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and DNA fragmentation in CGNs located in the external granule layer of the cerebellum.

Finding that TRPC3 and TRPC6 channels are crucial mediators of BDNF-dependent CREB phosphorylation and survival in CGNs is intriguing, but how does it fit into the known survival signaling network? TrkB activation independently activates PLC-γ and the canonical Shc-Grb2 pathway, and BDNF activates Erk and CREB phosphorylation through the Shc-Grb2 pathway[8]. PLC-γ also induces CREB phosphorylation, through Ca^{2+}-dependent activation of CaMKIV and Erk[9]. Furthermore, BDNF induces Ca^{2+} influx through TRPC1 and TRPC3 (ref. 10). The significance of the present study lies in its demonstration that, at least in CGNs, PLC-γ–dependent activation of TRPC3 and TRPC6 channels is the primary physiological pathway that supports BDNF-dependent Erk activation and CREB phosphorylation *in vitro* as well as neuronal survival *in vivo* (**Fig. 1**). BDNF-dependent Akt activation occurs independently of TRP channel function and therefore represents a distinct and parallel pathway affecting CGN survival.

The precise means by which PLC-γ activates the TRPC3 and TRPC6 channels in CGNs is not certain. PLC-γ generates the second messengers diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP_3). DAG directly activates TRP family channels. IP_3 triggers Ca^{2+} release, and the IP_3 receptor directly interacts with TRPC3 channels; both may contribute to store-operated mechanisms that open TRP channels[11]. Overexpression of TRPC3 and TRPC6 in CGNs increases CREB phosphorylation[1], and BDNF treatment enhances TRPC5 channel insertion into the plasma membrane in hippocampal neurons[12]. However, BDNF did not alter the cell surface levels of TRPC3 or TRPC6 in this setting[1], implying that the pathways downstream of PLC-γ directly affect channel conductance. TRP channels participate in a large number of physiological events, and the relative importance of channel insertion as compared to PLC-γ–induced conductance increase seems to vary widely between systems[7]. If TRP channel activation proves to be a widespread mechanism for supporting neuronal survival signaling, it seems likely that the regulatory mechanisms that impinge on this function will be complex. Indeed, determining exactly how PLC-γ activation, IP_3 receptor activation and TRPC3 and TRPC6 channels functionally intersect will be an important next step in resolving this issue.

Understanding the precise means by which Erk is activated by TRP-mediated calcium flux will also be an important challenge. There are several candidate mediators, but one particularly intriguing possibility for TRP-dependent ERK activation is RasGRP1, a unique guanine exchange factor that contains two atypical EF hands that bind Ca^{2+} and a C1 domain that binds DAG[13]. The Ca^{2+} and PLC-γ–dependent activation of RasGRP have been well established in immune cells, but the activation properties and physiological role of this protein in the brain, where it is highly enriched, remain unknown.

The identification of a role for TRP channels in neurotrophin signaling may have implications that extend to BDNF-induced synaptic plasticity. Intriguingly, the PLC-γ binding site in the TrkB intracellular domain is a key residue that is required for calcium-dependent CREB phosphorylation and the generation of late long-term potentiation (LTP)[9]. It is not certain that TRP channels are required for this effect, but it seems plausible, given that TRP channels seem to be required for mGluR-dependent LTP in interneurons[14].

Calcium entry is a pivotal event in neuronal signal transduction. This study, together with the discoveries that TRP channels facilitate axonal guidance[15] and some forms of LTP[14], place TRP channels alongside NMDA receptors and voltage-gated channels as being highly important in regulating calcium entry into neurons.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

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The feeling of looking

Marc A Sommer

Sensory cortex area 3a contains a map of the body. A new paper reports the location of eye position signals in this map, which should allow researchers to test the functions of eye position signals and visual gain fields in more detail.

Proprioception is a tongue-twisting word for a simple concept: monitoring the position of body parts. Proprioceptors occur throughout the musculature and continuously update a body map in area 3a of primate cerebral cortex[1,2] (**Fig. 1a**). But what a strange map! Some of its distortions are reasonable: the shrunken trunk and exaggerated hands, for example, reflect differing needs for fine positional information. There is one problem that has been inexplicable, however: the map seems to lack eyes. This may be fine for a cave creature, but not for primates with their ever-curious, darting glances. The eyes are the most mobile organs of the body, the eye muscles are packed with structures that look like proprioceptors[3], and knowing where the eyes are pointed should be useful for vision. Does the primate brain nonetheless ignore eye position? Or is there an eye proprioception zone yet to be found?

In this issue, Wang *et al.*[4] report that they have discovered the eye zone. It is in area 3a, but it is buried deep in a cortical wrinkle. In this day and age, it is quite an achievement to find any unexplored territory in the brain. Yet with all due respect to such an accomplishment, it is fair to wonder how much of an advance this represents. Why was so much effort spent to find a single body-part representation? Does the achievement signify the end of a narrow line of study or the beginning of a broader one?

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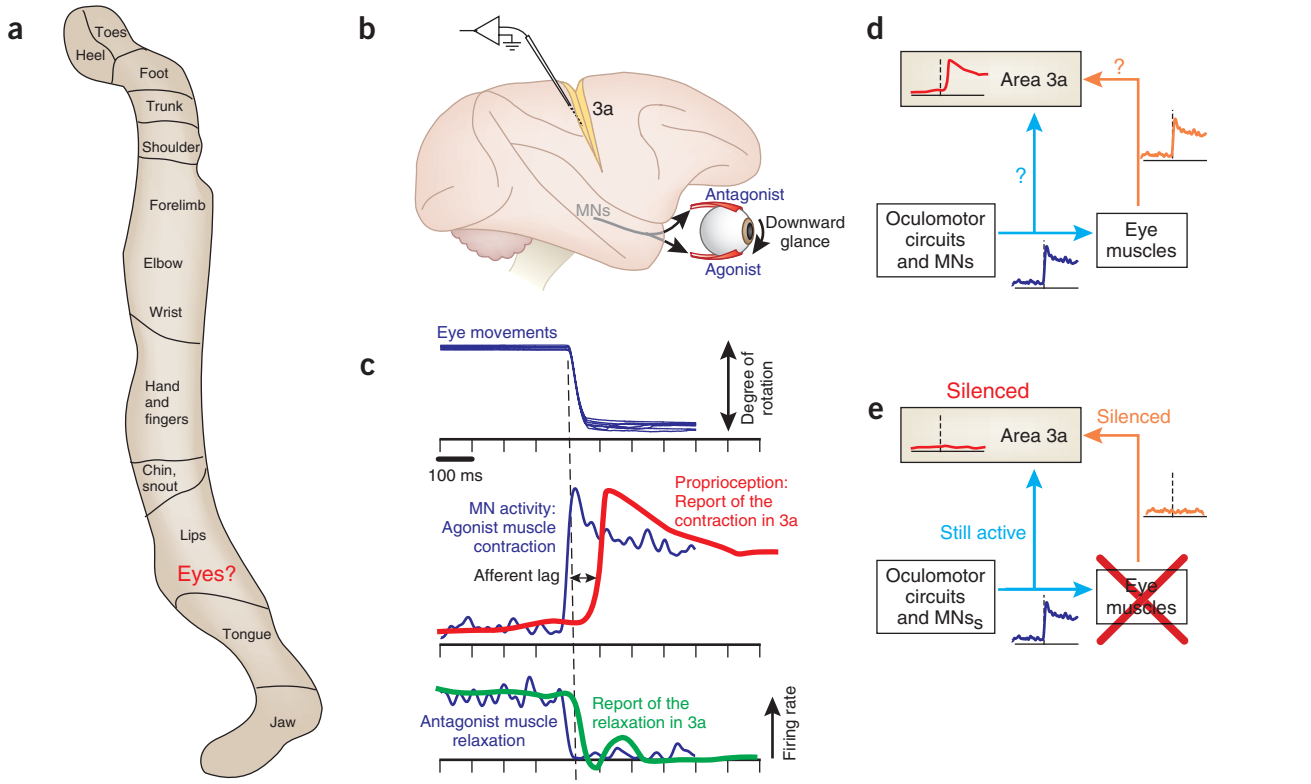

Figure 1 Discovery of a proprioceptive eye zone in primate cerebral cortex. (**a**) The body map in area 3a. Wang *et al.*[4] tested whether there is an eye representation in the face area. Medial is upward; anterior is rightward. Modified from ref. 2. (**b**) Lateral view of rhesus monkey brain with area 3a, in the central sulcus, exposed (yellow). Neurons were recorded in 3a while monkeys moved their eyes. Six muscles insert into the eye. (Only two are shown.) For a downward glance, as depicted, motor neurons (MNs) drive downward-pulling, agonist muscles and stop driving upward-pulling, antagonist muscles. (**c**) Top, position traces for repeated downward eye movements. Middle, MNs projecting to the agonist muscle show a sharp increase in activity and then a sustained firing (blue). Neurons in area 3a seem to report this activity (red) after a delay consistent with afferent lag (arrows). Bottom, MNs projecting to the antagonist muscle quickly cease their firing (blue), and neurons in area 3a seem to report this change dutifully (green). MN activity: M.A.S., unpublished data (courtesy S.-Y. Shin). Area 3a activity: modified from Figure 3c of Wang *et al.*[4] (**d**) Possible inputs to area 3a include corollary discharge from oculomotor circuits and MNs (blue signals and arrows) and proprioception from the eye muscles (orange signals and arrows). (**e**) Logic of the inactivation experiment. Paralyzing the eye muscles (red X) silences proprioception (orange) but not corollary discharge (blue).

Wang *et al.*[4] had ample rationale for their quest. Vision is useful only if you know where you are looking. If you are skiing and see a deer, your reaction depends on where your eyes are pointing: if leftward, you might want to smile; if straight ahead, you might want to dodge. Even in less dramatic moments, our brains must keep track of where we look. We move our eyes frequently, such that the images on the retinas resemble a high-speed slide show. The brain can reassemble these pieces into a stable percept only if information about eye motion or position (or both) is available. Furthermore, the mechanics of the eyes change with development and injury, thus requiring calibration that would be aided through feedback about eye position. Finding the eye position signal in the brain might facilitate treatment for eye disorders and traumas.

Empirical findings have been mixed regarding the existence of eye proprioception and whether area 3a may contain its cortical representation[3,5]. In favor of this premise is the observation that the density of proprioceptor-like sensory structures is higher in the eye muscles than in any other finely controlled muscles. Putative eye proprioceptive signals have been recorded subcortically and could ascend to cerebral cortex by way of trigeminal nerve–thalamus channels. Psychological experiments (some involving muscle vibration or paralysis) indicate that the brain uses eye proprioception. Yet many doubts remained. The competency of ocular proprioceptors is questionable because they fail to mediate a stretch reflex. Copies of eye movement commands (corollary discharge) reach cerebral cortex[6,7] and a running tab of these signals could estimate eye position in lieu of proprioception. Finally, an eye proprioception signal might not be represented in area 3a. The anterior neighbor of area 3a is primary motor cortex, and no one seems surprised that its map is eyeless. Movements of the eyes are controlled, instead, by the frontal eye field.

Into this fray stepped Wang *et al.*[4]. Using behaving rhesus monkeys, they tested the most optimistic hypothesis: that eye proprioception is indeed functional and that its representation lies in area 3a. First they advanced electrodes into area 3a (**Fig. 1b**) and found the upper face representation. Because area 3a lies in a wrinkle, or sulcus, of the brain, they had to go more than 9 mm deep (for comparison, cortex is ~3 mm thick). At the bottom of the sulcus, they got their first hint of success: neurons changed their activity with eye position. But was this activity due to proprioception, or to another source of input?

To predict what a proprioceptive signal would look like, it is important to review the principles of muscle contraction. When motor neurons in the brainstem command the eye muscles to contract (**Fig. 1c**, top), activity increases for agonist muscles (**Fig. 1c**, middle) and decreases for antagonist muscles (**Fig. 1c**, bottom). Proprioceptive signals should resemble the muscular signals plus

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a delay, and this is what Wang *et al.*[4] found (**Fig. 1c**, red traces). Temporally, it was a nice match: the putative proprioceptive signals had a transient-sustained sequence reminiscent of the muscle pattern. Spatially, however, the area 3a neurons failed to represent discrete muscle pulling directions; instead, preferred directions for the neurons were distributed homogeneously. This might have been due to the summation of signals from multiple muscles, but nonetheless it cast a shadow of a doubt onto the proprioceptive interpretation.

A skeptic might go even further and challenge the entire correlative basis of the recording results. Area 3a neurons changed their activity with eye position, but the source of the signal remained unknown. It might have arisen entirely from central calculations such as the running tab of corollary discharge mentioned above. Wang *et al.*[4] designed an experiment to test this (**Fig. 1d**). Proprioceptive signals necessarily depend on muscle contraction or relaxation, but corollary discharge signals do not. The next step, therefore, was to silence the muscle activity. This should silence proprioception while leaving corollary discharge signals active (**Fig. 1e**). The authors' prediction[4] was that neuronal signals in area 3a would go away.

To test this hypothesis, they injected anesthetic behind one eye to paralyze it. Others[8] had used this method to test neuronal modulations thought to be caused by corollary discharge; in that study, paralyzing the eye was predicted to have no effect on neuronal activity, which is what was found. Wang *et al.*[4] cleverly used the same method but with the opposite prediction: paralysis of the eye should silence neuronal activity. Their result fully confirmed their prediction. Area 3a activity was abolished with a full ocular paralysis, and with less complete blocks, the degree of neuronal silencing varied accordingly. When time courses could be followed, neurons recovered as the paralysis wore off. These data led the authors to conclude that the activity of neurons in area 3a depended critically on the actual contraction and relaxation of eye muscles: the source was proprioception, not corollary discharge.

A logical follow-up experiment would be to impose activation on the stretch receptors—for example, by passively rotating the eye of an anesthetized animal. If area 3a neurons are driven by proprioception, they should fire avidly for these imposed movements. Although such a manipulation is beyond the scope of the present work, it would be a useful future direction.

In summary, the eyes of the proprioceptive body map have been found. In a pleasing triumph of logic, they were in area 3a, right where they were supposed to be. The discovery has exciting implications. First, it settles the debate over whether the brain receives proprioception of eye position. It does. Second, it stokes another debate: what is the proprioceptive information used for? There is significant evidence, as the authors describe[4], that proprioception is not crucial for instantaneous eye movement behavior. Functions that demand high precision in time and space, such as stabilization of the visual percept across eye movements, probably rely on corollary discharge. A more likely role for proprioception is long-term calibration of the visual and oculomotor systems[9,10]. Among many oculomotor connoisseurs, however, there is concern that this dichotomy (corollary discharge underlies perceptual stability, and proprioception maintains calibration) is too simplistic. This raises the question of what happens when the eye position zone in area 3a is inactivated. Does loss of eye proprioception, like loss of corollary discharge[6,7], disrupt second-by-second eye movement planning and premovement remapping of the visual scene? Or does loss of proprioception have only long-term, calibrative influences?

An associated issue concerns neurons in posterior parietal cortex that show visual sensitivity modulated by eye position[11,12], a phenomenon known as 'gain fields'[13]. These neurons must receive eye position information from somewhere, and now there is a likely source area. More generally, area 3a could be a gateway for eye position signals to reach the entire cortical mantle. Wang *et al.*[4] raise the intriguing conjecture that if the proprioceptive signals are indeed used for calibrative purposes, then by association, gain fields may also serve such purposes. This goes against more ambitious ideas about gain field function and should provoke lively discussions in the coming years. At its core, the result of Wang *et al.*[4] should be welcomed by everyone. Now, with the cortical eye proprioception zone identified, debates about the role of eye position and gain fields can end productively with a simple, two-word challenge for each hypothesis: "test it."

COMPETING INTERESTS STATEMENT
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Of sleep, memories and trauma

Robert Stickgold

Contrary to the synaptic homeostasis theory, new work finds that reactivating memories during slow-wave sleep enhances learning and hippocampal activation. This may be useful for treating post-traumatic stress disorder.

Science sometimes moves forward only after experiments in one field unexpectedly find application in another. A recent study by Rasch and colleagues[1] in *Science* offers such potential. In this study, the authors provide strong evidence that experimentally reactivating memories during sleep on the night following learning can enhance those memories. This finding is an important addition to a rapidly growing literature showing that sleep contributes to processes changing memories after they are formed (encoded)—changing, stabilizing, strengthening, integrating and even moving memories into more permanent storage systems[2]. The results also have unexpected implications for the discussion on whether sleep serves to strengthen synapses or can only weaken them.

Memory structures active during encoding are normally reactivated, sometimes with remarkable temporal precision, during

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