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Neural mechanisms underlying human choice in the frontal cortex

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Introduction

In order to study how animals make choices, a good place to start is to consider *why* animals make choices. For the moment, discard your preconceptions of choice that come with visions of agonised Shakespearean characters making decisions of mortal consequence. Instead consider a much simpler example – the choice to do anything at all, rather than the alternative of doing nothing. This simple consideration leads us to a central theme in all decision sciences. We act because there is *value* in acting. It prevents starvation, thirst, and predation, and promotes procreation. Because different courses of action will lead to outcomes of different *values,* the decision-making problem, at its simplest, is to "often select courses of action with high value, and seldom those with low value".

In neuroscience experiments, the value of different decisions is often controlled experimentally. Different options may, for example, lead to different monetary outcomes in human experiments, or different quantities or qualities of food or drink in animal experiments. When subjects are asked to decide between such options, many brain regions, and even single cells within these brain regions, show activity that represents the worth or *value* of different options to an individual. High and low value options will lead to different activity patterns in a cell or cell population. This type of neural activity is notable, because it is neither a re-representation of a sensory stimulus – the brain's "input" – nor is it an "output" such as a motor command that will elicit a particular action. Instead, it is a signature of internal computations that are related to the choice itself. For example, neurons in the orbitofrontal cortex (OFC) will signal the amount of food that a choice will result in, but only when the animal is hungry (Rolls et al., 1989). FMRI signals recorded in the neighbouring ventromedial prefrontal cortex (vmPFC) will signal strongly when people are offered chocolate bars, but not if the subjects are dieting (Hare et al., 2011). Cells in the Anterior Cingulate Cortex that will increase their activity at the prospect of a rewarding

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drink, will also suppress their activity if the animal must exert effort in order to get that drink because the required effort reduces the overall worth to the animal (Kennerley et al., 2011).

Such value-related brain signals can be found in single neuron and fMRI responses across much of the brain (Rushworth and Behrens, 2008; Serences, 2008; Wallis and Kennerley, 2010). A major challenge, therefore, is to understand what different contributions these different brain regions might make to valuation, choice and behavioural control. In this essay, I will focus on three neighbouring cortical regions along the medial wall of the frontal cortex: The anterior cingulate cortex (ACC), the ventromedial prefrontal cortex (vmPFC), and the rostral dorsomedial prefrontal cortex (dmPFC) (figure 1, **p. xxx**). These three regions are of particular interest, partly because they demonstrate a paradigmatic example of how computational ideas can provide important insights into the different roles of apparently similar neural activity; but also because, despite their proximity in the brain, these three regions likely first appeared at very different points during mammalian evolution. By considering their different contributions to behavioural control, we can perhaps gain some insight into the evolution of the complex behaviours exhibited everyday by humans. The ACC is present in all mammals that have been studied; the granular layer iv in vmPFC makes this region likely to be an evolutionary adaptation specific to primates (Mackey and Petrides, 2010; Tsujimoto et al., 2011); it was thought possible that the dmPFC was a specialisation unique to humans or at least great apes, until the recent discovery of a possible homologous area in the macaque monkey (Sallet et al., 2011).

Behavioural adaptation and the Anterior Cingulate Cortex

Assuming that you have overcome the first hurdle, and are committed to doing something rather than nothing, you now face a new and very difficult problem: What should you do? Solving this task optimally is not only difficult; it is impossible. The array of actions you can take is infinite, and you are continually faced with this challenge at every moment in time. In order to constrain the problem, you need a mechanism that performs two key functions. First, it must tell you when is a good time to make a decision. I hope for example, that you will not decide to make a cup of tea between reading the next two words in this sentence. Second it must be able to reduce the candidate options to a number that might reasonably be compared.

One simple strategy that can help with such constraints is to give default preference to a particular course of action. Such an action might simply be the action that you are currently taking (reading this sentence), or might, for

example, be a habit that you have often followed in the same situation (Daw et al., 2005), such as going to work by the same route at the same time each morning. This strategy simplifies the decision-making problem dramatically. The problem is now one of knowing when to change your default strategy and adopt a new one. A wealth of evidence is suggestive that the dorsal ACC subserves computations that are tuned for exactly such a decision.

The ACC responds to changes in the world

In order to discern whether you should continue with your current policy, it is critical that you monitor the outcomes of your actions. Actions that often result in good outcomes should be repeated. Those that do not should be discarded. Neural responses in the ACC are tuned to the outcomes of actions, whether positive or negative (Jocham et al., 2009; Kennerley et al., 2011; Matsumoto et al., 2007; Shima and Tanji, 1998; Walton et al., 2004), and these responses are particularly strong if the outcome was a consequence of an action voluntarily selected by the subject (Walton et al., 2004). The ACC therefore has the opportunity to evaluate the quality of our current behavioural policy. To evaluate whether, and how well, it takes this opportunity, we must turn to some more mathematical ideas.

One reason why it might be important to change from your current preferred strategy is that something about the world has changed to mean that this strategy is no longer good. Your favourite apple tree has no apples, or your prey has moved away from the valley. But how do you know if a real change has occurred, or if your latest observation is just an aberration? The buffalo may have started their annual migration, or may have moved just for one day. This problem is equivalent to asking "How much should I learn from this latest piece of data in comparison to the rest of my experiences", and is a problem that Bayesian statistics is ideally placed to answer (Courville et al., 2006). A core idea in Bayesian statistics is that different pieces of information should be reconciled according to their respective predictive values. Hence in situations in which the most recent piece of information is a better predictor of the future than historical information (such as fast changing, or "volatile" environments) subjects should also learn at a fast rate by placing a great deal of weight on each new observation. By contrast, in situations where historical information is still informative (because the world changes only slowly), subjects should place little weight on new data points and instead, stay with their original policies.

Humans (Behrens et al., 2007; Nassar et al., 2010), macaques (Rushworth and Behrens, 2008) and rodents (Gallistel et al., 2001) do indeed learn faster when the environment is more volatile and, in Humans, each new obser-

vation causes more ACC activity in a volatile environment than that same observation would in a stable one (Behrens et al., 2007). Furthermore, individual subjects who display this ACC activity to a greater extent are the same subjects who are fastest to change their beliefs (Behrens et al., 2007). The anterior cingulate cortex is not simply monitoring the outcomes of our choices, but also using these outcomes to optimally adapt our future behaviour (Rushworth and Behrens, 2008). Indeed, if lesions are made to the ACC in macaque monkeys the impairment that can be observed is precisely this capacity to integrate past observations appropriately to guide future behavioural change (Kennerley et al., 2006).

These data reveal insights about the types of computations that occur in the ACC to guide choices, but more recently there have also been insights into how these computations occur at the level of cellular dynamics and neurochemicals. When Rats perform the simple task of choosing the correct location to find food, they are able to maintain a stable strategy even in the face of noisy outcomes. If the food is in the same place on 70 or 80% of occasions this will be the place they look first, even if it was somewhere else last time round. During these periods of stable belief, the pattern of activity amongst a population of cells in the ACC also remains stable (Karlsson et al., 2012) - each cell's activity will look the same on this trial as it did on the last. If the experimenter then plays a trick on the animal, and changes the best location to find the food, after several errors the rat will eventually learn to change strategy. However, before the rat commits to a new strategy, it undergoes a period of uncertainty when it is modifying its internal beliefs, displaying a decreased resolve to pursue a single strategy and, instead, exploring the different options seemingly at random. During this period, patterns of activity in ACC cells undergo volatile changes from trial to trial as the old belief is broken and the new one formed (Karlsson et al., 2012).

It is not clear what neural events lead to these rapid resets of the ACC cellular network, but one intriguing possibility is that they are mediated by the neuromodulator Norepinephrine (NE) (Yu and Dayan, 2005). The source of almost all of the brain's NE is the locus coeruleus (LC), a small nucleus in the mid-brain with a major input to the ACC. Release of NE from the locus coeruleus has broad ranging effects on the brain's arousal systems and, in particular, causes a dilation of the pupils. This convenient fact enables neuroscientists to measure an index of LC activity without harm to the subject. Matthew Nassar and colleagues have measured pupil diameter whilst subjects performed a change detection task (Nassar et al., 2012). In this task, there are two computational factors that should make

subjects amenable to changes of belief: The long-term probability that the world might change (akin to the environment volatility described above), and a term known as the relative uncertainty, which captures mathematically your doubt that your previous belief was correct. As these factors are varied by the experimenter throughout the experiment, they both exhibit strong and separable influences on the measured pupil diameter. Perhaps most impressively, if the experimenter introduces a surprising stimulus (a loud noise) at an unexpected time in the experiment, this not only causes an increase in pupil diameter, but also results in a rapid period of revising beliefs about the subject's completely unrelated task.

This causal intervention suggests that computations in the ACC are not simply responsible for detecting changes in the environment, but also for inducing resultant changes in behaviour. Such a computation is central to ecological theories of foraging animals(Charnov, 1976). If an animal is foraging for food in a field, the amount of food in that field will decline, but it is costly to leave the field and find a better one. If the animal's strategy is always to move to the best field, he will spend almost all of his time walking between fields! So when should he move from one field to the next? The mathematics of this problem can be solved, and there is indeed an optimal "foraging time" in each field(Charnov, 1976). When monkeys are asked to solve this problem in a laboratory they solve the problem almost exactly perfectly. They find the optimal foraging times no matter how rich is their own field, how rich is the competing field or how much it costs to travel between fields (Hayden et al., 2011). It seems that this remarkable capacity is due to this same ACC behavioural adaptation mechanisms. Whilst the animal is happily foraging in his patch, cells in the ACC are signalling exactly how good it would be to leave this patch right now. When these cells reach a threshold level of firing, the animal moves to the next patch (Hayden et al., 2011).

Two recent studies have demonstrated that these ancient foraging mechanisms are also at work when humans make decisions, and that they again rely on the anterior cingulate cortex. When humans are asked whether they would like to stay with a current option or to return to the world to see what they will get, FMRI signal in the ACC reflects the average value of everything else in the environment, and inversely reflects the cost of returning to the environment (Kolling et al., 2012). Just like the cells in Hayden's monkeys, signals in the human ACC reflect the expected value of changing from the current behaviour (Kolling et al., 2012). Furthermore, this signal works at the strategic level – exactly as is needed to solve the foraging problem. If subjects temporarily break from their long-term strat-

egy to try something new, the adaptation signal in the ACC both influences and later learns about the long-term strategy, and not the short term distraction (Boorman et al., in press).

Evaluative choices and the ventro-medial prefrontal cortex

Whilst many decision-making problems might be solved by the kinds of simple behavioural adaptation strategies such as those that I have attributed to the ACC, humans are certainly capable of choices that cannot be solved in such a simple fashion. We can decide to get married, to spend hundreds of thousands of pounds on a new house, or even make simple choices between restaurants where we havenever previously eaten. Two experiments that I have already described in the context of foraging-style choices above (Boorman et al., in press; Kolling et al., 2012) also compared these foraging choices with a particular type of 'evaluative choice' that can be examined in a laboratory. In both cases, whilst foraging-type activity was recorded in ACC, activity that reflected these evaluative choices could be recorded in the vmPFC (Boorman et al., in press; Kolling et al., 2012). That the vmPFC is particularly important for these types of choices has long been known from experiments that study patients with damage to vmPFC. Patients with vmPFC damage become indecisive about even trivial decisions (Barrash et al., 2000); choices that are made are often made poorly (Bechara et al., 1994; Bechara et al., 2000) according to unusual strategies (Fellows, 2006).

It is tempting to think that such subjective and complex behaviours as these might be immune to computational descriptions, but some progress has been made. Much like in the ACC, neural signals in vmPFC encode the value of potential choices at both the single cell (Bouret and Richmond, 2010)((Monosov and Hikosaka, 2012) and population level (FitzGerald et al., 2009; Kable and Glimcher, 2009; Rangel and Hare, 2010). However, vmPFC responses appear particularly flexible. Whilst many other brain regions rely on direct experience of previous outcomes to estimate the value of different courses of action, vmPFC can encode values that must be computed on the fly. These computations may, for example, rely on an understanding of the complex structure of the environment (Hampton et al., 2006); from the generalisation of concepts learnt in different situations (Kumaran et al., 2009); or from the integration of several disparate sources of information (Behrens et al., 2008). Perhaps most strikingly, if subjects are asked to ignore all of their own experiences and preferences, and instead to guess what a very different individual would choose, vmPFC value signals immediately reflect the preferences of this new individual (Janowski et al., 2012; Nicolle et al., 2012). If,

however, the problem at hand is best solved by considering values learnt from direct experience, the vmPFC can seamlessly revert to these more basic value computations (Wunderlich et al., 2012).

We are only now beginning to investigate the mechanisms that allow vmPFC and connected brain regions to perform these complex evaluations (Wimmer et al., 2012), but more progress has been made in understanding how a network of cells might use these computed values to select choices and guide behaviour. Such explicit or evaluative choices do not benefit from the simplifying strategies employed in foraging-style choices (Boorman et al., in press), so this system is once again faced with the problem of focussing attention on the option with the highest expected value from many possible alternatives. One possible solution to this problem is for different options to compete simultaneously for neural representation. Particular patterns of cellular activity associated with each option may become excited if that option is potentially valuable, and this activity may inhibit other representations from forming (e.g. (Wang, 2002)). Such a neural architecture implies a competition that is seamlessly resolved by options inhibiting each other until activity only remains in a single one. At this point, a decision has been made. If the competing neural representations are initially more excited by more valuable potential outcomes, then such architecture will, on average, make profitable decisions.

It is possible to construct neural networks with exactly this architecture in silico (e.g. (Wang, 2002, 2008)) and examine how they behave when faced with the same choices made by laboratory subjects. When the activity in such a simulated network is analysed, a complex and precise pattern can be seen in the average activity of the network that is a signature of this competitive inhibitory architecture. The activity of the network transforms its representation of value midway through the decision, does so with particular timings and at particular frequencies. When we look for a region that expresses this signature in the human brain, we find this exact pattern of activity in the vmPFC (Hunt et al., 2012). It appears that a competition mechanism exists in vmPFC that can highlight favourable options and suppress unfavourable or irrelevant ones. Indeed, when lesions are made to macaque vmPFC, unfavourable distracting options cannot be suppressed and interfere with the animal's choices (Noonan et al., 2010).

Again, however, modern methods allow us to go further and examine the neurochemistry that underlies these cortical computations. If it is indeed the case that competitions can be resolved by combining the excitation of favourable options with the inhibition of irrelevant ones then these competitions likely rely on the brain's major excitatory and inhibitory neuro-

transmitters, Glutamate and GABA. Indeed, using the same *in-silico* architectures that predicted dynamic signatures of choice above, one can predict exactly *how* variations in GABA and Glutamate concentrations should affect both subject choices and neural dynamics (Jocham et al., 2012). Increasing the GABAergic inhibition in such simulated networks results in choices that are resolved more slowly, but more accurately; increasing the glutamatergic excitation results in faster more erratic choices. Combined with the knowledge that cortical Glutamate and GABA concentrations may vary substantially across different individuals (Stagg et al., 2011), these observations make a rather surprising prediction: a behaviour as complex and personal as value-guided choice might depend predictably on basic neurochemistry. And indeed it does - People with high GABA concentrations in vmPFC exhibit slow neural dynamics and accurate decisions. Those with high vmPFC Glutamate concentrations exhibit fast dynamics and erratic decisions (Jocham et al., 2012).

Modelled choice and the dorsomedial prefrontal cortex

Sitting just above the vmPFC on the medial surface of the prefrontal cortex (figure 1) is a cortical area that is much less well studied and understood. The dmPFC is a region of cortex in which no single cell activity has ever been recorded because, until recently (Sallet et al., 2011), it has not been clear that the region even exists in any nonhuman species. In humans, the signals that can be recorded in this region are extremely alluring. The region, for example, appears to be particularly active in situations in which the experimental subject must attribute motive or intention to something in their surroundings. For example, dmPFC activity is weak when a subject is viewing triangles moving around a screen, but strong if one triangle appears to coax another to move in a particular direction (Castelli et al., 2002; Castelli et al., 2000). Responses such as these have led scientists to suggest that the region might play an important role in *social* cognition. The ability to infer the intentions and likely actions of others is of clear evolutionary value to all social animals, and humans are perhaps unique in the number and complexity of their social interactions (Dunbar and Shultz, 2007).

It is likely, then, that this brain region that has appeared relatively recently in human evolution might support a type of activity that underlies this complex human behaviour, but can we discover how? It seems to be a daunting challenge. Is it even possible to describe such mechanisms in a way that is amenable to scientific testing? It is very early days, but there are some indications that this problem might not be completely beyond our reach. One approach that has been taken is to look for parallels between mechanisms that

might underlie social behaviour, and those that are known about in non-social settings. We know, for example, that a key neural mechanism that controls reward learning is computation of the *reward prediction error* – the difference in reward between what was expected and what was received (Schultz et al., 1997). Neural signals that code for the reward prediction error are most famously found in the dopaminergic ventral tegmental area (Schultz et al., 1997) but can also be found in other brain regions including the vmPFC (Rutledge et al., 2010). Might a similar mechanism underlie our inferences about other individuals? Indeed, when subjects are asked to learn about the likely intentions of a confederate player in a game, FMRI activity in dmPFC first reflects first a prediction, and then a prediction error on the confederate's actions (Behrens et al., 2008; Hampton et al., 2008). Notably, in these studies the predictions and prediction errors did not concern the value of actions, but instead the truth of communicative intentions.

That the mechanisms at play in dmPFC (and related social regions (Frith and Frith, 2012)) might parallel those in vmPFC raises questions about whether there is really anything unique about the social nature of these computations. There is another intriguing possibility. By their very nature, representations of other individuals almost always require a model of that individual that is separate from the subject's current sensory and motor environment. In order to predict what another individual will do, the relevant environment is theirs, not yours. It is possible that it is this capacity to perform processing that is abstracted from the senses that was the key contribution brought by the evolution of dmPFC (Frith and Frith, 2003). If so, it is possible that the mechanisms and computations in dmPFC have a general similarity to those in vmPFC but take place in this abstracted frame of reference. Once abstracted, the values and goals that are represented in vmPFC activity might easily be misconstrued as dmPFC's motives and intentions.

It is possible to test such an idea by constructing an experiment similar to the simple value comparison task that was informative about vmPFC competition mechanisms, but with a twist. On some trials the subjects should choose not for themselves, but instead for another individual with very different preferences to their own. In these trials, then, the subject is choosing according to their own sensory and motor environment, but their partner's valuations (Nicolle et al., 2012). On trials when the subjects choose for themselves, signatures of their own choices can be seen vmPFC. In dmPFC, despite their irrelevance to the current task, the exact same signatures can be seen, but here computed according to the partner's values and the choices that the partner would have made. That it is the exact same signature that is recorded in the two regions supports the idea of similar un-

derlying computations. Crucially, however, when the subjects now choose on behalf of their partner, the two brain areas again exhibit the same signature but exchange agents so that the vmPFC now represents the partner's choices and the dmPFC the subject's. dmPFC activity is not required to model the other individual, but rather to abstract the choice from the immediate environment (Nicolle et al., 2012). Indeed, it is possible that the capacity to perform such abstract value processing has important functions that are completely divorced from social processing. For example, some decisions may rely on the ability to model ones own likely behavior in the context of future choices that ensue after the immediate action.

Conclusions

I have tried to demonstrate how modern scientists are attempting to dissect the neural mechanisms that control our behaviour. I have argued that humans display behaviours that are common to many other animals, and that in order to understand the neural processes that support these behaviours, we must first understand how the behaviours themselves evolved. Furthermore, I have argued that it is informative to consider the evolutionary precursors to human behaviours, even for behaviours (and perhaps neural processes) that are uniquely human. In making this argument, I have attempted to demonstrate several situations in which modern neuroscience has not only uncovered the computations that are being performed in different brain regions, but also how those computations might be performed in networks of cells and neurochemicals. Such an approach might even help us understand how the most complex human behaviours emerge - a major goal of neuroscience, and one that we are beginning to tackle.

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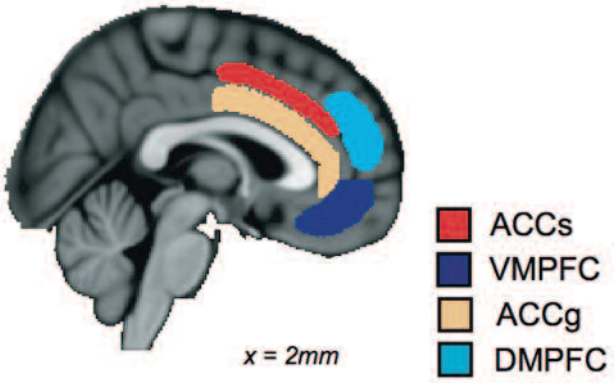

Figure 1. Medial frontal regions in a human brain. Saggital or medial view of the human brian. The frontal most part of the brain is on the right. ACCs – Anterior Cingulate Sulcus; VMPFC – ventromedial prefrontal cortex; ACCg – Anterior Cingulate gyrus; DMPFC – dorsomedial prefrontal cortex. Adapted from Behrens et al. Science 2009. For the purposes of the current review, I will not discuss the interesting differences between the sulcal (ACCs) and gyral (ACCg) portions of the anterior cingulate cortex. These are discussed at length in (Behrens et al., 2009; Behrens et al., 2008; Rudebeck et al., 2006).