Figure 3. DNA gyrase mechanistic scheme.

A basic reaction cycle for gyrase under normal conditions is shown on the right (**2–5**). Only the half wrap including the T segment is shown for clarity. Binding of ATP captures a T segment (red) (**2→3**), which may proceed to strand passage (**3→4**), or be freed by ATP hydrolysis and product release (**3→2**). After strand-passage and T segment exit from the complex (**4→5**), the clamp is opened on hydrolysis and rate-limiting (**RL**) product release (**5→2**). This cycle introduces two negative supercoils, and results in a rotor bead rotation of 720° in the single molecule experiment. Increasing tensile force will affect the wrapping/unwrapping equilibria, stabilising the unwrapped complexes (**6** and **7**), and reducing the processivity of the reaction by DNA dissociation from **7** or **2**. Product release is still the rate-limiting step, independent of force. Tensile force will perturb the equilibria as indicated by the red arrows, resulting in an increase in the efficiency of the strand-passage reaction (**3–4** equilibrium).

ATP binding and strand-passage. More speculatively, it would be fascinating to have a corresponding single-molecule method to analyse ATP hydrolysis simultaneously with DNA supercoiling, to really dissect the energy coupling aspects of these systems.

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Cognitive Neuroscience: Trickle-Down Theories of Vision

The visual cortex is not a passive recipient of information: predictions about incoming stimuli are made based on experience, partial information and the consequences of inferences. A combination of imaging studies in the human brain has now led to the proposal that the orbitofrontal cortex is a key source of top-down predictions leading to object recognition.

Jacinta O'Shea[1] and
Vincent Walsh[2]

The study of top-down processing often reveals a paradoxical feature of how we theorise about vision. It seems that in order to explain the workings of the brain we sometimes adopt the logic of Intelligent Design — smart things can only be made by, well, by smarter things. Every visual neuroscientist has had the experience, at the end of a lecture, of being asked by an engineer in the audience "why would anyone design a system like that?" (you know it's an engineer because they

always preface the question with "I am an engineer"). The answer, of course, is that nobody designed the system — it evolved. Yet when thinking about top-down control, the dominant assumption is that there must be a high-level 'smart' area that guides the less smart sensory cortex.

This is the thinking behind the idea that the parietal or prefrontal cortices are important in top-down visual control — they are higher level areas that can somehow direct visual cortical processes [1,2]. The same logic guided initial theorising about cognitive contours (Figure 1). It was argued that these contours are perceived because the brain makes inferences about what kinds of objects are consistent with the retinal images with which it is presented. Such an inferential process could only be carried out by a smart area, and it was therefore assumed that the inferotemporal cortex, in some senses the pinnacle of the visual system, must be the source of the perception of cognitive contours — and neurons responding to them were duly found. Subsequent studies, however, were able to show that the architecture of visual areas V2 [3] and V1 [4] could be sufficient to generate these illusory percepts: could the visual cortex be smart after all?

A new study [5] of visual recognition processes lends support to the idea that predictive visual processing follows a trickle-down path from frontal cortex to lower level visual areas. Previously, Bar *et al.* [6] had observed that object recognition elicited activity not only in the temporal cortex, as one might expect, but also in the orbitofrontal cortex, an area not traditionally associated with object recognition processes. In the new study, Bar *et al.* [5] presented subjects with line drawings or photographs of animals and everyday objects and subjects pressed a key if they recognised the object. Subjects underwent two types of brain imaging: functional magnetic resonance imaging (fMRI) to identify the areas activated by high or low spatial frequencies in the recognition task;

Figure 1. Two examples of 'cognitive' contours.

The lines forming the triangle and the long lines dividing the three sets of shorter horizontal lines are both illusory. Initial explanations of these percepts suggested that they must have been constructed by higher visual areas such as the inferotemporal cortex but we now know that V1 and V2 responses may produce these illusions.
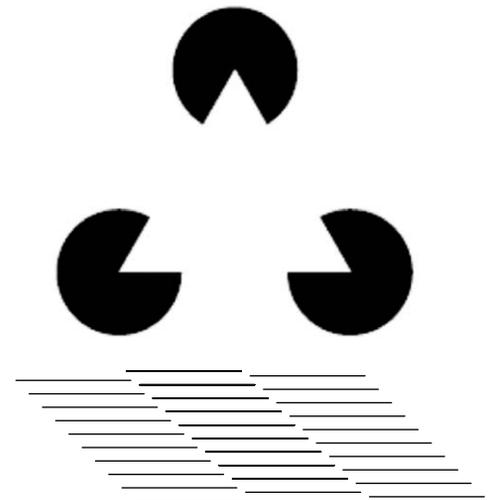
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and magnetoencephalography (MEG) to determine when these areas were activated.

The study has three core findings: First, the MEG data showed that the right orbitofrontal cortex was activated 50 milliseconds before the right fusiform gyrus and 85 ms before the left fusiform gyrus (Figure 2). Second, activity in the orbitofrontal cortex and activity in visual areas in the temporal (fusiform gyrus) and occipital (visual cortex) lobes was time locked on a trial-by-trial basis. And third, orbitofrontal cortex activity was found to differ in response to high versus low spatial frequency stimuli (Figure 3).

On the basis of these data, Bar *et al.* [5] propose that the orbitofrontal cortex "sensitises the representation of the most likely candidate objects in the temporal cortex as a predictive initial guess". The idea is that low spatial frequency information reaches the orbitofrontal cortex before it reaches the visual recognition areas, and that the orbitofrontal cortex sends a guiding signal to the visual recognition areas that says something like "here's a gistimate (*sic*) of what you're looking for".

Our engineering friend already has both hands in the air to ask the usual question, but perhaps we can also see a biologist wanting to ask a different question: why would something evolve like this? Trickle-down theories are based on movement of resources from the rich to the poor and in the case of

the orbitofrontal cortex, when it comes to cognitive functions we seem to be talking about the super-rich. As Bar *et al.* [5] note, the orbitofrontal cortex is not traditionally associated with visual recognition processes, but it is associated with emotion, reward-association, impulsivity and decision making [7,8]. It is also an area that receives inputs from all the senses. What we might consider, then, is whether the orbitofrontal cortex performs some function common to all its sensory inputs or whether its role in top-down visual control may be a special case.

If one were to look for an explanation of the orbitofrontal cortex activations in terms of what is already known about this area, some alternative explanations begin to present themselves. The orbitofrontal cortex is indispensable for forming normal stimulus–reward associations [8]. Hence it is possible that the orbitofrontal cortex activations seen in this study represent a prediction about the likelihood that one will identify an object correctly. In some conditions, subjects were required to indicate their level of knowledge about the object. Thus, the activations may be representative of subjects' emerging confidence in their performance on any given trial, and they could evolve in parallel and independently of visual predictive processes. Such a confidence judgement might also
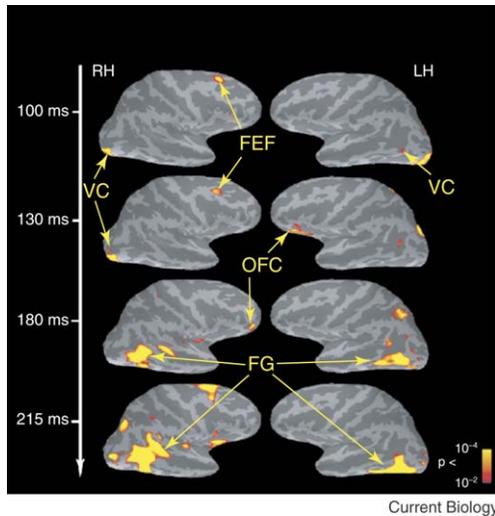
Figure 2. Trickle up or trickle down?

Time course of activity in the experiment reported recently by Bar et al. [5]. The first areas to be activated are the right frontal eye fields (FEF) and early visual cortex (VC). The second phase of activity involves the orbitofrontal cortex (OFC) and later phases involve the fusiform gyri (FG) and the right orbitofrontal cortex. Trickle-down: Bar et al. [5] suggest that the orbitofrontal cortex activity (130 milliseconds) provides an initial representation based on low spatial frequency information, which then guides object identification in the fusiform gyri. Trickle-up: Alternatively, the frontal eye field and visual cortex activity (100 milliseconds) may extract gist information and convey this to the fusiform gyri while, in parallel, the orbitofrontal cortex may be using low spatial frequency information to estimate the likelihood of making a correct perceptual judgment. (Modified from supplementary information in [5].)

correlate with recognised versus unrecognised objects on a trial by trial basis. Another recent study [9], for example, has shown that activity in orbitofrontal cortex can correlate with a subject's level of uncertainty when making a decision.

Another key question raised by the new work of Bar et al. [5] is whether activations in other areas that preceded orbitofrontal cortex activation could also reflect top down processing. There was greater activation for recognised versus non-recognised objects both in the early visual cortex (Figure 2) and in the right frontal

eye fields (Figure 2). There is compelling evidence that the frontal eye fields play a role in top-down visual processing. The frontal eye fields respond as early as 40 milliseconds after a stimulus is presented [10], have generated a representation of target location by 100–130 milliseconds [11], and share topographically organised connections with a wide range of visual areas [12]. They are also closer than the orbitofrontal cortex to the visual areas and therefore satisfy the constraint — or at least the common observation — that evolution, like an engineer, likes

to keep its wires short to limit the possibility of error [13].

There is a further reason to emphasise the role of interactions between the frontal eye field and the visual cortex. The visual areas connected to the frontal eye fields encode both low and high spatial frequency information, are closely connected to the fusiform recognition areas, and also respond to visual stimuli before the orbitofrontal cortex. It seems entirely possible that the activity in these areas preceding the orbitofrontal cortex activity (Figure 2) encapsulates all the information required for purely visual purposes prior to the fusiform activation, and that the source of the orbitofrontal cortex activity may be a parallel process representing confidence in the accuracy of the perceptual judgement that is being made under ambiguous conditions.

The work of Bar et al. [5] shows that even simple tasks can yield surprising and intriguing results and that understanding the temporal relationships between distant regions of cortex is a key to a more sophisticated understanding of the pathways from sense to action. The dual technique assault, adopted by Bar et al. [5], combining fMRI and MEG, provides a richness of data that will invite new interpretations — which we hope will be a flood rather than a trickle.

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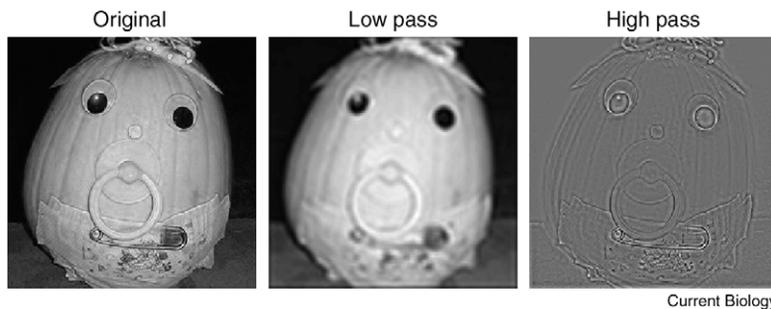
Figure 3. High and low spatial frequency information.

Images contain different spatial frequencies. Low spatial frequencies carry 'broad brush' information (centre image) and high spatial frequencies carry outline and fine contour information (far right image). The initial gist of a scene may be dominated by low frequency information. From the new Bar et al. [5] study the proposal is that low spatial frequency information reaches the orbitofrontal cortex via fast feedforward connections and that the information is then used to generate predictions about the more detailed higher spatial frequency information coming in through the visual cortex. (Figure courtesy of Elliot Freeman.)