Functional MRI of Reorganization in Rat Brain after Stroke

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INTRODUCTION Stroke regularly causes acute loss of sensorimotor function. Although often incomplete, some degree of functional recovery is common at later stages, which has been associated with brain plasticity. However, a clear causal link between cerebral reorganization and functional recovery has not been demonstrated.

Our goal was to correlate recovery of sensorimotor function with changes in brain activation patterns in relation to the cerebral pathophysiological status, as measured with functional MRI techniques, in a rat stroke model.

METHODS Focal cerebral ischemia was induced by occlusion of the right middle cerebral artery in rats. A specific limb placing test was used to assess sensorimotor function of the forelimb on a scale from 0 to 12, where 12 is maximally impaired.

MRI was done on a 2.0T SISCO/Varian system using a surface coil. Rats were anesthetized and paralyzed with alpha-chloralose (40mg/kg, i.v.) and pancuronium (2mg/kg, i.v.), resp. Diffusion-weighted MRI (TR/TE=2000/40ms; b=150,750,1350s/mm²; diffusion gradients in 3 directions) was performed to calculate maps of the trace of the apparent diffusion coefficient (ADC) of tissue water. Multiple boluses of monocrystalline iron oxide nanocolloid (MION) (an intravascular contrast agent with a relatively long blood half-life) were injected. During acquisition of these functional MR images, electrical stimuli (4V for 0.5ms at 3Hz during 10 and 4 runs of 30s and 60s, resp.) were delivered to the right and left forelimb, with a 1 or 1.5min time-interval. Functional activation maps were generated from the correlation between the calculated relative CBV response and a square-wave function corresponding to the stimulation paradigm for each pixel. Finally, the same technique was applied to measure the CBV response during 3min inhalation of 5% CO₂.

RESULTS Stimulation of the individual forelimbs resulted in a clear activation-induced CBV response in the forelimb area of the contralateral sensorimotor cortex in sham-operated rats. Forelimb placing was normal, and ADC values, hemodynamic parameters and cerebrovascular reactivity were similar in corresponding ipsi- and contralesional areas.

At 3 days after stroke, sensorimotor deficits were severe (forelimb placing score: 9.7±0.6); a unilateral focal ischemic lesion was characterized by profound perfusion loss and reduced tissue water ADC. A notable activation-induced CBV change was absent in the damaged hemisphere when the left, impaired forelimb was stimulated (Fig. 1). The CBF, CBV and water ADC in the sensorimotor cortex in the right, damaged hemisphere were 18±11%, 11±45% and 99±5% of contralateral, resp. The cerebrovascular response to 5% CO₂-inhalation was preserved: relative CBV increased to 11±7% and 10±2% in the left and right sensorimotor cortex, resp. In one animal, significant activation-induced responses were detected in the intact hemisphere, involving almost the entire neocortex.

After 2 weeks, when function of the impaired limb had largely recovered (forelimb placing score: 6.3±0.6), signs of activation were evident in the infarction borderzone, both in and adjacent to the sensorimotor cortex, and in the intact hemisphere (Fig. 1). The CBF and CBV in the sensorimotor cortex were 52±3% and 122±60% of contralateral, resp. The water ADC in the ischemic core was highly elevated. However, the ADC in the perifocal sensorimotor cortex was only 14±21% higher than contralateral. CO₂-inhalation led to a relative CBV increase of 134±4% in the left sensorimotor cortex, and 16±9% in the infarction borderzone.

At both time-points after stroke, stimulation of the right, unimpaired forelimb resulted in the same activation pattern as seen in the sham-operated rats. However, interestingly, in two animals bilateral activation in the thalamus was detected when stimulating the unimpaired forepaw.

DISCUSSION This study demonstrates that changes in activation patterns after stroke can be assessed with CBV-dependent MRI in a rat stroke model. Activation-induced CBV responses require preserved vasoactivity. Absence of the CBV response could theoretically occur when the vasculature is already maximally vasodilated, and/or when vasoactivity is lost. However, CBV was not significantly elevated, and the response to a CO₂-challenge was sustained in the sensorimotor cortex. Although CBF was lowered, there was still residual perfusion, and ADC maps did not show signs of serious tissue degeneration in these regions.

The findings of extension of forelimb representational areas into adjacent cortical areas, and activation responses in the intact hemisphere after unilateral stroke in rat brain, are consistent with the reorganization observed in human brain recovering from ischemic injury. Our data suggest that the degree of dysfunction of the impaired limb is related to loss of brain activation in the contralateral sensorimotor cortex. Restoration of sensorimotor function may be associated with recruitment of peri- and contralossional functional fields in the brain.