NEUROSCIENCE

Rewiring the adult brain

Arising from: S. M. Smirnakis *et al. Nature* 435, 300–307 (2005)

Any analysis of plastic reorganization at a neuronal locus needs a veridical measure of changes in the functional output — that is, spiking responses of the neurons in question. In a study of the effect of retinal lesions on adult primary visual cortex (V1), Smirnakis *et al.*[1] propose that there is no cortical reorganization. Their results are based, however, on BOLD (blood-oxygen-level-dependent) fMRI (functional magnetic resonance imaging), which provides an unreliable gauge of spiking activity. We therefore question their criterion for lack of plasticity, particularly in the light of the large body of earlier work that demonstrates cortical plasticity.

Plasticity in adult V1 has been demonstrated by multiple, independent lines of evidence from more than twenty studies in three species (see refs 2–6, for example). Physiologically, the evidence derives from measurements of lesion-induced shifts in the locations of V1 neuronal receptive fields. By plotting receptive fields before and at various points after making retinal lesions, it was shown that the affected cortex — with receptive fields originally inside the lesion — develops new, shifted receptive field positions after recovery. These shifts are cortically mediated because the lateral geniculate nucleus, the source of thalamic input to V1, shows limited reorganization[7]. All these measurements were made using suprathreshold spiking neuronal responses: this is an important point as the neuronal output from V1 to subsequent cortical stages is carried entirely by spikes. Any measure of V1 reorganization — and consequent functional remapping of visual information — therefore needs to assess the effect on spiking activity. These physiological results are buttressed by anatomical findings showing a selective increase in the density of axon collaterals in reorganized cortex[8], and the sequential expression of biochemical markers[9,10].

By contrast, the primary evidence for lack of plasticity offered by Smirnakis *et al.* is the observation that the V1 'silent zone', mapped with BOLD fMRI immediately following a retinal lesion, did not change over time. There are plausible reasons why fMRI maps may fail to change, despite re-emergent neuronal activity. The reorganization of cortex is believed to be mediated by long-range horizontal connections within V1 (refs 8,11,12). In normal V1, these connections mediate subthreshold modulation. Following retinal lesions, horizontal connections stretching from 'normal' cortex into the lesion projection zone (LPZ) are believed to strengthen their synapses — but not to change anatomical extent. They therefore induce re-emergent spiking activity, but only in neurons lying within their target zone in the silenced cortex.

Such re-emergent activity could involve reduction of inhibition as much as an increase in excitation. As the BOLD signal probably reflects synaptic input into a region rather than spiking output, the 'silent zone' observed by Smirnakis *et al.* immediately following a lesion may mark not the edge of the real LPZ but the inner edge of subthreshold activation spreading into the LPZ through horizontal connections. In subsequent measurements, the BOLD signal would continue to show the unchanging position of this inner boundary while being blind to synaptic reorganization, which would lead to re-emergent spiking activity over the extent of the horizontal connections. The single set of electrode recordings by Smirnakis *et al.* after months of recovery might simply show the extent of largely completed recovery and, not surprisingly, produce a border in register with the edge of the BOLD signal.

Furthermore, BOLD gives a local measure of the total cortical activity, a significant component of which comes from thalamocortical inputs, the contribution of which is probably further accentuated by the disproportionately high vascularization of layer 4, the cortical input layer. However, the neurons showing recovery may reside primarily in the superficial layers[12], which receive the long-range horizontal connections, as opposed to layer 4.

Owing to these uncertainties about the validity of BOLD fMRI as a yardstick of functional reorganization in V1, we believe that Smirnakis *et al.* do not present a convincing contradiction to the body of earlier evidence indicating substantial receptive field plasticity in adult animals following retinal lesion. The recovered activity demonstrated in the earlier studies has a likely corollary in the recovery of visual perception: human subjects suffering from macular degeneration, or with artificially induced retinal lesions, show improved perceptual fill-in over time after the lesions[13–15].

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Smirnakis et al. *reply*

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We disagree with Calford *et al.*[1] that there is a consensus on adult plasticity in primate V1 cortex: for example, macaque area V1 cytochrome oxidase levels remained depressed for several months after binocular retinal lesions[2]; no reorganization in macaque V1 after monocular retinal lesions was found[3]; and no area V1 reorganization in a patient with macular degeneration was detected[4].

Calford *et al.*[1] agree that subthreshold activity shows no long-term reorganization. They propose that plasticity comprises only an increase in the likelihood of transforming subthreshold signals into action

potentials. Their argument hinges on the claim that even our first BOLD (blood-oxygen-level-dependent) maps, obtained immediately after the lesion, reflect the full extent of reorganization (assumed to be equal in extent to subthreshold synaptic activity). Our results do not support this view. Rather, the BOLD-defined lesion projection zone (LPZ) border matches its anticipated location based on the retinotopic projection of the retinal lesion. Specifically, the BOLD-defined LPZ borders in Figs 1,2 of ref. 5 are within 1.5 mm of their expected retinotopic projection. This is commensurate with the expected vascular spread and considerably smaller than most estimates of reorganization (about 2–5 mm).

Calford *et al.*[1] defend a weak definition of plasticity. The prevalent view of long-term reorganization involves creation of new connections and increased efficacy of existing synapses[6], which is expected[7] to increase subthreshold activity. However, we observed no change in the slope or position of the BOLD profile at the LPZ border, suggesting that changes in subthreshold activity are weak or occur over a small scale (1 mm). Even if neuronal firing increases by down-regulation of inhibition, as proposed by Calford *et al.*, the BOLD signal in the neocortex should increase[8]. We note that functional magnetic resonance imaging is sensitive for detecting reorganization in human cortex[9,10], and that BOLD is strongest in the upper 1 mm of cortex[11], where long-range horizontal connections reside.

Calford *et al.* suggest that receptive field shifts at the LPZ border unequivocally demonstrate long-term plasticity. This is not necessarily so. Retinal recovery from thermal injury at the lesion border could produce similar shifts[2]. Moreover, the time course of this phenomenon is unclear, with some studies[12,13] reporting large (up to 4.5 mm), almost immediate activity shifts (discussed in ref. 5). Neither does perceptual 'filling-in' necessarily imply V1 reorganization. 'Filling-in' has been proposed to occur in higher areas[14], and macaque perceptual 'filling-in' has been demonstrated without area V1 reorganization[3]. Although anatomical and immunohistochemical changes occur inside the LPZ after deafferentiation[6,15], their functional significance is unclear.

Our multi-unit recordings from superficial and deep cortical layers confirm the BOLD measurements, showing that steady-state responses do not recover substantially inside the LPZ, and ruling out the possibility that BOLD missed reorganization by reflecting primarily activity in the thalamo–cortical afferents[5].

By monitoring aggregate neural activity, we may have missed reorganization in select neuronal subpopulations. As discussed[5], we cannot exclude short-term (minutes to hours) reorganization, or a limited form of plasticity expressed as adaptive gain adjustments affecting selectively transient extra-classical responses inside the LPZ while leaving steady-state responses largely unchanged. No method could convincingly show a complete lack of changes after deafferentiation, but our measurements define limits on the strength and spatial extent of any proposed reorganization.

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