trol mice following environmental enrichment. Other studies have shown robust synaptogenesis in the adult brain when synaptic activity is silenced pharmacologically[6,7]. The new spines form either when presynaptic release of neurotransmitter is blocked or when postsynaptic glutamate receptors are blocked, and new spines can last for at least eight hours without subsequent activation. Furthermore, induction of NMDA-receptor-dependent LTP in hippocampal area CA1 does not require the formation of new synapses[8,9]. Together with the findings from Tsien and colleagues, these studies show that dendritic spines can form in the mature brain without NMDA-receptor-dependent processes like LTP, and even without synaptic activity. Perhaps the new spine synapses can facilitate NMDA-receptor-independent processes within the hippocampus to enhance subsequent learning and memory in CA1-NMDA knockout mice.

How might the enrichment-induced dendritic spines within the hippocampus facilitate learning and memory? Hebb[10] originally suggested that learning and memory occurs by strengthening some connections and weakening other, inappropriate connections. Tsien and collegues show that the enrichment effects are specific to a particular type of spine synapse, causing an increase only in those with a continuous (that is, 'non-perforated') postsynaptic surface. There was no change in the frequency of large irregularly shaped synapses, those with 'perforated' postsynaptic surfaces. Thus, the non-perforated synapses might enhance some forms of learning and memory via NMDA-receptor-independent mechanisms. Other studies have shown a transient elaboration of a subset of perforated synapses with NMDA-receptor-dependent LTP[11]. An open question is whether NMDA-receptor-dependent changes at perforated synapses might be involved in refinement of synaptic connections during more complex learning protocols than those tested by Tsien and colleagues[2]. Either way, these findings are among the first to demonstrate a possible role for non-perforated synapses in learning and memory. Understanding the function of the small non-perforated synapses is especially important because these are normally the most abundant synapse type (> 75%) in both hippocampus and neocortex.

The second possible explanation for the findings of Tsien and colleagues[2] is that the hippocampus can be short-circuited altogether during learning and memory if environmental enrichment can induce enough connectivity outside the hippocampus, specifically within the neocortex. Tsien and colleagues did not examine the cortex, but previous evidence indicates that enriched experience increases intrinsic connectivity within the neocortex[12]. It is clear that memory is not mediated solely by CA1, or even by the entire hippocampus alone. Rather, the hippocampus is part of a memory system that prominently involves its bidirectional connections with diverse and interconnected regions of the cerebral cortex[13] (**Fig. 1**). Within this system, memories are likely 'stored' among large cell assemblies widespread across the cortex, and the organization of associations is mediated by the formation of links between the cell assemblies[10]. The role of the hippocampus may be to facilitate the consolidation of these cortical linkages by storing aspects of new information, or indices pointing to cortical loci of new representations, and using these to temporarily link otherwise separated cortical memories (**Fig. 1a**). We know that the role of the hippocampus is temporary because it is not necessary for the recall of long-established memories, suggesting that eventually new intracortical connections form to mediate permanent links[14]. The increase in synaptic connectivity in neocortex, likely to have occurred as a result of enriched training experience[12], might be so effective that lasting plasticity within the hippocampus is not required (**Fig. 1b**), at least for the relatively simple types of learning examined by Tsien and colleagues[2].

One way to distinguish the 'cortical hypothesis' from the 'hippocampal hypothesis' discussed above would be to determine whether the CA1-NMDA knockout mice after enrichment can tolerate loss of hippocampal area CA1 and still enjoy improved learning and memory. An early study[15] found that enriched experience reduced, but did not eliminate, the effects of hippocampal damage on spatial learning. These findings are consistent with the possibility that both putative mechanisms contribute to the effects of enrichment.

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Attention - brains at work!

Roger B.H. Tootell and Nouchine Hadjikhani

Two new studies use event-related fMRI to reveal a network of brain regions that are activated during different steps in the control of visual spatial attention.

The amount of information that is potentially available through our sense organs is far greater than our brains can handle. Much of this information must therefore be discarded, and the brain must select only those stimuli that are of greatest relevance for further processing. Understanding how this occurs is a major challenge for cognitive neuroscience, and two papers[1,2] in the current issue of *Nature Neuroscience* provide the most detailed spatio-tem-

The authors are at the Magnetic Resonance Imaging Center, Department of Radiology, Massachusetts General Hospital, 149 13th Street, Charlestown, Massaschusetts 02129, USA. e-mail: tootell@nmr.mgh.harvard.edu

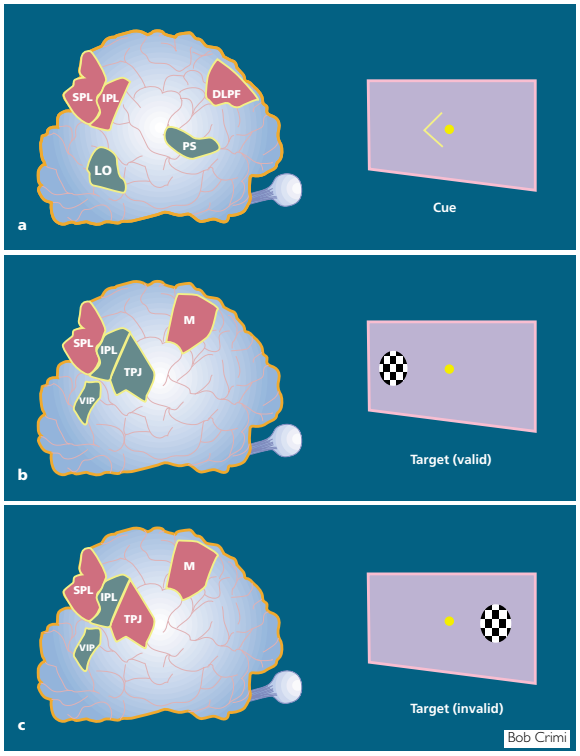

Fig. 1. Brain areas activated in a 'naked' eye and brain, from a subject who was facing a display screen and doing a covert attention task, similar that used in Hopfinger *et al.*[1] and Corbetta *et al.*[2] (**a**) A cue instructs the subject to attend to a given location: here to the subject's left. Then the attention target appears (here a checkerboard stimulus, but usually a more subtle stimulus change), at either the expected location (**b**) prompted by the 'valid' cue, or at an unexpected location (**c**), misdirected by the 'invalid' cue in (**a**). The activated areas described in Hopfinger *et al.* and Corbetta *et al.* include DLPF (dorsolateral prefrontal cortex), IPL (inferior parietal lobule), LO (lateral occipital region of visual cortex), M (supplementary motor region), PS (peri-sylvian), SPL (superior parietal lobule), TPJ (temporal-parietal junction) and VP (ventral parietal region). Additional areas were activated but are not visible from this vantage point (see refs. 1 and 2). High levels of activity are shown in red, and lower levels of activity are shown in green.

poral views yet of the brain structures that control the deployment of visual spatial attention.

Our focus of attention is constantly shifting, either automatically—in response to an 'attention-grabbing' stimulus—or voluntarily. Usually, an attentional shift is followed by an eye movement to the newly attended location, but it is also possible to attend to a location without looking at it; we are sometimes forced to do this during demanding visual tasks (such as driving on a busy road), where it is impossible to fixate all items of interest simultaneously. In the laboratory, these so-called 'covert' attentional shifts can be detected because reaction times are shorter for trials in which subjects know where to expect the stimulus, compared to trials in which they do not know or are misdirected.

Attention has sometimes been likened to a spotlight, and functional neuroimaging has recently allowed researchers to see the 'beam' directly[3–8]. Several studies have confirmed that attention is mapped topographically in all the early (retinotopic) visual cortical areas, and that when attention is directed to a particular location, the part of the cortex that represents that location becomes increasingly responsive. But where and how are attention signals first generated—in other words, how is the spotlight controlled? Answering this question is now an important goal for the field[9].

One problem with most previous neuroimaging studies of attention (as well as many other cognitive processes) is that they have used a 'block' design, in which the hemodynamic signal is averaged over many similar trials. This generates a static activation map that represents the average activation for a particular task, without giving any information about the individual steps involved. Yet spatial attention is inherently dynamic, and our brains are constantly choosing new locations of interest, disengaging attention and (often) eye position from previously attended locations, and shifting attention and eye position to new targets. It is difficult to resolve these different steps using a block design.

The new studies[1,2] avoid this problem by using 'event-related' designs. Event-related fMRI is a relatively new analytical method, in which the hemodynamic signal is analyzed on a trial-by-trial basis to identify patterns that occur at fixed times after a given event, such as cue or target presentation. Unlike block designs, event-related designs can reveal the time course of the response during an individual trial, making it possible to identify different patterns of activation associated with different components of the task.

Both groups used covert attention tasks, thus avoiding any complications due to eye movements. The subjects were instructed to fixate on the center of a screen and then shift their focus of attention to either the left or the right, as indicated by a cue at the fixation point. A few seconds later, a target appeared either at the cued location ('valid cue' condition)[1,2] or on the opposite side ('invalid' condition)[2], and subjects had to respond to it. Both groups confirmed that their subjects really were making attentional shifts during the task. Corbetta *et al.*[2] showed that their subjects' reaction times were faster after valid than invalid cues, and Hopfinger *et al.*[1] showed that the neural activity evoked by the arrow cue (which, being in the center, could activate both hemispheres) was greater in the hemisphere that represents the cued side.

Despite their similar techniques, the two studies addressed different questions and yielded complementary results. Hopfinger *et al.*[1] made few prior assumptions, and simply asked which brain regions were activated in response to the cues (reflecting an attentional shift) and which were activated by the subsequent target presentation (reflecting processing of the attended stimulus). Cues and targets both activated a number of different regions; the surprising finding was that there was relatively little overlap between the two sets of responses, suggesting that the brain structures that control spatial attention are largely distinct from those that participate in the processing of the attended stimulus.

In a more hypothesis-driven approach, Corbetta *et al.*[2] tested two specific proposals regarding the role of parietal cortex in attention. Based on studies of brain-damaged patients, it has been suggested that the region around the temporal-parietal junction (TPJ) is involved in reorienting attention toward stimuli at unexpected locations, and that the region around the intraparietal sulcus (IPs) is involved in voluntary orientation and maintenance of attention at cued locations. As described below, their data support both these ideas, and provide a view of parietal function that is complementary to, and largely consistent with, that of the other study.

Both groups agree on the role of a posterior parietal region in and around the

intraparietal sulcus; this region is activated in response to the cue and remains active as attention is maintained, but shows a reduced response once the target is presented (regardless of whether it appears at an expected or unexpected location)[2]. Similar responses have been observed in electrophysiological recordings from alert monkeys (see ref. 2 for references), and the combined evidence from physiology and neuroimaging strongly suggests that the posterior parietal cortex is involved in selecting a location and retaining it in working memory (although other areas may also be involved—see below). Interestingly, the greater region of posterior parietal activation may include the visual cortical area V7, which is retinotopically organized (albeit crudely), suggesting a possible role in the spatial allocation of attention[3,9,10].

Another popular candidate for storing spatial cues in working memory is the dorsolateral prefrontal cortex (see ref. 1 and references cited therein). Hopfinger *et al.*[1] observed activation of this region during the cueing period, but Corbetta *et al.*[2]—using a better analytical method that avoided prior assumptions about the time course of the hemodynamic response—found that the activation in the prefrontal cortex was more transient than that observed in the intraparietal cortex. Thus, the intraparietal cortex seems to be the stronger candidate for storing spatial working memories, although it is possible that both regions are involved, particularly as they are known to be interconnected in monkeys (and presumably in humans too).

Most previous models of visual attention have assumed that it is controlled by higher cortical regions, which regulate the processing of sensory inputs in lower regions via top-down projections. This makes sense because decisions about allocating attention are often based on high-level features that are not represented at the earliest stages of the cortical hierarchy. However, alternative, bottom-up models have also been proposed[11], in which attention arises as an emergent property from competitive interactions at each level in the hierarchy. The new findings do not completely exclude the latter model, but they are more consistent with a top-down model. In particular, both groups found that a cue instructing subjects to attend to a particular location caused increased activation of the corresponding parts of the early retinotopic visual areas, even before any stimulus appeared. It is difficult to see how this could happen except through top-down signals, and the challenge now will be to identify the anatomical connections that underlie these effects.

The Corbetta *et al.*[2] study has some interesting clinical implications. For many years, it has been known that damage to the right parietal cortex, particularly the temporal-parietal junction, causes a complex syndrome known as unilateral visual neglect (reviewed in ref. 12). Parietal neglect patients have problems attending to and responding to objects on in the left visual field; for instance, they often bump into objects on their left, and when asked to draw what they see, they tend to neglect what is in the left visual field. The syndrome has attracted a great deal of interest, not only for its clinical importance but also because of its implications for normal perceptual mechanisms. One interpretation of parietal neglect is that the TPJ is responsible for disengaging attention from its present focus and redirecting it to a new target.

Corbetta *et al.*[2] now provide elegant support for this hypothesis. Unlike other parts of the parietal cortex, the TPJ showed little or no response to the initial cue, but it responded strongly to the subsequent presentation of the target. Moreover, the TPJ response was much stronger for invalid than for valid targets, suggesting that it is specifically involved in reorienting of attention in cases where the target appears at an unexpected location. Finally, the TPJ response was always stronger in the right hemisphere than the left, regardless of the side where the target was presented. This right lateralization fits very well with the clinical literature on parietal neglect, and the link seems even more compelling given that the other activations seen in these studies were not lateralized.

In conclusion, these two papers demonstrate the power of new imaging techniques to resolve complex cognitive operations into their component steps, and to reveal the neural structures involved in each step. They are likely to stimulate many future studies, and by combining ever-better imaging methods with other approaches such as patient studies and physiology of non-human primates, we can hope to gain a new depth of understanding of how the brain controls attention.

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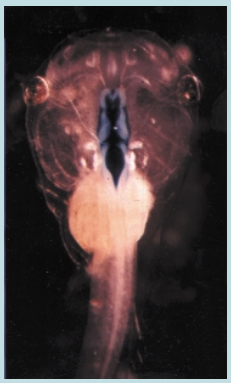
Signaling dendritic growth *in vivo*

Small GTPases of the Rho family affect cell morphology by regulating the cytoskeleton, and they have been implicated in neurite outgrowth. On page 217 of this issue, Holly Cline and colleagues (Cold Spring Harbor Laboratory, New York) report that RhoA, Rac and Cdc42 regulate different aspects of dendritic growth *in vivo*. The authors used vaccinia virus to express constitutively active or dominant-negative forms of these GTPases in albino *Xenopus* tadpoles. Time-lapse imaging of DiI-labeled neurons showed that constitutively active Rac and, to a lesser extent, Cdc42 increased branch addition and retraction. Activation of endogenous RhoA promoted the elongation of existing branches. Cline has previously shown that blocking NMDA receptors reduces dendritic growth, and the dominant-negative form of RhoA prevented this effect, suggesting that RhoA may act downstream of NMDA receptors to control dendritic development.



Sandra Aamodt