Now see this: Anti-inflammatory treatment reverses stroke-induced compromise in sensory learning

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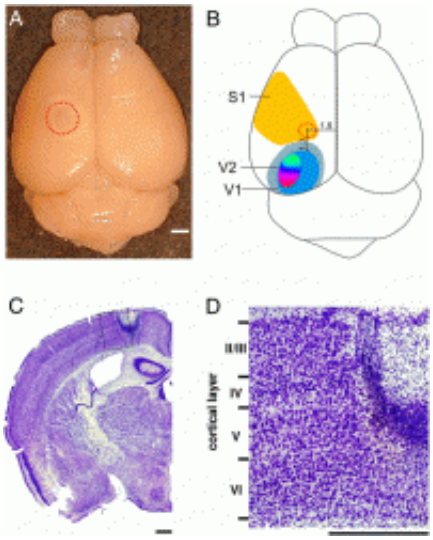

Localization, size, and demarcation of the photothrombotic (PT) lesion in the mouse cortex. (A) Top view of a mouse brain with a PT-lesion in the left hemisphere (red dotted circle). (Scale bar, 1 mm.) (B) Scheme illustrating average lesion location and size: lesion center was located in the left primary somatosensory cortex (S1), on average 1.3 mm anterior to (the anterior border of) the primary visual cortex (V1) and 1.8 mm lateral to the midline. We overlaid the scheme with an optically recorded retinotopic map from the binocular part of V1 to directly illustrate the spatial relationship of the PT-lesion and V1. (C) Nissl-stained frontal section through a lesion center 7 d after lesion induction. The left brain hemisphere is illustrated showing that the lesion was restricted to the cortex without affecting the underlying white matter or subcortical regions. (Scale bar, 500 μm.) (D) The higher magnification image of the lesion border (region demarcated by the black rectangle in C shows the intact

tissue and cortical layering in the perilesional zone. (Scale bar, 500 μm.)

(Medical Xpress) -- One of the many potential consequences of *ischemic stroke* – a lesion, or localized pathological change in the brain, in which blood flow insufficient to meet metabolic demand leads to poor oxygen supply (*cerebral hypoxia*) – is compromise to two different visual plasticity paradigms: sensory learning (the enhancement of visual acuity and contrast sensitivity of the open eye after monocular deprivation, or MD, in which vision in one eye is blocked) and *ocular dominance*, or OD, plasticity (a shift in the ocular dominance of neurons in the binocular part of the visual cortex toward the open eye after MD). A standard view holds that changes in the activity of the major thalamocortical afferents to the visual cortex (the afferents from the left and right eye) are sufficient to induce OD-plasticity.

Recently, however, research conducted at the Bernstein Fokus Neurotechnologie (BFNT) and Johann-Friedrich-Blumenbach Institut für Zoologie und Anthropologie at Universität Göttingen in Germany has shown that after a photothrombotically-induced stroke outside the visual system (a lesion induced in the mouse somatosensory cortex by intravenous injection of photosensitive dyes that, when irradiated, cause photochemical occlusion of the irradiated vessels with secondary tissue ischemia), there was neither an enhancement of visual acuity nor an OD-shift after MD – but OD-plasticity was present in the hemisphere *contralateral* to the lesion.

In addition, anti-inflammatory treatment restored sensory learning but *not* OD-plasticity – the same results obtained by implementing a two-week delay between photothrombosis and MD. The researchers were thus able to conclude that both sensory learning and OD-plasticity are

compromised in the areas surrounding a cortical lesion, and that transient inflammation is responsible for impaired sensory learning – suggesting that anti-inflammatory treatment may be useful adjuvant therapy in post-stroke rehabilitation. Moreover, in a finding significant to researchers modeling the visual system, the study clearly demonstrates that nonlocal influences – i.e., factors outside of the visual cortex or visual system – can modify the sensitivity of the visual cortex to changes in afferent activity patterns and are thus more important in OD-plasticity than has previously been thought.

Conducted by Franziska Greifzu, a graduate student in Prof. Siegrid Löwel's Systems Neuroscience Group, along with Silvio Schmidt, Karl-Friedrich Schmidt, Otto W. Witte, and Klaus Kreikemeier, the primary challenges facing the research team were selecting the lesion model that best addressed their questions, as well as controlling reproducible lesion size and location.

"To solve those challenges," says Löwel, "we didn't need to develop totally new techniques, but used well-establish ways of answering a question that is very often addressed using only *in vitro* techniques. The strength of our approach was to combine behavioral analyses and *in vivo* imaging of brain activities in the same animals."

The results were surprising given previous *in vitro* knowledge: One of the best-known model systems in neuroscience to study brain plasticity is visual cortex OD-plasticity, initially introduced in the 1960s by the subsequent Nobel Prize winners David Hubel and Torsten Wiesel[1]. "It was firmly believed," Löwel explains, "that one can induce ocular dominance plasticity in the visual cortex by depriving one eye of an animal" – i.e., monocular deprivation. "As a result, the MD-affected animal's visual cortex will be activated more strongly by visual stimulation of the non-deprived eye while deprived eye afferents get weakened. Our data clearly show that this plasticity does not just depend

on changes in the major thalamocortical afferents from the eyes to the visual cortex, but in fact must be modulated by non-local influences."

Despite the strength of the results, Löwel is cautious in speculating on how their findings may impact the development of post-stroke treatment and prophylaxis. "First of all, so far we have only analyzed mice and have to be very careful not to create more hope in patients than is justifiable. Nevertheless," she continues, "the observation that anti-inflammatory treatment had a therapeutic effect on the investigated learning paradigm might be the starting point for further investigations."

Turning to future research, Löwel notes that the team plans to analyze the cellular mechanisms underlying these plasticity changes using in vivo two-photon microscopy, which will allow then to visualize individual nerve cells and their changes after stroke. In terms of in *silico* computer modeling, however, she states that "If you want to analyze learning after brain lesions, one has to investigate real brains. There is no way around this conclusion. We do not yet know enough about brain mechanisms to switch to in *silico* protocols." She does point out that "We of course use computational neuroscience techniques for analyzing data properly and for creating hypothesis about brain mechanisms."

Other avenues for future research, adds Löwel, is the role of GABAergic neurons in post-lesion OD-plasticity, as well as having already started to investigate changes in inhibitory networks and interhemispheric interactions.

Of great promise, Löwel concludes, is applying their techniques to investigate other forms of neural plasticity. "I think the combination of behavioral analyses with imaging of neuronal activity in the same animals – perhaps even chronically to follow the same individual over time in a learning experiment – is very powerful. One can even perform so-called chronic two-photon calcium imaging experiments to follow

single neurons over time. It is therefore possible to follow the activity of larger nerve cell ensembles or even single nerve cells in the brains of individuals during a learning experiment."

More information: Global impairment and therapeutic restoration of visual plasticity mechanisms after a localized cortical stroke, *PNAS* published online before print August 24, 2011, doi: 10.1073/pnas.1016458108

[1]Related: An introduction to the work of David Hubel and Torsten Wiesel, Eric R. Kandel, doi: 10.1113/jphysiol.2009.170688, June 15, 2009, *The Journal of Physiology*, 587, 2733-2741