



## Has brain imaging discovered anything new about how the brain works?

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### ABSTRACT

There have now been roughly 130,000 papers on fMRI. While these have clearly contributed to our understanding of the functional anatomy of the human brain, it is less clear that they have changed the way in which we think about the brain. The issue, in other words, is whether they have established new principles about how the brain works. In this paper we offer as an example one new principle, partly to lay down the criteria that are required for establishing a new principle, and partly to encourage others to offer other principles.

Our example concerns the flexible flow of information through the cortex that must occur according to the demands of the task or current context. We suggest that this flexibility is achieved by feedback connections from the prefrontal and parietal cortex, and that these include connections to sensory and motor areas. However, the nature of the selective effect differs. The parietal cortex can select both within and across processing streams. By *across* streams we mean that it can have the same influence on different streams, for example the dorsal and ventral visual systems. However, only the prefrontal cortex can also select *between* processing streams. The difference between the prefrontal and parietal effects is due to their different positions within the processing hierarchy.

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### Introduction

The ability to image the brain at work has proved to be a potent stimulus in the development of cognitive neuroscience. It has allowed us to visualize activations while people carry out tasks of which animals are not capable. This has been true, for example, for grammatical speech (Friederici et al., 2006), for imagining objects (Ishai et al., 2000) and for reading the minds of others (Amodio and Frith, 2006). There have now been around 130,000 papers using fMRI to study the brain, and imaging has clearly fulfilled its promise as a tool for functional mapping.

There have, of course, been some who have argued that functional mapping tells us nothing about mental processes, that is about *psychology* (Coltheart, 2006). Others have responded to this argument (Henson, 2006) and we do not wish to rehearse the issue again here. Our question is different. It asks whether imaging has changed the way in which we think about the *brain*.

Our ideas about the brain have been formed from decades of research on animals, mainly rats, mice and monkeys, and these studies have provided fundamental insights into how the brain works. Furthermore,

these insights have established general principles. For example, it has become clear from studies of the visual system in macaque monkeys that there is hierarchical processing within each processing stream. The receptive field sizes increase as one moves by stages from the striate cortex to the inferotemporal cortex and the complexity of the effective stimuli also increases (Desimone et al., 1985). At the same time there is parallel processing in different processing streams. For example, the ventral visual system is involved in the identification of objects and the dorsal visual stream in the use of object information to guide actions such as grasping (Milner and Goodale, 2007). Both hierarchical and parallel processing can be regarded as general principles of cortical function. These have been confirmed by imaging studies, but not discovered by them (Grill-Spector et al., 1998; James et al., 2003).

It might be objected that we are asking too much of imaging as a method. But compare the introduction of the light microscope and the electron microscope. The light microscope revealed the fundamental principle that different cortical areas differ in their cytoarchitecture (Brodmann, 1909). The electron microscope revealed the fundamental principle that at chemical synapses one neuron influences another across a synaptic gap, and that there are presynaptic vesicles that are capable of releasing packets in accordance with the quantal hypothesis (Robertson, 1956).

So the challenge is to see whether brain imaging, as a new method, has also added new principles. We accept that imaging contributes to

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functional anatomy, but our question concerns principles of brain function. So in this paper we set the more radical challenge. Has brain imaging told us new principles concerning *how* the brain works? In other words, we contrast functional mapping with neurophysiology. The former tells us *what* functions are performed by individual areas, whereas neurophysiology tells us *how* these functions are performed, both within an area and in the interactions between different areas. Neurophysiology asks how cells *code* and how they *communicate* with other cells.

Imaging is not well placed to understand how cells code because it has a limited spatial resolution. It is true that there is promise for the future of a resolution with voxels of 5 mm<sup>3</sup> or less (Logothetis, 2008), and this is roughly the size of the functional patches as revealed by optical imaging in the inferotemporal cortex of monkeys (Wang et al., 1998). However, though fMRI can detect a population signal, only single unit recording in animals can show how that signal changes on a millisecond time base as the subject scans the paths (Crowe et al., 2005). The reason is that population vectors can only be measured by recording from cells.

This is not to deny that multivariate methods can be used to decode mental states from fMRI data. Thus, pattern analysers have been used to tell what object the person is viewing (Norman et al., 2006), what they are intending to do (Haynes et al., 2007) and what episodic memories they are retrieving (Chadwick et al., 2010). So these methods hold out the promise of decoding states of which people but not animals are capable.

They can also tell us something about the distribution of patches of cells which are similar in their coding. Jerde et al. (2008) showed that there are patches with different orientation specificity in the parietal cortex, and Chadwick et al. (2010) have demonstrated patches coding for particular memories in the hippocampus. That such patches may be important for the way in which the brain encodes stimuli or states is suggested by the work of Wang et al. (1998). Their work with optical imaging suggests an orderly progression in the coding of stimuli in the inferotemporal cortex in macaque monkeys.

However, fMRI does not have the spatial resolution to tell us how these stimuli or states are coded for within a patch. To understand this, we need the spatial resolution of microelectrodes, whether for recording from single cells with one electrode, from groups of cells with tetrodes or from widespread ensembles of cells with implanted electrode arrays (Crist and Lebedev, 2008). This is possible in humans under limited circumstances, for example prior to surgery for epilepsy (Mukamel and Fried, 2012), but it is not realistic for many of the cognitive neuroscience questions being asked.

If this is so, those who seek to use fMRI for neurophysiology should rely on its strengths. We list them here.

- 1) The images show all the areas that are involved at the same time. In other words, imaging is a whole brain method.
- 2) This means that it is possible to study the covariation between activations in different areas within the images.
- 3) The BOLD signal appears to be especially sensitive to modulatory effects (Logothetis, 2008).

### The analysis of interactions

In this paper we capitalize on these properties. Properties 1 and 2 mean that fMRI can be used to study the interactions between activations, and thus communication between areas. This is not to claim that fMRI can detect *what* is communicated though there are promising leads in that direction (Bogler et al., 2011; Lizier et al., 2011). Nor is it to claim that fMRI can be used to study the mechanisms via which the interactions occur. The temporal resolution of EEG and MEG is required to measure synchrony on a millisecond time scale (Siegel et al., 2008).

However, fMRI makes up for these deficiencies in two ways. First, it shows all the areas that are activated, and not just the activity of cells that lie in a particular orientation. Second, it does so with a

spatial resolution that is better than that achieved by source localization methods for EEG and MEG.

Imaging can measure interactions in several ways. Structural equation modelling has been adapted so as to interpret the covariance matrix for the activations in different areas (Penny et al., 2004b). Dynamic causal modelling has been devised so as to propose a simple but physiologically interpretable model of how the interactions occur (Penny et al., 2004b). Both methods interpret the data in terms of what is known about the anatomical connections between the activated areas. The aim is to produce a simplified anatomical model that is sufficient to test hypotheses concerning communication within the network. Structural equation modelling does this by identifying the pattern of interactions that best predict the observed pattern of covariation. Dynamic causal modelling uses Bayesian inversion of a generative model to obtain a free energy estimate of model evidence, rather than approximating covariance. This method thus enables a formal and principled Bayesian procedure for comparing different models (Penny et al., 2004a). Daunizeau et al. (2011) have recently reviewed the statistics, reliability and biophysical plausibility of the methods that are used to infer communication from imaging data.

Though these methods aim to infer influence, they are restricted to testing or comparing models that incorporate influences, and the influences cannot go beyond the range of the models tested. One way of checking whether the inference is plausible is to analyse the data in terms of Granger causality. If A causes B, it should occur before B, though even if A does occur before B that is not proof that A causes B. However, a problem for fMRI data is that the vasculature of areas A and B may differ such that the BOLD signal from A appears to occur before that from B, whereas in fact the apparent difference in timing results from the different shapes of the BOLD signals in the two areas. Nonetheless, it is still possible to test whether the signal from A precedes that from B in one condition but not in another. This was done for example in an experiment by Weilke et al. (2001) who compared the timing of the signal in the SMA and motor cortex in self-initiated and auditorily-prompted actions. The signal in the SMA only preceded that in the motor cortex in the self-initiated, but not the prompted condition, and this shows that the difference in timing in the self-initiated condition was not an artefact of differences in the haemodynamic response.

However, whichever of the analysis methods is used, they only provide *hypotheses* concerning causal influence; they do not provide proof of causal influence. So it is necessary, wherever possible, to check these hypotheses by methods that involve intervention in the system. In the present paper we cite examples both of the effects of lesions and of the effects of stimulation.

### A candidate principle

By analysing fMRI data by these and other methods, several authors have suggested a candidate principle concerning cortical function (Friston et al., 1997; McIntosh, 2000; Stephan, 2004; Stephan and Friston, 2010). The principle of context dependent connectivity is as follows:

#### 1. Area A interacts with area B in context 1 and with area C in context 2.

This principle is not simply that area A interacts with area B on some occasions, but not others. That suggestion has been discussed by Fries (2005) who argues that the mechanism may involve the synchronization of activity in areas A and B. The principle concerns 'switching'. In other words, given that area A is interconnected with many other areas, the principle is that it is the context that determines with which area it interacts.

Early evidence for this candidate principle comes from three studies.

- 1) Buchel and Friston (1997) used structural equation modelling to show that the interactions between the prefrontal and parietal cortex with area MT/V5 differed depending whether the subject was or was not attending to motion. The same effect has been analysed more recently by Stephan and Friston (2010) using dynamic causal modelling.
- 2) Rowe et al. (2005) required subjects to select between colours. In one condition four colours were presented, and in the control condition just one. Structural equation modelling was used to analyse the data. When the subjects selected between colours there was an increase in the interaction between the prefrontal and parietal cortex and the visual area V4.
- 3) The above examples show an increase in the interactions between the prefrontal and parietal cortex depending on whether the subject attended to motion or to colour. However, they do not show that the same prefrontal or parietal area was involved in both experiments. Mechelli et al. (2004) used dynamic causal modelling to analyse data from a study in which subjects were required to imagine either faces or houses. There was an increase in the interaction between the prefrontal cortex with the fusiform face area (FFA) or parahippocampal place area (PPA) depending on whether the subjects imagined faces or houses. This shows that the same area A – in this case prefrontal cortex – interacts with areas B (FFA) or C (PPA) as a function of the context or task.

The problem with candidate principle 1 as proposed is that it is not grounded in what we already know of the architecture and neurophysiology of the brain. Compare it with the principles of hierarchical and parallel processing.

Hierarchical processing within a stream involves the convergence of information from lower order cells onto higher order cells. It is this mechanism that explains the increase in receptive field sizes from V1 to V4 (Desimone et al., 1985). At the same time there is an increase in the number of basal spines on the layer III pyramidal cells as one goes from V1, through V4 to the inferotemporal cortex (Elston, 2007; Elston and Rosa, 1998). This trend provides a mechanism for the increase in integration as one ascends the hierarchy.

Parallel processing in the dorsal and ventral visual stream can be interpreted in terms of the different connections of the two streams. The parietal cortical area AIP is interconnected with the ventral premotor cortex whereas the inferotemporal cortex is not (Borra et al., 2008). It is this difference that explains the role of the dorsal visual stream in using the size and shape of an object for action, that is for grasping. In other words the dorsal stream is involved in the online guidance of action. Patients with optic ataxia as the result of parietal lesions are impaired at reaching and grasping online, but are paradoxically better when a delay is introduced such that they act from memory (Milner et al., 2003). This can be explained on the assumption that delayed action relies on the identification and memory of the object via the ventral visual stream, and it is the ventral stream that receives information about shape directly from V4 (Ungerleider et al., 2008).

It is clear that proposal 1 requires a similar grounding in neuroscience. The aims of the present paper are to present evidence in favour of this principle and to provide that grounding. In all the paper has six aims, and these are listed below.

- 1) To explore the nature of the influence of one area on another, and to establish that the influence is causal
- 2) To provide a grounding for the principle in terms of our current understanding of the anatomy and neurophysiology of the brain.
- 3) To establish whether the principle is a general principle rather than simply a statement about specific areas
- 4) To show why it would be difficult or less convenient to demonstrate the principle in animal experiments
- 5) To put the principle in its neuroscientific context, and thus to establish why it holds

- 6) To consider whether the principle, as reframed in this way, is a genuinely novel principle

### The nature of the influence

In experiments with human subjects the conditions are determined by the instructions that are given. The conditions may refer to different tasks. It is an advantage of imaging that people will carry out different tasks after verbal instructions, whereas it takes many months to train monkeys on different tasks such as matching or non-matching (Wallis et al., 2001).

#### *What does the interaction reflect?*

The first question is what is communicated when area A interacts with area B. Since the different contexts or conditions are established by giving different task instructions, one possibility is that the interaction simply reflects memory of the verbal instruction for that trial.

To find out, Sakai and Passingham (2003) gave one of four tasks on each trial. The subjects had to remember a sequence of locations or letters as presented (tasks 1 and 2) or to remember a sequence of locations or letters and then mentally reverse the order (tasks 3 and 4). A variable delay followed one of the instructions, then the task items were presented, and finally memory for the items was tested. The activations were measured during the delay period and before the items were presented.

The finding was that there were delay period activations in area 8 (including the frontal eye field) and the intra-parietal cortex when the tasks involved spatial items (tasks 1 and 3). By contrast the delay period activations were in Broca's area, Wernicke's area and the word form area when the tasks involved verbal items (tasks 2 and 4). This pattern of results shows that the delay period activity does not simply reflect memory of the verbal instructions. If this were so, the activations should have been the same in all conditions. The differential delay period activations reflect the upcoming task: in other words they reflect 'task set'.

In the study by Sakai and Passingham there was also a delay period activation in the anterior part of the ventral prefrontal cortex. So they correlated this with the delay period activation in the task specific areas (area 8 and Broca's area). There were significant correlations with area 8 when the tasks were spatial and with Broca's area when the tasks were verbal. However, the delay period activations in the prefrontal cortex were the same, whatever the task to be performed. This means that the prefrontal activation could merely reflect general non-specific preparation.

That this is not so is shown by a study by Haynes et al. (2007). They used multivariate methods to analyse the delay period activations so as to test whether it was possible to interpret them so as to predict which task the subjects were going to perform. Haynes et al. compared two tasks, adding and subtracting a pair of two digit numbers. Rather than providing an instruction on each trial as to whether to add or subtract, the subjects were required to make the decision themselves as to which task they would perform on each trial. It was possible to train a pattern analyser so as to predict at a level of between 60 and 70% whether the subject was preparing to add or subtract. The clusters of voxels that represented this information were found in the medial, polar, dorsal, ventral and orbital prefrontal cortex. This experiment disproves the suggestion that the delay period activations in the prefrontal cortex simply reflect non-specific preparation.

#### *Is the task set activity necessary for performance?*

If the prefrontal activations reflect the task to be performed, one possibility is that it is the prefrontal cortex that sets up the task. To find out, Sakai and Passingham (2006) correlated the prefrontal activations during the delay with the activations that occurred *later* in the

task specific areas while the task was actually being performed. Sakai and Passingham presented single nouns and the subjects had either to say if the noun was abstract or concrete or to say whether the noun was of two rather than one or three syllables. The activations while the subjects actually made the judgement occurred in the ventral prefrontal area 47 if the task was making a semantic judgement and in the ventral premotor cortex if the task was making a phonological judgement. Sakai and Passingham were able to show that on semantic trials the prefrontal activation during the delay correlated more highly with the activation during task performance in area 47, whereas on phonological trials it correlated more highly with the activation during task performance in premotor cortex, area 6.

If the delay period activation sets up the task, interference with this activation should lead to errors. So Rowe et al. (2007) studied patients with prefrontal lesions, and used fMRI to record the delay period activations. They tested the subjects on the memory for locations (task 1 from the earlier study) and memory for letters (task 2 from the earlier study). The patients in the study by Rowe et al. (2007) were impaired on the tasks, making errors by repeating the task that was appropriate on the previous trial. Furthermore, the correlations between caudal prefrontal and posterior spatial or verbal areas were significantly lower than in the control subjects.

These results suggest that the patient with prefrontal lesions failed to set up the new task adequately on each trial, and were unduly influenced by what had been done on the previous trial. That the previous trial can cause such an influence is shown by a study by Akaishi et al. (2010). The instruction was either to make a prosaccade or an antisaccade when a visual stimulus appeared. TMS was applied over the frontal eye field during the delay period, and it evoked activation in parieto-occipital areas. However, the effect was different depending on the task that had been performed on the preceding trial. This indicates that after the preceding trial there was a persistent, if temporary, change in the state of the network.

#### *Do the interactions reflect a causal influence?*

So far the fMRI evidence has come either from studies that have measured correlations or from studies that have analysed the data using structural equation modelling or dynamic causal modelling. These latter methods infer influence but they do not prove it. To do this one needs to intervene.

So Morishima et al. (2009) used TMS, as in the later study by Akaishi et al. (2010). Morishima et al. presented faces that were made up of moving dots, and the task was either to identify the direction of motion or to identify whether the face was that of a man or woman. Single pulse TMS was applied over the frontal eye and the current source density was measured via EEG in the MT complex and the fusiform face area. TMS had a selective effect on the MT complex when applied during the motion task, and a selective effect on the fusiform face area when applied during the gender task. In both cases the effect was to increase the current source density, that is an enhancement.

It might be objected that these results could be explained if, when the instruction was to attend to motion there was greater activation in the MT complex and when the instruction was to attend to gender there was greater activation in the FFA. If this were true, TMS over the frontal eye field could have a differential effect because of the differential activation in the two areas. However, Neubert et al. (2010) carried out an experiment which adequately copes with this objection. The subjects were set two tasks, and cues indicated whether the subjects should stay or switch on the current trial. Thus, on all trials, whether stay or switch, there was preparatory activity in the motor cortex, and the motor evoked potentials did not differ for these two trial types when the motor cortex was stimulated with TMS alone. However, if TMS was also applied over the ventral prefrontal cortex

(double pulse trials), it enhanced the motor evoked potential on stay trials and inhibited it on switch trials.

In summary, the evidence reviewed in this section supports principle 1. The differential interactions of area A with areas B or C reflect the transmission of information that is specific to the task, are necessary for performance, and reflect a directed causal influence of area A on the other areas.

## **Grounding in neuroanatomy and neurophysiology**

### *Neuroanatomy*

In all the cases discussed in the previous section, area A influences areas B or C via feedback paths. This is true, for example, of the experiment by Morishima et al. (2009) in which the task or context affected the degree of enhancement in early sensory areas. A direct demonstration of the operation of these paths comes from Garrido et al. (2007). They measured the effects of feedback on the late components of sensory evoked potentials, and used dynamic causal modelling to analyse the data.

It is known that, whereas feedforward paths terminate in the granular layer IV, feedback paths avoid this layer (Shipp, 2005). We are, of course, aware that the pattern of termination is not always the same for all feedforward or feedback pathways, and Shipp (2005) discusses this in detail. There are indeed problems with defining feedforward and feedback pathways purely in terms of the layers to which they project. However, the above generalization still holds.

It is, of true that, with current methods, the spatial resolution of fMRI is not adequate to distinguish activity in the different layers. To do this one would need to record with electrodes in macaque monkeys, as in the experiment by Takeuchi et al. (Takeuchi et al., 2011). However, where dynamic causal modelling indicates the operation of feedback paths (Daunizeau et al., 2011), it may be assumed that this involves layers other than layer IV. In this sense, principle 1 may be said to be grounded in neuroanatomy.

Shipp (2005) has proposed that the output (motor) pathways can also be regarded as being feedback pathways. The evidence is that, as in the case of feedback pathways to sensory areas, the output pathways do not go to a granular layer IV. The reason is that the premotor cortex and motor cortex lack a granular layer IV.

Brain imaging also suggests that there are similarities between the feedback pathways to sensory areas and the output pathways. In the study by Sakai and Passingham (2003), when the subjects were preparing to perform the verbal memory task, there was set activity both in Broca's area (an output area) and in the word form area (an input area). In both cases the activation reflected enhanced activity.

Imaging studies also show that the feedback paths to both sensory and motor areas are selective. Ishai et al. (2000) found that there was activation in the FFA (sensory) when subjects imagined faces and in the PPA (sensory) when they imagined houses. In parallel, Ehrsson et al. (2003) found that there was activation in the foot area of the premotor cortex (motor) when subjects imagined moving their toes and in the hand area (motor) when they imagined moving their fingers. In both experiments there was no change in the inputs during imagination, and thus the activations must have been driven by feedback paths.

### *Neurophysiology*

Shipp (2005) has made the further suggestion that feedback paths exert a modulatory influence. If so, they are distinct from feedforward paths which can be regarded as providing information. The results of the TMS studies by Morishima et al. (2009) and Neubert et al. (2010) are consistent with the claim that feedback paths exert a modulatory influence. The effect can either be an enhancement or a decrease in the activation.

### *The representation of the context*

In experiments with human subjects, the task instructions are given beforehand. Ruge and Wolfensteller (2010) used an event-related analysis of fMRI data to isolate the activations when the instruction is given. The degree of activation in the left prefrontal cortex was related to subsequent behavioural performance. The peaks lay in the middle frontal gyrus and in the inferior frontal junction. In a subsequent experiment Hartstra et al. (2011) showed that, at the time the instruction is given, the activation in the inferior frontal junction occurs irrespective of the nature of the task that is instructed.

These results suggest that it is the prefrontal cortex that first represents the context or task. It is true that for visuo-motor tasks one can find activations in the parietal and premotor cortex that also relate to the current task (Hartstra et al., 2011). And a multivariate analysis of the parietal activation indicates that it does indeed reflect the specific task (Bode and Haynes, 2009).

The authors in the latter study claimed that the activation in the parietal cortex represented the current task before the activation in the prefrontal cortex. And that this might indeed be the case is indicated by the findings of a study by Wallis and Miller (2003) in which they compared the relative times at which the current task, matching or non-matching, was specified by cells in the premotor and prefrontal cortex in monkeys. The evidence was that the specification occurred earlier in the premotor cortex. However, by this time the monkeys had been overtrained on the two tasks for very many months. It is possible that if recordings were taken simultaneously from the two areas during initial learning, the result would be different, in other words the specification would occur earlier in the prefrontal cortex.

There is good reason for making this prediction. Monkeys are taught the tasks by trial and error, and the information on the outcomes, that the value of rewards in relation to current needs is first processed in the orbital prefrontal cortex, and not the parietal cortex (Murray and Wise, 2010; Passingham and Wise, 2012). It is only after the tasks have been learned and overtrained that the task rules can be represented in other areas, such as the premotor or parietal cortex.

The crucial difference is that the prefrontal and parietal cortices occupy different positions within the processing hierarchy. While the parietal cortex receives information from several processing streams, for example from MT and V4 (Baizer et al., 1991; Ungerleider et al., 2008), the prefrontal cortex is unique in receiving information from all processing streams (Passingham and Wise, 2012). Thus, it receives visual information from the dorsal and ventral visual system, auditory and somatic information, and information about taste, smell and visceral sensation.

In other words, the prefrontal cortex lies at the top of the processing hierarchy. That the information that it receives is integrated is shown by the fact that it is possible to find cells in the prefrontal cortex that code both for shape (ventral visual stream) and location (dorsal visual stream) (Rao et al., 1997); others that are sensitive to information both about colour (inferotemporal cortex) and motion (MT complex) (Lauwereyns et al., 2001); and yet others that code for both vision and taste (Rolls et al., 1996).

In the imaging experiments the context was manipulated by verbal instructions but in the experiments on monkeys (Wallis and Miller, 2003) it was manipulated by presenting tones or juice as instruction cues. The prefrontal, but not the parietal cortex, receives information about both, and is thus in a position to establish the context for each trial. Passingham and Wise (2012) have argued that the prefrontal cortex lies at the top of the sensory hierarchy, and that for this reason it is in a position to identify the current context.

### *Serial versus parallel processing*

Given that the prefrontal cortex receives information from different processing streams, it can integrate information from those streams.

There are extensive interconnections between the different subareas of the prefrontal cortex (Barbas, 1988; Petrides and Pandya, 1999, 2002). Averbach and Seo (2008) have calculated that if one follows any input to the prefrontal cortex, the information can reach any other of the subareas of the prefrontal cortex in at most two steps. Evidence for the degree of integration within the prefrontal cortex comes from the observation that one can find cells that code for different tasks, matching or non-matching, throughout the lateral surface of the prefrontal cortex of the monkey (Wallis et al., 2001). And, as already mentioned, it is possible to use multivariate analysis to predict the current task in fMRI data from the medial, polar, dorsal, ventral and orbital prefrontal areas (Haynes et al., 2007).

The degree of integration is such that whereas the inputs to the prefrontal cortex can operate simultaneously and in parallel, there appear to be limits on the degree to which the prefrontal cortex can process information in parallel. In other words the prefrontal cortex seems to operate like a single processing stream. This can be demonstrated by requiring human subjects to perform two tasks simultaneously, both of which depend on prefrontal mechanisms. The result is a cost in terms of reaction time and errors, and this is true whether the tasks are judging the lengths of lines and selecting responses (Jiang and Kanwisher, 2003), learning a visuo-motor task and generating verbs (Grol et al., 2006) or learning to produce a sequence of forces while counting backwards in threes (Floyer-Lea and Matthews, 2004). That this interference occurs because of overlap in the prefrontal activations is shown by the fact that the cost greatly decreases when one of the tasks is practised until it is automatic, and when a motor task (Floyer-Lea and Matthews, 2004; Toni et al., 1998) or verb generation (Raichle et al., 1994) are practised repeatedly the activation in the prefrontal cortex decreases to near baseline levels.

In summary, principle 1 states that area A interacts with area B in task 1 and with area C in task 2. The current section has established the following.

- 1) Principle 1 depends on feedback paths that are modulatory
- 2) This is true for feedback paths to sensory and motor areas
- 3) The current task is represented at the time of instruction in the prefrontal cortex, though it can also be represented later in the parietal and premotor cortex
- 4) The reason why the prefrontal cortex can represent the task is that it lies at the top of the processing hierarchy, and is thus able to construct the current context
- 5) Because the prefrontal cortex integrates information from all processing streams, processing within the prefrontal cortex occurs serially, as in a single stream.

### **Is principle 1 a general principle?**

Principle 1 depends on the properties of feedback pathways. And it is common to all feedback pathways that they are selective. Consider first a single stream. Breckfzyski and DeYoe (1999) instructed subjects to attend covertly in turn to locations at different distances from central vision into the periphery. The enhancement of activation occurred in turn at the corresponding locations in visual areas that were retinotopically mapped, and this included V1. Kosslyn et al. (1995) also showed that if subjects are asked to imagine figures, there is activation in visual areas including V1. In both cases these activations occurred without any change in the visual inputs, and thus they must result from the operation of feedback pathways. Thus, these studies show that feedback pathways continuing back to V1 are involved in selecting by the location or the identity of the object.

The study by Breckfzyski and DeYoe (1999) also shows that feedback pathways can be selective across different processing streams. By this we mean selection which occurs at the same time in different streams. Thus, when the subjects attended covertly to location, the localized enhancements of activation occurred in both the dorsal and ventral visual streams.

Finally, the evidence that we have reviewed earlier shows that feedback pathways can select *between* streams. We have provided examples of selection between the MT complex and the FFA (Morishima et al., 2009) and between spatial (dorsal) and verbal (ventral) streams (Sakai and Passingham, 2003).

While it true that it is a general principle that feedback paths, whether to sensory or motor areas, are selective, this does not mean that all feedback pathways select *between* areas. Principle 1 states that area A interacts with area B in context 1 and with area C in context 2. This is not a principle that relates to all feedback paths. To illustrate this point we consider the feedback pathways from the prefrontal and parietal cortex.

Both prefrontal (Petrides and Pandya, 2002; Stanton et al., 1995) and parietal cortex (Ungerleider et al., 2008; Webster et al., 1994) project to sensory areas, and both prefrontal (Wang et al., 2002, 2005) and parietal cortex (Rizzolatti and Luppino, 2001) project to premotor areas. Yet the feedback pathways from the two areas differ in the way in which they operate.

Ruff et al. (2009) compared stimulation with TMS over either the right frontal eye field or the right intra-parietal sulcus, while recording activations with fMRI in areas MT and V4. Stimulation over both areas in the right hemisphere increased activation in the peripheral representation within V4, but stimulation over the frontal eye field in the left hemisphere led to changes in the central representation with V4. Stimulation over the parietal cortex selectively affected activation in area MT only when motion stimuli were presented. Though no formal task was presented, the subjects would have been attending to the motion in this condition.

In a related experiment, Blankenburg et al. (2010) instructed their subjects to attend to a coloured pattern either on the right or on the left. TMS was applied over the intra-parietal sulcus while scanning the subjects with fMRI. Attending to the pattern on one side led to greater activation in the contralateral than ipsilateral fusiform gyrus and V4. And this effect was increased by TMS over the parietal cortex.

These results indicate that the feedback pathways to sensory areas from both prefrontal and parietal cortex have a selective or modulatory influence. However, the nature of that influence differs as a result of the position of the prefrontal and parietal cortex within the processing streams. The parietal cortex forms part of the dorsal visual stream, and thus it selects by location, that is by where within the visual field attention is paid. The parietal cortex sends projections to prefrontal area 8d (Petrides and Pandya, 1999), and so applying TMS to area 8d also has a selective effect according to location.

However, prefrontal areas 8v and the inferior frontal convexity area 12/47 receive information from the ventral visual stream (Webster et al., 1994). Thus these areas are in a position to have a selective effect according to shape and colour. In the experiment on imagining objects by Mechelli et al. (2004), the interactions of the prefrontal cortex with the FFA and PPA differed depending on whether the subjects were imagining faces or houses, whereas the interaction of the parietal cortex with these areas did not. In other words, while it is true that the prefrontal cortex influences areas B or C depending on the task, the parietal cortex has an influence that does not depend on *what* is imagined.

If this is correct, principle 1 relates to the influence of the prefrontal cortex, whether on sensory and motor areas. While it is true that the interactions of the parietal cortex with sensory areas also depend on the context, the selective influence operates *within* and *across* areas, but not *between* areas.

This conclusion is backed up by the findings of a combined fMRI and EEG study by Zanto et al. (2010). The subjects were required either to discriminate the direction of motion or to discriminate colour, and the activity in areas MT/V5 and area V4 was enhanced when attention was paid to the relevant feature. However, whereas the prefrontal cortex interacted with MT/V5 or V4 according to the feature, the parietal cortex only interacted with activity in MT/V5 in the motion condition. That the prefrontal effect was causal was suggested

by a later study in which TMS over the prefrontal cortex both led to a decrease in the enhancement and also a fall off in performance (Zanto et al., 2011).

In the earlier experiment by Zanto et al. (2010) the parietal cortex did not interact with area V4 during the colour task. The reason is that the task was to discriminate between the colours, that is to say *what* the colour was. In an experiment by Rowe et al. (2005) there was a significant change in the interaction between the parietal cortex and area V4 when the subjects were required to select one of four colours. In this case the colours were presented in an array, and the selection involved the choice of a colour by its location, that is by *where* it was in the array.

We are, of course, aware that it is possible to record cell activity in the parietal cortex of monkeys that reflects object features such as colour (Toth and Assad, 2002) and shape (Murata et al., 2000) as well as spatial location (Toth and Assad, 2002). This activity could be transmitted from area V4 (Ungerleider et al., 2008) or from the ventral prefrontal cortex (Gerbella et al., 2010). However, where it is the context that establishes whether it is colour, shape or spatial location that is relevant, the information concerning context must be derived in the first case from the prefrontal cortex since the animal learns the relevance of context via the outcomes that follow action (Passingham and Wise, 2012).

So we conclude that whereas the prefrontal cortex is in a position to select what cue is relevant, the parietal cortex selects mainly on the basis of location. This is also true for the feedback paths to the motor system. Both prefrontal and parietal cortices send projections to the dorsal premotor cortex (Rizzolatti and Luppino, 2001). However, in two experiments Rowe and Passingham used structural equation modelling to show that when subjects select (Rowe et al., 2005) or prepare (Rowe et al., 2002) a specific finger response, there is a change in the interaction between the prefrontal and premotor cortex, but not between the parietal and premotor cortex. The reason is that the projections from the parietal to the dorsal premotor cortex are involved in reaching (Caminiti et al., 1998), that is in selecting the location to which to move the arm. In the experiments by Rowe and Passingham the responses involved different finger movements.

We are now ready to restate principle 1. It can be expanded so as to form principle 1a, as follows:

**1a.** *The flow of information within and between streams, both sensory and motor, is flexible according to the demands of the task, and this flexibility is achieved by feedback connections from the prefrontal and parietal cortex. These include connections to sensory and motor areas. However, the nature of the selective effect differs between the parietal and prefrontal cortex. The parietal cortex can select within and across processing streams but only the prefrontal cortex can also select between streams. This difference is due to the different positions of the two areas within the processing hierarchy.*

### **Why would it be difficult to establish principle 1a in animal experiments?**

That one area can have a differential influence on another according to condition can be demonstrated in experiments on animals, though it is technically difficult to do so. It has been shown that stimulation of the frontal eye field in monkeys can enhance visual responses in corresponding parts of the visual field in area V4 (Moore and Armstrong, 2003). Furthermore, Zhou and Desimone (2011) have recorded simultaneously in the frontal eye field and V4. They isolated cell pairs, one in the frontal eye field and one in V4, that had the same receptive field. They then manipulated attention to an object by using a visual search task. There was enhancement of activity in both areas when the monkeys attended to the relevant object, and the data suggested that the frontal eye field influenced the enhancement in V4. The evidence was that the optimal timing of firing involved a spike from the frontal eye field preceding

the enhanced local field potential in V4. The data were consistent with the proposal that areas interact optimally when the spikes in the two areas occur in synchrony (Fries, 2005; Womelsdorf et al., 2007).

While these studies suggest a mechanism for communication, it remains that it would be difficult to demonstrate in animals that area A interacts with area B or C depending on the task. The best evidence is that cortico-cortical cells do not have collaterals (DeYoe and Van Essen, 1985), and we know for certain that different cells in the frontal eye field connect with MT and V4 (Ninomiya et al., 2012). So, to demonstrate that the interactions of area A with B or C differ by condition, one would need to find cell pairs in A and B, and in A and C, that have the same receptive fields, and to record simultaneously in areas A, B and C.

This may be possible in the future with implanted electrode arrays (Lehew and Nicolelis, 2008). But for the moment it is more feasible to demonstrate principle 1a using a method such as fMRI that has a more coarse spatial resolution. Methods such as this could also be used to follow up principles such as 1a that have initially been demonstrated with imaging.

### Is principle 1a novel?

We do not pretend that principle 1a is other than a working out of the proposals concerning effective connectivity made in a series of papers by Friston and colleagues (Büchel and Friston, 1997; Daunizeau et al., 2011; Garrido et al., 2007; Stephan and Friston, 2010). However, we do claim to have given this principle a firm grounding in neuroanatomy and neurophysiology; to have generalized it to output as well as sensory streams; and to have clarified both the importance of the prefrontal cortex in identifying the context, and the difference between the feedback influence of the prefrontal and parietal cortex. Furthermore, we hope that our discussion has made clear what criteria must be met for a principle to be accepted as new.

Nor do we wish to ignore the major contribution of Desimone and Duncan (1999) in identifying the need for top-down effects to explain the effects of visual attention. However, principle 1a is more general, since it concerns the flexibility between processing streams as a function of the task, and these include motor as well as sensory streams.

As already mentioned we have also claimed that imaging (fMRI with and without TMS) has also clarified the difference between the top-down effects from the prefrontal and parietal cortex. There is a further difference. Desimone and Duncan stressed that within a processing stream such as the ventral visual stream, there is local competition between representations as in the experiment by Moran and Desimone (1985). In this two objects were presented within the receptive field of the cells in V4 or the inferotemporal cortex from which recordings were taken. Attention to the object at one location led to a decrease in the firing to the object at the other location.

Attention is limited for the same reason that there is a limit to eye movements. You cannot look right and left at the same time, and you cannot attend right and left at the same time. The constraint occurs because of location. In the same way you cannot both raise and press your forefinger at the same time. Doing one necessarily means that you cannot do the other. It is for this reason that there can be competition *within* a processing stream. Desimone (Desimone, 1999) accounted for the results of the study by Moran and Desimone (Moran and Desimone, 1985) by suggesting that there were top-down effects that exerted a bias on this local competition.

But the same limit need not apply *between* streams. Suppose that one were to present a sequence of four letters, but with the difference that in one condition the subjects had to remember the letters, and in the other the location of the letters. There is no reason why the subjects should not be able to remember *both* the letters (what) and their locations (where) simultaneously. The only reason why it was difficult to do this in the experiment by Sakai and Passingham (2003) is that in each

frame a letter and a square were presented at different locations. In one condition the subjects had to remember the sequence of letters and in the other the sequence of locations (squares).

Although one might have thought that there need be no competition between streams, the task does impose a limit. As suggested by Allport (1987), at any one time the subject is working for a desired outcome, and that outcome will only be achieved by coherent action towards that outcome. Only some of the sensory information currently available will be relevant to the appropriate action. So there must be selection both of the sensory information and of the action if the desired outcome is to be achieved. It is the prefrontal cortex that is primarily involved in selecting the sensory information and the appropriate action since it is the prefrontal cortex that also processes information concerning current needs (Murray and Wise, 2010). Passingham and Wise (2012) have argued that the prefrontal cortex generates the action that is appropriate to the current context and current needs. We have suggested that it does so serially, acting like a single processing stream. So, though information in the sensory streams is processed in parallel, there is a limit on the processing of information across these streams, and that is imposed by the demands of serial processing for action.

### Is principle 1a a statement about functional anatomy or neurophysiology?

We have suggested that the flexible routing of information through processing streams depends on feedback pathways from the prefrontal cortex. It could be argued that this is simply a statement about the functions of the prefrontal cortex, that is what it does. And, of course, we are suggesting that the prefrontal cortex exerts a selective influence both on input and output pathways. Passingham and Wise (2012) have used data on macaque monkeys to argue that the key role of the prefrontal cortex is to generate the action that is appropriate to the current context. However, the imaging data reviewed here go beyond that. They suggest *how* the prefrontal cortex does this.

This, then, is a statement about neurophysiology. We have reviewed the imaging and TMS data that indicate that the prefrontal cortex can enhance representations in other areas, whether these be sensory or motor. The data reviewed relate also to the top down influence of the parietal cortex, and to the operations of the cortex as a whole. Principle 1a concerns the flow of information through the cortex as a function of the task. Thus, it is not simply a statement about the functions of one area.

### What is the mechanism underlying principle 1a?

There is no need to invoke any new mechanism to explain principle 1a. Selection between processing streams could be achieved by the same mechanism that explains selection within a processing stream, and this is true both for sensory and motor pathways. Consider the results of studies on imagination. Selection of faces versus houses (within the ventral visual stream) or selection of hand versus foot movements (within the premotor output stream) is achieved by the enhancement of specific representations within an area. The same mechanism can select between operations in different areas, for example spatial versus verbal. What we call an 'area' is arbitrary. We typically use Brodmann divisions to define an area, but within the motor cortex, area 4, the cells in the medial surface (foot) are larger than those in the lateral surface (hand), and we could in principle call these two different areas. Similarly it is not clear whether we should regard the FFA and PPA as lying in parallel visual streams or as representing the central and peripheral part of a single visual stream (Levy et al., 2001). So we do not believe that a new mechanism is needed to account for flexible processing across streams.

Nonetheless, it remains true that we understand little about the mechanism that explains selection within a processing stream. Somehow one

subpopulation of cells within area A becomes active whereas another subpopulation does not, and an accumulator-racetrack model has been suggested for one area (Gold and Shadlen, 2007). That there can be changes between active subpopulations we know from the work of Takeda and Funahashi (2004) who recorded during the delay on an oculomotor delayed response task. There was a change in the population vectors as the monkeys converted from a cue at one location to a response at a location at 90° to this. The explanation is not that the same cell changes its coding (Takeda and Funahashi, 2007) but that different subpopulations of cells are active at any one time.

Thus, it is plausible that in one context one subpopulation could be active and in another context another subpopulation. It is not clear, however, how the switch occurs. Hussar and Pasternak (2009) have shown that, when a monkey views a complex stimulus, it is the interneurons in the prefrontal cortex that are more sensitive to the relevant dimension than the pyramidal cells. However, we do not know how the interneurons influence the output cells so as to enhance the activity of one subpopulation rather than another.

## Conclusions

We started by asking whether brain imaging has discovered any new principles. We have argued that it has, and have provided one example. We may call this the principle of the flexible flow of information as a function of the current task or context. This involves the flexible routing of information within and between the processing streams, both sensory and motor, depends on the feedback architecture of the brain.

We have also claimed that the different effects of the feedback paths from the prefrontal and parietal cortex depend on the different position of these areas within the hierarchy. Finally, we have claimed that the prefrontal cortex acts as a single processing stream, integrating information from parallel processing streams, and thus acting in a serial fashion.

None of this is totally new to this paper, nor has it been established by imaging alone. But imaging has played a major part in putting this principle forwards. It has done so because it is so easy to instruct people to perform different tasks, because fMRI visualizes activations throughout the cortex, because it is possible to study the covariance between those activations, and because it is possible to use TMS together with EEG or fMRI to establish causal influence.

Apart from discovering new principles, imaging can also be used to test principles that have been proposed on the basis of animal data. An example concerns the proposal by Passingham et al. (2002) that the coding of an area is determined by the inputs and outputs of that area. Saygin et al. (2011) have used imaging to show that the activation in the fusiform face area can be predicted on the basis of the connections as suggested by diffusion tensor imaging.

The rapid development of imaging and the flood of papers on fMRI have shown that it is easy to use it to study the functional anatomy of cognition. The argument here concerns our understanding of *how* the brain works. It is less easy to find good examples of progress made here. In concentrating on one example our intention has been to lay down the criteria that need to be met if new principles are to be established. We hope also to challenge the community to come forward with other principles that meet these criteria.

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