Adult Cortical Plasticity

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Introduction

Plasticity of the brain is a lifelong phenomenon. In general, cortical plasticity describes changes of neuronal wiring and function in the cerebral cortex in response to new challenges of external or internal origin. External stimuli are environmental conditions that impose new tasks on the system. Internal stimuli can be normal developmental demands or pathological lesions in the widest sense – structural, biochemical, or genetic – leading to severe functional impairment. Extrinsic as well as intrinsic neuronal activity can shape wiring and strength of connectivity. Developmental plasticity, as opposed to adult plasticity, has a stronger potential and can include axonal and dendritic growth at a larger scale. Many factors that guide normal development of the brain (e.g., growth factors, netrins) are downregulated after the critical periods of development. In response to lesions in adulthood, some factors can eventually be upregulated to again allow more extensive neuronal plasticity. In that case, neuronal plasticity is the response of the system in an attempt to repair or compensate loss of function. In development as well as in adult cortical plasticity, neuronal activity can change functional connections; however, the effectiveness of synaptic plasticity is usually reduced following postnatal development and critical periods. In the case of adult cortical plasticity, functional and structural adaptations remain, as a rule, spatially localized and restricted to the level of axonal terminals and synapses. New functional connections can be formed by increase of synaptic efficacy in a preexisting network. The principles of reorganization and remapping are common features of the adult auditory, somatosensory, and visual cortices. This article, however, focuses on plasticity in the visual system.

Transition from Visual Cortical Development into Adult Cortical Plasticity

Some principles of adult sensory cortex plasticity can be understood by comparing development in early postnatal life and reorganization after injury of sensory cortical maps. Sensory cortices are characterized by topographic maps that are arranged according to the neighborhood principle. Cells that are close in the sensory periphery are also close in the cortical representations, be it sound frequency in the auditory, body surface in the somatosensory, or retinal surface and visual space in the visual system. The representational maps remain stable throughout adulthood once they have formed through dependence on use in early postnatal life. Accordingly, the postnatal development of the visual cortex is characterized by use-dependent sculpturing of the necessary, correct connections. Characteristic cortical maps of retinal topography and stimulus specificity are formed. At the end of the critical periods, the functional connections are stabilized, and the programs that prevailed during this period, such as axon growth and guidance, removal of incorrect connections, strengthening of optimal, and weakening nonoptimal inputs (synaptic plasticity) are modified in a way to foster stability without sacrificing flexibility in adulthood. Finally, the ability to change synaptic weights by long-term potentiation (LTP) or long-term depression (LTD) persists throughout adult life into senescence. This is exemplified by the lifelong ability for perceptual learning. Use, disuse, and lesions are the strong stimuli for plasticity and reorganization in the adult visual cortex. For example, when challenged by central or peripheral lesions, the visual system displays characteristic patterns of remodeling. While the observed subcortical changes remain limited, more widespread reorganization is seen in the cortex. In the early phase, cortical reorganization appears more restricted and based on functional modifications of cortical connections governed by subtle changes in the balance of excitation and inhibition. In later stages, more extended reprogramming of connections, based on long-term changes in synaptic connectivity (LTP, LTD), is observed and can ultimately involve anatomical reorganization including local growth mechanisms.

There are many different types of adult cortical plasticity. One type is purely use-dependent and closely related to perceptual learning as observed in humans. This plasticity is operating in everyday life when cellular properties are modified in response to repetitive use in demanding tasks. This use-dependent plasticity is closely related to 'synaptic learning' based on mechanisms like LTP and LTD. Other types of visual cortical plasticity are observed after lesions; they are less specific and generally lead to changes in single cell properties and reorganization of cortical representations (maps). The following sections focus on adult use-dependent plasticity and two different types of lesion-induced plasticity in the visual cortex.

Use-Dependent Adult Visual Cortical Plasticity

Fast associative plasticity of visual cortical cells has been shown *in vitro* with electrical stimulation as well as *in vivo* by pairing of natural stimuli with artificial depolarization of single cells. The *in vitro* experiments were performed with intracellular recordings in brain slices of adult rats and cats and showed that adult visual cortical cells are capable of synaptic plasticity. High-frequency repetitive stimulation of specific inputs results in LTP, which is expressed in long-lasting increases of synaptic potentials.

To induce changes in cellular responses *in vivo* on a fast timescale, natural sensory stimuli have been paired with electrical or pharmacological stimulation of cells in the visual cortex of anesthetized animals. Properties such as orientation specificity (e.g., vertical vs. horizontal) or ocular dominance (left vs. right) were shifted toward the property reinforced by repetitive pairing with a facilitating stimulus during supervised learning. These experiments provide *in vivo* evidence that the modifiability of mature visual cortical connections follows the Hebbian rule, which requires both pre- and postsynaptic activity within a defined time window. While many experiments used electrical or pharmacological stimuli to facilitate synaptic plasticity, is was also shown in experiments with anesthetized animals that purely natural repetitive stimulation can induce long-lasting changes of visual cortex cell properties such as receptive field (RF) size and substructure. Visual costimulation of the central parts of an excitatory RF with an unresponsive region located just outside was applied to elicit 'associative' synaptic changes. With this paradigm visual cortical cells did specifically 'learn' to respond to an originally subthreshold region outside their excitatory RF or to change the subfield composition within their RF.

Recently, sophisticated *in vivo* studies have shed additional light on the possible properties and mechanisms of use-dependent adult visual cortical plasticity by examining short-term changes of orientation specificity induced by adaptation to certain orientations. Repulsive shifts of preferred orientation were observed that involved time-dependent processes of depression as well as enhancement. This kind of short-term plasticity was dependent on the location of cells within the layout of the orientation preference map of the visual cortex that is characterized by large coherent orientation domains and 'pinwheel centers' or singularities, where all orientations meet within a small circumscribed region. In the vicinity of singularities, the capacity for adaptive changes in response to oriented gratings is much stronger than in orientation domains. It has further turned out that certain forms of short-term plasticity in the adult visual cortex are stimulus timing-dependent. In respective experiments, plasticity of orientation selectivity *in vivo* depended on stimulus timing within a ± 40 ms window like the crucial parameters for spike timing-dependent plasticity. This suggests that underlying mechanisms are modifications of synaptic weights of intracortical connections.

Beyond the single cell level, use-dependent adult visual cortex plasticity can be shown in whole cortical networks. When optical imaging of intrinsic signals was combined with localized electrical intracortical microstimulation, profound changes in orientation preference maps were observed in the adult cat visual cortex. After a few hours of high-frequency focal electrical stimulation, the cortical representation of the orientation represented at the stimulation site increased because surrounding cells with previously different orientation preferences shifted toward the stimulated orientation at sites as distant as 4 mm. These widespread changes did not involve attention, special training, or reinforcement; they were purely dependent on high-frequency synchronized activation of the cortical network.

When monkeys are trained for several months to identify the orientation of a small grating, they show a marked increase in performance. Single cell recordings from primary visual cortex (V1) of these monkeys after successful training reveal significantly increased orientation sensitivity of only those cells and orientations that represented the trained orientation. This proves that use-dependent single cell plasticity in the adult visual cortex can be linked directly to behavior and perceptual learning.

Lesion-Induced Cortical Plasticity

Retinal lesions remove afferent input to thalamus and cortex. Cortical lesions destroy cortical cells that have a dual function, being targets for topographic retinal projections via the thalamus on one hand, and being the origin of intracortical connections on the other. These completely different types of lesion, retinal versus cortical, pose very different problems for reorganization and restitution of function to the visual system. In the case of retinal lesions, the option is to reinnervate intact cortical cells that have lost their sensory input; however, the topographically correct fibers are no longer available due to retinal destruction. In the case of cortical lesions, the retinal afferent information is still completely on hand, but the cortical target cells are lost. Accordingly, the options for reorganization are different, and so is the outcome of functional reorganization: after retinal lesions, a blind cortical region is filled in with retinal topography redundantly spreading across the cortical surface and resulting in many cortical cells newly

representing the same retinal topography, whereas after cortical lesions, the surviving cells in the surround receive new suprathreshold information from geniculocortical afferents and acquire additional topographical representations from the retina. While the former fills in a cortical region of still existing but blind cells with new but topographically redundant activity, the latter enables true functional improvement by recovering previously lost afferent information for further cortical processing. The lesion-induced changes can be roughly subdivided into acute, subacute, and chronic effects. The pathology of cell death and functional suppression that is predominant in the acute phase (first day postlesion) is followed by events of neuronal plasticity in the subacute (second day to 1 week postlesion) and chronic phases (weeks to months after a lesion). It is interesting that the different types of lesions seem to trigger similar effects that lead to receptive field plasticity, topographical remapping, and a limited recovery of function.

Plasticity in the Primary Visual Cortex after Cortical Lesions

Focal lesions of the visual cortex lead to a local visual field loss (scotoma). The size of the scotoma mirrors cell death and functional depression of cortical neurons. However, the dimension of functional loss following cortical lesions can diminish in both animals and humans with time and especially when specific training is performed. A possible basis for restoration of function is a reactivation of 'silent' cells in the only partially damaged, functionally suppressed surround of the lesion (the penumbra) by strengthening of subthreshold synaptic inputs. Another possibility is the increase in size of receptive fields of intact cells at the border of the lesions, that is, an additional representation of lost parts of the visual field by cells that also maintain their original topographical representation of space and thereby enable the perception of previously lost parts of the visual field. It is interesting that in the first weeks after a lesion in the visual cortex, an increase of excitability is observed in its surround. This increased excitability seems to support the theory of increased plasticity of cells surrounding the lesion. Changes of receptive field size that do not occur spontaneously in the first days following a lesion develop months later close to the border of lesions in the cat visual cortex.

Faster changes in receptive field size can be experimentally induced by repetitive visual stimuli. This can be achieved even in neurons of the normal adult cat visual cortex. Repetitive stimulation associated with high response rates in the neurons under study can lead to a significant and stimulus-specific widening of receptive fields. The observed effects last from 20 min to several hours and are reminiscent of effects similar to short-term potentiation and LTP. Such LTP-like mechanisms might be enhanced because of locally increased excitability in the surround of visual cortical lesions and might be associated with the RF enlargements observed in the surround of cortical lesions. LTP is the best candidate to explain cellular learning and memory and can be studied in brain slices *in vitro* following high-frequency electrical stimulation of inputs. LTP is characterized by strengthened synaptic transmission over a span from more than 1 h to days and weeks. LTP was first described in the mammalian hippocampus and can also be observed in the visual cortex of mice, rats, and cats. During early postnatal development, when synaptic plasticity is highly expressed – as in the visual cortex during the critical period – very effective LTP is observed. In fact, lesion-induced reorganization after lesions in the visual cortex is associated with increased LTP, as was shown by increased synaptic plasticity in slices of the lesioned rat visual cortex *in vitro*.

Reorganization of the Primary Visual Cortex Following Retinal Lesions

Retinal lesions trigger chronic reorganization in the afferent visual pathway. This follows the interruption of visual signal flow from the destroyed retinal area to the visual cortex that locally deprives cells in the thalamus (lateral geniculate nucleus) and the primary visual cortex of their normal input. The excitability of cells in the visual thalamic relay nucleus (dorsal lateral geniculate nucleus, dLGN) that are primarily deafferented by a monocular photocoagulator lesion of the retina changes in a characteristic way: initially the cells show a complete loss of visual drive and a significant decrease in spontaneous activity; then spontaneous activity increases in deafferented cells, and some cells inside the deafferented region regain visual input originating from the retina directly adjacent to the lesion. Accordingly the RFs of these newly connected cells change their retinotopy and shift to a new position located at the border of the retinal lesion. This reorganization of the retinotopic map leads to a partial filling in of the scotoma on the subcortical level and is associated with a lateral spread of excitation in the dLGN of up to 300 μm. With the same type of lesion, a much more extended reorganization can be observed in the visual cortex. Apart from the longer distances involved, the reorganization was exactly of the same kind as observed in the dLGN: originally silenced cells regained visual input that originated from the border of the retinal lesion, a retinal region that did not excite these cells

before. The same kind of plasticity was found in cat and monkey visual cortex. The reorganization gradually fills in cortical regions that were depleted of retinal inputs with new excitability over distances up to 5 mm. This distance conforms to the range of lateral horizontal connection in the visual cortex. This chronic retinotopic remapping is preceded by fast changes in visual RF properties that follow acute disuse induced by retinal lesions and are elicited as well when selective surround stimulation is applied to artificial retinal scotomata.

The cortical region affected by loss of input after retinal lesions constitutes an anatomically defined lesion projection zone (LPZ, Figure 1(a)). A characteristic imbalance of input occurs in and outside the LPZ as cells with normal afferent input are situated in direct proximity to visually silenced cells. In addition, excitation is upregulated and inhibition downregulated inside the LPZ. This situation leads to changes in cortical cell RF size and topography when the active cells gain influence on their inactive neighbors through the intracortical horizontal fiber systems. The filling in follows a characteristic spatiotemporal pattern in which hyperactive and visually hyperexcitable cells are first found close to the order of normal cortex in the LPZ, then progressively deeper inside the LPZ (Figure 1(b)). The long-range horizontal fibers are the most probable basis of a low-level perceptual filling in of retinal scotomata. In fact, artificial scotomata (produced in normal people by stabilized retinal images) take considerable time to fill in whereas scotomata are filled in immediately in patients with chronic

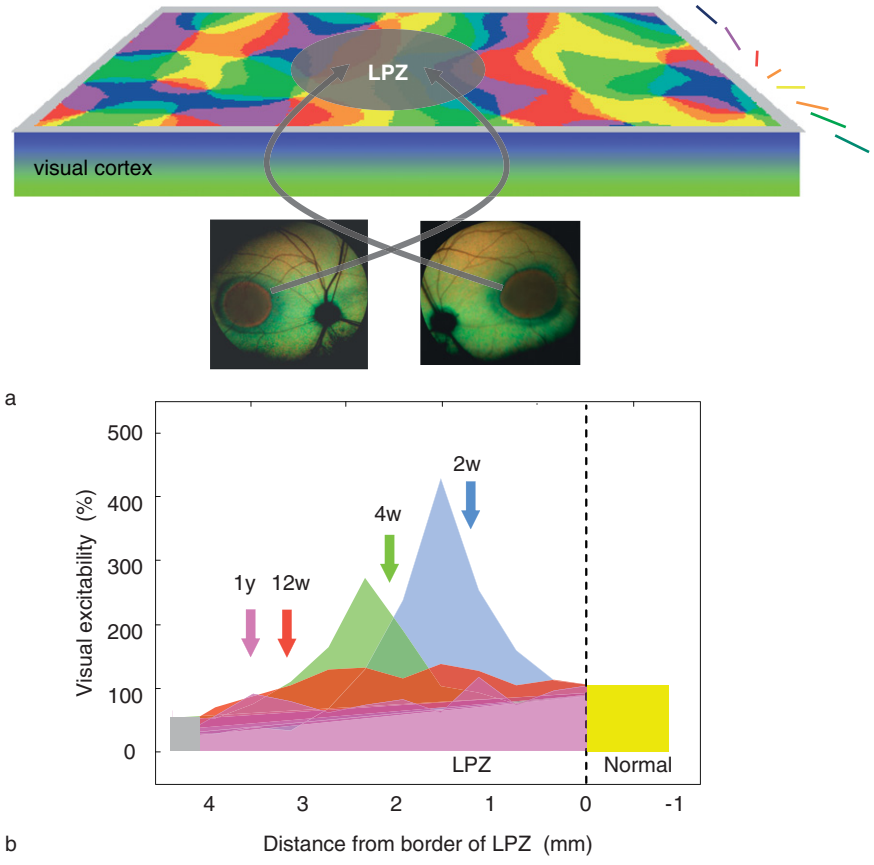

Figure 1 Spatiotemporal pattern of filling-in of the lesion projection zone (LPZ) in the cat visual cortex. (a) Schematic representation of the projection from the left and right eye retinae (with central 10° diameter photocoagulator lesions) to the primary visual cortex. The resulting binocular LPZ is surrounded by normal cortex as shown on top of a topographic map with color-coded orientation preferences. (b) Visual excitability inside the LPZ as a function of distance from the border between LPZ and normal cortex. Normal activity outside the LPZ is shown in yellow; the nonreorganized, and after 1 year visually nonresponsive center of the LPZ is shown in gray. Visual excitability in general moves gradually with time into the LPZ and is associated in the first weeks with a peak of significant hyperexcitability at the front of reorganization. Arrows indicate the first, well defined receptive fields plottable at the different time points. (b) Adapted from Giannikopoulos DV and Eysel UT (2006) Dynamics and specificity of cortical map reorganization after retinal lesions. *Proceedings of the National Academy of Sciences of the United States of America* 103: 10805–10810.

retinal lesions. This observation further supports the proposition that cortical connectivity is profoundly and permanently changed after chronic lesions. This proposition is corroborated by the above-mentioned experimental evidence that shows primary cortical reorganization taking place on the basis of functional changes in synaptic weights of preexisting connections but followed in a final step by anatomical stabilization associated with terminal sprouting, as observed more than 8 months after retinal lesions in the adult cat visual cortex.

It is interesting that when state-of-the-art high-resolution functional magnetic resonance imaging (fMRI) was applied in the visual cortex of adult monkeys, no changes of the visuotopic projection were observed. This seems to indicate that fMRI, a method prone to predominantly detect population responses and presynaptic activity, does not reflect the subtle changes found in suprathreshold performance of individual neurons. On the other hand, the lesion-induced remapping detected on the single-cell level shows close correlation with the psychophysical observations in humans with retinal lesions, indicating the functional relevance of cortical reorganization and filling in.

Mechanisms of Lesion-Induced Cortical Plasticity

Hyperactivity after Cortical and Retinal Lesions

Suppression and facilitation of activity was observed at different distances from the border of heat lesions in the visual cortex. Subnormal activity was seen in a region of <1 mm around the lesion whereas hyperactivity prevails at 1–2.5 mm from its border; at more distant positions (>2.5 mm) the activity was normal. This hyperactivity after heat lesions was already present 1 day after the lesion, became maximal after 3–7 days, and was still visible 30 days postlesion. One possible mechanism for the increase of activity in the surround of lesions is an imbalance between γ-aminobutyricacidergic (GABAergic) inhibition and glutamatergic excitation. This is supported by experimental evidence: in the immediate surround of neocortical lesions, inhibitory transmission is downregulated and a widespread reduction of GABA receptors is observed; then 1–5 days postlesion and up to 2 mm from the border of the lesions, the fast $GABA_A$- and late $GABA_B$-induced inhibitory postsynaptic potentials show reduction in amplitudes and peak currents.

At the same time, the glutamatergic excitation is increased, as substantiated by higher amplitudes and longer durations of *N*-methyl-D-aspartate (NMDA) receptor-mediated excitatory postsynaptic potentials. In addition, excitatory field potentials were significantly larger than normal. These enlarged potentials were NMDA-dependent as shown by blockade with d-amino-phosphonovaleric acid.

It is interesting that also after retinal lesions, a hyperactive zone was found within the LPZ in the visual cortex (**Figure 1(b)**), and an increase in glutamate immunoreactivity was observed at the same time. Hyperactivity and hyperexcitability appear to be a common feature associated with postlesion functional rewiring in the adult visual cortex following deafferentation.

The GABAergic and glutamatergic systems have been investigated with immunhistochemical methods 2 weeks after homonymous lesions in the retina (central 10°) and reveal a characteristic pattern of transmitter system immunoreactivity (IR) inside and in the surround of the deafferented region (LPZ). The glutamic acid decarboxylase (GAD) IR was downregulated inside the LPZ where the number of positive profiles was extremely reduced in the neuropil while the GAD IR in the cell somata remained rather unchanged. IR of the excitatory neurotransmitter glutamate revealed glutamate-positive cells in cortical layers II to VI of area 17. The retinal lesions caused a clear reduction (by 15–26%) in the number of glutamate-immunoreactive cells in the supra- and infragranular layers of the cortical LPZ, compared with normal cortex. Furthermore, close to the border of the LPZ inside the deafferented region, glutamate IR displayed a sharp increase (by 50–100%) throughout layers II to VI of area 17. This glutamate peak was largest in layer VI and had a width of 600–800 μm.

Both the changes in GAD and glutamate IR diminished with time. When the central and the peripheral portions of area 17 were compared in cats with postlesion survival times of more than 12 weeks, no significant differences in the number of glutamate IR-positive cells and in the GAD IR of the neuropil were observed. Obviously the initial imbalance of the excitatory and the inhibitory immunhistochemical reactions returns to normal once the functional reorganization is completed.

Enhanced LTP-Like Effects

Pharmacological studies in brain slices have shown that reduced inhibition and/or increased excitation facilitates the expression of LTP. This situation is mimicked in the visual cortex following lesions in which a decreased strength of inhibition and an increased excitation are observed. Accordingly, electrophysiological

recordings in slices of rats with cortical lesions revealed a significantly elevated level of LTP at synapses from neurons located at a defined distance of 1–4 mm from the border of the lesion and up to 1 week following induction of the injury.

This enhanced synaptic plasticity is accompanied by changes in the intracellular calcium concentration $(Ca^{2+})_i$. Both the neuronal resting calcium concentration and the stimulus-evoked calcium influx are moderately increased at the border of the lesion. The origin of this increase of intracellular calcium was investigated by means of specific neuronal calcium permeation blockers for ionotropic NMDA and AMPA receptors, revealing an increase of Ca^{2+} influx mediated through both of these glutamate receptor types postlesion. While a previously present calcium permeability is just increased in the case of the NMDA receptors, there is a fundamental lesion-induced change in the functional properties of the ionotropic AMPA receptors. AMPA receptors are known to be calcium-impermeable under physiological conditions in rat neurons after postnatal day 15. However, after cortical lesions in animals more than 23 days old, a neuronal calcium influx was measured in the presence of pharmacological blockers of all known sources of intraneuronal calcium influx. This calcium influx was blocked by an antagonist for AMPA. This unusual calcium permeability mediated by AMPA receptors can be explained by a lesion-induced change in the specific composition of the AMPA receptor protein subunits: a reduction in the expression of the glutamate receptor 2 subunit, which is normally observed only in the young postnatal brain, is also observed after lesions in the adult.

A similar reversion to more juvenile patterns is observed for the NMDA receptors. Cortical lesions change the relative expression levels of the messenger RNA for the ionotropic NMDA receptor subunits NR2A and NR2B. Experimental data suggest an increased relative expression of the NR2B subunit of the NMDA receptor at the border of the lesion (due to downregulation of the amount of NR2A subunits). It is interesting that this relatively high amount of NMDA receptors containing the NR2B subunit has also been described in the early postnatal cortex in the phase when enhanced synaptic plasticity (LTP) is observed. Following cortical lesions the true relevance of NR2B subunits for the lesion-induced facilitation of LTP has been clearly shown: blockade of NR2B subunit-containing receptors with ifenprodil reduces the increased LTP in lesioned rat cortex to control values.

Calcium imaging with Fura2-AM (a fluorescent probe) combined with LTP induction can be utilized to record the stimulus-evoked and field potential-correlated calcium influx in the lesion-treated cortex. In fact, significantly increased calcium levels are observed during the induction of LTP by theta burst stimulation as well as 55 min thereafter. This increase of the stimulus-correlated calcium influx postlesion might explain the expression of facilitated LTP as elevated intracellular calcium levels directly correlate with the strength of synaptic LTP.

Growth Factors and Morphological Correlates of RF Plasticity

The neurotrophins brain-derived neurotrophic factor (BDNF), neurotrophin-3, nerve growth factor, and the insulin-like growth factor IGF-1 have been found elevated in the visual cortex as early as 3 days after binocular retinal lesions. The related neurotrophin receptors were elevated as well. Furthermore, increased transcription levels of calcium/calmodulin-dependent kinase II, microtubule-associated protein 2, and synapsins are observed in the area undergoing cortical reorganization. There is increased neuronal activity in regions with elevated BDNF expression. Thus, BDNF appears directly linked to the activity-dependent early unmasking of existing connections on one hand, and as a growth factor, it might also represent a link to the late morphological changes involving axonal sprouting.

See also: Activity in Visual Development; BDNF in Synaptic Plasticity and Memory; Developmental Synaptic Plasticity: LTP, LTD, and Synapse Formation and Elimination; Hebbian Plasticity; Long-Term Potentiation and Long-Term Depression in Experience-Dependent Plasticity; Metaplasticity; Neuronal Plasticity after Cortical Damage; Pain and Plasticity; Perceptual Learning and Sensory Plasticity; Plasticity, and Activity-Dependent Regulation of Gene Expression; Plasticity of Intrinsic Excitability; Somatosensory Plasticity; Spike-Timing Dependent Plasticity (STDP); Synapse Formation: Competition and the Role of Activity; Synaptic Plasticity: Neuronal Sprouting; Synaptic Plasticity: Short-Term Mechanisms; Visual Cortex: Mapping of Functional Architecture Using Optical Imaging.

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