

## DO WE UNDERSTAND THE PREFRONTAL CORTEX?

Richard E. Passingham<sup>1</sup>, Hakwan Lau<sup>2</sup>

1. Department of Experimental Psychology, University of Oxford, UK
2. RIKEN Center for Brain Science, Japan

Correspondence: [dick.passingham@psy.ox.ac.uk](mailto:dick.passingham@psy.ox.ac.uk), [hakwan.lau@riken.jp](mailto:hakwan.lau@riken.jp)

### Abstract

Many suggestions have been made as to the functions of the PF cortex. However, they involve labelling areas using psychological terminology. But what we need to know is *how* the PF cortex operates. We argue that understanding this must start with describing the flow of information.

We illustrate this argument by considering three PF areas. Each has a unique pattern of inputs and outputs, and we suggest that the implication is that each performs a unique transformation from the inputs to the outputs. The caudal PF cortex transforms input that is maintained by attention or short-term memory into the target of the appropriate eye movement. The mid-dorsal PF cortex transforms input concerning the order of objects or actions into the target of the appropriate eye and hand movements, thus supporting sequences of action. The ventral PF cortex transforms input concerning an object or sound into prospective activity that encodes the associated object or sound.

However, it is important to appreciate that the mid-dorsal and ventral PF cortex are specialized for encoding *abstract* transformations, irrespective of the specific actions or objects. The advantage is that this enables generalization to novel problems that have the same underlying logic. We account for the difference between fast learning and slow learning in this way.

The human brain has co-opted these mechanisms so as to support intelligence. Non-verbal tests of IQ typically use sequences of letters, numbers or designs. These test the ability to understand the abstract rules that apply. Here the activations lie in the mid-dorsal PF cortex. Verbal tests typically assess the ability to understand semantic associations. These can be presented either in pictorial or verbal form. Here the activations lie in the ventral PF cortex.

### Abbreviations

FEF = frontal eye field  
lip = lateral intraparietal cortex  
PF = prefrontal  
PFG = intermedial area in inferior parietal cortex  
PG = posterior part of the inferior parietal cortex  
PreSMA = presupplementary motor cortex  
SII = secondary somatosensory area  
STS = superior temporal sulcus  
TE = anterior inferotemporal cortex  
TEO = posterior inferotemporal cortex  
vip = ventral intraparietal cortex  
V4 = fourth area in the hierarchy of the ventral visual system

## Introduction

There has been a prolonged debate about the function of the prefrontal (PF) cortex. Sixty years ago Teuber (1964) thought it to be a 'riddle'. Then Goldman-Rakic (1995; Goldman-Rakic, 1996) proposed that it provided a mechanism for working memory, and there are those who still support this view (Constantinidis and Qi, 2018; Miller et al., 2018). Others have suggested a role in response selection (Passingham, 1993), conditional learning on the basis of single events (Passingham and Wise, 2012) or planning (Shallice, 1982). And more generally it is often said that the PF cortex has executive functions and acts in cognitive control (Menon and D'Esposito, 2022).

Duncan (2010) has taken a different tack, arguing that any proposals are misguided if they were based on a narrow choice of behavioural tasks. He suggests that in fact the PF cortex is engaged by (Fedorenko et al., 2013) and can learn (Duncan, 2001) a very wide variety of tasks. He therefore suggests that it should be regarded as a 'multiple demand system'.

A recent book has reviewed the literature at length (Passingham, 2021) with the bold title 'Understanding the Prefrontal Cortex'. The present paper outlines one of the themes of the books, suggesting general principles on how the problem should be approached. This is based on considering the anatomical properties of the brain. The conclusions explain how the different account of the functions of the PF cortex outlined above can be accounted for if this anatomical approach is adopted.

## Transformation

In cognitive neuroscience, functions are often described in psychological terms, rather as in phrenology. There are two limitations. The first is that these terms were introduced to explain performance on laboratory tasks, and these have often taken no account of the ecological conditions in which the primates evolved. The second is that the aim of neuroscience is not to simply label the brain, but to understand *how* it works.

This involves describing the transformation that is performed from the inputs of an area to its outputs. This depends not only on the extrinsic connectivity of the area, its inputs and outputs, but also on its intrinsic connectivity, the internal wiring (Passingham et al., 2002). Rather than describing the flow of information in terms of black box models (Broadbent, 1958), the aim is to produce an account that describes the anatomical inputs and thus the information that an area receives, specifying how that is converted into the outputs and thus the influence that the area exerts within the system. In the conclusions we point to the need to produce models of how this conversion occurs, given the internal wiring of the area.

There is an important advantage in viewing the problem in terms of the transformation from inputs to outputs or computation. This is that it avoids positing a homunculus that acts as a controller. Baddeley's working memory model has several components, a short-term buffer and a central executive for example. But as he admitted he could be criticised for treating the central executive as a homunculus (Baddeley, 1996).

Yet the PF cortex is no homunculus. It lies at the top of the sensory hierarchy and at the top of the action hierarchy (Passingham and Wise, 2012). There are three implications.

The first is that the PF cortex is in a position to transform sensory inputs, whether current or memory, into action. For example, the inferotemporal cortex sends connections to the ventral PF cortex (Webster et al., 1994), not the premotor cortex, and this means that it is the PF cortex that transforms visual information about the context into action.

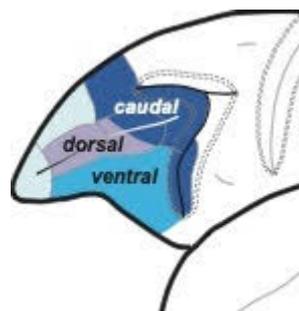
The second implication is that the PF cortex does not actually specify the movement itself. Instead it specifies the goal of the action by which we mean the target of either an eye movement or a hand movement (Passingham and Wise, 2012). For example, when a macaque monkey moves a cursor on a visual maze, the cell activity in the mid-dorsal PF cortex relates to the goal, not to the direction in which the joystick has to be turned for the cursor to reach that goal (Mushiake et al., 2006).

The final implication is the fact that the PF cortex lies at the top of the sensory and action hierarchy means that it can both select the sensory cues that are relevant for the current task as well as selecting the goal of the action for the motor system. As Shipp (2005) pointed out the cortical feedback pathways are similar to the output pathways – and unlike the feedforward pathways - in that they do not project to layer 4 (Shipp, 2005). The selection occurs via the mechanism of attentional enhancement. Thus, the PF cortex influences and enhances the activity in task-relevant sensory association areas via feedback pathways (Gee et al., 2008; Heinen et al., 2014; Siegel et al., 2015). And similarly, it influences and enhances activity in the premotor association areas including the preSMA and anterior cingulate cortex via output pathways (Rowe et al., 2002a; Rowe et al., 2002b; Westendorff et al., 2016).

### Three subdivisions of the PF cortex

Since each area of the brain has a different overall pattern of inputs and outputs (Passingham et al., 2002), the transformation will differ from one area to another within the PF cortex. To illustrate the transformations, the discussion that follows considers three broad regions of the PF cortex, the caudal, mid-dorsal and ventral PF cortex. These were chosen because the debate as described above has been primarily about the function of these areas.

Figure 1 shows these areas for the brain of a macaque monkey.



*Figure 1. The caudal, mid-dorsal and ventral PF cortex shown on the brain of a macaque monkey. The figure also shows the orbital PF cortex. Adapted from Price and Drevets (2010).*

In the macaque monkey and human brain these subdivisions include the following areas as defined by cytoarchitecture (Petrides and Pandya, 1999) and connectivity (Neubert et al., 2014; Sallet et al., 2013):

- 1) The caudal PF cortex (navy blue) includes areas 8B, 8Ad, 8Av and 45B
- 2) The mid-dorsal PF cortex (pink) includes areas 9/46 and 46vV
- 3) The ventral PF cortex (light blue) includes areas 45B and 47/12.

### Caudal PF cortex

The caudal PF cortex transforms information in short-term memory into the goal of a saccade (Passingham, 2021). Area 8Ad receives inputs concerning location (LIP, VIP, PG) (Stanton et al., 1995) and area 8Av inputs concerning objects (V4, TE, TEO) (Stanton et al., 1995). In turn area 8 can influence eye movements via outputs to the superior colliculus both directly (Kunzle et al., 1976) and indirectly via the medial caudate and substantia nigra, pars reticulata (Hedreen and DeLong, 1991).

There are cells that respond to the visual stimuli (V cells), cells that respond both to the visual stimulus and eye movement (VM cells) and cells that respond to the eye movement alone (M cells) (Schall, 1991), though each of these three types can be further subdivided into more specialized cells (Lowe and Schall, 2018). It is the existence of cells with these properties that explains how the area can transform visual inputs concerning location into the goal of the saccade.

There is activity in macaque monkeys (Blacker and Courtney, 2016; Chafee and Goldman-Rakic, 1998) and humans (Rowe et al., 2000; Sala et al., 2003) in the caudal PF cortex during the delay period on a short-term memory task. But it is persistent activity in posterior areas that is critical for the maintenance of the items, whether in short-term memory (Mackey and Curtis, 2017; Sreenivasan et al., 2014) or as the focus for attention (Colby et al., 1996; Jerde et al., 2012). Lesions whether in macaque monkeys (Mackey and Curtis, 2017; Tsujimoto and Postle, 2012) or human subjects (Ferreira et al., 1998; Mackey et al., 2016) fail to abolish the ability to remember items. Instead, they cause errors in the accuracy of the eye movement (Mackey et al., 2016; Mackey and Curtis, 2017) or the focus of attention (Keller et al., 2008).

Thus, the caudal PF cortex transforms the visual input from posterior areas into the goal of the response. This transformation was illustrated in a study by Takeda and Funahashi (2004) in which they trained macaque monkeys on a task in which they had to remember a location but make a saccade to a location at 90 degrees. Population vectors were calculated for the cells in the caudal PF cortex. As shown in Figure 2 there was a change in the direction of these vectors during the delay, indicating the gradual transformation of the memory of the visual input into the goal of the saccade.

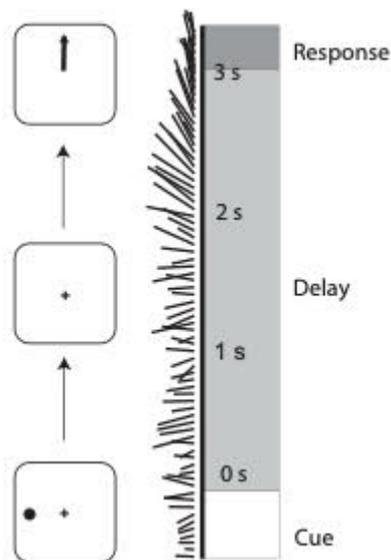


Figure 2. Population vectors showing the gradual transformation during a delay period from the input location to the target location at 90°. Adapted from Takeda and Funahashi (2004).

### Mid-dorsal PF cortex

The mid-dorsal PF cortex differs in that it is specialized for transforming information concerning the *order* of items into the goals of the action and generates sequences of goals (Passingham, 2021). The inputs (lip, 8A) and outputs (FEF and superior colliculus) of area 9/46 enable it to transform a location into the goal of the next eye movement (Borra et al., 2014; Borra et al., 2019; Gerbella et al., 2013). By contrast, the inputs (SII, PFG) and outputs (premotor and presupplementary motor cortex or preSMA) of area 46 enable it to transform an action as performed or viewed into the goal of the next hand movement (Borra et al., 2019; Gerbella et al., 2013).

The original evidence that order was critical came from a study of macaque monkeys with lesions in the dorsal PF cortex; they made errors on reporting the order of items with which they have been presented (Petrides, 1991). More recent neurophysiological and fMRI studies have provided clues as to the mechanism. There are cells that are active while monkeys commit a sequence of items to short-term memory (Lundqvist et al., 2018; Miller et al., 2018), while they report the order of items in a sequence (Warden and Miller, 2010), and while they plan a sequence of goals (Averbeck et al., 2006; Mushiaké et al., 2006). Similarly, there is activation while human subjects commit a sequence of items to short-term memory (Amiez and Petrides, 2007), while they

maintain the order before repeating it (Pochon et al., 2001), and while they generate a sequence of actions on a planning task (Rowe et al., 2001; Spreng et al., 2010; Unterrainer et al., 2005) or generate a random sequence of goals by monitoring what they have just done (Phillips et al., 2018).

Furthermore, lesions that include the mid-dorsal PF cortex severely impair the ability of patients to repeat the order in which items were presented (Ferreira et al., 1998). This is not due to a failure to maintain the items in memory since the patients can recognize the order if testing on a matching design (Ferreira et al., 1998; Pochon et al., 2001). In other words, the problem is one of transforming the order of the items into a sequence of goals.

Sequences require the transformation from one item or goal to the next one in time. Tsujimoto et al. (2008) found pairs of cells in the mid-dorsal PF cortex of macaque monkeys in which one coded for the previous goal and the other for the current goal. At the time that the animal chose the current goal there was transient synchrony between the activity of the cells representing the previous and current goal. On a planning task there is also maximal synchrony between a cell coding for a subgoal and another coding for the goal during the transformation from one goal to the next one in time (Sakamoto et al., 2008).

### Ventral PF cortex

The ventral PF cortex differs yet again in that it associates one member of a pair with the other (Passingham, 2021). Area 47/12 has visual and tactile inputs concerning objects (Petrides and Pandya, 2002; Saleem et al., 2008) whereas area 45A has mainly auditory ones not only from the superior temporal cortex but also from Broca's 45B (Petrides and Pandya, 2002). The ventral PF cortex can influence choice via indirect projections to the premotor cortex via the preSMA (Takahara et al., 2012).

Unlike the mid-dorsal PF cortex, the ventral PF cortex associates objects irrespective of the order in which they are presented, and even if they are presented simultaneously (Bussey et al., 2001; Rushworth et al., 1997; Wang et al., 2000). Though a delay period is sometimes presented between each associate, it is not essential as inactivation of the ventral PF area 45A does not disrupt performance on a delayed visual-visual associative task (Plakke et al., 2015).

Figure 3 illustrates the activity of cell populations while macaque monkeys associate two pictures (Rainer et al., 1999). After the presentation of picture A, there is prospective activity that encodes picture B, and this increases up to the time that picture B is presented. In other words, there is a transformation between the input for picture A and the output of specifying picture B as the goal.

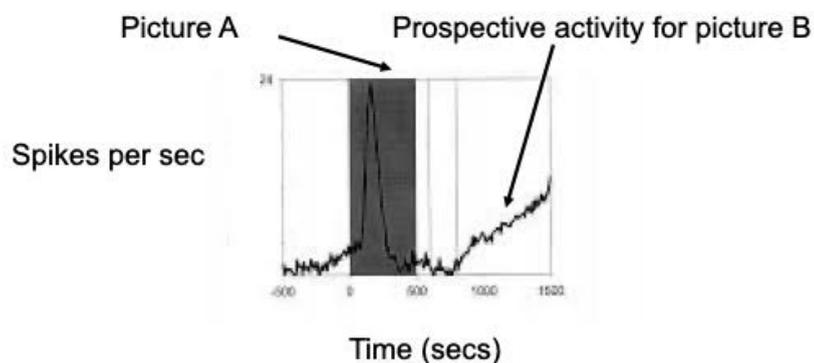


Figure 3. The filled box shows the time at which the input picture was presented. The ascending line shows the prospective population activity encoding the target picture. Adapted from Rainer et al. (1999).

Inactivation and lesion studies show that the ventral PF cortex is critical for learning associations. This has been shown for the association between faces and vocalizations (Hwang and

Romanski, 2015) and the association between a visual cue and a spatial target (Bussey et al., 2001; Wang et al., 2000). Freedman et al. (2002) also found cells in the ventral PF cortex that associated stimuli that were morphed in appearance, such as cats and dogs. These cell populations act to classify objects (Cromer et al., 2010).

However, the ventral PF contributes mainly to the learning of new associate pairs because it has access to information about rewards via its connections with the orbital PF cortex (Petrides and Pandya, 2002). There are cells that encode these associations (Andreau and Funahashi, 2011). It is less critical for the retrieval of overlearned associates (Boettiger and D'Esposito, 2005; Wang et al., 2000). It is true that Bussey et al. (2001) reported an impairment in retrieval of visual-spatial associates. But the reason may be that the lesions in this study included not only the ventral but also the orbital PF cortex.

### Abstract rules and fast learning

Though the PF cortex transforms from sensory input to action output, this cannot be the full story because rodents and other mammals can do this. Yet they lack a granular PF cortex including the lateral PF areas described above (Preuss, 2007; Wise, 2017). This raises the question as to what the granular PF cortex adds.

The answer is that it supports the ability to learn *abstract* rules or transformations. It is in a position to do this because it lies at the top of the sensory and action hierarchies, and it is this hierarchical organization (Markov and Kennedy, 2013) that allows the abstraction of specific features. For example, the projections from the inferotemporal cortex to the perirhinal cortex support view invariance of objects (Buckley and Gaffan, 1998; Wang et al., 1998). Cadieu et al. (2007) produced a model that was able to achieve invariance for position or shape by combining units in a hierarchical fashion.

There are cells in the mid-dorsal PF cortex that code for abstract sequences, that is the structure of sequences independently of the specific actions (Shima et al., 2007). Figure 4 shows the population activity for cells firing in advance of sequences of four actions. The upper traces show the activity for actions in which the animal had to alternate what it did. The same cell populations did not fire for sequences with a different structure, for example repetition of actions.

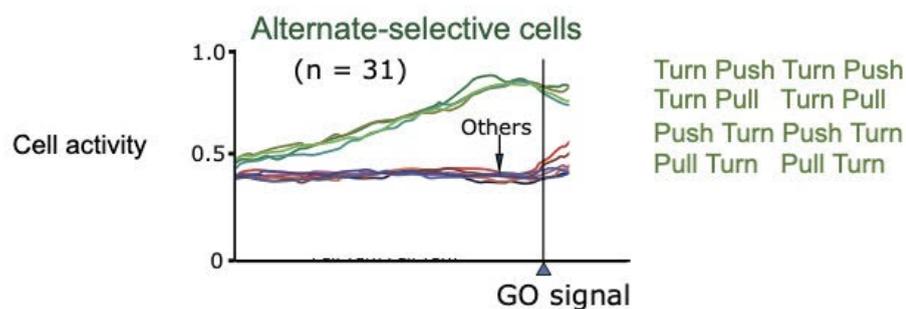


Figure 4. The green lines show cell populations encoding the abstract structure of sequences in which the actions alternated. The response to sequences with a different abstract structure is labelled 'others'. Adapted from Tanji et al. (2007)

There are also cells in the ventral as well as the mid-dorsal cortex that code for abstract matching rules. These encoding whether the rule is matching or non-matching, irrespective of the actual objects presented (Wallis et al., 2001).

The advantage of learning abstract rules is that it means that anthropoid primates can show transfer or generalize from solving one problem to solving others with the same (Harlow and Warren,

1952) or related (Warren, 1974) logic. In other words, they can develop a learning set. Rather than starting from scratch on each problem (slow learning) they can show rapid improvement across problems (fast learning).

The distinction between slow and fast learning was illustrated by a study in which macaque monkeys learned visuo-spatial associations (Bussey et al., 2001). The animals with ventral and orbital PF lesions could learn visuo-spatial associations over very many sessions, presumably because there was still a visual input to the basal ganglia (Hoshi, 2013). However, they showed no improvement at all on new visuo-spatial problems within a session. Improvement within a session depends on learning the abstract rules 'repeat-stay' and 'change-shift', and Genovesio et al. (2008) have described subpopulations of cells that code for these abstract strategies.

Fast learning involves the development of statistical assumptions or priors (Botvinick et al., 2019; Costa et al., 2015). Wang et al. (2018) take the example of a two-bandit problem and suggest that, whereas the basal ganglia can support slow learning via reinforcement, the dopamine system also trains up the PF cortex so that it can operate independently as an algorithm that supports fast learning. They describe this as 'meta-learning'.

### **Selective advantage**

Given that the granular PF cortex is unique to primates, it is important to consider the selection pressures that led to its evolution. Primates differ from other mammals in two critical respects. One is that they have hands with which to grasp their food. That is why the mid-dorsal and ventral PF areas have outputs to the oculomotor system and hand areas of the premotor system (Borra et al., 2019).

The second difference is that their food sources exist in patches. The caudal PF cortex exists in prosimians as well as monkeys and apes (Wise, 2017), and it supports the ability to move the gaze within a patch (Collin et al., 1982).

The mid-dorsal and ventral PF cortex are unique to anthropoid primates (Wise, 2017). The mid-dorsal PF cortex supports the ability to prospectively encode an ordered search using the eye and hand (Owen et al., 1990; Owen et al., 1996; Passingham, 1985). The ventral PF cortex differs in that it supports the ability to learn which *types* of fruit and leaves should be the target for search, these being defined in terms of their look and taste (Passingham, 2021).

However, during the evolution of the anthropoid primates the availability of particular fruits and leaves varied dramatically within a year and from year to year (Chapman et al., 1999; Janmaat et al., 2006). This meant that the anthropoids faced challenges as the result of the volatility of resources. It was these challenges that led to selection pressures for the ability to learn abstract rules, and thus the ability to solve novel problems rapidly if they shared an underlying logic with previous problems. To put it another way, they promoted intelligence.

### **Human intelligence**

Human intelligence depends on the fact that our brain has co-opted this system and has reused it for novel purposes. Its potential has been greatly amplified by the fact that language provides a tool for instruction and thus formal education. The prolonged period of education further encourages the ability to transfer knowledge from one type of problem to another.

Intelligence can, of course, be assessed by non-verbal IQ tests. Solving these tests does not necessarily require facility with language (Woolgar et al., 2018). Indeed a patient with severe aphasia and no inner speech could succeed on the Raven's Matrices (Levine et al., 1982).

Typically tests of fluid intelligence present sequences of letters, numbers or designs and the task is to find the abstract rule that the sequences obey. There is extensive activation in the mid-dorsal PF cortex when subjects are tested on a task such as the Raven's Matrices (Crone et al., 2009). The reason why the activation is in the mid-dorsal PF cortex is that the area is specialized for learning abstract rules concerning sequences (Shima et al., 2007).

Sequences are defined by order, and that is why there is activation in the same area when subjects are required to re-order or manipulate sequences of letters in their head (D'Esposito et al., 1999), calculate using numbers which lie on an ordinal scale or perform the n-back task in which the correct response depends on the order in which the items are presented (Assem et al., 2020). All these tasks require the subjects to appreciate the order in which A is followed by B and C, and 3 by 4 and 5.

An alternative way of testing intelligence is to present problems that assess semantic knowledge. Wendelken et al. (2008) presented problems in verbal form. For example, the subjects had to complete 'brain is to thought as stomach is to?'; and when they did so there was activation in the ventral PF cortex. Price and Friston (1999) presented an adaptation of the pyramid and palm trees test (Howard and Patterson, 1992) in which the subject has to decide which of two semantically similar pictures or words is closest to a third semantically related picture or word. The frontal activation was in the left ventral PF cortex.

They argued, however, that this activation was not necessary for correct performance because a patient with a ventral PF lesion could succeed on the task. But the tasks were deliberately made easy. That difficulty matters was shown by a study in which rTMS was applied to the left ventral PF cortex. The subjects were not impaired if the correct associate 'salt' was 'pepper'; but they were impaired if the correct associate was 'grain' (Whitney et al., 2011).

These tests of semantic knowledge assess the ability to appreciate associations, and that is why the activations are in the ventral PF cortex. Just as there is cell activity in this area when macaque monkeys are tested on associative learning (Asaad et al., 1998; Rainer et al., 1999), so there are activations there when human subjects learn verbal paired associates (Fletcher et al., 1995). Tasks of this sort require the transformation from A to X and B to Y.

### **Objections and limitations**

It is important to consider possible objections to the approach recommended here. There are three.

First, it could be argued that if area A performs a unique transformation from its inputs to outputs, then areas X, Y and Z should not be able to take over after a lesion in area A. Yet, we know that patients with neurological disorders can show recovery (Sampaio-Baptista et al., 2018; Tomassini et al., 2012). There could be several explanations. First, if the lesion is unilateral, the other hemisphere may be able to support recovery. For example, monkeys with unilateral mid-dorsal PF lesions can relearn delayed responses tasks (Ainsworth et al., 2018; Rosen et al., 1975); but monkeys with bilateral lesions fail to relearn delayed alternation in 2000 trials (Goldman et al., 1971). Second, recovery is possible by learning a new strategy, for example attending to a location during the delay period rather than depending on short-term memory (Ainsworth et al., 2018). Finally, given the astonishing complexity of the neural networks, alternative routes from vision to action may remain, even if performance is sub-optimal.

Second, it could be objected that if each area performs a transformation from its inputs to its outputs, this is incompatible with the flexibility shown by the anthropoid brain. But that flexibility can be accounted for in two ways. First, the PF cortex enhances activity in different sensory areas depending on the current task (Heinen et al., 2014). Second, the PF cortex enhances activity in different output areas depending on the current task (Sakai and Passingham, 2006). This means that each PF area has different inputs and outputs as a function of the task demands.

The third potential objection is that the clearest evidence for distinguishing the mid-dorsal and ventral PF cortex comes from lesion studies (Passingham, 1975). But in the intact brain, cell recordings do not indicate such a clear distinction between areas (Brincat et al., 2018). For example, as already mentioned there are cells in the mid-dorsal PF cortex, and not just the ventral PF cortex, that encode abstract visual matching rules (Wallis et al., 2001). Yet the inferotemporal cortex (Webster et al., 1994) and perirhinal cortex (Kondo et al., 2005) project to the ventral and orbital PF cortex, but not to the mid-dorsal PF cortex. The implication is that the cell activity in the mid-dorsal

PF cortex during visual matching is derived from the interconnections between the ventral and mid-dorsal PF cortex (Petrides and Pandya, 2002). A lesion in the ventral PF cortex cuts these connections.

However, this does not mean that in the intact brain the mid-dorsal PF cortex makes no contribution to performance on visual matching. For example, it provides one route, though not the only one, to the premotor areas (Borra et al., 2019; Takahara et al., 2012). Thus, even though a lesion that includes the mid-dorsal PF cortex has no effect on visual matching (Passingham, 1975), this does not mean that it makes no contribution to the intact brain. And it is the intact brain we are trying to understand.

## Conclusions

It is not possible to say whether we understand the PF cortex in a short paper. It demands a book (Passingham, 2021). But the hope is that reframing the problem as describing the transformations that are performed by each region within the PF cortex, given specific inputs and outputs, helps to clarify what we need to know.

So does this way of framing the problem help us to appreciate why so many apparently different suggestions have been made concerning the functions of the PF cortex. First, it abolishes the *riddle*. Then it encompasses the proposal that the PF cortex supports *conditional* learning in which the response depends on a single event (Passingham and Wise, 2012). In a sequence A leads to B, whereas in an association A is linked with B. In both cases B is conditional on A. Furthermore, in both cases the *selection* of B depends on A. And attentional selection via enhancement of the sensory inputs or specific outputs is an *executive* mechanism involved in *cognitive control*.

However, it is not always possible in nature to select B immediately. This means that the transformation is delayed, and the representation of B must be encoded and maintained during the delay period. Prospective activity of this sort was illustrated in figure 3, an aspect of *working memory*. Furthermore, A may lead not just to B but also to C and D, in other words a sequence. And figure 4 illustrates activity encoding the upcoming sequence. To put it another way the activity encodes the *plan*.

Finally, claims that the PF cortex serves as a *multiple-demand system* was originally based on an imaging study (Fedorenko et al., 2013) in which the statistical analysis was not corrected for multiple comparisons. When Duncan used corrected thresholds (Assem et al., 2020), the activation was much more restricted. It lay in area 9/46v and area 46. The activation in the mid-dorsal PF cortex reflects the fact that two of the three tasks involved sequences. The activation in area 9/46v reflects the fact that the third task was associative, and there are strong interconnections between ventral PF cortex and area 9/46v (Petrides and Pandya, 2002); in other words the activation is derived.

We take the description in terms of information flow to be more fundamental than the description using psychological terminology because it is not restricted simply to labelling. Instead, it provides an account of how the different PF areas work and how they interact with each other, given known anatomical inputs and outputs. Future studies can aim to explain other psychological phenomena within the same framework. For example, is the activation in the ventral PF cortex when subjects are perceptually aware (Lau and Passingham, 2006) to be explained because the experienced percept (the input) is associated with and thus codes prospectively for stimuli that are alike in their category (the output)?

But there are two more requirements for a full understanding. First, we need an account of how each PF area interacts with the rest of the cortical network. We have a very detailed connectome (Ercsey-Ravasz et al., 2013), and as already mentioned very heavy interconnections have been described between the different PF areas (Harriger et al., 2012). The mechanism for interaction may depend on oscillatory activity. This is ubiquitous throughout the hierarchy, with higher frequencies in the PF cortex (Lundqvist et al., 2020), and it may play a role in changes in functional connectivity between areas depending on the current task (Pariz et al., 2021). The inputs and

outputs are fixed, though they may differ in strength with experience. We need to know whether the flexibility supported by the PF cortex depends on changes in functional connectivity.

Second, a full understanding requires an account of how the particular cells within each area interact so as to enable its transformation from inputs to outputs. And that account may well differ from area to area. Heinzle et al. (2007) have produced such an account for the frontal eye field, and they specifically compared the columnar structure with that in visual areas. Similar detailed comparisons of the columnar structure need to be made in each of the PF areas and the results incorporated into computational models of how they perform their particular transformation.

These computational theories need to be tested against each other to see which makes the best predictions. It is one thing to produce a computational account, but quite another to demonstrate that it makes correct and novel predictions that other accounts do not. We are still a long way from the sorts of neuronal accounts with detailed predictions that Marr (1969) gave for the cerebellum. And that was 50 years ago.

## REFERENCES

- Ainsworth, M., et al., 2018. Functional reorganisation and recovery following cortical lesions: A preliminary study in macaque monkeys. *Neuropsychologia*. 119, 382-391.
- Amiez, C., Petrides, M., 2007. Selective involvement of the mid-dorsolateral prefrontal cortex in the coding of the serial order of visual stimuli in working memory. *Proc Natl Acad Sci U S A*. 104, 13786-91.
- Andreau, J.M., Funahashi, S., 2011. Primate prefrontal neurons encode the association of paired visual stimuli during the pair-association task. *Brain Cogn*. 76, 58-69.
- Asaad, W.F., Rainer, G., Miller, E.K., 1998. Neural activity in the primate prefrontal cortex during associative learning. *Neuron*. 21, 1399-1407.
- Assem, M., et al., 2020. A Domain-General Cognitive Core Defined in Multimodally Parcellated Human Cortex. *Cereb Cortex*. 30, 4361-4380.
- Averbeck, B.B., Sohn, J.W., Lee, D., 2006. Activity in prefrontal cortex during dynamic selection of action sequences. *Nat Neurosci*. 9, 276-82.
- Baddeley, A., 1996. Exploring the Central Executive. *Quarterly Journal of Experimental Psychology*. 49, 5-28.
- Blackler, K.J., Courtney, S.M., 2016. Distinct Neural Substrates for Maintaining Locations and Spatial Relations in Working Memory. *Front Hum Neurosci*. 10, 594.
- Boettiger, C.A., D'Esposito, M., 2005. Frontal networks for learning and executing arbitrary stimulus-response associations. *J Neurosci*. 25, 2723-32.
- Borra, E., et al., 2014. Projections to the superior colliculus from inferior parietal, ventral premotor, and ventrolateral prefrontal areas involved in controlling goal-directed hand actions in the macaque. *Cereb Cortex*. 24, 1054-65.
- Borra, E., et al., 2019. Rostro-caudal Connectional Heterogeneity of the Dorsal Part of the Macaque Prefrontal Area 46. *Cereb Cortex*. 29, 485-504.
- Botvinick, M., et al., 2019. Reinforcement Learning, Fast and Slow. *Trends Cogn Sci*. 23, 408-422.
- Brincat, S.L., et al., 2018. Gradual progression from sensory to task-related processing in cerebral cortex. *Proc Natl Acad Sci U S A*. 115, E7202-E7211.
- Broadbent, D., 1958. *Perception and Communication*, Vol., Oxford University Press, Oxford.
- Buckley, M.J., Gaffan, D., 1998. Perirhinal cortex ablation impairs visual object identification. *J Neurosci*. 18, 2268-75.
- Bussey, T., Wise, S., Murray, E., 2001. The role of ventral and orbital prefrontal cortex in conditional visuomotor learning and strategy use in rhesus monkeys (*Macaca mulatta*). *Behav Neurosci*. 115, 971-82.
- Cadieu, C., et al., 2007. A model of V4 shape selectivity and invariance. *J Neurophysiol*. 98, 1733-50.

- Chafee, M.V., Goldman-Rakic, P.S., 1998. Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *J Neurophysiol.* 79, 2919-40.
- Chapman, C.A., et al., 1999. Fruit and flower phenology at two sites in Kibale National Park, Uganda. *Journal of Tropical Ecology.* 15, 189-211.
- Colby, C.L., Duhamel, J.R., Goldberg, M.E., 1996. Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *J Neurophysiol.* 76, 2841-52.
- Collin, N.G., et al., 1982. The role of frontal eye-fields and superior colliculi in visual search and non-visual search in rhesus monkeys. *Behav Brain Res.* 4, 177-93.
- Constantinidis, C., Qi, X.L., 2018. Representation of Spatial and Feature Information in the Monkey Dorsal and Ventral Prefrontal Cortex. *Front Integr Neurosci.* 12, 31.
- Costa, V.D., et al., 2015. Reversal learning and dopamine: a bayesian perspective. *J Neurosci.* 35, 2407-16.
- Cromer, J.A., Roy, J.E., Miller, E.K., 2010. Representation of multiple, independent categories in the primate prefrontal cortex. *Neuron.* 66, 796-807.
- Crone, E.A., et al., 2009. Neurocognitive development of relational reasoning. *Dev.Sci.* 12, 55-66.
- D'Esposito, M., et al., 1999. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain Cogn.* 41, 66-86.
- Duncan, J., 2001. An adaptive coding model of neural function in prefrontal cortex. *Nat Rev Neurosci.* 2, 820-9.
- Duncan, J., 2010. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn Sci.* 14, 172-9.
- Ercsey-Ravasz, M., et al., 2013. A predictive network model of cerebral cortical connectivity based on a distance rule. *Neuron.* 80, 184-97.
- Fedorenko, E., Duncan, J., Kanwisher, N., 2013. Broad domain generality in focal regions of frontal and parietal cortex. *Proc Natl Acad Sci U S A.* 110, 16616-21.
- Ferreira, C.T., et al., 1998. Spatio-temporal working memory and frontal lesions in man. *Cortex.* 34, 83-98.
- Fletcher, P.C., et al., 1995. Brain systems for encoding and retrieval of auditory-verbal memory. An in vivo study in humans. *Brain.* 118 ( Pt 2), 401-16.
- Freedman, D.J., et al., 2002. Visual categorization and the primate prefrontal cortex: neurophysiology and behavior. *J Neurophysiol.* 88, 929-41.
- Gee, A.L., et al., 2008. Neural enhancement and pre-emptive perception: the genesis of attention and the attentional maintenance of the cortical salience map. *Perception.* 37, 389-400.
- Genovesio, A., Wise, S.P., 2008. The neurophysiology of abstract response strategies. In: *Neuroscience of Rule-Guided Behavior. Vol.*, S.A. Bunge, J. Wallis, ed. ^eds. Oxford University Press, Oxford, pp. 81-106.
- Gerbella, M., et al., 2013. Connectional heterogeneity of the ventral part of the macaque area 46. *Cereb Cortex.* 23, 967-87.
- Goldman, P.S., et al., 1971. Analysis of the delayed-alternation deficit produced by dorsolateral prefrontal lesions in the rhesus monkey. *Journal of Comparative and Physiological Psychology.* 77, 212-220.
- Goldman-Rakic, P.S., 1995. Cellular basis of working memory. *Neuron.* 14, 477-485.
- Goldman-Rakic, P.S., 1996. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philos Trans R Soc Lond B Biol Sci.* 351, 1445-53.
- Harlow, H.F., Warren, J.M., 1952. Formation and transfer of discrimination learning sets. *J Comp Physiol Psychol.* 45, 482-9.
- Harriger, L., van den Heuvel, M.P., Sporns, O., 2012. Rich club organization of macaque cerebral cortex and its role in network communication. *PLoS One.* 7, e46497.

- Hedreen, J.C., DeLong, M.R., 1991. Organization of striatopallidal, striatonigral and nigrostriatal projections in the macaque. *Journal of Comparative Neurology*. 304, 569-595.
- Heinen, K., et al., 2014. Direct evidence for attention-dependent influences of the frontal eye-fields on feature-responsive visual cortex. *Cereb Cortex*. 24, 2815-21.
- Heinzle, J., Hepp, K., Martin, K.A., 2007. A microcircuit model of the frontal eye fields. *J Neurosci*. 27, 9341-53.
- Hoshi, E., 2013. Cortico-basal ganglia networks subserving goal-directed behavior mediated by conditional visuo-goal association. *Front Neural Circuits*. 7, 158.
- Howard, D., Patterson, K., 1992. *Pyramids and Palm trees: a test of semantic access for pictures and words.*, Vol., Thames Valley Tests Company, Bury St Edmunds.
- Hwang, J., Romanski, L.M., 2015. Prefrontal neuronal responses during audiovisual mnemonic processing. *J Neurosci*. 35, 960-71.
- Janmaat, K.R., Byrne, R.W., Zuberbuhler, K., 2006. Primates take weather into account when searching for fruits. *Curr Biol*. 16, 1232-7.
- Jerde, T.A., et al., 2012. Prioritized maps of space in human frontoparietal cortex. *J Neurosci*. 32, 17382-90.
- Keller, E.L., et al., 2008. Effect of inactivation of the cortical frontal eye field on saccades generated in a choice response paradigm. *J Neurophysiol*. 100, 2726-37.
- Kondo, H., Saleem, K.S., Price, J.L., 2005. Differential connections of the perirhinal and parahippocampal cortex with the orbital and medial prefrontal networks in macaque monkeys. *J Comp Neurol*. 493, 479-509.
- Kunzle, H., Akert, K., Wurtz, R.H., 1976. Projection of area 8 (frontal eye field) to superior colliculus in the monkey. An autoradiographic study. *Brain Res*. 117, 487-92.
- Lau, H.C., Passingham, R.E., 2006. Relative blindsight in normal observers and the neural correlate of visual consciousness. *Proc Natl Acad Sci U S A*. 103, 18763-8.
- Levine, D.N., Calvanio, R., Popovics, A., 1982. Language in the absence of inner speech. *Neuropsychol*. 20, 391-409.
- Lowe, K.A., Schall, J.D., 2018. Functional Categories of Visuomotor Neurons in Macaque Frontal Eye Field. *eNeuro*. 5.
- Lundqvist, M., Herman, P., Miller, E.K., 2018. Working Memory: Delay Activity, Yes! Persistent Activity? Maybe Not. *J Neurosci*. 38, 7013-7019.
- Lundqvist, M., Bastos, A.M., Miller, E.K., 2020. Preservation and Changes in Oscillatory Dynamics across the Cortical Hierarchy. *J Cogn Neurosci*. 32, 2024-2035.
- Mackey, W.E., et al., 2016. Human Dorsolateral Prefrontal Cortex Is Not Necessary for Spatial Working Memory. *J Neurosci*. 36, 2847-56.
- Mackey, W.E., Curtis, C.E., 2017. Distinct contributions by frontal and parietal cortices support working memory. *Sci Rep*. 7, 6188.
- Markov, N.T., Kennedy, H., 2013. The importance of being hierarchical. *Curr Opin Neurobiol*. 23, 187-94.
- Marr, D., 1969. A theory of cerebellar cortex. *J Physiol*. 202, 437-70.
- Menon, V., D'Esposito, M., 2022. The role of PFC networks in cognitive control and executive function. *Neuropsychopharmacology*. 47, 90-103.
- Miller, E.K., Lundqvist, M., Bastos, A.M., 2018. Working Memory 2.0. *Neuron*. 100, 463-475.
- Mushiake, H., et al., 2006. Activity in the lateral prefrontal cortex reflects multiple steps of future events in action plans. *Neuron*. 50, 631-41.
- Neubert, F.X., et al., 2014. Comparison of human ventral frontal cortex areas for cognitive control and language with areas in monkey frontal cortex. *Neuron*. 81, 700-13.
- Owen, A.M., et al., 1990. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia*. 28, 1021-1034.

- Owen, A.M., et al., 1996. Double dissociation of memory and executive functions in working memory tasks following frontal excisions, temporal lobe excisions or amygdala-hippocampectomy in man. *Brain*. 119, 1597-1615.
- Pariz, A., et al., 2021. Transmission delays and frequency detuning can regulate information flow between brain regions. *PLoS Comput Biol*. 17, e1008129.
- Passingham, R.E., 1975. Delayed matching after selective prefrontal lesions in monkeys. *Brain Research*. 92, 89-102.
- Passingham, R.E., 1985. Memory of monkeys (*Macaca mulatta*) with lesions in prefrontal cortex. *Behavioral Neuroscience*. 99, 3-21.
- Passingham, R.E., 1993. *The Frontal Lobes and Voluntary Action*, Vol., Oxford University Press, Oxford.
- Passingham, R.E., Stephan, K.E., Kotter, R., 2002. The anatomical basis of functional localization in the cortex. *Nat Rev Neurosci*. 3, 606-16.
- Passingham, R.E., Wise, S.P., 2012. *The Neurobiology of Prefrontal Cortex*, Vol., Oxford University Press, Oxford.
- Passingham, R.E., 2021. *Understanding The Prefrontal Cortex: selective advantage, connectivity, and neural operations*, Vol., Oxford University Press, Oxford.
- Petrides, M., 1991. Functional specialization within the dorsolateral frontal cortex for serial order memory. *Proc Biol Sci*. 246, 299-306.
- Petrides, M., Pandya, D.N., 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur J Neurosci*. 11, 1011-36.
- Petrides, M., Pandya, D.N., 2002. Comparative cytoarchitectonic analysis of the human and macaque ventrolateral prefrontal cortex and corticocortical connection pattern in the monkey. *Eur. J. Neurosci*. 16, 291-310.
- Phillips, H.N., et al., 2018. Monitoring the past and choosing the future: the prefrontal cortical influences on voluntary action. *Sci Rep*. 8, 7247.
- Plakke, B., Hwang, J., Romanski, L.M., 2015. Inactivation of Primate Prefrontal Cortex Impairs Auditory and Audiovisual Working Memory. *J Neurosci*. 35, 9666-75.
- Pochon, J.-B., et al., 2001. The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: an fMRI study. *Cereb. Cortex*. 11, 260-266.
- Preuss, T.M., 2007. Primate brain evolution in phylogenetic context. In: *The Evolution of Nervous Systems*. Vol. 4, J. Kaas, T.M. Preuss, ed. Elsevier, New York, pp. 3-34.
- Price, C.J., Friston, K.J., 1999. Scanning patients with tasks they can perform. *Hum Brain Mapp*. 8, 102-8.
- Price, J.L., Drevets, W.C., 2010. Neurocircuitry of mood disorders. *Neuropsychopharmacology*. 35, 192-216.
- Rainer, G., Rao, S.C., Miller, E.K., 1999. Prospective coding for objects in primate prefrontal cortex. *J Neurosci*. 19, 5493-505.
- Rosen, J., et al., 1975. Effects of one-stage and serial ablations of the middle third of sulcus principalis on delayed alternation performance in monkeys. *J Comp Physiol Psychol*. 89, 1077-82.
- Rowe, J., et al., 2000. Prefrontal cortex: response selection or maintenance within working memory. *Science*. 288, 1656-1660.
- Rowe, J., et al., 2002a. Attention to action: specific modulation of corticocortical interactions in humans. *Neuroimage*. 17, 988-98.
- Rowe, J., et al., 2002b. Attention to action in Parkinson's disease: impaired effective connectivity among frontal cortical regions. *Brain*. 125, 276-89.
- Rowe, J.B., et al., 2001. Imaging the mental components of a planning task. *Neuropsychologia*. 39, 315-27.
- Rushworth, M., et al., 1997. Ventral prefrontal cortex is not essential for working memory. *Journal of Neuroscience*. 17, 4829-4838.

- Sakai, K., Passingham, R.E., 2006. Prefrontal set activity predicts rule-specific neural processing during subsequent cognitive performance. *J Neurosci.* 26, 1211-8.
- Sakamoto, K., et al., 2008. Discharge synchrony during the transition of behavioral goal representations encoded by discharge rates of prefrontal neurons. *Cereb Cortex.* 18, 2036-45.
- Sala, J.B., Rama, P., Courtney, S.M., 2003. Functional topography of a distributed neural system for spatial and nonspatial information maintenance in working memory. *Neuropsychologia.* 41, 341-56.
- Saleem, K.S., Kondo, H., Price, J.L., 2008. Complementary circuits connecting the orbital and medial prefrontal networks with the temporal, insular, and opercular cortex in the macaque monkey. *J Comp Neurol.* 506, 659-93.
- Sallet, J., et al., 2013. The organization of dorsal frontal cortex in humans and macaques. *J Neurosci.* 33, 12255-74.
- Sampaio-Baptista, C., Sanders, Z.B., Johansen-Berg, H., 2018. Structural Plasticity in Adulthood with Motor Learning and Stroke Rehabilitation. *Annu Rev Neurosci.* 41, 25-40.
- Schall, J.D., 1991. Neuronal activity related to visually guided saccades in the frontal eye fields of rhesus monkeys: comparison with supplementary eye fields. *J Neurophysiol.* 66, 559-79.
- Shallice, T., 1982. Specific impairments of planning. *Philosophical Transactions of the Royal Society of London, series B.* 298, 199-209.
- Shima, K., et al., 2007. Categorization of behavioural sequences in the prefrontal cortex. *Nature.* 445, 315-8.
- Shipp, S., 2005. The importance of being agranular: a comparative account of visual and motor cortex. *Philos Trans R Soc Lond B Biol Sci.* 360, 797-814.
- Siegel, M., Buschman, T.J., Miller, E.K., 2015. Cortical information flow during flexible sensorimotor decisions. *Science.* 348, 1352-5.
- Spreng, R.N., et al., 2010. Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage.* 53, 303-17.
- Sreenivasan, K.K., Curtis, C.E., D'Esposito, M., 2014. Revisiting the role of persistent neural activity during working memory. *Trends Cogn Sci.* 18, 82-9.
- Stanton, G.B., Bruce, C.J., Goldberg, M.E., 1995. Topography of projections to posterior cortical areas from the macaque frontal eye fields. *J Comp Neurol.* 353, 291-305.
- Takahara, D., et al., 2012. Multisynaptic projections from the ventrolateral prefrontal cortex to the dorsal premotor cortex in macaques - anatomical substrate for conditional visuomotor behavior. *Eur J Neurosci.* 36, 3365-75.
- Takeda, K., Funahashi, S., 2004. Population vector analysis of primate prefrontal activity during spatial working memory. *Cereb Cortex.* 14, 1328-39.
- Tanji, J., Shima, K., Mushiake, H., 2007. Concept-based behavioral planning and the lateral prefrontal cortex. *Trends Cogn Sci.* 11, 528-34.
- Teuber, H.L., 1964. The riddle of frontal lobe function in man. In: *The Frontal Granular Cortex and Behavior.* Vol., J.M. Warren, K. Akert, ed. ^eds. McGraw-Hill, New York.
- Tomassini, V., et al., 2012. Neuroplasticity and functional recovery in multiple sclerosis. *Nature Reviews Neurology.* 8, 635-646.
- Tsujimoto, S., Genovesio, A., Wise, S.P., 2008. Transient neuronal correlations underlying goal selection and maintenance in prefrontal cortex. *Cereb Cortex.* 18, 2748-61.
- Tsujimoto, S., Postle, B.R., 2012. The prefrontal cortex and oculomotor delayed response: a reconsideration of the "mnemonic scotoma". *J Cogn Neurosci.* 24, 627-35.
- Unterrainer, J.M., et al., 2005. The influence of sex differences and individual task performance on brain activation during planning. *Neuroimage.* 24, 586-90.
- Wallis, J.D., Anderson, K.C., Miller, E.K., 2001. Single neurons in prefrontal cortex encode abstract rules. *Nature.* 411, 953-6.

- Wang, G., Tanifuji, M., Tanaka, K., 1998. Functional architecture in monkey inferotemporal cortex revealed by in vivo optical imaging. *Neurosci Res.* 32, 33-46.
- Wang, J.X., et al., 2018. Prefrontal cortex as a meta-reinforcement learning system. *Nat Neurosci.* 21, 860-868.
- Wang, M., Zhang, H., Li, B.M., 2000. Deficit in conditional visuomotor learning by local infusion of bicuculline into the ventral prefrontal cortex in monkeys. *Eur J Neurosci.* 12, 3787-96.
- Warden, M.R., Miller, E.K., 2010. Task-dependent changes in short-term memory in the prefrontal cortex. *J Neurosci.* 30, 15801-10.
- Warren, J.M., 1974. Possibly unique characteristics of learning by primates. *J Hum Evol.* 3, 445-454.
- Webster, M.J., Bachevalier, J., Ungerleider, L.G., 1994. Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys. *Cerebral Cortex.* 4, 471-483.
- Wendelken, C., et al., 2008. "Brain is to thought as stomach is to ??": investigating the role of rostralateral prefrontal cortex in relational reasoning. *J Cogn Neurosci.* 20, 682-93.
- Westendorff, S., et al., 2016. Prefrontal and anterior cingulate cortex neurons encode attentional targets even when they do not apparently bias behavior. *J Neurophysiol.* 116, 796-811.
- Whitney, C., et al., 2011. The neural organization of semantic control: TMS evidence for a distributed network in left inferior frontal and posterior middle temporal gyrus. *Cereb Cortex.* 21, 1066-75.
- Wise, S.P., 2017. The evolution of the prefrontal cortex in early primates and anthropoids. In: *The Evolution of Nervous Systems.* Vol., L. Krubitzer, J. Kaas, ed. Elsevier, New York.
- Woolgar, A., et al., 2018. The multiple-demand system but not the language system supports fluid intelligence. *Nat Hum Behav.* 2, 200-204.