Frontal circuit specialisations for decision making

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<u>Author Accepted Manuscript</u>

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Running title: *PFC and decision making*

Keywords: prefrontal cortex, reward, neurophysiology, computational model, neuroeconomics

Word count: 6737 words

There is widespread consensus that distributed circuits across prefrontal and anterior cingulate cortex (PFC/ACC) are critical for reward-based decision making. The circuit specialisations of these areas in primates were likely shaped by their foraging niche, in which decision making is typically sequential, attention-guided and temporally extended. Here, I argue that in humans and other primates, PFC/ACC circuits are functionally specialised in two ways. First, *microcircuits* found across PFC/ACC are highly recurrent in nature and have synaptic properties that support persistent activity across temporally extended cognitive tasks. These properties provide the basis of a computational account of time-varying neural activity within PFC/ACC as a decision is being made. Second, the *macrocircuit* connections (to other brain areas) differs between distinct PFC/ACC cytoarchitectonic subregions. This variation in macrocircuit connections explains why PFC/ACC subregions make unique contributions to reward-based decision tasks, and how these contributions are shaped by attention. They predict dissociable neural representations to emerge in orbitofrontal, anterior cingulate and dorsolateral prefrontal cortex during sequential attention-guided choice, as recently confirmed in neurophysiological recordings.

When collecting food from trees, early primates were unusual in that they moved dextrously between fine arboreal branches, reaching precisely for berries and insects. Their forward-facing eyes, with large binocular fields of view, supported these behaviours by facilitating depth perception and a visual-centred frame of reference for reaching movements. The subsequent development of a fovea in anthropoid primates facilitated rapid identification of high value fruits within the cluttered visual environment of the fine-branch niche. It is within this ecological niche that the circuitry of the granular prefrontal cortex – which supports sequential, temporally extended, and attention-guided behaviour – evolved (Wise, 2008; Passingham & Wise, 2012).

Such foraging behaviours seem quite different from the kind of decisions that we humans typically make on a daily basis (for example, on a trip to the supermarket). Yet several features are in fact similar (Hayden, 2018). Most decisions that we make are sequential in nature (Cisek, 2012): unlike in many lab experiments used to study decision making, it is rare for humans to be suddenly confronted with two alternatives appearing next to one another. Most decisions are temporally extended: even in situations where options are presented simultaneously, reaction times depend upon the difficulty of the decision, and this implies a process of internal evidence accumulation across time (Shadlen & Shohamy, 2016). And, perhaps most significantly in primates, most decisions are attention-guided: there is a close interplay between where humans shift their foveal gaze by saccading around the environment and the unfolding of a decision process (Krajbich, 2019).

The sequential, temporally extended and attention-guided properties of reward-based decision making immediately give rise to questions about how the neural circuitry of the prefrontal (PFC) and anterior cingulate cortex (ACC) is specialised to support these different processes. If we are to answer these questions, it makes sense to study them in

primates. As we shall see, there is functional specialisation in the cellular microcircuits of the primate PFC/ACC, a specialisation that is far less pronounced in rodents (Gilman *et al.*, 2017). Anatomical homologies can also readily be drawn between ACC and PFC subregions in macaque monkeys and corresponding subregions of the human brain, but this is more challenging in other mammalian species (Ongur & Price, 2000; Ongur *et al.*, 2003; Neubert *et al.*, 2015). The primate PFC is also unique in having areas with a granular cytoarchitecture with an expanded layer IV (Passingham & Wise, 2012), whereas the rodent brain lacks a granular PFC and as a consequence the homologies between rodent and primate PFC remain strongly debated (Laubach *et al.*, 2018) (figure 1). During primate evolution, cytoarchitectonically new areas emerged in anthropoid primates (such as macaques, marmosets, apes and humans) that do not exist even in strepsirrhine primates (such as lemurs, lorises and galagos) (Preuss & Goldman-Rakic, 1991), let alone in other mammals. And in addition to these anatomical homologies, primate cognition is also unique. For example, primates can flexibly combine individual cues across extended periods of time to construct goal-directed behaviour (Passingham & Wise, 2012). This is perhaps because the primate way of foraging relies heavily upon visual attention; anthropoid primates typically gather information about the environment with their eyes and then select or reject different food items that they encounter in accordance with their current needs (Coe, 1984). Thus, eye gaze provides a unique window into cognition as a decision is unfolding. While certain observable behaviours in rodents can also be used as indicators of deliberative processing (Redish, 2016), these do not provide such direct insight into what is currently the focus of attention in a manner analogous to human decision making.

In this review, I examine how the neural circuitry of the primate prefrontal cortex is functionally specialised to support temporally extended, attention-guided behaviours such as
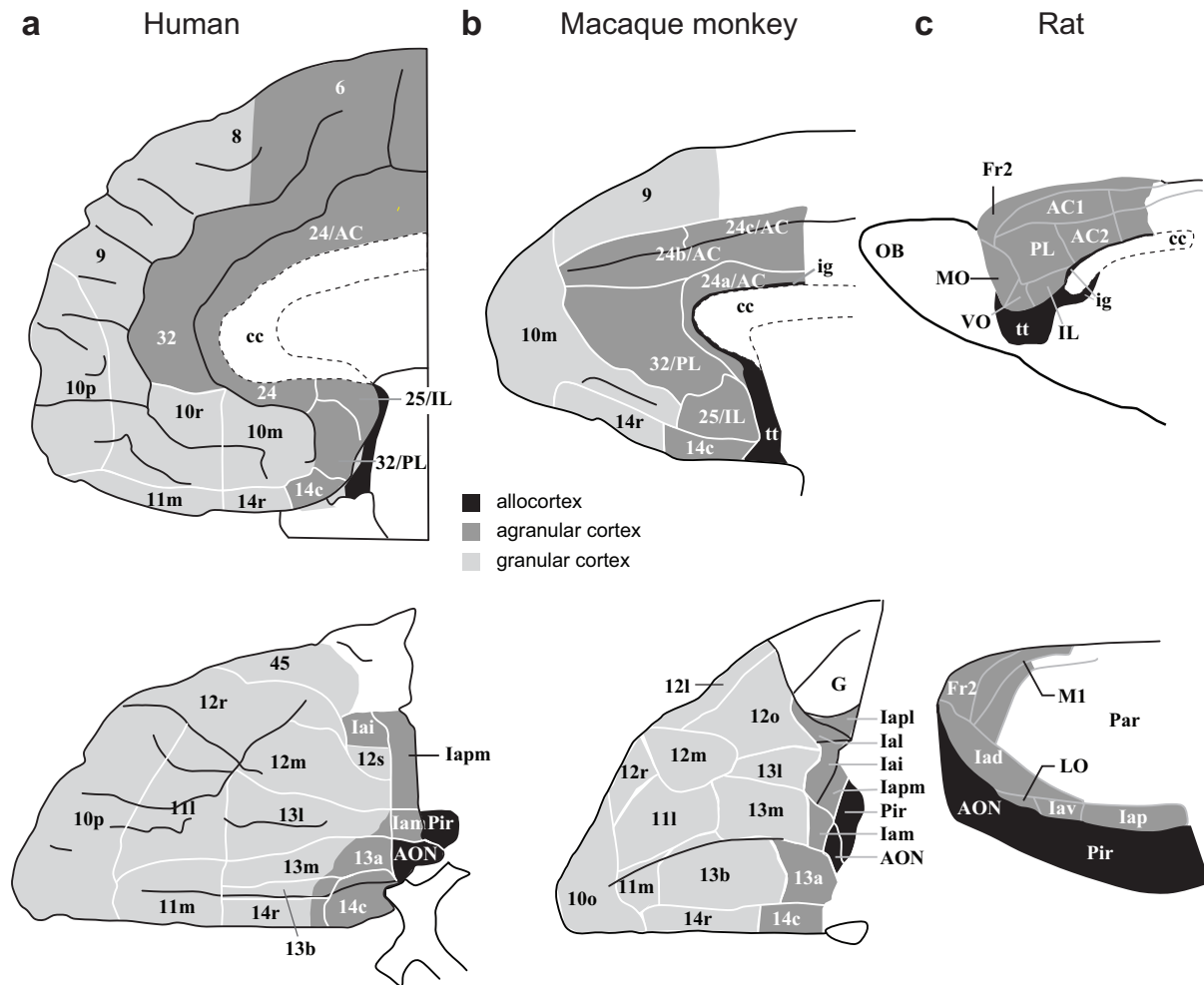
*Figure 1. **Comparison of surface anatomy and antomical subregions in human, macaque and rat frontal cortex.** (a) Medial (top) and orbital (bottom) views of the human frontal cortex. (b) Medial (top) and orbital (bottom) views of the macaque frontal cortex. (c) Medial (top) and lateral (bottom) views of the rat frontal cortex. Many of the areas found in the human frontal cortex, in particular granular prefrontal cortex, have homologues in the macaque brain but are absent in the rat brain, which lacks a granular prefrontal cortex. Note that in this review, I refer separately to prefrontal cortex (PFC) from anterior cingulate cortex (ACC) based on the convention that the PFC denotes the granular parts of the frontal lobe, whereas ACC is agranular. When I refer to orbitofrontal cortex (OFC), I am primarily referring to recordings made in granular area 13m of the macaque; however, as can be seen in (b), more posterior parts of the macaque OFC are agranular, and in rodents OFC in entirely agranular. Figure reproduced from (Passingham & Wise, 2012) with permission of Oxford Publishing Limited through PLSclear, Copyright 2012 Oxford University Press.*

decision making. I use this to contextualise recent work that I have performed, studying the neural correlates of decision making in temporally extended decision tasks. I begin by reviewing how primate PFC and ACC are functionally specialised at the level of their *microcircuitry* – the local connections within the cortical circuit – to perform temporally extended computations in recurrent circuits. I argue that these specialisations are found broadly across PFC/ACC as a whole, and can explain the temporal dynamics of decision-related signals that I and others have observed in several different PFC subregions. I then

describe how functional specialisation at the level of *macrocircuitry* – the anatomical connections of different PFC/ACC subregions to other brain areas – enables these subregions to make distinct contributions to sequential, attention-guided decision making. I describe findings from my recent work that demonstrates these functionally distinct contributions, and link this to frameworks proposing that even simple economic choices can be described as a temporally extended process of evidence accumulation guided by visual attention.

The PFC Microcircuit is Functionally Specialised for Temporally Extended Information Processing

Several features distinguish the microcircuit properties of the primate PFC/ACC from other parts of the neocortex (figure 2).

Firstly, the local connectivity of PFC and ACC pyramidal neurons is highly recurrent in nature. Across the neocortex of anthropoid primates, there is a gradient in neuronal density (figure 2a) such that neurons in early sensory areas are more densely packed, whereas neurons in frontal cortex are more sparsely distributed (Collins *et al.*, 2010). Frontal cortex is therefore marked by a greater amount of neuropil between neuronal cell bodies, which is a difference that becomes most extreme in the most anterior regions of human PFC (Semendeferi *et al.*, 2010). This increase in neuropil reflects each individual neuron having a far greater number of dendrites, dendritic spines and terminals in PFC than in other regions, shown in studies that directly compare the morphology of layer III pyramidal neurons between primate PFC and those of other brain areas and species (Elston *et al.*, 2001; Elston, 2007; Gilman *et al.*, 2017). In particular, the hierarchical position of a cortical area (determined by its anatomical connections to other areas) correlates strongly with the
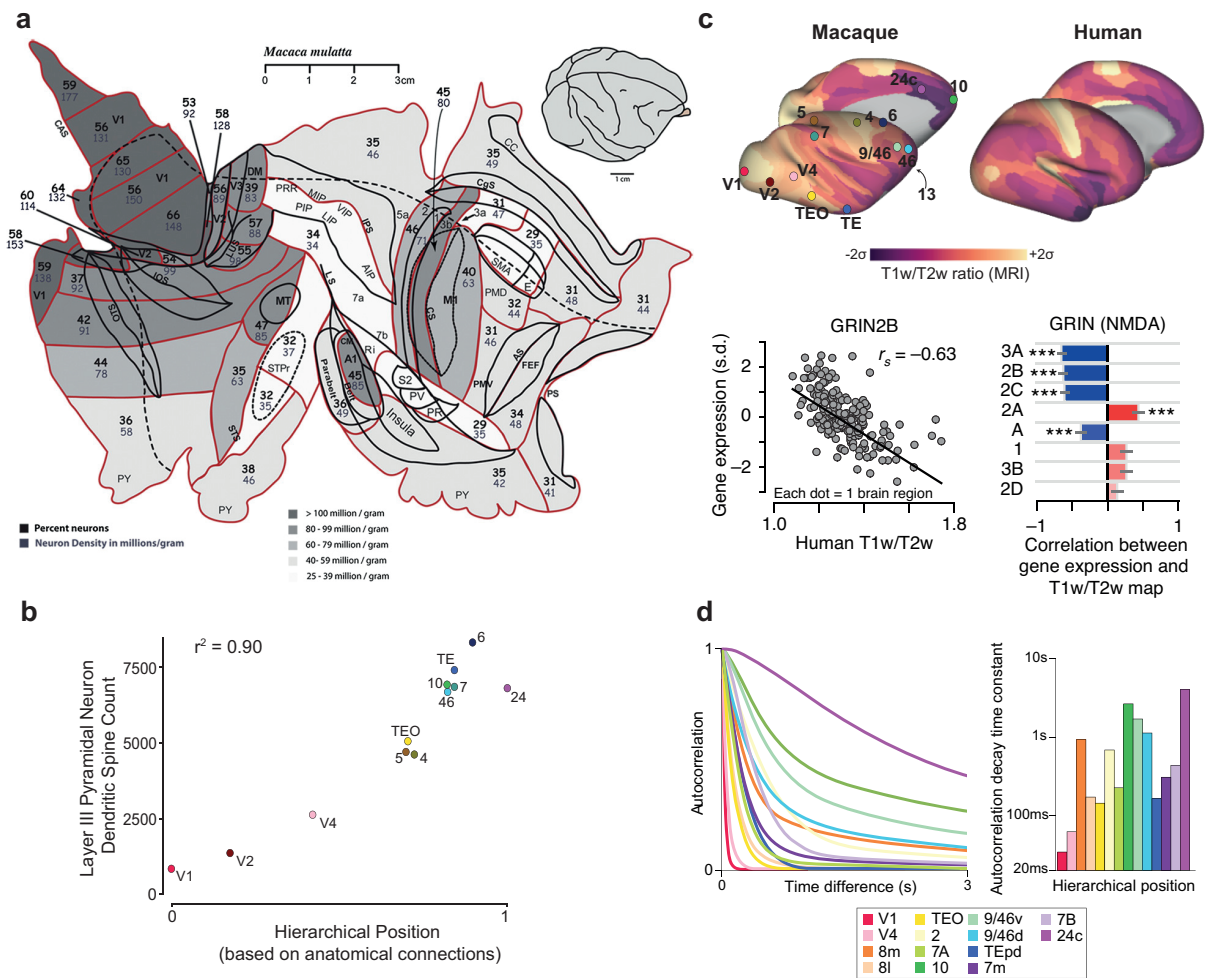
*Figure 2. **Microcircuit properties vary across the cortical hierarchy, with PFC/ACC subregions at one end of the hierarchy.** (a) A flat map of macaque cortex (with occipital areas on the left of the figure and frontal areas on the right) in which the shading of each area reflects the neuronal density in that tissue. Neuronal density was estimated using the isotropic fractionator method; red lines indicate locations of cuts made in the tissue before estimating neuronal density. Whereas V1 is the most neuron dense region, most of frontal cortex has a low neuronal density. Taken from (Collins et al., 2010). (b) Layer III pyramidal neuron spine count varies across the cortex, and correlates with a region's position in the anatomical hierarchy. V1 has the least spinous neurons, whereas PFC and ACC regions (e.g. 46, 10, 24) are among the regions with the most spinous neurons and hence the most recurrent circuitry. Note that this 'hierarchy' is defined in terms of anatomical connections (Markov et al., 2014) rather than in terms of receptive field properties or a temporal sequence of activations (for instance, regions high in the anatomical hierarchy can still have relevant or predictive activity even before stimulus onset (Durschmid et al., 2019)). Adapted from (Chaudhuri et al., 2015). (c) Top row: variation in MR-derived T1w/T2w ratio (used as a proxy for myelination (Glasser & Van Essen, 2011)) across the cortex, showing frontal cortex to have lower myelin density than other areas. Bottom row: this map was then correlated with transcriptomic data measuring gene expression of a wide range of neuron-related genes; it is found that regions with a low T1w/T2w ratio, such as frontal cortex, have higher expression of the long-time constant NR2B subunit of the NMDA receptor (left); there is similar across-brain variation in other NMDAR subunits (right) and many other neuronal genes. Adapted from. (d) The physiological consequence of these anatomical and ultrastructual features: PFC and ACC regions (such as 24c, 9/46, and area 10) have the longest decay time constant of their resting autocorrelation function, meaning that their activity is more persistent over time. Panel (a) Copyright 2010 National Academy of Sciences. Panels (b) and (d) reprinted from Neuron, vol. 8, (Chaudhuri et al., 2015), "A Large-Scale Circuit Mechanism for Hierarchical Dynamical Processing in the Primate Cortex", pp.419-431, Copyright 2015, with permission from Elsevier. Panel (c) Reprinted by permission from Springer Nature: Nature Neuroscience, "Hierarchy of transcriptomic specialization across human cortex captured by structural neuroimaging topography." (Burt et al., 2018), Copyright 2018.*

dendritic spine count of layer III pyramidal neurons in that area (Chaudhuri *et al.*, 2015) (figure

2b).

As a result, the average layer III pyramidal neuron in primate PFC/ACC receives ~5-10 times the number of excitatory synaptic inputs compared to an equivalent neuron in primary visual cortex. Because these connections are primarily local corticocortical projections from other nearby neurons, this means that PFC/ACC connectivity is highly recurrent. This increase of recurrent excitatory connections within a circuit can change its response properties in a highly non-linear fashion, causing persistent activity to emerge as a stable state of the network (Wang, 2020). This ability to stably maintain activity across time is a prerequisite for temporally extended information processing during cognitive tasks.

In addition to this recurrent local circuitry, PFC and ACC also differ from other areas in terms of their expression of receptor subunits that determine the electrochemical properties of neurotransmitter receptors in the dendritic membrane. This again determines how neural activity can persist across time within these regions. For example, NMDA receptors for the neurotransmitter glutamate are found across cortex and have slow excitatory post-synaptic currents; the subunit composition of the NMDA receptor determines the time course of these slow currents. In PFC/ACC, there is greater expression of the GRIN2B gene encoding the NR2B subunit, and reduced expression of GRIN2A encoding the NR2A subunit (Burt *et al.*, 2018) (figure 2c). The resulting subunit composition leads to a longer synaptic NMDA receptor decay time-constant when compared to other areas (Cull-Candy *et al.*, 2001), as confirmed in patch clamp recordings from medial frontal cortex versus visual cortex (Wang *et al.*, 2008). Theoretical work has demonstrated the importance of this long time-constant NMDA receptor for supporting persistent activity within the network (Wang, 1999; Wong & Wang, 2006). This has also been confirmed empirically, as selective pharmacological antagonism of NR2B-containing NMDA receptors abolishes persistent activity in dorsolateral PFC during working memory (Wang *et al.,* 2013), and more recently systemic antagonism of NMDA

receptors has been shown to affect evidence integration in temporally extended decision making tasks (Cavanagh *et al.*, 2020b; Salvador *et al.*, 2020).

Beyond gradients in NMDA receptors and recurrent excitation, gradients in expression of other neurotransmitter receptors (Burt *et al.*, 2018), inhibitory cell subtypes (Kim *et al.*, 2017; Burt *et al.*, 2018) and long-range cortico-cortical projections (Goulas *et al.*, 2018) will further affect the circuit properties of PFC relative to other regions. It would be conceivable that these factors might vary independently to one another across different cortical areas, meaning that this variation would be high dimensional. However, transcriptomic studies have in fact shown that a single principal component accounts for nearly 30% of the between-area variance in expression of brain-specific genes, there is a single, dominant axis of variation in circuit properties across the brain (Burt *et al.*, 2018). PFC and ACC sit at one end of this dominant axis, placing them at the top of an overall gradient of excitation and inhibition across the entire cortex (Wang, 2020). Although the rodent brain is far less differentiated than the primate (Gilman *et al.*, 2017), a similar set of conclusions can nevertheless be drawn for the mouse (Fulcher *et al.*, 2019).

What are the physiological consequences of these microcircuit properties? To measure the persistence of neural activity directly, one can examine the firing rates of neurons recorded while monkeys are at rest, and compare the temporal autocorrelation structure of single units recorded from different cortical areas (Murray *et al.*, 2014). The decay time constant of the autocorrelation function is found to be longest in frontal regions, and shortest in early sensory regions (figure 2d), implying that activity is most persistent across time in PFC and ACC. The average resting time constant of each cortical area corresponds closely to its position in the anatomical hierarchy and the number of recurrent excitatory connections in that area (Chaudhuri *et al.*, 2015). More recently, similar organising principles

of resting time constants have also been found in the rodent (Siegle *et al.*, 2021) and human brain (Vidaurre *et al.*, 2018; Demirtaş *et al.*, 2019; Gao *et al.*, 2020). Several studies have also shown that neurons with longer resting time constants are more likely to be functionally involved in temporally extended cognitive tasks (Nishida *et al.*, 2014; Cavanagh *et al.*, 2016; Cavanagh *et al.*, 2018; Wasmuht *et al.*, 2018; Fascianelli *et al.*, 2019; Cavanagh *et al.*, 2020a).

It is therefore unsurprising that in order to successfully model the response properties of neurons recorded during temporally extended tasks, computational models of PFC circuits rely heavily upon recurrent local connections. These endow such networks with the ability to perform temporally extended operations such as working memory, evidence integration and motor sequence production (Wang, 2001; 2002; Mante *et al.*, 2013; Hennequin *et al.*, 2014; Constantinidis *et al.*, 2018). In the next section, I discuss specific predictions that arise from recurrent neural networks for the neural correlates of reward-based decision making, and how these predictions have been tested empirically.

Dynamic Neural Correlates of Value Arising from Temporally Extended Processing

When deciding between competing courses of action, neural correlates of the value of choice alternatives are found widely distributed over prefrontal cortex and other brain regions (Hunt & Hayden, 2017). Crucially, these value representations are not static but evolve across time as a decision is being made. The temporal evolution of value representations is one of the most salient features that can be captured by recurrent microcircuit models of PFC.

Even before an animal commits to an externally observable choice, it may be possible to observe the unfolding of an internal process of evidence accumulation and decision formation. For example, consider the responses of single units shown in figure 3a, recorded
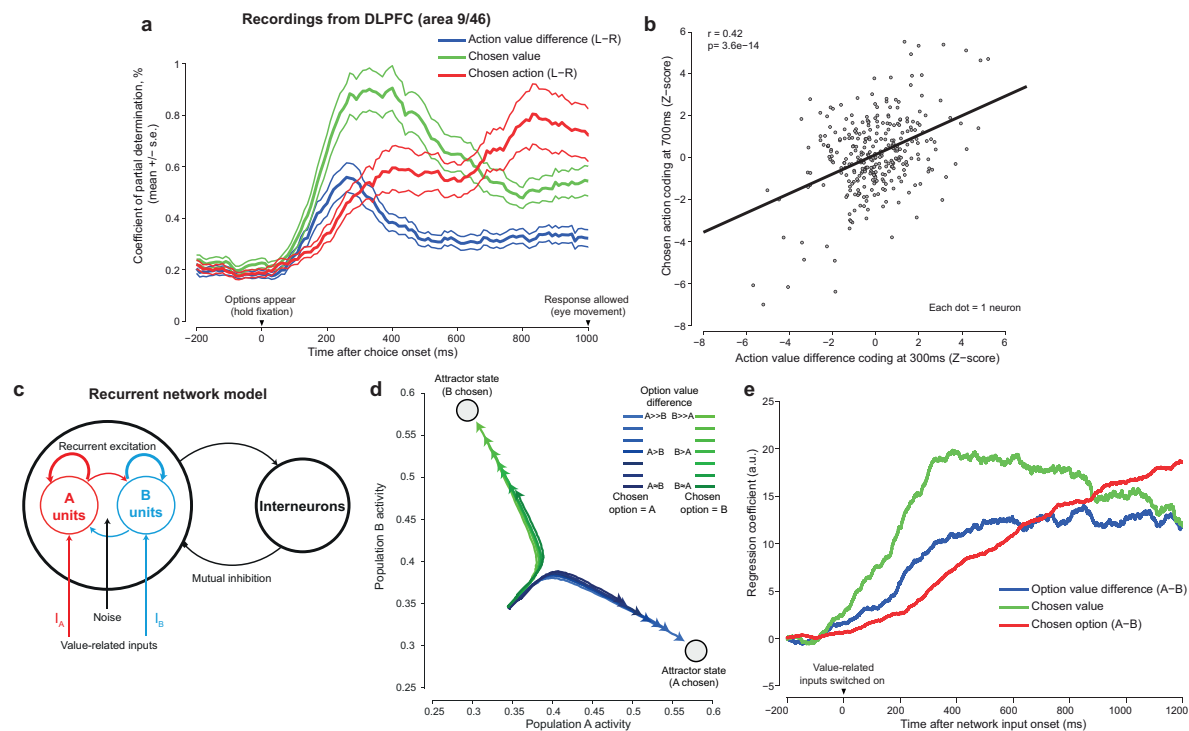
*Figure 3. **Temporal dynamics of value correlates in PFC during reward-guided decision making, and explanation via a recurrent microcircuit model with winner-take-all dynamics. (a)** Value correlates during a fixation period, prior to eye-movement choice, in area 9/46. The lines show, across the neuronal population (n=303 single units), the mean +/- s.e. of the coefficient of partial determination for each regressor (variance explained that cannot be accounted for by other regressors in the model). The DLPFC population initially reflects the different in value between the left and right options (blue), but later in the trial reflects the actual choice made (red). Between these two timepoints is the strongest representation of the chosen value (green). **(b)** The same neurons that strongly represent the action value difference at 300ms also strongly represent the chosen action at 700ms. **(c)** A recurrent network model of decision making, first introduced in (Wang, 2002), in which two selective excitatory populations receive noisy inputs that reflect the evidence (value) in favour of each option. Strong recurrent excitatory connections in the network allow integration of these inputs, and a pool of non-selective interneurons mediates an effective competition via mutual inhibition, where only one selective population reaches a high-firing attractor state. **(d)** Activity in the network approximately 500ms into the decision process, with arrowhead locations showing the current state of the network on trials of differing value/chosen option. On easy trials (A>>B or B>>A), the attractor state has almost been reached, whereas on difficult trials (A≈B) the network activity is far less advanced towards the final decision. At this point in time, network activity therefore correlates with both the option value difference and the chosen value. The representation of the chosen option will become strongest later, once all the arrows have reached the attractor state. **(e)** The value correlates that arise from these network dynamics vary across time; the same sequence of value correlates is found in the network model as in the data. Adapted from (Hunt et al., 2015).*

from area 9/46 in the dorsal bank of the principal sulcus in dorsolateral PFC (DLPFC) (Hunt *et al.*, 2015). These recordings were made while the animal fixated a central fixation point, and two pictures were presented on either side of the screen with different values. As the monkey fixated, value correlates were observed in these DLPFC neurons that evolved over time (figure 3a). Initially the neuronal population reflected the difference in values between making a

leftward versus a rightward saccade (blue line), but later in the decision process they reflected the eventual choice that the animal was about to make (red line). These quantities were not represented by separate subpopulations of neurons; instead, those neurons that encoded action value difference 300ms into the decision also encoded the chosen action 700ms into the decision (figure 3b). Between these two timepoints, there was a representation of the value of the chosen option (green line). Similar temporal dynamics separating value and choice encoding have also been observed in previous studies (Kim *et al.*, 2008; Louie & Glimcher, 2010).

How might a recurrent microcircuit give rise to such time-evolving correlates of a decision process? A number of studies (Hunt *et al.*, 2015; Rustichini & Padoa-Schioppa, 2015; Song *et al.*, 2017) have used variations of the recurrent circuit model shown in figure 3c to make predictions of value correlates that might emerge as a consequence of mutual inhibition between competing pools of neurons that are selective for different alternatives. The input to the selective units is modelled as reflecting the strength of decision evidence for each option. Recurrent excitatory connections combined with slow NMDA receptor dynamics (as described in the previous section on PFC/ACC microcircuits) support the gradual accumulation of evidence in favour of each alternative. Pooled inhibition across the network leads to a winner-take-all process, whereby there is a stable attractor state in which one pool of selective neurons effectively inhibits the other pools of neurons, a process termed 'competition through mutual inhibition' (figure 3d).

This model architecture builds upon earlier work that used the same circuit to capture the dynamics of cell activity during perceptual evidence integration (Wang, 2002; Wong & Wang, 2006), as well as persistent activity during working memory (Wang, 1999). These cellular responses are not exclusively found within frontal cortex; indeed, the model was first

used to explain data collected from posterior parietal cortex (Shadlen & Newsome, 1996; Shadlen & Newsome, 2001). However, it can be seen in figure 2b that area 7 within the parietal cortex has similar microcircuit and macrocircuit properties to PFC areas, and so temporally extended information processing in these areas can be explained using the same principles. It is only because the recurrent network has sufficient recurrent excitation and long time-constant NMDA receptors that it can sustain persistent activity over long periods of time. It therefore provides a biologically plausible mechanism for the implementation of temporally extended evidence accumulation within a neural circuit.

When such a recurrent network is used to simulate a range of value-based decisions, the same regression analysis that was applied to the neuronal data (figure 3a) can also be applied to the time-varying network activity. Strikingly, the same sequence of value correlates can be found in the network model as in the data (figure 3e) (Hunt *et al.*, 2015). A similar approach can also be used to model the temporal dynamics of value correlates observed at a mesoscopic (rather than cellular) level: by summing the postsynaptic potentials across *all* the units in the network and using this as a proxy for the local field potential. This reveals an initial correlation with the overall sum of presented values (=chosen + unchosen values), followed by a later correlation with value difference (=chosen – unchosen values) (Hunt *et al.*, 2012). This sequence of value correlates was found both at the level of the macaque local field potential (Hunt *et al.*, 2015) and also using magnetoencephalography in humans (Hunt *et al.*, 2012) which is known to relate to the local field potential (Hämäläinen *et al.*, 1993). The network model makes clear that these value correlates emerge as a consequence of a dynamical decision process unfolding at different speeds on different trials (figure 3d) (Hunt, 2014; Hunt & Hayden, 2017), and this was empirically validated in the macaque local field

potential: value correlates emerge at the times when the temporal derivative (i.e. rate of change) of the field potential was greatest (Hunt et al., 2015).

Although the responses in figure 3 are from area 9/46, it is worth noting that such a model also describes value correlates in many other subregions, including the orbitofrontal cortex (Hunt et al., 2015; Rustichini & Padoa-Schioppa, 2015), ventromedial prefrontal cortex (Hunt et al., 2012), and anterior cingulate cortex (Hunt et al., 2015). This suggests that competition through mutual inhibition may be a general property of PFC/ACC microcircuits, but that the frame of reference in which competition takes place varies depending upon the inputs to each subregion (Cisek, 2012; Hunt & Hayden, 2017).

It is important to note that none of these models rely upon a direct fit of the model dynamics to neural data; instead, the central predictions concern the *sequence* of value correlates, which can be shown to be robust to the exact parameterisation of the model (Hunt et al., 2012). While the model parsimoniously accounts for several features of neural data, it is also clear that some of this parsimony is an oversimplification. For instance, whereas the model consists of discrete pools of selective units, there is much evidence for neurons being both positively and negatively tuned for different task features (Kennerley et al., 2009), and for this selectivity being mixed (Rigotti et al., 2013) and distributed across the population (Mante et al., 2013; Hunt et al., 2018; Yoo & Hayden, 2020). While the nature of population coding in PFC/ACC has recently been contested (Hirokawa et al., 2019; Onken et al., 2019), it is nevertheless clear that the model simplifies the diversity of neuronal populations in PFC, and it does not speak to other properties such as layer-specific computations and interneuron diversity. In addition, it assumes that the stimulus values can be directly fed into the network, rather than learnt over time via reinforcement; more recent versions of recurrent networks address this issue directly (Song et al., 2017). It may also be interesting to consider approaches

that directly fit the response properties of the model to neural data (Dezfouli *et al.*, 2018), and those that are trained on performing a more diverse array of temporally extended cognitive tasks (Yang *et al.*, 2019).

The PFC Consists of Multiple Subregions, whose Functional Specialisation is Determined by their Macrocircuit Connections

Whereas microcircuit specialisations can be considered a property of PFC/ACC circuits as a whole, there is functional specialisation within PFC/ACC that arises as a consequence of variation in macrocircuit connections. The anatomical connections that a brain area receives will determine the information that it receives, and therefore the computations that it can perform. This provides a neuroanatomical basis of functional specialisation in the cortex (Passingham *et al.*, 2002). PFC and ACC are not unitary brain areas, but instead consist of a large number of subregions that can be distinguished based on cytoarchitecture (Petrides & Pandya, 1999; Ongur & Price, 2000; Ongur *et al.*, 2003) and, more recently, multimodal neuroimaging (Glasser *et al.*, 2016). These subregions are also distinguished from one another in terms of their anatomical connections (Ongur & Price, 2000; Haber & Behrens, 2014), and this variation can in turn be used to explain the contribution that different subregions make to reward-guided decision making and other cognitive tasks.

A straightforward way of illustrating the connections of a given cortical area is to plot its "connectivity fingerprint" – a polar plot that shows the strength of connectivity to a range of other areas of the brain. This allows one to directly compare the similarities and differences between different subregions in terms of their connectivity. Connectivity fingerprinting was initially performed using data compiled from injection of tract tracers, collated into databases to allow statistical comparison of different areas' fingerprints (Kötter *et al.*, 2001; Passingham

et al., 2002). More recently, the advent of neuroimaging techniques such as diffusion tensor imaging and resting state functional imaging has allowed connectivity fingerprints to be directly studied in the living human brain (Jbabdi *et al.*, 2015; Mars *et al.*, 2018a). This has facilitated cross-species comparison of anatomical connectivity between humans and other primates, supporting direct homologies to be drawn between different species' cortical subregions (Mars *et al.*, 2011; Jbabdi *et al.*, 2013; Sallet *et al.*, 2013; Neubert *et al.*, 2014; Neubert *et al.*, 2015; Mars *et al.*, 2018b).

One key study (Neubert *et al.*, 2015) performed such a cross-species comparison between resting state connectivity in the human brain and the macaque brain, assessing a range of brain areas on the orbital and medial surfaces that are central to reward-guided decision making. This was also linked to diffusion imaging data collected in the human brain. Figure 4a and figure 4b show the results of this analysis for two regions that have frequently been studied by neurophysiologists studying neural correlates of reward-guided decision making: area 13m in the orbitofrontal cortex (Tremblay & Schultz, 1999; Padoa-Schioppa & Assad, 2006; Kennerley *et al.*, 2011; Rudebeck *et al.*, 2013; McGinty *et al.*, 2016; Rich & Wallis, 2016; Xie *et al.*, 2018), and area 24c in the anterior cingulate cortex (Shidara & Richmond, 2002; Amiez *et al.*, 2006; Seo & Lee, 2007; Kennerley *et al.*, 2009; Hayden *et al.*, 2011; Kennerley *et al.*, 2011; Cai & Padoa-Schioppa, 2012; White *et al.*, 2019).
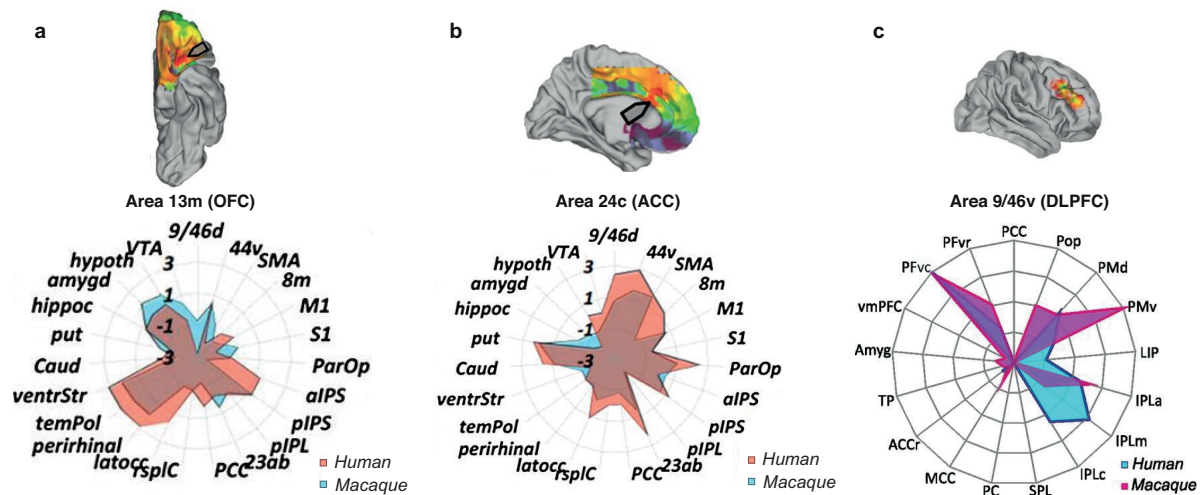
Figure 4. **Connectivity fingerprints of three subregions of PFC and ACC associated with reward-guided decision making.** *The resting state connectivity for each subregion shown in the bottom row was determined using functional MRI in humans and macaque monkeys. In each fingerprint, the polar axis reflects the degree of coupling between the subregion and a range of other key brain regions. **(a)** Area 13m in orbitofrontal cortex has particularly strong positive functional coupling with regions containing highly processed sensory information in the ventral visual stream (ventrStr), temporal pole (temPol) and perirhinal cortex, amongst others. **(b)** Area 24c in ACC does not show positive coupling with these areas, but instead with parts of striatum associated with motor control (caudate/putamen), area 9/46d in the DLPFC, and the supplementary motor area (SMA), amongst others. **(c)** Area 9/46v in the DLPFC shows strong coupling with parts of the parietal cortex in the inferior parietal lobule (IPL) that have been associated with attentional reorienting, amongst other regions. n.b. Panel **(c)** is taken from a different study (Sallet et al., 2013) to panels **(a)/(b)** (Neubert et al., 2015); the same methodology is used, but the target regions of interest are different. In panel **(c)**, only positive coupling is shown on the connectivity fingerprint, whereas in panels **(a)/(b)** both positive and negative coupling is shown. It is important to note that connectivity fingerprints measured by tractography or functional imaging are not directional (and not all connections are bidirectional, as shown by tract-tracing studies (Markov et al., 2014)). Panels (a) and (b) Copyright 2015 National Academy of Sciences.*

Area 13m (but not area 24c) is shown to have particularly strong connections to areas in the ventral visual stream and temporal pole amongst others. These contain highly processed sensory information, with cells responding to objects that are currently in the animal's field of view (Ito *et al.*, 1995; Booth & Rolls, 1998; Hung *et al.*, 2005; DiCarlo *et al.*, 2012) (figure 4a). Other studies have also highlighted the connectivity of this region to processed sensory information from other modalities, as well as gustatory and olfactory cortices (Carmichael & Price, 1995a; Carmichael & Price, 1995b); therefore, this region receives multimodal information that can be combined across multiple senses, and may serve as a basis for linking this sensory information with reward expectations (Noonan *et al.*, 2012).

By contrast, area 24c (but not area 13m) possesses strong connections to the dorsolateral prefrontal cortex and insula, and also to motoric areas such as the supplementary

motor area and the caudate/putamen (figure 4b). This suggests that instead of being positioned for linking sensory information to reward, it may be better positioned to guide appropriate selection of actions to obtain reward. Although this region does not project directly to the spinal cord, it has strong connections to a more posterior part of the cingulate sulcus that has direct connections to both spinal cord and primary sensorimotor areas (Van Hoesen *et al.*, 1993).

These connections help to explain the distinct contributions of these areas to reward-guided decision making. For example, lesions to OFC and ACC produce dissociable impairments on learning stimulus-outcome and action-outcome contingencies, respectively (Rudebeck *et al.*, 2008; Camille *et al.*, 2011). Area 13m in OFC has neurons that are selective for specific juice identities and their values (Padoa-Schioppa & Assad, 2006; Xie & Padoa-Schioppa, 2016), whereas area 24c in ACC has neurons that are particularly sensitive to the movement needed to obtain that juice (Cai & Padoa-Schioppa, 2012).

It is also important to distinguish area 13m in OFC from another area that has been shown to play a central role in valuation for economic choice, in ventromedial PFC. Ventromedial PFC is one of the most commonly activated brain regions in human studies of economic choice (Bartra *et al.*, 2013; Clithero & Rangel, 2014), and there is some evidence for this region also performing value comparison in macaque single cell recordings (Strait *et al.*, 2014). However, tracer studies in macaques (Ongur & Price, 2000; Saleem *et al.*, 2008) and diffusion imaging studies in humans (Neubert *et al.*, 2015) indicate that it belongs to a different connectional network from area 13m. It has recently been shown that VMPFC is particularly involved when primates are asked to make novel choices that they have not previously made before (Bongioanni *et al.*, 2021). This may explain why it is particularly commonly found in human imaging studies, where subjects are performing the task for the

first time, as opposed to animal single-unit recordings, where the animals have often been trained for many months on the same task.

Further studies have also investigated the connectivity fingerprints of subregions within the dorsal frontal cortex - including those on the lateral surface, which is sometimes referred to as dorsolateral PFC (DLPFC) (Sallet *et al.*, 2013). Figure 4c shows the connectivity fingerprint of one DLPFC subregion on the ventral bank of the principal sulcus, which is the ventral portion of area 9/46. Amongst other connections, this subregion has connectivity to parts of the inferior parietal lobule such as IPLa that are associated with reorienting of visual attention (Thiel *et al.*, 2004). Tract tracer studies from area 9/46 have also highlighted its connectivity to a more caudal area around the arcuate sulcus, area 8, which contains the frontal eye field (Petrides & Pandya, 1999).

Amongst other functions, this region might therefore be particularly concerned with decisions over where to saccade next when searching for rewards. Indeed, neurons recorded from this area have been studied by several groups in the context of eye movement decisions based on sensory evidence (Kim & Shadlen, 1999), working memory and attention (Lebedev *et al.*, 2004), reinforcement history (Kim *et al.*, 2008), or value-associated stimuli (Cai & Padoa-Schioppa, 2014; Hunt *et al.*, 2015). These recordings indicate selectivity of these neurons for spatial attention or eye movement preparation. Indeed, it is this area that shows the transformation over time from action value encoding to chosen action in figure 3, where the choice was made with an eye movement (Hunt et al., 2015). OFC and ACC neurons recorded in the same study showed chosen and unchosen value signals, indicating that they were involved in the decision process, but they did not show the eye movement-related decision signals.

This provides an overview of only three ACC/PFC subregions. Yet it is clear that these three subregions have very different connectivity fingerprints, and this can be linked to their functional specialisation. This contrasts with 'neurochemical fingerprints', which as discussed in the section on microcircuits appear fundamentally similar across different PFC/ACC subregions, but with a single dominant axis of variation across the brain (Geyer *et al.*, 1998; Burt *et al.*, 2018).

Different PFC Subregions Make Distinct Contributions to Temporally Extended, Attention-Guided Choice

There has been an unacknowledged tension between accounts of decision making that focus primarily on functional localisation (Fellows & Farah, 2005; Lee *et al.*, 2007; Buckley *et al.*, 2009; Rushworth *et al.*, 2011; Murray & Rudebeck, 2018) or perhaps emphasise the contribution of one particular brain region (Padoa-Schioppa & Conen, 2017), versus those that focus on computations that may be common across multiple areas (Duncan, 2001; Cisek, 2012; Siegel *et al.*, 2015; Hunt & Hayden, 2017). Comparatively few neurophysiological studies have compared responses across multiple PFC/ACC subregions within the context of a single paradigm – but those that have often found subtle and quantitative rather than qualitative differences between PFC/ACC subregions (Wallis & Kennerley, 2010; Lee *et al.*, 2012).

The two accounts are of course not mutually exclusive, and it is possible that there is an element of truth to both. In other words, there may be similarities between PFC/ACC subregions in terms of supporting temporally extended cognitive tasks due to their microcircuit properties, but differences between which tasks they support due to their anatomical connections. However, if we are to identify these differences using

neurophysiology, it is crucial to design tasks that contain sufficiently rich behaviour to distinguish the computations being performed by distinct subregions as a decision unfolds.

For example, we have seen that microcircuit models (as shown in figure 3c) can be used to describe value-based decision making as a process of evidence accumulation across time when fixation is being held. But simple introspection tells us that attention must also play a role in the deliberation process. When making a choice, we do not maintain fixation on one point in space, but instead we shift our gaze in order to foveate different choice alternatives, considering one option at a time. How do we decide where to look next? How do our shifts in gaze, which determine the information that we sample from the environment, affect the decisions that we ultimately make? How do we decide when to stop sampling information, and commit to a final decision? Patterns of shifting eye gaze can be used as a window into this process of information sampling (Krajbich *et al.*, 2010; Krajbich, 2019), especially in decisions where each option consists of several different attributes that are separated in space (Arieli *et al.*, 2011; Glöckner & Herbold, 2011; Stewart *et al.*, 2016). Given the close association of certain parts of the PFC/ACC circuitry with brain regions that identify currently attended objects and/or reorient attention to new locations in space (figure 4), it would be natural to think that neural correlates of decision processes may be strongly shaped by attention.

One recent study (Hunt *et al.*, 2018) recorded neural activity across area 13m in OFC, area 24c in ACC, and area 9/46 in DLPFC (cf. figure 4) during a temporally-extended, attention-guided choice task that involved information sampling across multiple cues. Monkeys were trained to make choices using a joystick between two options that consisted of a reward probability and a reward magnitude (figure 5a). Crucially, the monkey had to sample this information sequentially by making saccadic eye-movements to different locations on the
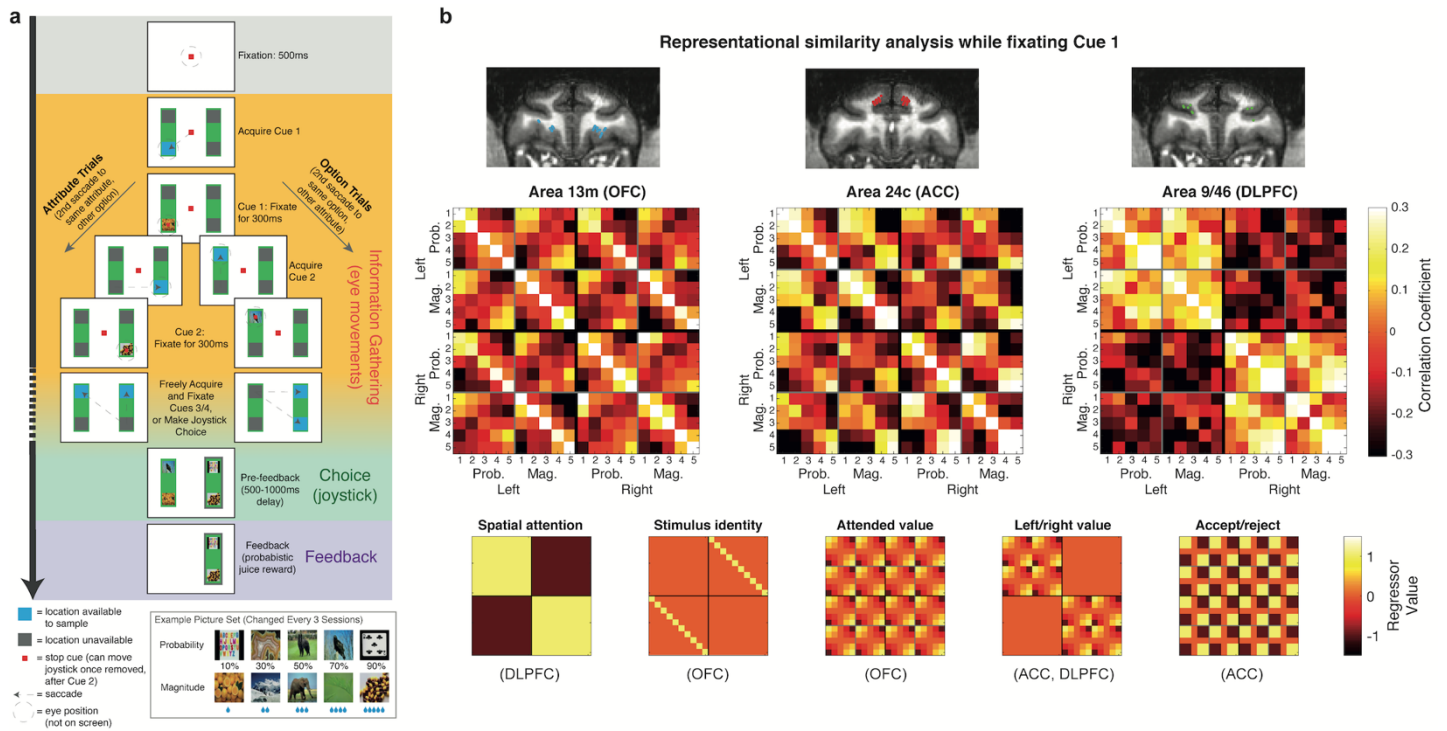
Figure 5. **Triple dissociation of attention and decision computations across three PFC subregions during a temporally extended, sequential, attention-guided choice task. (a)** *Task design. Macaque monkeys were presented with a choice between two options (left/right of screen), each consisting of two cues (denoting reward probability and magnitude). They revealed the cues by saccading to different locations (blue/grey boxes). After two cues had been revealed, monkeys could sample the remaining cues or could make a joystick response to indicate their choice. The first two cue locations were experimenter-controlled, such that all locations were equally sampled at the first cue, and half of all trials were "attribute" trials (i.e. the second cue was the same attribute (probability/magnitude) on the other option) whereas the other half were "option" trials (i.e. the second cue was the other attribute on the same option).* **(b)** *Representational similarity analysis (RSA) of each region's population firing rates, ~300ms after the first cue has been acquired. Each 'pixel' in the matrix reflects the degree of similarity (correlation) between two conditions, sorted by whether the picture is on the left/right of the screen, whether it represents reward probability/magnitude, and how valuable the picture is (1=least valuable, 5=most valuable). Several key task features can be encoded using 'templates' (bottom row) which are then regressed onto the RSA matrices; each of these are found to be strongly represented in some subregions but not in others. Adapted from (Hunt et al., 2018).*

screen. This type of experimental design has been used for many decades by psychologists and economists interested in how information search unfolds during choice (Payne, 1976; Fellows, 2006; Hunt *et al.*, 2016; Stewart *et al.*, 2016).

As the cues were being sampled, it was possible to examine how their different features were represented across the neuronal populations recorded from the three PFC/ACC subregions. Each cue was distinguished by its picture identity, how this stimulus was predictive of reward value, where it was located on screen, and how it affected the subject's eventual choice. Figure 5b shows the results of a representational similarity analysis (Kriegeskorte *et al.*, 2008) performed on the neuronal firing rates shortly after the first cue was sampled by the animal. The results showed a clear and qualitative triple dissociation of

function between the three subregions. Area 13m in OFC encoded the identity of the currently attended stimulus and the value of that stimulus, but has little information about its spatial position. Area 9/46 in DLPFC most strongly encoded the spatial location of where the monkey deployed their (overt) attention to sample this stimulus, as well as a value signal in the frame of reference of left/right spatial position. Area 24c in ACC also carried this left/right value signal. However, its dominant feature was a value coding signal that appeared to categorise stimuli into whether they were better than the average stimulus (and so might eventually be 'accepted') or worse than average (and so might eventually be 'rejected').

In addition to this dissociation at the first cue, it was possible to study how information was combined when further cues were sampled in order to form a decision (figure 6a). In OFC, when monkeys sampled a cue on one option and a second cue on the other option, these cues should be compared in order to start to make a decision. It was found that there was a *negative* relationship between the value code for the currently attended cue and that for the previously attended cue (figure 6b) (Strait *et al.*, 2014). Moreover, on trials where the animal sampled two cues on one option and a third cue on the other option, the two *remembered* cues were now *positively* correlated in terms of their value code (figure 6c), but were both *negatively* correlated with the value code of the currently attended option. In other words, the memory of two previously attended cues appeared to be flexibly combined in OFC, allowing for comparison with the currently attended cue.

How did this attention-guided value comparison support the animal's commitment to a final choice? Two key signals in the ACC provided insight into this process (figure 6d/e). First, it was possible to define each cue according to whether it *confirmed* what the animal currently might believe to be the best option, or *disconfirmed* it. A stable ACC population subspace was

found to encode this "belief confirmation" regressor. Activity in this subspace peaked
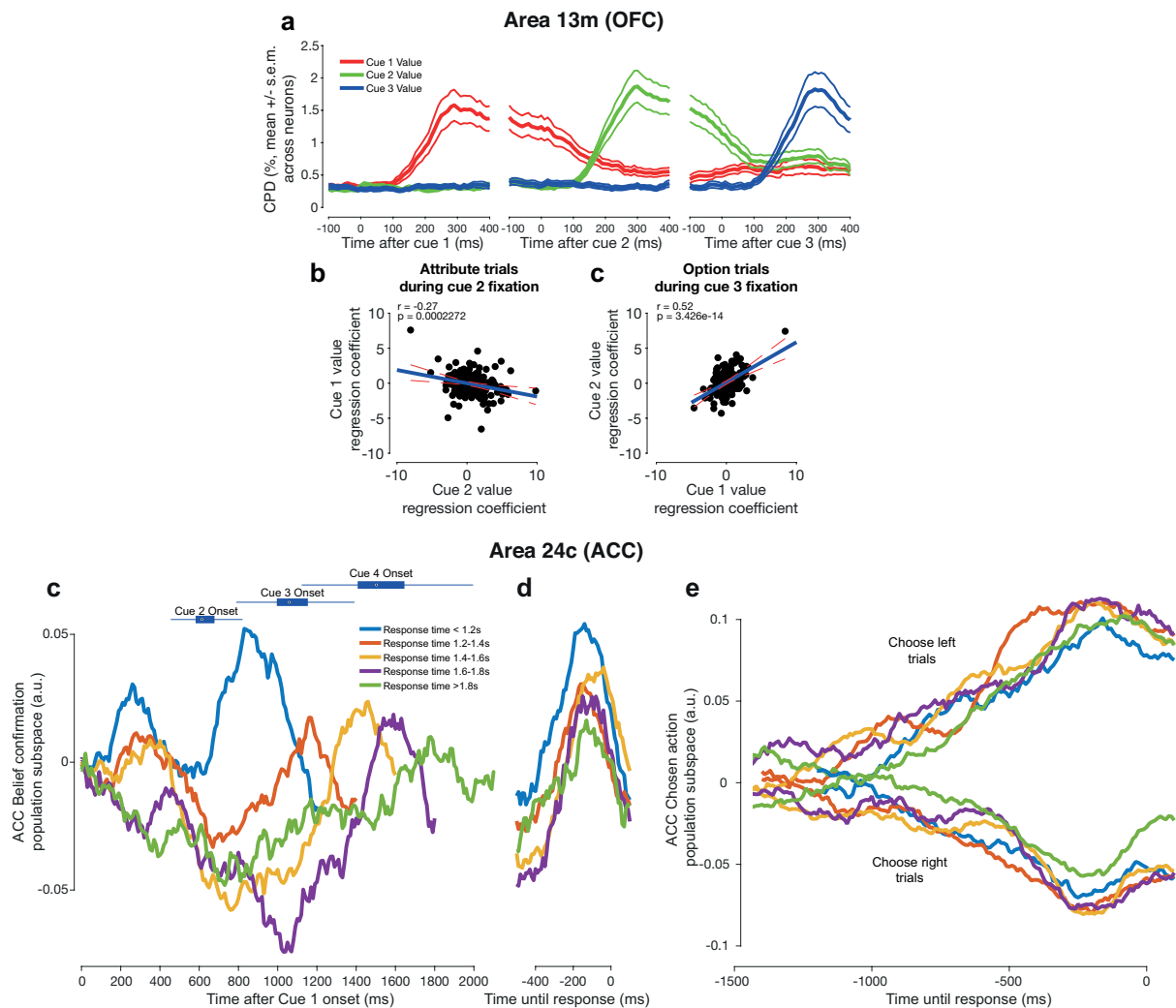
Figure 6. **Value comparison, and commitment to a final decision, during sequential attention-guided choice.** *The data shown are from the paradigm in figure 6a, as the subject moves beyond sampling the first cue (figure 6b) and samples further information then commits to a choice. **(a)** In OFC, the value of the currently attended cue is strongly represented ~300ms after it is sampled, but previously attended cues do not return to baseline – instead, there is a 'memory trace' of these cues in OFC activity. **(b)** On 'attribute' trials (see figure 6a for details), when cue 2 is fixated there is a negative relationship between encoding of the currently attended value versus the previously attended value. **(c)** On 'option' trials, when cue 3 is fixated there is a positive relationship between encoded of the two previously attended attributes (cue 1 value and cue 2 value), both of which are on the other option. These are also both negatively correlated with the currently attended, cue 3 value (not shown). **(d)** Population activity in ACC, projected along a subspace which is defined by whether the currently attended cue confirms the animal's belief as to which option is best. Trials are sorted into bins of different joystick reaction time; it is shown that activity ramps in this subspace immediately prior to a final commitment to a decision. **(e)** Population activity in ACC, projected along an orthogonal subspace defined by the final left/right joystick choice of the animal. It is shown that activity in this subspace gradually ramps towards a final leftward/rightward choice. Adapted from (Hunt et al., 2018).*

immediately prior to the time when the animal committed to a joystick choice (figure 6d). At

the same time, an orthogonal subspace in ACC represented an emerging plan for *which* choice

(left or right) the animal was going to make with the joystick; this also peaked immediately

prior to the decision (figure 6e). These two signals are in some ways an elaboration of the

signals observed in ACC at the first cue (figure 5b) - the "accept/reject" code is akin to a belief updating signal (but in the absence of any prior belief), and the "left/right value" code is the precursor to the commitment to a final left/right choice. It is likely that these two codes should influence one another, such that the belief confirmation signal can inform the plan for a choice, but this remains to be directly tested.

The results from this study could be interpreted in different ways. On the one hand, the presence of an attention-guided value comparison code in OFC, and an accumulator-like signal in ACC for the final action plan, corresponds very well to the core components of 'attentional drift diffusion' models of reward-based choice. This is an extension of the classical drift diffusion model (Ratcliff & McKoon, 2008) in which evidence accumulation is biased by the locus of visual attention (Krajbich *et al.*, 2010; Krajbich, 2019). Notably, the drift diffusion model can be shown to be formally related to the microcircuit models introduced earlier in this review (Bogacz *et al.*, 2006). A similar neuroanatomical account of the attentional drift diffusion framework was first introduced by Rangel and colleagues, largely on the basis of functional imaging evidence (Rangel & Hare, 2010; Hare *et al.*, 2011; Lim *et al.*, 2011; McGinty *et al.*, 2016).

On the other hand, some of the signals observed in ACC – the accept/reject code at the first cue, and the belief confirmation code as further cues are sampled – may fit more neatly into accounts of economic choice where decisions are framed as serial 'accept/reject' choices rather than between two mutually exclusive alternatives (Cisek, 2012; Hayden, 2018). The decisions that primates (and other animals) evolved to make rarely consisted of a few mutually exclusive alternatives, but instead of decisions about how to forage for food. These might consist of a sequence of decisions about whether to accept or reject a currently presented choice alternative. It is likely the brain will be functionally specialised to support

such foraging decisions (Kolling *et al.*, 2012), and many economic choices could be reframed as sequential decisions about whether to accept or reject a currently favoured alternative (Hayden, 2018).

Reconciling the 'evidence accumulation' framework for economic choice and the 'foraging' or 'accept/reject' framework may require a step towards even more naturalistic decision paradigms. Formal algorithms have been developed to account for choice behaviour in such foraging decisions (Stephens & Krebs, 1986; Mobbs *et al.*, 2018), but only recently have attempts been made to directly link foraging decisions to accumulator models (Davidson & El Hady, 2019). Decisions need not only include information sampling (Kaanders *et al.*, 2020), but also consist of multiple alternatives that are encountered in a sequential rather than simultaneous fashion. There have been recent movements towards studying such decision making in the field (Kolling *et al.*, 2012; Sweis *et al.*, 2018; Yoo *et al.*, 2020), and it is perhaps the study of these types of sequential decision that provide scenarios even closer to those faced by the decision-maker in the supermarket or the early primate amongst the arboreal branches.

Conclusions and future directions

Since the first studies began to investigate the neural basis of economic decision making just over 20 years ago (Shizgal, 1997; Platt & Glimcher, 1999), the field has made tremendous progress. This review has focussed on circuit specialisations supporting the sequential, temporally extended and attention-guided computations that are common to humans and other primates in making these decisions. I have argued that PFC/ACC as a whole contains recurrent microcircuit specialisations that support temporally extended information processing, but that the distinct anatomical connections of PFC/ACC subregions lead to them

making distinct contributions to reward-guided choice. In both cases, it has been possible to link the properties of neurophysiological recordings to these circuit specialisations.

A number of outstanding questions remain to be addressed. Firstly, the study of circuit specialisations at the microcircuit level and functional specialisations at the macrocircuit level have been treated as broadly separate problems; very few circuit models have been developed that encompass multiple interacting regions in the service of solving cognitive tasks. This raises the question as to how best to specify such a model of PFC and ACC circuits, how it should be tested, and what benefits might arise from having regional specialisation in such a model (as opposed to, for example, all-to-all connectivity). It seems likely that such an account may benefit from initially avoiding questions of biological plausibility; indeed, inspiration may be drawn from recent findings in developing recurrent neural networks in machine learning, where modularity and hierarchy conveys certain advantages in performing temporally extended tasks (Chung *et al.*, 2016). On the other hand, it is also possible that certain biological constraints are essential for considering why the PFC and ACC consist of multiple subregions with some degree of functional specialisation - for example, this may be necessary to constrain wiring length within the circuit. Such a hypothesis could again be explored in silico, by training networks to approximate multi-region neuronal data (Perich *et al.*, 2020) while introducing sparsifying constraints on network connections into the cost function used to train the network.

Secondly, although the studies discussed in this review have focussed on the introduction of attention as one means to study more naturalistic decision problems, it is also clear that primates have other unique cognitive capabilities that need to be incorporated into experimental tasks, and considered in terms of circuit specialisation. For instance, primates are advanced in their abilities of flexibly generalising and reusing knowledge from one

decision problem to other closely related problems (Behrens *et al.*, 2018), and they also have unique abilities to learn about the hierarchical structure of decision problems, and execute long-term sequences of behaviour in accordance with this structure (Conway & Christiansen, 2001). These questions have now been well formalised at the algorithmic level in the framework of reinforcement learning, and neural correlates of task state representations (Niv, 2019), generalisation and hierarchical structure (Ribas-Fernandes *et al.*, 2011; Donoso *et al.*, 2014) have been observed in various subregions of PFC. However, it is unclear what PFC circuit specialisations are fundamental for these kinds of behaviours, and whether these can also be considered at the microcircuit and macrocircuit level.

Thirdly, many of the key predictions of the framework outlined in this review remain to be tested. For example, is variation in the local correlates of a decision process predicted by the anatomical connections and microcircuit properties of the circuit? Although many of the regions studied in this review appear to carry multiple signals during the course of a decision process, a natural hypothesis is that these should actually be separable and align with the anatomical connections of the circuit. For example, neurons in area 13m that receive direct projections from sensory areas should be those best positioned to learn the value associated with specific stimuli, whereas neurons in layer III that have mostly recurrent connectivity should be primarily responsible for subserving competition through mutual inhibition. The development of new tools for interrogating neural circuits, such as novel recording techniques to sample many neurons from multiple layers and brain regions simultaneously (Siegel *et al.*, 2015; Steinmetz *et al.*, 2019), alongside circuit manipulation tools, should allow such questions to be tested more directly.

Addressing these challenges means that advances cannot be made only in circuit modelling, data recording and analysis techniques, but it will also be crucially important to

think about studying far richer, more naturalistic behavioural repertoires. The study of rich, ethologically valid behaviour can build upon the foundations laid by studying simpler, mutually exclusive forced-choice scenarios, which are the basis of much of the work presented in this review.

Competing Interests

The author declares no actual or potential conflict of interest.

Author contributions statement

L.H. wrote the paper and prepared the figures.

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