Increased connectivity of the contralesional sensorimotor cortex at a chronic stage after stroke as studied by manganese-enhanced MRI in rats

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Introduction

Functional recovery after stroke has been associated with changes in neuronal connectivity. Manganese-enhanced MRI (MEMRI) provides a unique tool for *in vivo* detection of alterations in connections within ipsi- and contralesional networks after experimental stroke[1-3]. However, the pattern of structural modifications in the ipsi- and contralesional hemispheres in relation to restoration of function is still largely unidentified. Neuroanatomical alterations in contralesional cortical regions have been suggested to play a significant role in post-stroke functional recovery[4]. In the present study we applied MEMRI to assess changes in contralesional sensorimotor cortex connections at 10 weeks after unilateral stroke in rats. The hypothesis was that manganese accumulation is enhanced in contra- and ipsilesional sensorimotor areas after injection in the contralesional sensorimotor cortex at this chronic post-stroke time-point as compared to controls.

Methods

Experimental stroke was induced by transient (90 minutes) intraluminal occlusion of the right middle cerebral artery (tMCA-O) in male Wistar rats[5]. Sensorimotor function was measured repeatedly by scoring neurological deficiency[3] and adhesive removal from forelimb[3]. At 10 weeks after tMCA-O, when recovery of sensorimotor function had plateaud, rats (n=5) received an injection (0.2 μL) of $MnCl_2$ (1 M) in PBS in the left, contralesional forelimb region of the primary sensorimotor cortex. Three normal rats served as controls.

Two days prior to tracer injection, T_2- (multiple spin echo; TR/TE = 3000/17.5 ms; echo train length = 8) and T_1-weighted MRI (gradient echo; TR/TE = 60-6000/2.5 ms) (FOV = 32×32 mm^2; data matrix = 128×128; 19 1-mm slices) were performed on a 4.7T horizontal bore Varian Instruments MR system. These experiments were repeated at day 2, 4 and 8 after tracer injection. During MRI rats were mechanically ventilated with 1.8% isoflurane in air/O_2 (2:1). Longitudinal relaxation rate R_1 ($1/T_1$)-maps were coregistered to a T_2-weighted template using SPM2 software. This template was coregistered with a rat brain atlas[6] using in-house developed software. Based on this atlas, six ipsi- and contralateral regions-of-interest (ROIs) were selected within the sensorimotor network, i.e., primary motor cortex (M1), primary somatosensory cortex of the forelimb (S1fl), external globus pallidus (EGP), thalamus (Th), substantia nigra (SN) and internal capsule (IC). An additional ROI was placed in the primary visual cortex (V1) to check for non-specific distribution of manganese. Voxels within ipsilesional ROIs with R_1 values ≤ mean−2SD of contralesional brain tissue before $MnCl_2$ injection, were considered to be part of the lesion and excluded from the ROI analysis. ΔR_1 was calculated from the pre- and post-manganese R_1 maps. Data are expressed as mean ± SEM.

Results

Manganese-induced R_1 increase was found in all six ROIs of the sensorimotor network ipsilateral to the injection site, both in control rats and at 10 weeks after stroke (Fig 1). The ΔR_1 time-course demonstrated that manganese enhancement in subcortical ROIs was increased in the contralesional hemisphere (i.e., ipsilateral to tracer injection site) at all time points as compared to the control group (Fig 2). Small manganese-induced R_1 increases were also detected contralateral to the tracer injection site. The contralateral ΔR_1 changes were larger in ipsilesional cortical ROIs M1 and S1fl at 2 days and 4 days post-injection in stroke animals as compared to controls (Fig 3).

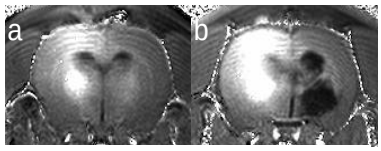

Fig 1. R1-maps of corresponding brain slices of (a) control rat and (b) stroke rat after 10 weeks, at 2 days after $MnCl_2$ injection in left (contralesional) primary sensorimotor cortex.

Discussion

Our MEMRI study demonstrates increased accumulation of the neuronal tract tracer manganese in ipsi- and contralateral sensorimotor areas after injection in the contralesional sensorimotor cortex at a chronic stage after stroke. Increased tracer uptake and distribution may be associated with structural remodelling in the contralesional cortex, e.g., neuronal sprouting and synaptogenesis[4]. Resulting increased connectivity of the contralesional sensorimotor cortex with other sensorimotor network areas may play an important role in post-stroke functional recovery.

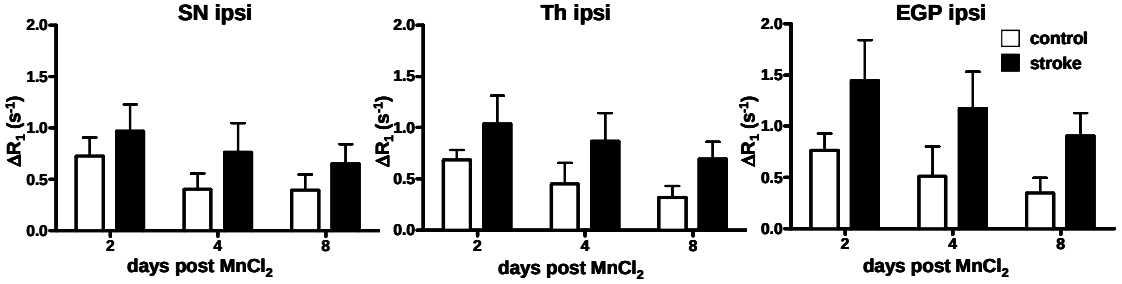

Fig 2. Time-course of manganese-induced ΔR_1 in subcortical ROIs ipsilateral to $MnCl_2$ injection.

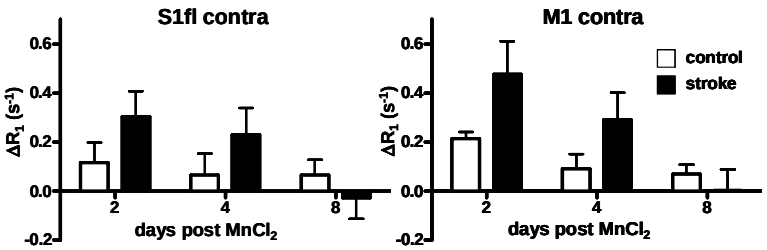

Fig 3. Time-course of manganese-induced ΔR_1 in cortical ROIs contralateral to $MnCl_2$ injection.

References

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