MRI-based measurement of longitudinal contralesional white matter volume changes after unilateral stroke in rat brain

W. M. Otte[1,2], K. van der Marel[2], M. P. van Meer[2], K. P. Braun[1], and R. M. Dijkhuizen[2]
[1]Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Utrecht, Netherlands, [2]Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands

Introduction

The temporal pattern of sensorimotor function after unilateral stroke has recently been shown to correlate with changes in functional connectivity between the ipsi- and contralesional gray matter[1]. However, the role of possible underlying alterations in structural integrity of connecting white matter tracts, particularly in not directly affected areas, remains unresolved. In this study we aimed to measure longitudinal changes in contralesional white matter volume in relation to functional recovery in rats up to ten weeks after unilateral stroke. Therefore we acquired serial multimodal MRI datasets and applied three supervised segmentation algorithms to it, allowing us to accurately characterize white matter volumes in controls and after experimental stroke.

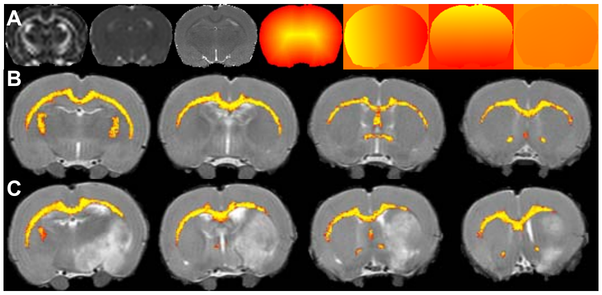

Figure 1. A: from left to right: coronal slice maps of fractional anisotropy, mean diffusivity, T_2, distance-to-brain-border and x-, y-, z-coordinates. B, C: Random forest-based white matter segmentation on multislice T_2-weighted images (B: control; C: subcortical stroke).

Methods

MRI was conducted on a 4.7T Varian MR system at 3, 7, 21, 49 and 70 days after 90-min right middle cerebral artery occlusion in rats[1], and included T_2-weighted MRI (TR = 3600 ms; TE interval = 15 ms; number of echo's = 12; matrix size = 256 × 128; FOV = 32 × 32 mm^2; 19 1-mm slices) and diffusion tensor imaging (four-shot EPI; TR/TE = 3500/26 ms; b = 1250 s/mm^2 with diffusion-weighting in 50 directions; matrix size = 64 × 64; FOV = 32 × 32 mm^2; 25 0.5-mm slices). Sensorimotor performance score (SPS)[1] was measured at the same time points. For rat brain white matter segmentation, we first compared three supervised segmentation methods, based on generalized linear model (glm), support vector machine (svm) and random forest (rf) algorithms[3]. For validation purposes, white matter was manually delineated in twenty MRI datasets (four at each time point) by an independent neuroanatomist. Training data included both intensity (fractional anisotropy (FA), mean diffusivity (MD), T_2) and spatial (distance-to-brain-border, x-, y-, z-coordinates) features (Figure 1A), and were randomly and equally divided in two subsets. The three methods were trained with one subset and validated (using the area under the curve (AUC) of the sensitivity versus specificity ROC curve and similarity index (SI)) on the other subset. Feature ranking was performed by using the prediction error on the out-of-bag dataset portion[3]. Absolute (determined as the sum of all contralateral voxel probabilities × voxel size; $V_{WMAbsolute}$) and relative (determined as $V_{WMAbsolute}$ / hemispheric volume; $V_{WMRelative}$) white matter volumes were determined by restricting the prediction maps to the contralesional hemisphere masks. Group comparisons and correlations were made using a repeated measures linear mixed model (R, *nlme*). Group comparisons included factors 'group', 'day' and 'group × day' with a continuous autocorrelation structure.

Results

SPS was significantly reduced ($p < 0.01$) after stroke, but recovered faster in rats with a subcortical lesion (S_{Medium} (n = 5) than in rats with a subcortical and cortical lesion (S_{Large} (n = 8) ($p < 0.01$) (Figure 2, left panel). The rf method obtained high predictability with an AUC of 0.992 and SI of 0.76 ± 0.02 (mean ± sd), which was significantly higher than the svm and glm methods (p = 0.003, $p < 0.0001$, respectively), and was therefore selected as the classification method for further analyses. The rf method provided accurate white matter segmentations in both stroke and age-matched controls (n = 13), as shown in Figure 1. Feature priority was as follows: FA > distance-to-brain-border > z-coordinate > T_2 > y-coordinate > x-coordinate > MD. White matter volume in the left hemisphere increased progressively in healthy rats (Figure 2, middle and right panel). However, after right-sided stroke the absolute and relative white matter volumes were significantly lowered in the left, contralesional hemisphere over time ($p = 0.02$, $p = 0.04$, respectively). Contralesional white matter recovered over time in S_{Medium}, but remained low in S_{Large}. A significant interaction between 'group' and 'day' was found for $V_{WMRelative}$ ($p = 0.03$).

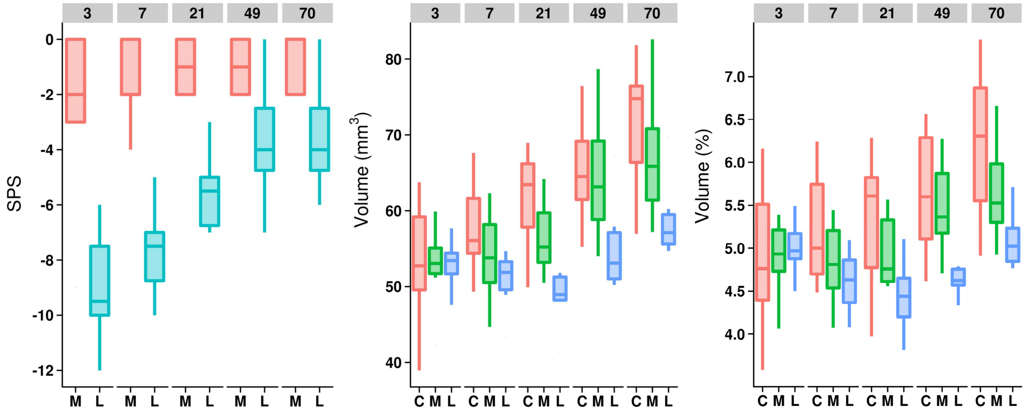

Figure 2. Serial box plots for sensorimotor performance (SPS) (left panel), absolute white matter volume in the left (contralesional) hemisphere ($V_{WMAbsolute}$; middle panel) and relative left (contralesional) white matter volume ($V_{WMRelative}$), in controls (C), S_{Medium} (M) and S_{Large} (L).

Discussion

Our study shows that (a) white matter volume estimation in rat brain is feasible using supervised segmentation based on multiparametric MRI; (b) substantial changes in development of white matter volume occur in the non-affected hemisphere after unilateral stroke. These results indicate that the contralesional white matter is significantly involved in post-stroke brain reorganization and may play an important role in functional recovery.

References

[1] van Meer *J Neurosci* 30 (2010); [2] Pantoni *Stroke* 27 (1996); [3] Breiman *Machine Learning* 45 (2001)