Procyk E (2020) Local inhibitory control of frontal network metastability underlies the temporal signature of cognitive states. *bioRxiv* 28:319.
- Gehring WJ, Goss B, Coles M, Meyer DE (1993) A neural system for error detection and compensation. *Psychological ...*
- Gemba H, Sasaki K, Brooks VB (1986) “Error” potentials in limbic cortex (anterior cingulate area 24) of monkeys during motor learning. *Neurosci Lett* 70:223–227.
- Gruber T, Zuberbühler K, Neumann C (2016) Travel fosters tool use in wild chimpanzees. *Elife* 5:93.
- Hahn G, Bujan AF, Frégnac Y, Aertsen A, Kumar A (2014) Communication through Resonance in Spiking Neuronal Networks Brunel N, ed. *PLoS Comput Biol* 10:e1003811–e1003816.
- Hanes DP, Schall JD (1996) Neural control of voluntary movement initiation. *Science* 274:427–430.
- Harlow HF (1949) The formation of learning sets. *Psychol Rev* 56:51–65.
- Hayden BY, Pearson JM, Platt ML (2009) Fictive reward signals in the anterior cingulate cortex. *Science* 324:948–950.
- Hayden BY, Pearson JM, Platt ML (2011) Neuronal basis of sequential foraging decisions in a patchy environment. *Nat Neurosci* 14:933–939.
- He SQ, Dum RP, Strick PL (1995) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere. *J Neurosci* 15:3284–3306.
- Holroyd CB, Yeung N (2012) Motivation of extended behaviors by anterior cingulate cortex. *Trends Cogn Sci (Regul Ed)* 16:122–128.
- Hunt LT, Malalasekera WMN, Berker AO, Miranda B, Farmer SF, Behrens TEJ, Kennerley SW (2018) Triple dissociation of attention and decision computations across prefrontal cortex. *Nat Neurosci* 21:1–17.
- Hyman JM, Holroyd CB, Seamans JK (2017) A Novel Neural Prediction Error Found in Anterior Cingulate Cortex Ensembles. *Neuron* 95:447–456.e3.
- Janmaat KRL, Byrne RW, Zuberbühler K (2006) Primates Take Weather into Account when Searching for Fruits. *Current Biology* 16:1232–1237.
- Jueptner M, Stephan KM, Frith CD, Brooks DJ, Frackowiak RS, Passingham RE (1997) Anatomy of motor learning. I. Frontal cortex and attention to action. *J Neurophysiol* 77:1313–1324.
- Karlsson MP, Tervo DGR, Karpova AY (2012) Network Resets in Medial Prefrontal Cortex Mark the Onset of Behavioral Uncertainty. *Science* 338:135–139.

- Kawai T, Yamada H, Sato N, Takada M, Matsumoto M (2015) Roles of the Lateral Habenula and Anterior Cingulate Cortex in Negative Outcome Monitoring and Behavioral Adjustment in Nonhuman Primates. *Neuron*:1–16.
- Kawai T, Yamada H, Sato N, Takada M, Matsumoto M (2019) Preferential Representation of Past Outcome Information and Future Choice Behavior by Putative Inhibitory Interneurons Rather Than Putative Pyramidal Neurons in the Primate Dorsal Anterior Cingulate Cortex. *Cereb Cortex* 29:2339–2352.
- Kennerley SW, Behrens TEJ, Wallis JD (2011) Double dissociation of value computations in orbitofrontal and anterior cingulate neurons. *Nat Neurosci*.
- Kennerley SW, Walton ME, Behrens TEJ, Buckley MJ, Rushworth MFS (2006) Optimal decision making and the anterior cingulate cortex. *Nat Neurosci* 9:940–947.
- Khamassi M, Quilodran R, Enel P, Dominey PF, Procyk E (2015) Behavioral Regulation and the Modulation of Information Coding in the Lateral Prefrontal and Cingulate Cortex. *Cereb Cortex* 25:3197–3218.
- Kolling N, Behrens T, Wittmann MK, Rushworth M (2016a) ScienceDirect Multiple signals in anterior cingulate cortex. *Curr Opin Neurobiol* 37:36–43.
- Kolling N, Behrens TEJ, Mars RB, Rushworth MFS (2012) Neural Mechanisms of Foraging. *Science* 336:95–98.
- Kolling N, Wittmann MK, Behrens TEJ, Boorman ED, Mars RB, Rushworth MFS (2016b) Value, search, persistence and model updating in anterior cingulate cortex. *Nat Neurosci* 19:1280–1285.
- Kopell N, Kramer MA, Malerba P, Whittington MA (2010) Are Different Rhythms Good for Different Functions? *Front Hum Neurosci* 4:1–9.
- Kouneiher F, Charron S, Koehlin E (2009) Motivation and cognitive control in the human prefrontal cortex. *Nat Neurosci* 12:939–945.
- La Camera G, Fontanini A, Mazzucato L (2019) Cortical computations via metastable activity. *Curr Opin Neurobiol* 58:37–45.
- Loh KK, Hadj-Bouziane F, Petrides M, Procyk E, Amiez C (2018) Rostro-Caudal Organization of Connectivity between Cingulate Motor Areas and Lateral Frontal Regions. *Frontiers in Neuroscience* 11:13786–17.
- Loh KK, Procyk E, Neveu R, Lambertson F, Hopkins WD, Petrides M, Amiez C (2020) Cognitive control of orofacial motor and vocal responses in the ventrolateral and dorsomedial human frontal cortex. *Proceedings of the National Academy of Sciences* 117:4994–5005.
- Mansouri FA, Tanaka K, Buckley MJ (2009) Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex. *Nat Rev Neurosci* 10:141–152.
- Markov NT, Ercsey-Ravasz M, Van Essen DC, Knoblauch K, Toroczkai Z, Kennedy H (2013) Cortical high-density counterstream architectures. *Science* 342:1238406.
- Mars RB, Sotiropoulos SN, Passingham RE, Sallet J, Verhagen L, Khrapitchev AA, Sibson N, Jbabdi S (2018) Whole brain comparative anatomy using connectivity blueprints. *Elife* 7:870.
- Medalla M, Gilman JP, Wang J-Y, Luebke JI (2017) Strength and Diversity of Inhibitory Signaling Differentiates Primate Anterior Cingulate from Lateral Prefrontal Cortex. *J Neurosci* 37:4717–4734.
- Meder D, Kolling N, Verhagen L, Wittmann MK, Scholl J, Madsen KH, Hulme OJ, Behrens TEJ, Rushworth MFS (2017) Simultaneous representation of a spectrum of dynamically changing value estimates during decision making. *Nature Communications* 8:1–11.
- Miller EK, Lundqvist M, Bastos AM (2018) Working Memory 2.0. *Neuron* 100:463–475.
- Miltner WHR, Braun CH, Coles MGH (2001) Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a “generic” neural system for error detection. *Journal of Cognitive Neuroscience* 9:788–798 Available at: <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23964600&retmode=ref&cmd=prlinks>.
- Mitchell DJ, Bell AH, Buckley MJ, Mitchell AS, Sallet J, Duncan J (2016) A Putative Multiple-Demand System in the Macaque Brain. *Journal of Neuroscience* 36:8574–8585.
- Mongillo G, Rumpel S, Loewenstein Y (2018) Inhibitory connectivity defines the realm of excitatory plasticity. *Nat Neurosci*:1–14.
- Monosov IE (2017) Anterior cingulate is a source of valence-specific information about value and uncertainty. *Nature Communications*:1–11.
- Morecraft RJ, Schroeder CM, Keifer J (1996) Organization of face representation in the cingulate cortex of the rhesus monkey. *Neuroreport* 7:1343–1348.
- Murakami M, Shteingart H, Loewenstein Y, Mainen ZF (2017) Distinct Sources of Deterministic and Stochastic Components of Action Timing Decisions in Rodent Frontal Cortex. *Neuron* 94:908–919.e7.
- Murray JD, Bernacchia A, Freedman DJ, Romo R, Wallis JD, Cai X, Padoa-Schioppa C, Pasternak T, Seo H, Lee D, Wang X-J (2014) A hierarchy of intrinsic timescales across primate cortex. *Nat Neurosci* 17:1661–1663.
- Nächer V, Hassani SA, Womelsdorf T (2019) Asymmetric effective connectivity between primate anterior cingulate and lateral prefrontal cortex revealed by electrical microstimulation. *Brain Struct Funct* 224:779–793.

- Németh G, Hegedüs K, Molnár L (1988) Akinetic mutism associated with bicingular lesions: clinicopathological and functional anatomical correlates. *Eur Arch Psychiatry Neurol Sci* 237:218–222.
- Niki H, Watanabe M (1979) Prefrontal and cingulate unit activity during timing behavior in the monkey. *Brain Res* 171:213–224.
- Noser R, Byrne RW (2007) Mental maps in chacma baboons (*Papio ursinus*): using inter-group encounters as a natural experiment. *Anim Cogn* 10:331–340.
- Palomero-Gallagher N, Mohlberg H, Zilles K, Vogt B (2008) Cytology and receptor architecture of human anterior cingulate cortex. *J Comp Neurol* 508:906–926.
- Palomero-Gallagher N, Vogt BA, Schleicher A, Mayberg HS, Zilles K (2009) Receptor architecture of human cingulate cortex: Evaluation of the four-region neurobiological model. *Hum Brain Mapp* 30:2336–2355.
- Parvizi J, Rangarajan V, Shirer WR, Desai N, Greicius MD (2013) The will to persevere induced by electrical stimulation of the human cingulate gyrus. *Neuron* 80:1359–1367.
- Passingham RE (1996) Attention to action. *Philos Trans R Soc Lond, B, Biol Sci* 351:1473–1479.
- Passingham RE, Wise SP (2012) *The Neurobiology of the Prefrontal Cortex: Anatomy, Evolution, and the Origin of Insight*. OUP Oxford.
- Pearson JM, Watson KK, Platt ML (2014) Decision Making: The Neuroethological Turn. *Neuron* 82:950–965.
- Petrides M, Pandya DN (1994) Comparative architectonic analysis of the human and the macaque frontal cortex. In: *Handbook of Neuropsychology*. (Boller F, Grafman J, eds), pp 17–58. Amsterdam.
- Pettine WW, Louie K, Murray JD, Wang X-J (2020) Hierarchical Network Model Excitatory-Inhibitory Tone Shapes Alternative Strategies for Different Degrees of Uncertainty in Multi-Attribute Decisions. *bioRxiv*.
- Picard N, Strick PL (1996) Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* 6:342–353.
- Powell NJ, Redish AD (2016) Representational changes of latent strategies in rat medial prefrontal cortex precede changes in behaviour. *Nature Communications* 7:12830.
- Premereur E, Janssen P, Vanduffel W (2018) Functional MRI in Macaque Monkeys during Task Switching. *Journal of Neuroscience* 38:10619–10630.
- Procyk E, Joseph J-P (2001) Characterization of serial order encoding in the monkey anterior cingulate sulcus. *The European Journal of Neuroscience* 14:1041–1046.
- Procyk E, Tanaka YL, Joseph J-P (2000) Anterior cingulate activity during routine and non-routine sequential behaviors in macaques. *Nat Neurosci* 3:502–508.
- Procyk E, Wilson CRE, Stoll FM, Faraut MCM, Petrides M, Amiez C (2016) Midcingulate Motor Map and Feedback Detection: Converging Data from Humans and Monkeys. *Cereb Cortex* 26:467–476.
- Quilodran R, Rothé M, Procyk E (2008) Behavioral Shifts and Action Valuation in the Anterior Cingulate Cortex. *Neuron* 57:314–325.
- Rich EL, Wallis JD (2016) Decoding subjective decisions from orbitofrontal cortex. *Nat Neurosci* 19:973–980.
- Rothé M, Quilodran R, Sallet J, Procyk E (2011) Coordination of High Gamma Activity in Anterior Cingulate and Lateral Prefrontal Cortical Areas during Adaptation. *Journal of Neuroscience* 31:11110–11117.
- Sallet J, Mars RB, Quilodran R, Procyk E, Petrides M, Rushworth MF (2011) **Neuroanatomical Basis of Motivational and Cognitive Control: A Focus on the Medial and Lateral Prefrontal Cortex**. In: *Neural Basis of Motivational and Cognitive Control* (Mars RB, Sallet J, Rushworth MFS, Yeung N, eds). The MIT Press.
- Sallet J, Quilodran R, Rothé M, Vezoli J, Joseph J-P, Procyk E (2007) Expectations, gains, and losses in the anterior cingulate cortex. *Cogn Affect Behav Neurosci* 7:327–336.
- Schaeffer DJ, Hori Y, Gilbert KM, Gati JS, Menon RS, Everling S (2020) Divergence of rodent and primate medial frontal cortex functional connectivity. *Proceedings of the National Academy of Sciences* 5:202003181–202021689.
- Scholl J, Kolling N, Nelissen N, Stagg CJ, Harmer CJ (2017) Excitation and inhibition in anterior cingulate predict use of past experiences. *Elife*.
- Seo H, Barraclough DJ, Lee D (2007) Dynamic signals related to choices and outcomes in the dorsolateral prefrontal cortex. *Cereb Cortex* 17 Suppl 1:i110–i117.
- Seo H, Lee D (2007) Temporal filtering of reward signals in the dorsal anterior cingulate cortex during a mixed-strategy game. *Journal of Neuroscience* 27:8366–8377.
- Shen C, Ardid S, Kaping D, Westendorff S, Everling S, Womelsdorf T (2015) Anterior Cingulate Cortex Cells Identify Process-Specific Errors of Attentional Control Prior to Transient Prefrontal-Cingulate Inhibition. *Cereb Cortex* 25:2213–2228.
- Sheth SA, Mian MK, Patel SR, Asaad WF, Williams ZM, Dougherty DD, Bush G, Eskandar EN (2012) Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. *Nature* 488:218–221.
- Shidara M, Richmond BJ (2002) Anterior cingulate: single neuronal signals related to degree of reward expectancy. *Science* 296:1709–1711.

- Shima K, Tanji J (1998) Role for cingulate motor area cells in voluntary movement selection based on reward. *Science* 282:1335–1338.
- Silvetti M, Vassena E, Abrahamse E, Verguts T (2018) Dorsal anterior cingulate-brainstem ensemble as a reinforcement meta-learner. O'Reilly J, ed. *PLoS Comput Biol* 14:e1006370–32.
- Spitmaan M, Seo H, Lee D, Soltani A (2020) Multiple timescales of neural dynamics and integration of task-relevant signals across cortex. *Proc Natl Acad Sci USA* 21:202005993–10.
- Stoll FM, Fontanier V, Procyk E (2016) Specific frontal neural dynamics contribute to decisions to check. *Nature Communications* 7:11990.
- Sul JH, Kim H, Huh N, Lee D, Jung MW (2010) Distinct roles of rodent orbitofrontal and medial prefrontal cortex in decision making. *Neuron* 66:449–460.
- Talairach J, Bancaud J, Geier S, Bordas-Ferrer M, Bonis A, Szikla G, Rusu M (1973) The cingulate gyrus and human behaviour. *Electroencephalogr Clin Neurophysiol* 34:45–52.
- Tervo D, Kuleshova E, Manakov M, Proskurin M, Karlsson M, Lustig A, Behnam R, Karpova AY (2020) Anterior Cingulate Cortex Directs Exploration of Alternative Strategies. *bioRxiv*.
- Tervo DGR, Proskurin M, Manakov M, Kabra M, Vollmer A, Branson K, Karpova AY (2014) Behavioral Variability through Stochastic Choice and Its Gating by Anterior Cingulate Cortex. *Cell* 159:21–32.
- Tremblay R, Lee S, Rudy B (2016) GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits. *Neuron* 91:260–292.
- Vogt BA (2016) Journal of Chemical Neuroanatomy. *Journal of Chemical Neuroanatomy* 74:28–46.
- Vogt BA, Nimchinsky EA, Vogt LJ, Hof PR (1995) Human cingulate cortex: surface features, flat maps, and cytoarchitecture. *J Comp Neurol* 359:490–506.
- Vogt BA, Paxinos G (2012) Cytoarchitecture of mouse and rat cingulate cortex with human homologies. *Brain Struct Funct* 219:185–192.
- Voloh B, Womelsdorf T (2018) Cell-Type Specific Burst Firing Interacts with Theta and Beta Activity in Prefrontal Cortex During Attention States. *Cereb Cortex* 28:4348–4364.
- Walsh MM, Anderson JR (2011) Modulation of the feedback-related negativity by instruction and experience.
- Wang X-J (2020) Macroscopic gradients of synaptic excitation and inhibition in the neocortex. *Nat Rev Neurosci*:1–10.
- Wasmuht DF, Spaak E, Buschman TJ, Miller EK, Stokes MG (2018) Intrinsic neuronal dynamics predict distinct functional roles during working memory. *Nature Communications* 9:1–13.
- White JK, Bromberg-Martin ES, Heilbronner SR, Zhang K, Pai J, Haber SN, Monosov IE (2019) A neural network for information seeking. *Nature Communications* 10:1–19.
- Williams ZM, Bush G, Rauch SL, Cosgrove GR, Eskandar EN (2004) Human anterior cingulate neurons and the integration of monetary reward with motor responses. *Nat Neurosci* 7:1370–1375.
- Wilson CRE, Vezoli J, Stoll FM, Faraut MCM, Leviel V, Knoblauch K, Procyk E (2016) Prefrontal Markers and Cognitive Performance Are Dissociated during Progressive Dopamine Lesion. *PLoS Biol* 14:e1002576.
- Womelsdorf T, Valiante TA, Sahin NT, Miller KJ, Tiesinga P (2014) Dynamic circuit motifs underlying rhythmic gain control, gating and integration. *Nat Neurosci* 17:1031–1039.
- Zilles K, Palomero-Gallagher N (2017) Multiple Transmitter Receptors in Regions and Layers of the Human Cerebral Cortex. *Front Neuroanat* 11:e1000489–26.