

fact that it is not defined by modes of ossification, but by the embryonic cell populations that form the attachment points. A conclusion that can therefore be drawn is that the endochondral scapular spine of mammals is the ghost of the cleithrum [5].

The discovery of the important contribution of the neural crest to the structures of the neck and shoulder has also allowed an explanation the aetiology of some poorly understood human syndromes [5]. These include Klippel-Feil disease, Sprengel's deformity, cleidocranial dysplasia, Arnold-Chiari I/II malformation and 'cri-du-chat' syndrome, all of which present dysmorphologies of the neural crest derived structures of the neck and shoulder and swallowing problems. It can now thus be appreciated that these syndromes are united by a common cellular aetiology.

This elegant new study [5] obviously raises questions as to how the neural crest contribution to the neck is organised. It is

currently unclear from which axial level of the developing neural tubes these neural crest cells arise. The regulatory elements used in this study will result in most neural crest cells being labelled. The path of migration of these neural crest to the region of the developing pectoral girdle is also unclear. These are interesting issues the investigation of which should shed further light on the mechanisms that act to order the connectivity of attachment of the neck muscles. It is probable, based on a previous study in chick [6], that these cells will arise from caudal hindbrain, migrate out between the otic vesicle and the anterior somite and then track posteriorly along the base of the somites. It would, however, given the power of the single cell fate mapping that can be achieved using transgenic mice and the advantages of mouse genetics, be of great worth if regulatory elements could be identified which would allow the mapping of crest cells

specifically from the caudal hindbrain.

#### References

1. Kardong, K.V. (1998). *Vertebrates, Comparative Anatomy, Function, Evolution*, second edition (New York: WCB McGraw Hill).
2. McGonnell, I.M. (2001). The evolution of the pectoral girdle. *J. Anat.* 199, 189–194.
3. Kontges, G., and Lumsden, A. (1996). Rhombencephalic neural crest segmentation is preserved throughout craniofacial ontogeny. *Development* 122, 3229–3242.
4. Chevallier, A., and Kiény, M. (1982). On the role of connective tissue in the patterning of the chick limb musculature. *Wilhelm Roux Arch. Dev. Biol.* 191, 277–280.
5. Matsuoka, T., Ahlberg, P.E., Kassaris, N., Iannarelli, P., Dennehy, U., Richardson, W.D., McMahon, A.P., and Koentges, G. (2005). Neural crest origins of the neck and shoulder. *Nature* 436, 347–355.
6. McGonnell, I.M., McKay, I.J., and Graham, A. (2001). A population of caudally migrating cranial neural crest cells: functional and evolutionary implications. *Dev. Biol.* 236, 354–363.

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## Neuroimaging: Seeing the Trees for the Forest

New functional imaging studies demonstrate that it is possible to decode a sensory visual pattern, and even an internal perceptual state, by combining seemingly insignificant feature selective signal biases present in a large number of voxels.

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“But what has really been learned by functional imaging?” Whispered quips such as this were often overheard in past years at neuroscience meetings amid rows of colorful posters. Spatial maps of brain activity were initially met with skepticism by electrophysiologists who, while perhaps ready to concede defeat in the aesthetics of data presentation, claimed to prefer their more serious science. Yet in the past years, functional magnetic resonance imaging (fMRI) has moved forward at an enviable pace, and many of the

initial skeptics are now themselves ensnared in its details.

As in many fields of science, descriptions of the brain arise from, and are ultimately shaped by, contemporary technology. In visual neurophysiology, the predominance of single unit recordings during the last decades has provided concepts such as feature selectivity and receptive field structure, which now serve as the building blocks for theories of how we see. These concepts are, nonetheless, strongly linked to a particular experimental paradigm, and may therefore be limited in their capacity to support a general theory of visual processing. This

issue becomes apparent when trying to understand fMRI data using conceptual frameworks originally derived from single unit recordings. In fMRI, *voxels* are the fundamental spatial unit of measurement. Unlike single neurons, a voxel is a volumetric entity that does not map directly onto any particular functional quantity. Instead, each contains thousands to millions of neurons, whose collective activity is usually measured indirectly through its impact on the vasculature. But along with these potentially undesirable aspects of fMRI is the great advantage of being able to monitor many thousands of voxels at once, throughout the entire brain.

But how is it possible to keep track of thousands of simultaneously measured signals? From the start of functional imaging, the answer has been to create activity maps. In these maps, each voxel is typically analyzed independently from the

others, with its activation level reflecting how closely it follows a prescribed or “expected” function based on the stimulus presentation [1,2]. This massively univariate approach, while providing useful and robust visualizations of how the brain responds to stimuli, has undeniable shortcomings. For example, even though brain mapping aspires to paint a global picture of sensory processing, its maps ultimately consist of a large array of localized responses, in which the temporal modulation of each voxel is compared only to the external stimulus, rather than to the state of other voxels in the brain. It is increasingly clear that a major intellectual hurdle facing systems neuroscience is to understand the parallelism and cooperative processes that are at the core of sensory processing, and for this, innovative techniques are required.

Recently, two groups [3–5] have followed the lead of Haxby *et al.* [6] and strayed from traditional brain mapping approaches, asking instead what kinds of stimulus-related information can be extracted from fMRI data when signals from a large number of voxels are considered in parallel. Haynes and Rees [3] and Kamitani and Tong [5] independently applied multivariate techniques to voxel responses in the early cortical areas of human subjects viewing grating patterns differing in their orientation. Both groups found that, while individual voxels had only very subtle sensitivity to orientation, insignificant with traditional analyses, the entire spatial pattern of voxels, considered together, showed highly reliable “orientation tuning” (Figure 1). Thus, according to the interpretation of the authors, information in the population of voxels was able to unveil the tuning properties of the underlying neurons – seeing the trees for the forest, in a sense.

But perhaps the most spectacular results emerging from this approach so far relate not to the registration of sensory patterns, but rather to the “reading” of internal perceptual and attentional states. Haynes and Rees [4], for example, found that by applying this multivariate technique during

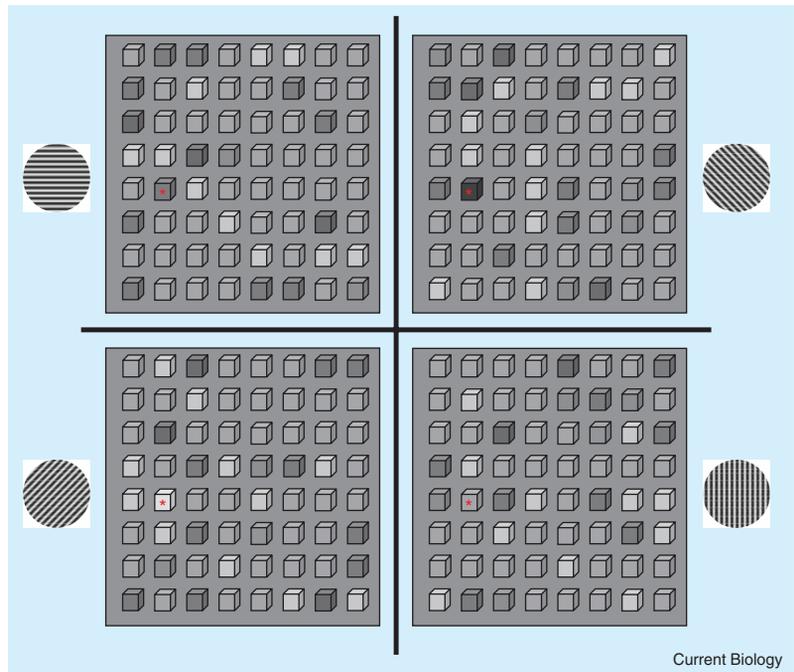


Figure 1. How does the primary visual cortex register different orientations—and how is this expressed in the language of fMRI?

In this cartoon, the voxel with the asterisk depicts the only voxel that, alone, possesses significant orientation selectivity when standard, univariate analysis is applied. However, many other voxels have small and “insignificant” biases. Yet, the new studies find that when these small biases are jointly considered using multivariate methods, the experimenter can accurately and reliably determine which stimulus was presented on each trial.

an unstable visual percept, the time course of subjective fluctuations could be reliably decoded. Using binocular rivalry, a well-studied paradigm in which the presentation of two conflicting stimuli shown to opposite eyes gives rise to alternation in their perceptual dominance, they were able to continuously track which of the stimuli was perceived as the dominance slowly changed back and forth over periods lasting several seconds (Figure 2). In this case, the decoding exploited the small color and ocularity biases present in each of many individual voxels.

Kamitani and Tong [5] were similarly able to monitor another subjective quantity—visual attention. In their study, the act of simply concentrating on one or the other of two overlapping oriented patterns was sufficient to sway the multivoxel signal in the direction of the attended orientation. These results, while consistent with previous fMRI studies—but in some ways discrepant with neurophysiology studies; for reviews see [7,8] — are particularly

interesting because they demonstrate that an external observer can monitor what a subject is perceiving without the subject saying or doing anything.

Multivariate methods in general are not new to brain physiologists. They are an important tool in the design and implementation of brain-machine interfaces [9,10], and have been previously applied to imaging data as well. Some earlier studies have used highly data-driven multivariate methods, such as independent component analysis (ICA) and therein successfully disentangled overlapping spatial patterns of shared activation when knowledge of the ‘expected’ response was poor [11–13]. The most direct precursors of the present studies were, however, experiments exploring the nature of categorical representations in brain areas associated with object processing [6,14]. These studies found widely distributed, consistent activity patterns elicited by individual objects.

Both of the new studies [3,5] offer concrete explanations why

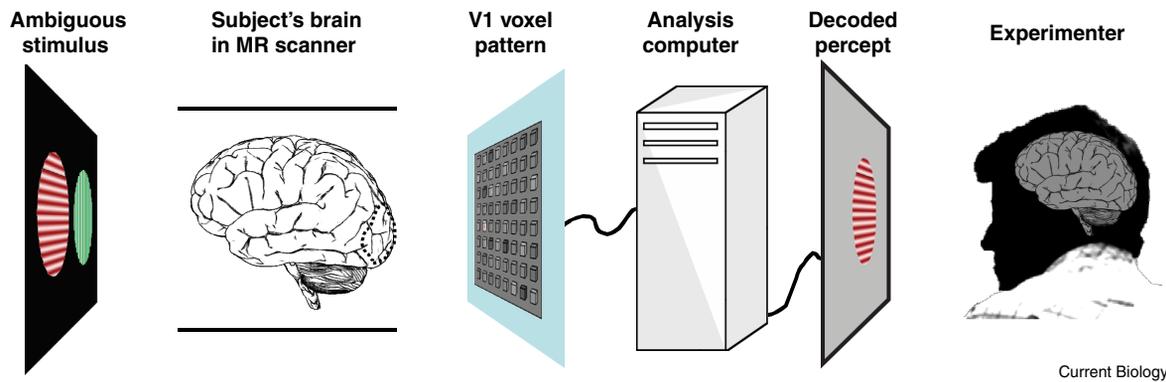


Figure 2. As an ambiguous binocular rivalry stimulus is shown, a subject lying in an MR scanner registers two images, which compete for perceptual dominance.

During rivalry, the brain arrives at a unique solution such that the subject only perceives one of the competing patterns (in this case, the red grating). Remarkably, using the methods presented in the highlighted studies, it is now possible to extract with a high degree of accuracy, the time course of perceptual alternation. The key is to monitor the waxing and waning of activity in spatially intermingled voxel patterns that have been previously identified as showing shared response biases.

voxels should show small orientation biases based on the functional architecture of V1 (see [15]). Their models, describing how the coarse sampling of a functional orientation map should lead to imbalances in responses to orientation are plausible and likely to be at least partly responsible for their observations. It might be argued, however, that other interpretations of the data are possible, and that this new technique might allow us to discover new, higher-level, aspects of stimulus representation in the striate and extrastriate areas. Is it not conceivable, for example, that there exist multiple, parallel representations of a given stimulus in V1, one expressed according to the topographic arrangement of primitives, and the other operating according to entirely different principles? In answering this and similar questions, it is important to explore what sorts of stimuli can or cannot be differentially ‘read out’ in this way, and whether the brain’s discrimination between two stimuli can always be traced to the functional organization of local feature analysis. As always, the brain is likely to surprise us.

Finally, being able to peer into subjective human experience by looking at brain activity is an exciting new scientific direction which is likely to improve with time. While this ability has various implications for different interested parties, the neuroscientist should remain focused on always striving

for a deeper understanding of brain physiology. The studies highlighted above reveal that fMRI can be highly sensitive to information in extended activity patterns, which can be detected even on a single trial. This is an important new methodological insight that is not simply an extension of standard fMRI analyses. But just as brain-machine interfaces do not guarantee a deeper understanding of the neural circuits underlying voluntary behavior, nor does “mind-reading” necessarily reveal the brain’s strategies for sensory or subjective processing unless we always keep this focus in mind. In the study of perception, generations of neuroscientists have been plagued by the idea of a mystical *homunculus* living inside our head and interpreting sensory responses in the brain. In applying new techniques to brain imaging data, we must continually push for new discoveries that relieve us of this spectre. We must avoid the trap of endowing the existing homunculus with, say, an aptitude for multivariate analysis.

#### References

1. Friston, K.J., Jezzard, P., and Turner, R. (1994). The analysis of functional MRI time series. *Hum. Brain Mapp.* 1, 153–171.
2. Boynton, G.M., Engel, S.A., Glover, G.H., and Heeger, D.J. (1996). Linear systems analysis of functional magnetic resonance imaging in human V1. *J. Neurosci.* 16, 4207–4221.
3. Haynes, J.D., and Rees, G. (2005). Predicting the orientation of invisible stimuli from activity in human primary visual cortex. *Nat. Neurosci.* 8, 686–691.
4. Haynes, J.D., and Rees, G. (2005).

5. Kamitani, Y., and Tong, F. (2005). Decoding the visual and subjective contents of the human brain. *Nat. Neurosci.* 8, 679–685.
6. Haxby, J.V., Gobbini, M.I., Furey, M.L., Ishai, A., Schouten, J.L. and Pietrini, P. (2001). Distributed and overlapping representations of faces and objects in ventral temporal cortex. *Science* 293, 2425–2430.
7. Posner, M.I., and Gilbert, C.D. (1999). Attention and primary visual cortex. *Proc. Natl. Acad. Sci. USA* 96, 2585–2587.
8. Blake, R., and Logothetis, N.K. (2002). Visual competition. *Nat. Rev. Neurosci.* 3, 13–21.
9. Laubach, M., Shuler, M., and Nicolelis, M.A. (1999). Independent component analyses for quantifying neuronal ensemble interactions. *J. Neurosci. Methods* 94, 141–154.
10. Schwartz, A.B. (2004). Cortical neural prosthetics. *Annu. Rev. Neurosci.* 27, 487–507.
11. McKeown, M.J., Makeig, S., Brown, G.G., Jung, T.P., Kindermann, S.S., Bell, A.J., and Sejnowski, T.J. (1998). Analysis of fMRI data by blind separation into independent spatial components. *Hum. Brain Mapp.* 6, 160–188.
12. Bartels, A., and Zeki, S. (2004). The chronoarchitecture of the human brain—natural viewing conditions reveal a time-based anatomy of the brain. *Neuroimage* 22, 419–433.
13. Friston, K.J. (1998). Modes or models: a critique on independent component analysis for fMRI. *Trends Cogn. Sci.* 2, 373–375.
14. Cox, D.D., and Savoy, R.L. (2003). Functional magnetic resonance imaging (fMRI) “brain reading”: detecting and classifying distributed patterns of fMRI activity in human visual cortex. *Neuroimage* 19, 261–270.
15. Boynton, G.M. (2005). Imaging orientation selectivity: decoding conscious perception in V1. *Nat. Neurosci.* 8, 541–542.

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