Making holes in the visual world

Michael Morgan

The finding that transcranial magnetic stimulation can be used to create a perceived 'hole' in a visual pattern could provide new ways to test the relationship between brain events and consciousness.

Many questions posed directly to the Deity are computationally flawed. "How long, oh Lord, how long?" is the question that psychologists have passionately asked for over a hundred years about the temporal relationship between neural activity and sensation. How long does a brain event need to be before it can result in conscious experience? If a briefly presented visual stimulus is followed closely in time by a bright flash or 'pattern mask', it will be rendered invisible. This phenomenon of 'backward masking' tells us that the neural processing of a visual stimulus can be disrupted before it reaches the part of the brain where consciousness arises. The problem with backward masking, however, is that one does not know precisely when either the masked or the masking stimulus reaches the relevant part of the brain. The recent technique of transcranial magnetic stimulation (TMS) overcomes at least one of these problems by delivering a disruptive stimulus directly to a specific brain area. A brief (millisecond) electromagnetic pulse to the cortex from an induction coil on the scalp can suppress awareness of a visual stimulus presented 100 milliseconds or so previously. In this issue of *Nature Neuroscience*, Kamitani and Shimojo describe how they have used spatially localized TMS to make 'holes' in visible patterns[1].

Their technique is to present a large textured pattern, such as a grid (**Fig. 1**), followed by a TMS pulse, briefly to a human observer. The effect of the pulse, when delivered with appropriate timing, was to make a gray hole in the otherwise visible pattern. The location of the hole in the pattern varied according to the position of the coil on the scalp, in a manner consistent with known cortical topography. The authors refer to the missing part of the pattern as an 'artificial scotoma', by analogy with the missing parts of the visual field that follow localized damage to the retina or cortex. A crucial difference, however, is that patients are not normally aware of their scotomata as missing regions of the pattern: they tend to complete their conscious experience across the gaps, in the same way that normal observers do with their 'blind spot'. This difference may be due to the brief exposure of the pattern: 'filling-in' may require cortical rewiring taking place over days rather than tens of milliseconds.

An unexpected finding was that the perceived holes in the pattern were not always circular. When the pattern was a horizontal grating, the apparent hole was an ellipse, compressed in the horizontal direction. The holes in vertical gratings were compressed vertically. The authors speculate that this compression was caused by cortical activity propagating in a direction parallel to the bars, through horizontal connections between cells with the same orientation selectivity. This amounts to saying that there is a tendency to complete across gaps in gratings. A similar effect has been extensively studied in the form of 'phantom gratings' crossing small gaps[2]. However, these phantoms are of opposite contrast to the background grating, and would thus provide no basis for the compression effect reported by Kamitani and Shimojo[1].

What do we learn from TMS-induced scotomata that we would not learn from looking at patterns with real holes in them? Would a fuzzy round hole in a grating look circular? If we cut a hole in a pattern with a pair of scissors there will be a sharp edge to the hole, which betrays its presence. Under these circumstances, we have little tendency to see anything in the hole other than the background that it reveals. The situation with the TMS-induced scotoma is different in two ways: it has not got a 'hard' edge, and there is presumed to be an absence of activity within it. Under these circumstances, why do observers see gray, or indeed any color at all, within the scotoma? Kamitani and Shimojo very interestingly suggest that the perceived gray of the scotoma is filled in by the gray field that followed the presentation of the pattern. If the next field is colored red, for example, then the scotoma is tinged with that color, rather than being gray.

An alternative to TMS for producing an artificial scotoma is the humble afterimage. Visual scientists sometimes pass their time during a boring lecture by staring at a light on the ceiling until it produces a vivid afterimage. The afterimage can be used to blot out the lecturer's head, or to test Emmert's Law, which states that an afterimage looks much larger when projected onto a distant wall than onto a nearby object. It would be interesting if TMS-induced scotomata did not obey Emmert's law, and much less interesting if they did. Another phenomenon that the reader can observe with afterimages is that their color can be strongly influenced by context. If one projects an afterimage onto a piece of white paper with a strong blue surround, it will tend to look blue, exactly as if it were being interpreted as a hole in the white paper through which the blue background is seen. Again, it would be

Fig. 1. The figure represents the appearance of a visual stimulus (a grid) with an artificial scotoma (the fuzzy gray region) produced by transcranial magnetic stimulation. In the study by Kamitani and Shimojo[1], the position of the artificial scotoma corresponded to the region of the visual cortex under the TMS coil. The perceived color of the scotoma was similar to the color of the field following it, suggesting a temporal 'filling in' process.

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interesting to do this experiment with the TMS-induced scotomata, to see whether they are colored by expectation in space as well as time.

The wider significance of TMS is in its potential for answering questions about the relationship between brain events and consciousness. If we have a candidate brain event for a conscious experience, we could test our hypothesis by using TMS to erase the brain event, and seeing whether the conscious experience does or does not survive. There are some very hard conceptual problems here, however. Most neuroscientists think that brain events cause conscious experiences, rather than the other way around. Does this mean that brain events precede conscious experiences in time, or that the two are simultaneous? As Bertrand Russell pointed out in his destructive analysis of the notion of causality in general, if two events are simultaneous, it is unjust to pick out one as the cause of the other. If on the other hand they follow in time, there will always be room for a chain of events between them. What would such events be in the case of sensations and brain events: further sensations, or further brain events?

1. Kamitani, Y. & Shimojo, S. *Nat. Neurosci.* **2**, 767-771 (1999).
2. McCourt, M. *Vision Res.* **34**, 1609–1617 (1994).

Digging for gold in the human genome

Peter Mombaerts

A large family of human cadherin-like genes shows an unusual genomic organization, suggesting that the nervous system might use DNA rearrangements during development.

Despite their very different structures, the nervous system and the immune system both consist of highly organized networks of many different cell types. The complexity of the immune system arises though gene rearrangements in lymphocyte precursors, allowing a limited number of genes to encode an enormous repertoire of antigen binding receptors[1]. This mechanism was first described for immunoglobulin genes[2], and we now know that similar rearrangements occur in seven different gene families, accounting for the diversity of both immunoglobulins (Ig) and T-cell receptors (TCR).

It is attractive to speculate that the nervous system might make use of similar mechanisms to impart identities to individual neurons, but specific hypotheses are lacking; the only plausible candidates so far are the odorant[3] and vomeronasal[4] receptor genes, but there is no evidence yet that they are rearranged during differentiation. In a recent issue of *Cell*, however, Wu and Maniatis identify another candidate family encoding transmembrane proteins, whose organization provides the strongest hint so far that gene rearrangement may occur in the nervous system[5]. By combining experimental work with analysis of data from the human genome project, the authors have identified a family of 52 novel cadherin-like genes whose genomic organization is strikingly reminiscent of the Ig and TCR loci. Because some cadherins are known to be localized at synapses and to mediate specific cell–cell adhesion, these results provide new insights into the origin of the molecular complexity assumed to underlie the formation of neural circuitry.

Cadherins are transmembrane proteins that mediate calcium-dependent, selective cell–cell interactions in a wide range of processes[6]. The cadherin superfamily consists of a large number of genes and has been divided into several families, including classical cadherins and so-called protocadherins. Last year, Yagi and colleagues described eight members of a new family of mouse genes encoding cadherin-like molecules, the first of which was isolated based on its ability to associate with the tyrosine kinase fyn[7,8]. The choice of fyn was inspired by the profound disruption of neural and lymphocyte function observed in fyn knockout mice[9]. These cadherin-like genes are expressed in neurons of the cerebellum, neocortex, hippocampus and olfactory bulb, and in the one case for which an antibody was available, the protein was found to be localized at synapses[8]. The authors therefore termed the new family 'cadherin-related neuronal receptors' (CNRs).

A comparison of the cDNA sequences for the eight CNRs revealed a striking observation: the N-terminal region was variable, but the C-terminal region was 100% identical for all eight sequences. Yagi and colleagues refer in the discussion[8] somewhat cryptically to an unusual organization of the exons that may explain the bipartite nature of the cDNAs. At around the same time, another group reported a similar chimerism in three rat protocadherin sequences[10]. This pattern of variable and constant domains is highly reminiscent of the Igs and TCRs, and it was this striking similarity that encouraged Wu and Maniatis to examine the genomic organization of the human cadherin superfamily in more detail.

Using publicly available data from the human genome project, the authors identified 52 novel cadherin-like genes within a 700 kb region on chromosome 5. These genes fall into three clusters. The first of these contains 15 genes that appear to be human orthologs of the mouse *Cnr* genes. (The authors refer to them as the protocadherin α (Pcdhα) cluster, a confusing term because they are in fact distinct from other protocadherins.) The N-terminal domains (which are presumed to be extracellular, transmembrane and partially cytoplasmic) are encoded by fifteen large (2.4 kb) exons, arrayed in head-to-tail fashion over 200 kb. Downstream of the last of these lie three small exons that together encode the constant (intracellular) region. Between the variable and constant exons are consensus splice sites, suggesting that they may be joined by RNA splicing.

A second gene cluster, which the authors term Pcdhβ, consists of a further 15 variable-region exons. (No putative constant-region exons have yet been found.) Unlike the human *Cnr* (Pcdhα) cluster, these sequences show homology to rat Pcdh-3 and can therefore be regarded as true 'protocadherins'. A third clus-

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