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Visual Neuroscience: A Hat-Trick for Modularity

A new study using transcranial magnetic stimulation of the brain shows that each of three neighboring areas of visual cortex plays a specific and causal role in perceiving faces, bodies and other kinds of objects.

Paul E. Downing

Vision provides the human brain with its main source of information about the surrounding world. Accordingly, the visual cortex is large and complex — considerable machinery is required quickly and accurately to decode the wealth of information that is latent in the retinal input. How is visual cortex organised? Much of it can be partitioned into multiple maps of space that analyse the input for primitive features such as edges. But a large part of the visual brain plays a more complex role in comprehending what we see — for example, identifying objects across changing perspectives or lighting — and this has been a fertile ground for debate.

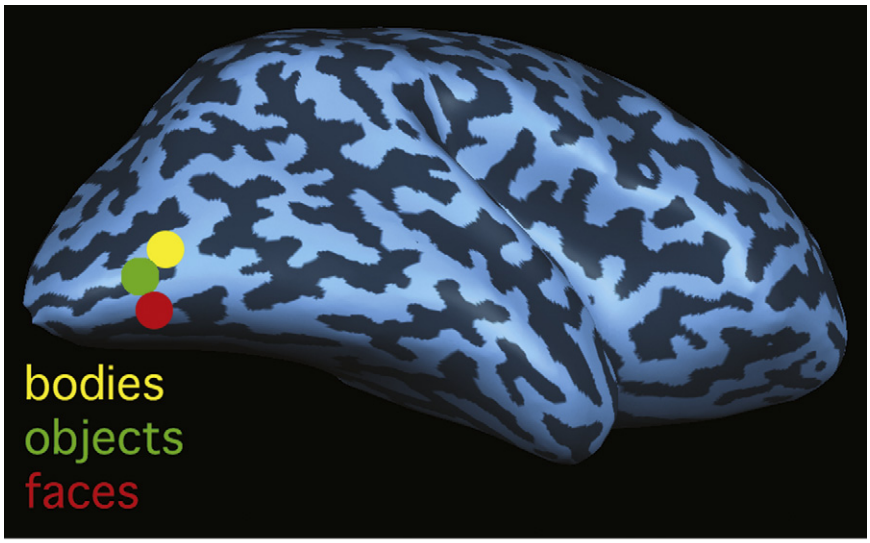
A lightning rod for this debate is the issue of whether and to what degree the organization of visual areas is modular. Are there focal brain areas that specialise in the perception of certain classes of things? This idea takes support from neurological patients who can perceive everyday objects without difficulty but fall down on faces (and others who show the reverse dissociation), although such 'pure' deficits are rare [1]. Observations like these have inspired neuroimaging studies that identified small areas of visual cortex that respond highly selectively — to faces, for example [2]. When neuroimaging data are analysed with sophisticated pattern recognition methods, however, it appears that broad swathes of visual cortex contain diffuse, distributed information about many visual kinds, contrary to the modularity hypothesis [3].

Hence a key question in the field is whether brain areas that respond strongly to a single category are uniquely and causally involved in perceiving items of that kind. Neuroimaging methods can only provide correlational evidence, so transcranial magnetic stimulation (TMS) steps in to cross the gap. TMS works by driving a strong electrical current through a coil placed over the scalp. The resulting magnetic field induces an electrical current into the neurons that lie beneath the coil — effectively adding noise to neuronal activity and hence interfering with normal processing. The effects of TMS are temporary, working on a time scale of milliseconds to tens of minutes (depending on the protocol), making it the ideal tool for reversibly impairing the function of a brain area in order to probe its workings.

Conveniently, several apparently category-selective regions of visual cortex lie on the lateral surface of the brain, where they are in reach of TMS (Figure 1). These include the occipital face area [4] and the extrastriate body area [5] — selective for human faces and bodies, respectively — and the lateral-occipital complex [6], selective for general object form but not especially for bodies and faces. Some recent studies [7–9] of neurological patients indicate, for each of these regions, a causal role in perceiving a particular category. Similarly, in each case, initial TMS studies support the same view. For one example, TMS over the extrastriate body area, but not over primary visual cortex or prefrontal cortex, impairs tasks requiring subtle judgments of the form of the human body [10]. Similar tasks on other object types were unaffected. In all of these TMS studies to date, the category-selective area of interest has been compared to sites elsewhere in the brain — typically not even in visual cortex — leaving open the question whether this method can distinguish among them with precision.

As they report in this issue of *Current Biology*, Pitcher *et al.* [11] were bold enough to seek a triple-dissociation among the occipital face area, the extrastriate body area, and the lateral occipital complex. Each region was localised individually in each participant with an fMRI scan, to provide a target for TMS. Participants performed carefully balanced tasks that involved making subtle discriminations about images of faces, bodies, or novel objects. The results showed that in each test, TMS over a given area (such as the occipital face area) impaired accuracy only for that area's 'preferred' stimulus (for example, faces). Performance on the other categories was just as good as when no TMS was applied. This spatial precision is remarkable given the close proximity of these regions (Figure 1) and is good news for researchers hoping to use TMS as a tool to investigate visual cortex.

Thus, brain areas that respond selectively in fMRI appear to be uniquely involved in analysing their preferred categories, strongly favouring a modular view in which at least some visual kinds are analysed in focal brain areas. Caveats apply: in principle there could be minute but undetected effects of TMS on the other categories, and there could still be some other, untested category that will activate these areas equally well, although many have been tested [12]. But on the whole this triple-dissociation pattern is very hard to accommodate with a model in which the information about object form (or at least bodies and faces) is spread diffusely across visual cortex.



Current Biology

Figure 1. Category specificity in lateral visual cortex.

An inflated rendering of the right hemisphere of the human brain, highlighting some of the posterior areas that respond selectively in neuroimaging studies to bodies (extrastriate body area), faces (occipital face area), and other object kinds (lateral occipital complex). A recent study used transcranial magnetic stimulation (TMS) to interfere with neural processing in each of these areas in turn while volunteers performed simple tasks on face, body, or object images. In each case, TMS over a given area uniquely impaired tasks involving that area's preferred category. This result provides evidence on the practical spatial resolution of TMS. It also supports a 'modular' account of the organization of visual cortex, in which the representations of some natural kinds is anatomically focal. Future TMS studies will be able to build on these findings in order to build a picture of the properties, connectivity, and functional roles of these brain areas.

Besides the three areas described here, other focal brain regions respond selectively to the same categories. All three areas are mirrored on the underside of the brain, and also to varying degrees across both hemispheres. Indeed, recent work indicates the possibility of still more such patches in human and particularly monkey cortex [13]. To what extent do the scattered areas that respond to a given category work in concert? A new study in monkeys has combined fMRI with microstimulation — direct application of current to stimulate activity in a patch of cells — in order to explore the connectivity of face-selective patches [14]. Combining TMS with fMRI may provide a parallel source of evidence on the organization of human visual cortex, by revealing the remote consequences of disrupting activity in one brain area.

What visual features drive the activity in these regions? TMS studies can address this question by comparing different types of visual discrimination. For example, TMS over the occipital face area interferes with perceiving face parts but not their configuration into a whole face [15]. Similarly, TMS over the extrastriate body area impairs subtle judgments on body shape but not the posture of limbs [10]. Evidence from studies like these will build a picture of the kinds of analysis performed by category-selective regions.

How do category-specific cortical modules arise? There is relatively little evidence on this question, most of it concerning faces. The neural responses to faces develop gradually to reach the adult pattern [16]. It appears that certain cortical areas are prepotent in their ability to acquire face-selective responses [17] and that normal visual experience during certain periods of development is key in order for this to occur [18]. In some individuals face perception appears to go awry without any evident triggering neurological incident [19]. More evidence on the development of category-specific regions will be essential to improving our understanding of the visual brain.

Why do category-selective areas fall where they do in visual cortex? Researchers continue to search for a set of principles [20] that will explain why the adult visual cortex looks the way it does. Pitcher *et al.*'s [11] results provide some of the clearest evidence yet that any such account must take into account the strongly localised and selective representations of faces, bodies, and other objects. Perhaps equally important, the findings of that study, and of other recent TMS work, indicate that this technique will be a key source of evidence on the organization of visual cortex in the near future.

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Cytokinesis: GAP Gap

The central spindle regulates cleavage furrow formation and cytokinesis and is composed of antiparallel microtubules bundled by microtubule-associated proteins and kinesin motors. One key protein in the central spindle is a Rho family GTPase-activating protein, CYK-4/MgcRacGAP, whose target is the subject of two new studies that arrive at divergent models.

Michael Glotzer

An actomyosin-based contractile ring is responsible for generating the force that drives cell division in animal cells. The position of the contractile ring is cooperatively determined during anaphase by astral microtubules that emanate radially from the spindle poles and the central spindle [1], a set of antiparallel bundled microtubules that lies between the two spindle poles. Assembly of the contractile ring is regulated by the small GTPase RhoA. Like most GTPases, RhoA is active when bound to GTP and inactive when bound to GDP. The balance between these two states is regulated by guanine nucleotide exchange factors (GEFs) that activate RhoA and GTPase-activating proteins (GAPs) that stimulate GTP hydrolysis. One critical Rho GEF in cytokinesis, ECT2, is recruited to the central spindle by a putative Rho family GAP, CYK-4/MgcRacGAP (hereafter called CYK-4) [2]. The isolated GAP domain of CYK-4 promotes GTP hydrolysis by Rho family members *in vitro*; however, it is more active against Rac1 and Cdc42 than against RhoA, despite the fact that RhoA plays a central role in cytokinesis and Rac1 and Cdc42 do not, creating an apparent paradox.

Two new papers [3,4] now investigate the requirement for the GAP activity of CYK-4 in cytokinesis and explore the identity of the target GTPase of CYK-4. While one study concluded that the GAP domain acts on RhoA, the other concluded that it acts on Rac1. Can these divergent observations be reconciled?

CYK-4/MgcRacGAP: A Signaling Nexus

Although the CYK-4 protein has a reasonably simple domain structure, containing a coiled-coil domain, a C1 domain and a RhoGAP domain, it has numerous interaction partners. In addition to acting upon Rho family GTPase(s), the protein forms a stable complex with the kinesin-6 family member ZEN-4/MKLP1 to form the centralspindlin complex, which bundles microtubules at the central spindle. In human and *Drosophila* cells, and probably in other eukaryotes, CYK-4 also binds to the Rho GEF ECT2 [2,5,6]. In human cells this interaction is critical for RhoA activation and is subject to multiple levels of phosphoregulation by kinases such as Cdk1–Cyclin B and Polo-like kinase 1 [7]. Additional evidence points to an interaction between CYK-4 and the actin-, myosin-, and RhoA-binding protein anillin [8]. While these interactions have been mapped to isolated domains and have been reconstituted in bimolecular reactions, there may be interplay between the binding proteins such that mutations in one domain may affect interactions mediated by another part of the protein.

Phenotypic Fingerprinting

In one of the new studies, Miller and Bement [3] used morpholino oligonucleotides to deplete endogenous CYK-4 from *Xenopus* blastomeres and reintroduced CYK-4 variants — either wild-type CYK-4, or a mutant lacking the GAP domain, or one in which the conserved catalytic arginine [9], the so-called arginine finger, within the GAP domain of CYK-4 is substituted by alanine. In the other study, Canman *et al.* [4] isolated temperature-sensitive mutations in *Caenorhabditis elegans cyk-4* that conditionally inactivated CYK-4 as a consequence of amino-acid substitutions in regions reasonably close to the catalytic center. Although substitution of the catalytic arginine with alanine has previously been shown to diminish — but perhaps not fully inactivate [10] — the GAP activity of CYK-4, the effects of the new temperature-sensitive mutations have not been documented to date.

In the *Xenopus* study, replacement of endogenous CYK-4 with a GAP-deficient variant resulted in a broader and more intense accumulation of F-actin at the furrow (Figure 1) [3]. In this study, the activity of Rho family GTPases was monitored by following the cortical localization of GFP fused to protein domains that bind the active form of RhoA, Rac, and Cdc42. Expression of the GAP-deficient variant resulted in hyper-accumulation of active RhoA at the furrow. Notably, the zone of active RhoA widened significantly. No changes in the cortical accumulation of active Rac or Cdc42 were detected. The phenotypes caused by GAP-deficient CYK-4 were quite similar to those observed when constitutively active RhoA was injected. These data point to RhoA being a critical target of the CYK-4 GAP domain, implying that the GAP activity ensures a tightly focused zone of active RhoA. Interestingly, the authors observed oscillations of the contractile ring in embryos expressing a CYK-4 variant that lacked the entire GAP domain. These oscillations are reminiscent of those observed in cultured human cells depleted of the cytokinetic scaffold protein anillin, which binds to both CYK-4 and Rho [8,11,12]. The authors conclude that the CYK-4 GAP domain continuously inactivates RhoA during the process of ingression and that the GAP domain itself may play a mechanical role by