Oscillations as a window into neuronal mechanisms underlying dorsal anterior cingulate cortex function

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Abstract

The function of dorsal Anterior Cingulate Cortex (dACC) remains poorly understood. While many methods, spanning bottom-up and top-down approaches, have been deployed, the view they offer is often conflicting. Integrating bottom-up and top-down approaches requires an intermediary with sufficient explanatory power, theoretical development, and empirical support. Oscillations in the local field potential (LFP) provide such a link. LFP oscillations arise from empirically well-characterized neuronal circuit motifs. Synchronizing the firing of individual units has appealing properties to bind disparate brain regions and propagate information, including gating, routing, and

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coding. Moreover, the LFP, rather than single unit activity, more closely relates to macroscale recordings, such as the electroencephalogram and functional magnetic resonance imaging. Thus, LFP oscillations are a critical link that allow for the inference of neuronal micro-circuitry underlying macroscopic brain recordings.

1. Introduction

The dorsal anterior cingulate cortex (dACC) is an enigmatic structure located on the medial wall of the cerebral cortex. It is associated with executive control, learning, adjustment, economic choice, and self-control (Heilbronner & Hayden, 2016; Morecraft et al., 2012; Paus, 2001; Shenhav et al., 2017). It has prominent anatomical connections to other structures in the prefrontal cortex, including the orbitofrontal cortex and pre/motor structures, as well as to the amygdala (Barbas & Pandya, 1989; Morecraft et al., 2012; Vogt & Pandya, 1987). It even includes direct connections to the spinal cord, as well as the hypothalamus, suggesting a role in autonomic control (Passingham & Wise, 2012). Dysregulation of the dACC is associated with several psychiatric diseases, including depression, obsessive compulsive disorder, and drug addiction, and it has been argued to play a central role in integrating and communicating information across the cortex (Goodkind et al., 2015).

Like other brain structures, dACC is amenable to study via multiple experimental methods. Single unit electrophysiology and anatomy, which we have called bottom-up methods, are two sources (Heilbronner & Hayden, 2016). Another source of information comes from top-down methods, which include functional neuroimaging (fMRI), electroencephalography (EEG), magnetoencephalography, and lesion studies. Reconciling a portrait of the dACC derived from the different methods has proven to be a challenge. Indeed, there is perhaps no other brain region wherein the disagreement over methods—epitomized by the debate over conflict detection – has proven to be so central to discussions of its function (Cole, Yeung, Freiwald, & Botvinick, 2009; Ebitz & Hayden, 2016; Holroyd, Nieuwenhuis, Mars, & Coles, 2004; Schall & Emeric, 2010).

In theory, we should be able to leverage the large number of approaches into the dACC, triangulate across methods, and obtain a better understanding of its function. Our central argument is that the consideration of multiple methods can indeed provide a better and more accurate understanding of the dACC. But for that to happen, the methods need to be compared in a sophisticated way that respects the strengths and weaknesses of each. In particular, while the bottom-up approaches continue to provide the gold standard ground truth, they provide only a part of the story, one that is impoverished by failures to be integrated with other methods.

An important lemma of our argument will be that the local field potential (LFP) serves as a critical intellectual intermediary between top-down and bottom-up methods. The LFP is recorded intracranially, and thus, typically in animal models (although there is growing interest in human recordings (Widge, Heilbronner, & Hayden, 2019)). The LFP represents the summed transmembrane currents in a $\sim 200 \,\mu m$ radius (Einevoll, Kayser, Logothetis, & Panzeri, 2013). The relative prominence of different frequency components f comprising the signal can be determined with a spectrogram. An LFP spectrogram typically has a 1/fstructure. Frequency-specific "bumps" above this 1/f structure can shed insights on engaged neuronal circuits. Typically, these bumps are centered around canonical frequencies, such as theta (4–10 Hz), alpha/beta (10 - 30), or gamma (30 - 100 Hz). The frequency of interest can change with age (e.g., Tran, Rolle, Gazzaley, & Voytek, 2020), and does exhibit some inter-species variability (Javitt et al., 2020), though it remains convenient to discuss results in terms of these canonical bands (Javitt et al., 2020).

The present work is organized as follows. First, we briefly review insights derived from bottom-up approaches of dACC function (covered in detail in Heilbronner & Hayden, 2016). Second, starting with the observation that task-dependent changes in dACC single unit activity is modulated as a function of LFP oscillation phase, we describe circuit and network insights from LFP oscillations. Third, we elucidate key computational properties of phase modulated spiking. Finally, we describe efforts to reconcile micro- and macro-scale insights that leverage LFP recordings.

2. Insights from single unit studies: dACC as an economic structure

Neurons in the dACC clearly participate in economic computations (Heilbronner & Hayden, 2016). Key findings include the fact that firing rates of neurons in dACC encode the values of offered options and of chosen options, as well as values of obtained options (Amiez, Joseph, & Procyk, 2006; Azab & Hayden, 2018; Cai & Padoa-Schioppa, 2012; Hayden, Heilbronner, Pearson, & Platt, 2011; Rudebeck, Mitz, Chacko, & Murray, 2013; Seo & Lee, 2007). Those responses are modulated by the prior

likelihood of the outcome and by the surprisingness of the outcome (Hayden et al., 2011). It is well established that dACC has a strong motor repertoire; consequently, it is not surprising that dACC neurons track the positions of offers and of choices (Hayden & Platt, 2010; Strait et al., 2016).

Recent work from our lab has further clarified the economic computations of the dACC (Azab & Hayden, 2017, 2020). That work puts dACC precisely in the middle of two key value-related computations, namely, value formation and value comparison. Specifically, we examined responses of dACC neurons in an economic choice task in which subjects chose between two staggered gambles defined by varying probabilities. Behavior depended systematically on the values of both outcomes, as did firing rates of single neurons (Azab & Hayden, 2020). This type of pattern has been observed before, and has been used to argue that neurons represent an *abstract* value signal, that is, one that is independent of the factors that influence value.

However, we used some novel statistical techniques to ask whether dACC neurons carry a *pure* value signal—that is, whether dACC neurons had fully shed information about the components of value. Surprisingly, we found that value-related encoding in dACC is only partial. That is, dACC responses partially integrate the values of the two offers, much as if they reflect the middle of a hierarchical process that transforms discrete information channels into integrated abstract value signals (Balasubramani, Moreno-Bote, & Hayden, 2018; Yoo & Hayden, 2018).

A complementary study used the same analysis technique to ask about value comparison signals. We had initially identified an anti-correlation between regression weights for the values of two offers, and argued that these weights were signatures of value comparison processes (Azab & Hayden, 2018; Strait, Blanchard, & Hayden, 2014; Strait, Sleezer, & Hayden, 2015). These anti-correlations reflect frank encoding of the key decision variable predicted from value comparison processes, namely, value difference. We had previously argued that such signals reflect the completion of a value comparison process. However, we showed that this comparison process is only partially complete, even relatively late in the trial (Azab & Hayden, 2017). That is, the outputs of dACC reflect only partial comparison of values, suggesting, as before, occupation of a middle stage in a hierarchical value comparison process. These works, together with other studies showing similar responses in other value-sensitive regions, suggests that dACC does not have a specific and unique role in economic choice, but is better

understood as part of a larger distributed hierarchy for economic decisionmaking, and thus reflects the interaction of multiple distributed processes (Chen & Stuphorn, 2015; Cisek & Kalaska, 2010; Hunt & Hayden, 2017; Kolling, Behrens, Wittmann, & Rushworth, 2016; Maisson, Cash-padgett, & Hayden, 2020).

2.1 Linking economic function with other roles of dACC

The economic view of dACC function emphasizes its role in value formation and comparison. Critically, the values of options may change, and must be updated. This dovetails with a second viewpoint that sees dACC as critical to *learning* option values. In support of this, neurons in dACC encode feature-specific reward prediction errors, and do so earlier than the lateral prefrontal cortex (LPFC) or striatum (Oemisch et al., 2019; Voloh, Oemisch, & Womelsdorf, 2020). Furthermore, dACC neurons show individual selectivity for errors with different sources (Shen et al., 2015). These studies thus suggest a neural substrate for attributing general outcomes to their specific attendant sources.

A second viewpoint links valuation to concepts from foraging theory, where dACC is thought to reflect switching from a default option to a new one (e.g., exploring a new patch, (Hayden et al., 2011; Kolling, Behrens, Mars, & Rushworth, 2012)). Indeed, neurons in ACC have a higher degree of task selectivity than LPFC when switching to a new task set (Johnston et al., 2007). When multiple options are available (for example, multiple patches that can be (re)visited), the dACC must be able to maintain a memory trace for different options, even if they do not affect choice on the current trial. Indeed, neurons in dACC can track correct targets even when the trial was ultimately unsuccessful (Westendorff, Kaping, Everling, & Womelsdorf, 2016). This is in line with evidence that the dACC tracks counter-factual outcomes (what could have been), as has been demonstrated in macaques in both single unit (Hayden, Pearson, & Platt, 2009), and macroscopic BOLD (Fouragnan et al., 2019) studies. Presumably, the dACC evaluates if a different option could have had a better outcome, and generates a signal to switch to it.

Taken together, single unit studies have identified economic computations that are likely expressions of a broader fronto-striatal circuitry designed for the selection and instantiation of action that maximize future rewards.

3. Oscillations as a window into circuit interactions

To optimize behavior, the computations performed by dACC neurons must be coordinated and disseminated with other brain regions (Heilbronner & Hayden, 2016; Kolling, Wittmann, et al., 2016; Shenhav, Cohen, & Botvinick, 2016; Womelsdorf & Everling, 2015). A key feature of coordination between ACC and distal structures is that spikes in ACC are concentrated to certain phases of distal oscillations. Many studies of primates have shown such task-specific spike-phase synchrony, including between the ACC and frontal eye fields (Babapoor-Farrokhran, Vinck, Womelsdorf, & Everling, 2017), ACC and LPFC (Smith et al., 2019; Voloh, Valiante, Everling, & Womelsdorf, 2015; Voloh & Womelsdorf, 2017; Womelsdorf, Ardid, Everling, & Valiante, 2014), ACC and ventro-medial PFC (Womelsdorf, Ardid, et al., 2014), ACC and striatum (Voloh et al., 2020), and ACC and amygdala (Taub, Perets, Kahana, & Paz, 2018). Further evidence from rodents suggests that the ACC also synchronizes to hippocampus (Benchenane et al., 2010; Fujisawa & Buzsáki, 2011; Hyman, Ma, Balaguer-Ballester, Durstewitz, & Seamans, 2012; Sirota et al., 2008), ventral tegmental area (Fujisawa & Buzsáki, 2011), and infra-limbic cortex (Totah, Jackson, & Moghaddam, 2013), although care must be taken in translating results from rodents to primates (Heilbronner & Hayden, 2016). Such synchrony selectively emerges when attentional (Voloh & Womelsdorf, 2017; Womelsdorf, Ardid, et al., 2014), or control (Smith et al., 2019) demands are high. This suggests that communication between ACC and distal structures may be modulated and controlled by band-limited, populationlevel oscillatory activity, arising from distinct neuronal circuits.

3.1 Oscillatory timescales arise from specific dynamic circuit motifs

Local circuits of cells can generate oscillatory activity. The period of this activity is determined by the specific configuration of inhibitory and excitatory cells, the kinetics of transmembrane channels, axonal delays, and the nature of arriving inputs (Womelsdorf, Valiante, Sahin, Miller, & Tiesinga, 2014). For example, a well-characterized circuit motif that generates activity in the gamma (30–100 Hz) band is the pyramidal-interneuron gamma (PING) motif. Depolarizing pyramidal cells excite inhibitory parvalbumin-positive (PV+) interneurons, which subsequently inhibit those same pyramidal cells. The frequency of the generated oscillation is thus determined by the timescale of $GABA_A$ -ergeric inhibition, and how quickly pyramidal cells can recover from inhibition. It is important to note that this sort of circuit can thus generate oscillatory activity even when the input is non-oscillatory. Different circuit motifs can generate oscillations with different periods (reviewed in (Womelsdorf, Valiante, et al., 2014) as well as (Wang, 2010)).

Oscillatory circuit motifs are likely computational units that are conserved across brain areas (Fries, 2015; Womelsdorf, Valiante, et al., 2014), yet still support processing of region-dependent information. For example, in dACC and LPFC, electrophysiological classification of neuronal subtypes revealed a similar interneuron type in both dACC and LPFC, likely corresponding to PV + interneurons (Boroujeni, Tiesinga, & Womelsdorf, 2020). This neuron type encoded different information in the two areas, with choice probabilities being encoded in LPFC, and reward prediction errors in dACC. These same cells also showed gamma band synchrony that mirrored the cells' encoding preferences. Thus, the same neuronal circuits, conserved across dACC and LPFC, may nevertheless be leveraged to process area-specific information.

Importantly, activity at multiple frequency bands can be generated by the same circuit, with the faster oscillation being nested within the slower one. This can be evident as "phase-amplitude coupling," where the amplitude of a fast oscillation is modulated by the phase of a slow one (see Hyafil, Giraud, Fontolan, & Gutkin, 2015 for a review of this and other forms of cross frequency interactions). At the circuit level, different instantiations are possible. One option, most extensively studied in the hippocampus, suggests that a separate population of cells, whose activity is dominated by a slow Ca²⁺ I_h hyper-polarizing current, provides theta-pulsed inhibition (Malerba & Kopell, 2013; Neymotin et al., 2013; Stark et al., 2013; Tort, Rotstein, Dugladze, Gloveli, & Kopell, 2007). Alternatively, phasic and/or tonic excitation of inhibitory and excitatory populations in the PING motif (described above) can generate different phase-amplitude coupling profiles (Onslow, Jones, & Bogacz, 2014). This implies that information contained in highfrequency oscillations can be organized according to a low-frequency scaffold (Lisman & Jensen, 2013; Panzeri, Brunel, Logothetis, & Kayser, 2010; Voloh & Womelsdorf, 2016).

The maintenance and generation of oscillatory activity does not only depend on neuronal cell types. Even within the same neurons, different spike profiles have a differential impact on local oscillations. This is evident when comparing the relation of regular spiking vs burst spiking (spike occurring <5 ms apart) to local LFP activity in dACC and LPFC (Voloh &

Womelsdorf, 2017). Bursts of putative interneuron cells are associated with increased local theta power that peaks after the burst has occurred, as well as increased beta phase synchronization, compared to non-bursts. On the other hand, bursts, rather than non-bursts, of putative pyramidal cells were associated with a stronger phase-dependent variation in beta power. These results are suggestive of the neuronal circuits at play, such as a role for Martinotti cells in theta maintenance, and/or the coactivation of proximal and dendritic inputs of a network of excitatory and inhibitory cells for beta generation (*see* Voloh & Womelsdorf, 2017 for detailed discussion).

In summary, the frequency of a particular rhythm being engaged in a task-dependent manner is suggestive of the neuronal circuitry at play.

3.2 Oscillations index inter- and intra-laminar coordination

Intriguingly, frequency specific activity can often be localized to specific cortical layers (Voloh & Womelsdorf, 2016; Wang, 2010; Womelsdorf, Valiante, et al., 2014). Slower oscillations are prevalent in infra-granular layers, whereas faster ones are reported in granular and supragranular layers (Bastos, Loonis, Kornblith, Lundqvist, & Miller, 2018; Bollimunta, Chen, Schroeder, & Ding, 2008; Buffalo, Fries, Landman, Buschman, & Desimone, 2011; Ninomiya, Dougherty, Godlove, Schall, & Maier, 2015; Van Kerkoerle et al., 2014; Wang, 2010). Varying task demands changes the strength of activation but not the pattern of functional connectivity, suggesting such activity propagation proceeds along conserved anatomical paths (Van Kerkoerle et al., 2014). Intriguingly, this segregation of frequency by layer also indexes feedforward and feedback connectivity between (Van Kerkoerle et al., 2014; Voloh & Womelsdorf, 2016; Bastos et al., 2018), and within (Van Kerkoerle et al., 2014; Voloh & Womelsdorf, 2016) columns. Indeed, it is possible to recapitulate a large swath of the visual hierarchy based on oscillatory coordination alone, both in macaques (Bastos et al., 2014) and humans (Michalareas et al., 2016).

Evidence suggests that even within a column, oscillations between layers can interact (Bollimunta et al., 2008; Florez et al., 2013; Lee, Whittington, & Kopell, 2013; McGinn & Valiante, 2014; Ninomiya et al., 2015; Spaak, Bonnefond, Maier, Leopold, & Jensen, 2012). For example, in human neocortical slices, theta activity is prevalent in supra and infra-granular layers (Florez et al., 2013). The phase of the former lags behind that of the latter, suggesting a directional influence. Importantly, gamma amplitude in supragranular layers is modulated by the phase of theta. Taken together, both inter- and intra- columnar coordination may be realized via oscillatory interactions.

Visual areas are a major source of evidence for a role of oscillations in widespread coordination, but have a unique architectonic fingerprint, raising the question of whether these results can be extended to agranular cortex such as the dACC (Voloh & Womelsdorf, 2016). An important piece of evidence is offered by a study of macaque SEF (Ninomiya et al., 2015), an agranular structure much like dACC (Barbas, 2015). In SEF, unlike in V1, deep layer slow oscillations did not modulate superficial layer fast oscillations (Ninomiya et al., 2015). Instead, the interaction was localized to layer 3. As the authors note, this may be due to the propensity of inputs and output to be localized to the (same) layer 3 (Ninomiya et al., 2015). Thus, a more general principle of oscillatory organization may be that oscillations index the input and output of local circuits, rather than simply the depth of the layer.

The inter-laminar patterns of oscillatory coordination may support a role for the dACC in the modulation of local computations in downstream regions (Helfrich & Knight, 2016; Womelsdorf & Everling, 2015). This possibility was probed in a study of selective attention in macaques (Voloh et al., 2015). Monkeys were cued to attend to a target, and had to report the direction of rotation, while ignoring a distractor. After the attention cue came on, but not before, high-frequency gamma amplitudes was modulated as a function of low-frequency theta phase (Fig. 1A and B). Critically, such theta-gamma phase-amplitude coupling selectively emerged when monkeys made a subsequent correct choice, but not an erroneous one (Fig. 1B). This directly suggests that coordination of oscillatory activity across timescales can support the successful deployment of attention. Importantly, theta and gamma activity was anatomically distinct; theta phases were more likely to arise in dACC, whereas gamma amplitudes were more likely to be found in LPFC (Fig. 1C). This is in line with the putative functional distinction between dACC as a controlling region that modulates task-relevant representations in LPFC (Kolling, Wittmann, et al., 2016; Shenhav et al., 2016). Further evidence directly implicates theta phases in the modulation of gamma amplitudes. First, a theta-phase reset was evident on correct, but not incorrect, trials (Fig. 1D). Second, gamma amplitudes were more tightly coupled to theta phases than the attention cue itself. Taken together, this suggests that dACC modulation of downstream LPFC is instantiated via theta phasic influence of gamma amplitudes, a suggestion borne out by computational modeling (Verguts, 2017).



Fig. 1 See figure legend on opposite page.

4. Computational principles of oscillatory coordination

The excitatory-inhibitory push-pull of local circuits creates periods where spiking activity is more or less likely to occur (Fries, 2015; Voloh & Womelsdorf, 2016; Wang, 2010; Womelsdorf, Valiante, et al., 2014). This has a number of important implications.

4.1 Gating input

Information transmission can be gated to the excitable periods of the oscillation cycle. In this scenario, incoming spikes only have an effect on the downstream neurons if these neurons are not prohibitively inhibited. Optogenetic experiments provide some of the strongest, causal evidence for this suggestion. Gamma oscillations can be optogenetically induced by specifically targeting fast-spiking interneurons (Cardin et al., 2009). Importantly, pyramidal cell activity, induced by a single whisker deflection, strongly depended on the gamma phase at which it was delivered. Thus, local oscillations gate input in such a way that may facilitate (or inhibit) incoming information.

Perhaps more surprisingly, it seems that neurons have inherent mechanisms that can sensitize them to synchronized inputs. Evidence for this comes from in vivo recordings in cat striate cortex (Azouz & Gray, 2003). Slow depolarization is associated with increasing spike threshold, indicating that the probability of firing decreases when cells are depolarized slowly. On the other hand, the same mechanism *decreased* the spike threshold in response to fast depolarizations, as occur during synchronized spike input. This adaptive spike threshold mechanism can help tune task-relevant representations,

Fig. 1 Theta-gamma coupling predicts successful attentional deployment. (A) Example theta-gamma phase-amplitude coupling on one trial. Blue and red traces correspond to LFPs from two different sites. After attention cue onset, gamma amplitudes (red) were modulated as a function of theta phases (blue) (gamma peaks highlighted with vertical gray/green lines). (B) Phase-amplitude coupling, dissociated by frequency, task epoch, and outcome. Theta-gamma coupling increased in the post-cue epoch relative to the pre-cue epoch, but only for correct trials (black box). (C) Likelihood of a phase-providing channel (values left from zero) and an amplitude-providing channel (right from zero) in the vmPFC, dACC, and LPFC during cross-area theta-gamma coupling. (D) Progression of the average phase (y-axis) for all phase- providing LFP channels engaging in significant theta-gamma coupling around the time of the attention cue onset (x-axis). Each gray line represents the average phase across trials of one such LFP. Top and bottom panels show the progression of mean phases on correct trials and on error trials, respectively. More channels exhibited a cue-induced reset on correct, rather than error, trials.

and is tightly correlated with gamma band activity (Azouz & Gray, 2003). Although such a correspondence has not, to our knowledge, been shown in the frontal cortex, a similar mechanism may be in play. An interesting future direction would be to determine if synchronous firing in dACC leverages such intrinsic cellular adaptation to tune downstream, task-relevant representations.

4.2 Gating output

If neuronal output is synchronized, the impact on downstream targets can be maximized. This follows from the well-known phenomenon of temporal summation; if spikes from different neurons arrive around the same time, the probability of depolarization of their target is increased. For example, periods of higher coordination in earlier visual areas increases the probability of spiking in later visual areas (Zandvakili & Kohn, 2015). This effect is specific to retino-topically aligned, rather than non-aligned, cells in V1 and V2 (Zandvakili & Kohn, 2015).

Likewise, rodent studies of the medial prefrontal cortex (likely an analogue to primate dACC) also suggest synchronizing output can have a powerful gating effect. A clear example of this is from an optogenetic study of conditioned fear responses in rodents (Courtin et al., 2013). Here, optogenetic inhibition (or activation) of inhibitory interneurons resulted in the synchronization of local pyramidal cells, also evident as an increase in phase-locking to local theta activity. The synchronization of pyramidal output could be traced to a theta-phase reset, similarly induced either via optogenetic manipulation, or by the onset of the conditioning cue. Furthermore, antidromic stimulation revealed that the synchronized output of pyramidal cells had preferential downstream targets involved in fear expression. The results of (Courtin et al., 2013) are shadowed by those of (Voloh et al., 2015) (described earlier), who also found that cue-related theta-phase resetting is predictive of behavioral outcome. Taken together, these results suggest that synchronizing dACC output mediates a powerful effect on downstream effector regions.

4.3 Routing

By aligning the phase of distal oscillations, information can be selectively routed. Intuitively, this follows from the points above; spikes from a sending region that arrive at an excitable phase can be processed, while those arriving at an inhibited phase cannot. Thus, manipulating the relative phase between sending and receiving regions may mediate the flow of information

(Fries, 2015; Hahn, Ponce-Alvarez, Deco, Aertsen, & Kumar, 2019; Palmigiano, Geisel, Wolf, & Battaglia, 2017). Testing this proposition requires simultaneous recording from two separate upstream regions that project to the same target. This has been done in macaque visual cortex during a selective attention task (Bosman et al., 2012). The investigators found that while gamma activity in V1 was prevalent at sites with different receptive fields, downstream sites in V4 whose receptive field encompassed both upstream sites were only coherent with the attended receptive field sites (Bosman et al., 2012). Thus, relative phase differences between sites can be leveraged to selectively route information. This is true even if oscillations are short-lived and occur stochastically (Palmigiano et al., 2017), as seems to be the case in in vivo recordings in frontal cortex (Bastos et al., 2018; Lundqvist et al., 2016). One question that arises is how phase differences may be controlled in order to route information. Modeling suggests that increasing tonic firing rate activity of the target site is sufficient to modify relative phases and route information transmission (Palmigiano et al., 2017). While this has not yet been demonstrated in the dACC, we hypothesize that such routing may underlie the ability of the dACC to selectively modulate downstream, task-relevant targets such as in the LPFC. This would require careful dissection of network level variables that determine information propagation via synchronous (or asynchronous) firing (Hahn et al., 2019; Kumar, Rotter, & Aertsen, 2010).

4.4 Coding

One consequence of phase-specific sensitivity to input is that information can be encoded as a function of phase. Put another way, a downstream reader can deduce the informational content of spikes based on which phase they arrive at. Phase-of-firing coding has been shown to increase the informational content of spikes (Kayser, Montemurro, Logothetis, & Panzeri, 2009; Montemurro, Rasch, Murayama, Logothetis, & Panzeri, 2008), and to carry information about stimulus orientation (Vinck et al., 2010; Womelsdorf et al., 2012), object in memory (Siegel, Warden, & Miller, 2009), spatial navigation parameters (Huxter, Senior, Allen, & Csicsvari, 2008; Turesson, Logothetis, & Hoffman, 2012), and learning variables (Hawellek, Wong, & Pesaran, 2016; Voloh et al., 2020) (*see* below for further details). This may be achieved through a rate-to-phase conversion (Buzsáki & Draguhn, 2004; Fries, Nikolić, & Singer, 2007; Mehta, Lee, & Wilson, 2002); neurons that are activated most strongly will be able to escape oscillatory inhibition earliest, thus firing on earlier phases. Importantly, this also provides a mechanism to multiplex different streams of information (Akam & Kullmann, 2014). A downstream reader can decode a packet of information by determining the phase (relative to a reference oscillation) at which it arrived (Lisman & Jensen, 2013; Akam & Kullmann, 2014; *see* Akam & Kullmann, 2014 for other oscillationbased multiplexing schemes). Such a reference oscillation may be instantiated by a phase reset of ongoing oscillations (Voloh & Womelsdorf, 2016), thus bringing sending and receiving regions into phase alignment.

Recent evidence suggests that, like primary and associative areas reviewed above, spike-phase interactions in dACC (as well as LPFC and striatum) also boost information content (Voloh et al., 2020). Monkeys performed a reversal learning task, whereby they had to learn the color associated with reward in a block of trials. All considered brain areas encoded key learning variables, including outcome, reward prediction error (RPE), and the history of outcomes. The critical question was whether the phase at which spikes occurred conveyed information about these three critical learning variables; if they did, differences in firing rate would be modulated as a function of phase, whereas if a pure firing rate code was in effect, differences would be flat across phases (Fig. 2A). Indeed, we found evidence of the former for all three learning variables (Fig. 2B and C). This effect was specific to a 10-25 Hz beta band (Fig. 2D), and only for sites that synchronized to distal LFPs. Importantly, the encoding phase gain was greatest in the dACC as compared to the LPFC or the striatum (Fig. 2E). Similar phase-of-firing coding has been observed in humans when control demands are high (Smith et al., 2019). Thus, phase-of-firing encoding of key learning variables is prevalent across the dACC, LPFC, and striatum, and is strongest in the dACC.

One might expect that spikes concentrated on a cell's preferred firing phase are the richest carriers of information. However, this was not the case in the aforementioned study. Specifically, for neurons encoding a reward prediction error, maximal information gain occurred on approximately the anti-preferred firing phase (Fig. 2F). It is unclear how this may be mechanistically instantiated. One possibility, suggested by previous rodent work (Benchenane et al., 2010), is that a dopaminergic influence may shift encoding phases during learning. Alternatively, keeping in mind that a prediction error is a comparison of two signals (expected and observed outcomes), such a phase offset may be the result of a latency difference between these incoming signals (*see* Voloh et al., 2020 for further discussion). These and other studies suggest



Fig. 2 See figure legend on next page.

that spiking activity in dACC synchronized to LFP phases have an important role in disseminating task-relevant information.

Do these results indicate a bona-fide phase-code, or rather a phase gain of rate encoding? Indeed, both may be true. Outcome cells showed a significant difference in phase synchronization between conditions, suggesting phasic modulation of rate encoding. On the other hand, RPE and Outcome History cells tended to synchronize on different phases between conditions, consistent with a bona-fide phase code (Voloh et al., 2020). This suggests that different phase coding schemes may co-exist. This is in line with evidence that, in monkey visual cortex (in the same dataset), phase may both modulate rate encoding (Womelsdorf et al., 2012), as well as act as a scaffold for bona-fide phase-coding (Vinck et al., 2010). Future studies should critically assess the mechanisms and conditions under which different phase-coding schemes are dominant.

Fig. 2 Spike-phase encoding in dACC. (A) Phase-dependent encoding analysis. Spikes were segregated according to the phase of the LFP. In a pure firing rate code (right, middle), firing rates on different conditions (solid vs dotted lines) would be consistent across phase bins. This would emerge as a flat firing rate difference (i.e., encoding strength, derived from a Generalized Linear Model (GLM) analysis) across phase bins (right, bottom). Alternatively, a phase-of-fire code would show phasic encoding strength (left, middle, bottom). (B) Example cell showing phase-dependent outcome encoding, comparing correct (dashed lines) and error (solid) trials. Color represents firing on the preferred (orange) or anti-preferred (blue) encoding phase. The gray box between [-0.1 0.2] was not analyzed. Firing rate differences emerged after reward onset, but only on preferred firing phases. (C) Example of phase-of-firing encoding for Outcome, Reward Prediction Error, and Outcome History cells. Colored dots reflect the encoding metric for a corresponding phase bin (derived from GLM model coefficients). Zero radians correspond to the preferred (mean) firing phase. Numbers on concentric circles are the value of the encoding metric. The gray dotted line represents the encoding metric estimated using all spikes, whereas the black dotted line represents the average across many permutations of spike phases. The red line is the average direction. Colored borders represent phase bin size. These cells show stronger encoding near the Orad phase, and weaker encoding on opposite phases. (D) Median encoding phase gain per frequency for encoding and locking cells. Phase gain was above chance at [1020] Hz. (E)Violin plots of the encoding phase gain, split by the spike area. Black circle and vertical bars depict the median and standard error. All areas showed some evidence of significant phase gain, with stronger encoding in ACC rather than LPFC or striatum. (F)Distribution of the relative phase of maximal encoding of cells (0 corresponds to the preferred phase), split by functional cell types. Outcome and Outcome History cells did not show an encoding phase preference, whereas RPE cells did.

5. Oscillations in dACC as a link between the micro and macro

Up to this point, we have reviewed evidence that band-limited oscillations emerge from specific neuronal circuit motifs, index anatomical and functional connectivity, provide a key substrate for neural coding, and are functionally relevant. These properties allow building links between insights using micro- and macro-scale recordings.

Two major macro-scale recording techniques, particularly prevalent in human studies due to their non-invasive nature, are the EEG and fMRI. Both have a strong relationship with the LFP that can be leveraged to build links between the micro- and macro-scale.

5.1 Linking EEG theta to neuronal circuits

A rich source of evidence implicating the dACC in cognitive control is based on EEG in humans, where frontal midline theta power increases when cognitive control demands are high (Cohen, 2014; Cavanaugh and Cohen, 2014). Theta as an index of control is stable throughout life (Cooper et al., 2019). Overall theta power is associated with negative prediction errors (thus disambiguating the valence of errors), but can also signal the degree of surprise (Cavanagh, Figueroa, Cohen, & Frank, 2012). Such a surprise signal may serve to instantiate top-down control, or focus attentional resources (Cavanagh & Frank, 2014; Womelsdorf & Everling, 2015). In so doing, if theta is indeed a medium by which dACC exerts control over downstream circuits, we would expect to see dACC synchrony with such regions. This has indeed been shown to be true, both in humans (*see* Cavanagh & Frank, 2014) and non-human primates (Phillips, Vinck, Everling, & Womelsdorf, 2014).

The control-indexing theta evident in human EEG has also been observed in macaques (Womelsdorf, Johnston, Vinck, & Everling, 2010). A promising line of research uses inverse modeling techniques (critically reviewed in (Cohen, 2017)) to determine how theta rhythmogenesis may arise from a columnar circuit of layer 5 pyramidal cells and inhibitory Martinotti cells (Herrera, Sajad, Woodman, Schall, & Riera, 2020). In this work, conflict detection is conceptualized as coincidence detection between an efferent motor copy and a task rule. Activated L5 pyramidal cells then activate Martinotti cells, which then (indirectly) inhibit the apical dendrites of the L5 cells. The dynamics of this circuit instantiate deep layer theta, which may be detected at the level of scalp recordings. This is in line with optogenetic work that has shown that optogenetic activation of even a single Martinotti cell can generate synchronized activity in nearby pyramidal cells (Hilscher, Leão, Edwards, Leão, & Kullander, 2017). Leveraging such work, in conjunction with detailed laminar encoding preferences (Sajad, Godlove, & Schall, 2019) and translational studies of EEG in macaques (e.g., Godlove et al., 2011), is critical for understanding the micro-circuitry of dACC (Cohen, 2014; Sajad et al., 2019).

5.2 BOLD and LFP

A second major source of evidence of dACC function comes from human fMRI experiments, which measure the blood-oxygenation level dependent (BOLD) response. The bi-directional translation of knowledge from invasive experiments in animals on the one hand, and non-invasive BOLD measurements on the other, is of great importance when studying complex cognitive processing in associative cortex such as the dACC. BOLD responses are widely employed not only to map brain activation, but also as a means for studying the dynamics of neural networks across spatial and temporal scales (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Fox & Raichle, 2007; He, Snyder, Zempel, Smyth, & Raichle, 2008; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). The BOLD response seems to correlate most closely with low-frequency activity (Shi et al., 2019; Wang, Saalmann, Pinsk, Arcaro, & Kastner, 2012), although other investigators find a closer correspondence to high-frequency activity (Logothetis et al., 2001). This may depend on whether recordings are task-dependent or obtained from resting state (Wilson, Yang, Gore, & Chen, 2016). Critically, the BOLD response is more closely correlated with LFP activity than with single- or multi-unit activity (Logothetis et al., 2001). These findings have led the field to assume that the BOLD contrast mechanism reflects the input and intracortical processing of a given area rather than its spiking output. Linking BOLD activity to band-limited LFP activity further allows us to infer the neuronal circuits at play.

6. Conclusion

The breadth of research into the function of the dACC is impressive and accelerating. It spans multiple recording hierarchies, and is supported by multiple computational theories. Such richness of evidence has a cost; namely, that paradoxes and conflict between competing theories/methodologies naturally arise. This is fertile ground to build a more nuanced understanding of dACC function. LFP oscillations are a critical link between micro- and macroscopic recording techniques; they are both grounded in specific inter-neuronal interactions, and correlate more closely with EEG and BOLD measurements than do individual neurons. Importantly, oscillatory coordination between regions has key and attractive properties for gating, propagation, and encoding of information. Thus, they offer a unique perspective on understanding the function of the dACC within the broader fronto-striatal circuits.

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