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Changes in resting-state functional connectivity after stroke in a mouse brain lacking extracellular matrix components

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ABSTRACT

In the brain, focal ischemia results in a local region of cell death and disruption of both local and remote functional neuronal networks. Tissue reorganization following stroke can be limited by factors such as extracellular matrix (ECM) molecules that prevent neuronal growth and synaptic plasticity. The brain's ECM plays a crucial role in network formation, development, and regeneration of the central nervous system. Further, the ECM is essential for proper white matter tract development and for the formation of structures called perineuronal nets (PNNs). PNNs mainly surround parvalbumin/GABA inhibitory interneurons, of importance for processing sensory information. Previous studies have shown that downregulating PNNs after stroke reduces the neurite-inhibitory environment, reactivates plasticity, and promotes functional recovery. Resting-state functional connectivity (RS-FC) within and across hemispheres has been shown to correlate with behavioral recovery after stroke. However, the relationship between PNNs and RS-FC has not been examined. Here we studied a quadruple knock-out mouse (Q4) that lacks four ECM components: brevican, neurocan, tenascin-C and tenascin-R. We applied functional connectivity optical intrinsic signal (fcOIS) imaging in Q4 mice and wild-type (129S1 mice) before and 14 days after photothrombotic stroke (PT) to understand how the lack of crucial ECM components affects neuronal networks and functional recovery after stroke. Limb-placement ability was evaluated at 2, 7 and 14 days of recovery through the paw-placement test. Q4 mice exhibited significantly impaired homotopic RS-FC compared to wild-type mice, especially in the sensory and parietal regions. Changes in RS-FC were significantly correlated with the number of interhemispheric callosal crossings in those same regions. PT caused unilateral damage to the sensorimotor cortex and deficits of tactile-proprioceptive placing ability in contralesional fore- and hindlimbs, but the two experimental groups did not present significant differences in infarct size. Two weeks after PT, a general down-scaling of regional RS-FC as well as the number of regional functional connections was visible for all cortical regions and most notable in the somatosensory areas of both Q4 and wild-type mice. Q4 mice exhibited higher intrahemispheric RS-FC in contralesional sensory and motor cortices compared to control mice. We propose that the lack of growth inhibiting ECM components in the Q4 mice potentially worsen behavioral outcome in the early phase after stroke, but subsequently facilitates modulation of contralesional RS-FC which is relevant for recovery of sensory motor function. We conclude that Q4 mice represent a valuable model to study how the elimination of ECM genes compromises neuronal function and plasticity mechanisms after stroke.

1. Introduction

Stroke is a major cause of death and severe disability worldwide and is associated with a limited degree of functional recovery (Benjamin et al., 2017). Rehabilitative training is the current evidence-based strategy to improve outcome in stroke patients, although electromagnetic stimulation of the brain and computer gaming show promising results in clinical studies (Hatem et al., 2016). In experimental models, pharmacological interventions and environmental influences stimulate lost brain function (Pekna et al., 2012; Wieloch and Nikolich,

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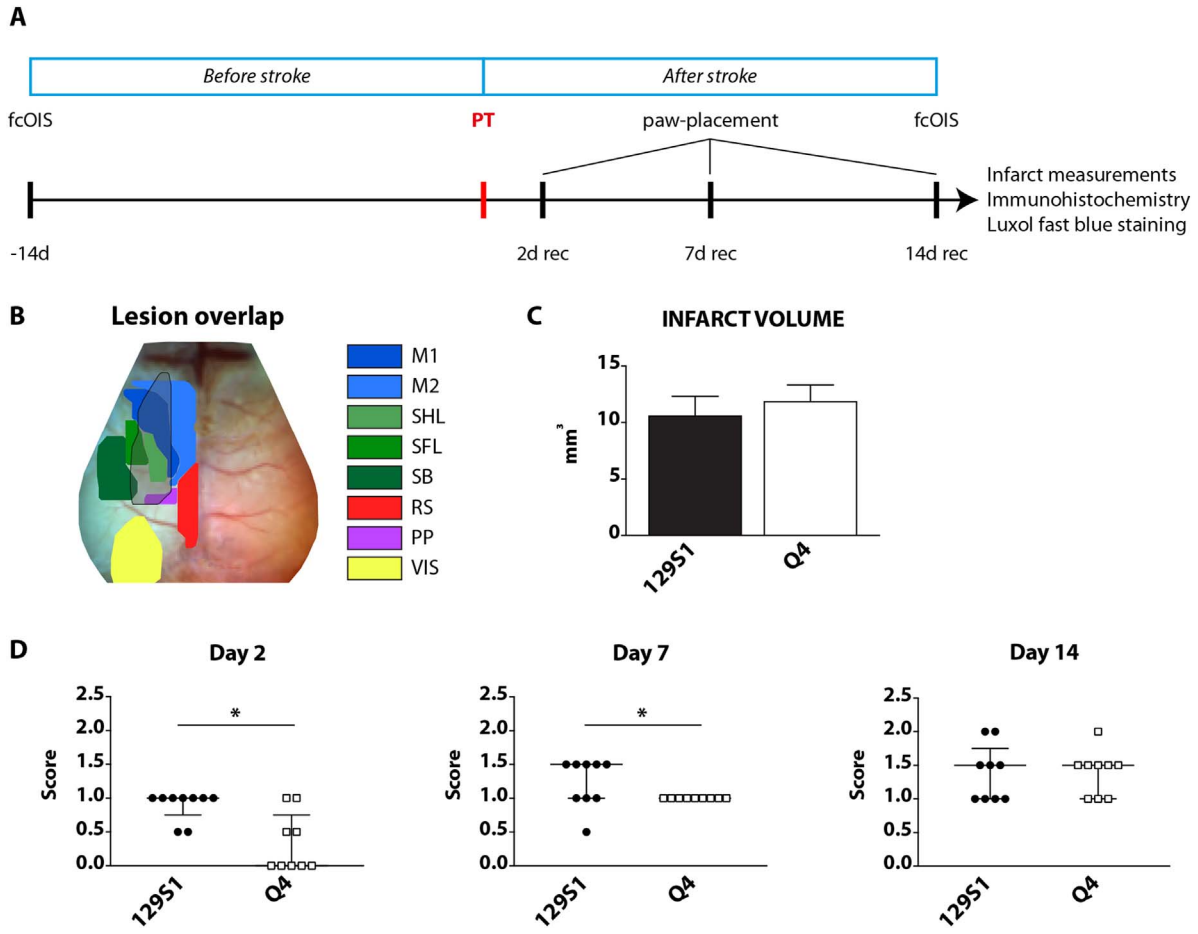

Fig. 1. Experimental design, infarct volume and paw-placement test. (A) Time line of the experiments performed in this study. (B) Lesion overlay (in grey) and anatomical regions according to (Paxinos and Franklin, 2001). Primary motor (M1), secondary motor (M2), somatosensory hindlimb (SHL), somatosensory forelimb (SFL), somatosensory barrel (SB), retrosplenial (RS), posterior parietal (PP), visual (VIS). (C) Infarct volume measurements of NeuN-stained slices 14 days after stroke. Two-tailed unpaired Student's *t*-test, n = 9 for each group, mean ± SEM. No statistical difference was observed when comparing the two experimental groups (129S1 vs Q4 mice, P = 0.57). (D) Combined score for the paretic right forelimb and hindlimb in the paw-placement test at 2, 7 and 14 days of recovery. Scores are shown as individual data points with group median and interquartile range. Mann-Whitney *U* test, n = 9 for each group (day 2 and day 7: *P < 0.05).

2006). Following stroke, undamaged neurons can undergo plastic responses and neuroanatomical reorganization to replace damaged structural and functional connections. However, the extent of reorganization remains limited by factors that hamper neuronal growth such as extracellular matrix (ECM) molecules (Overman and Carmichael, 2014).

The ECM is known to regulate important processes in brain development, neuronal growth and network formation. It is associated with the structural stabilization of neuronal processes and synaptic contacts during the maturation of the central nervous system (CNS). Remodeling of the ECM both during development and after CNS injury affects synaptic plasticity, neuronal guidance and their regenerative responses (Kwok et al., 2011). Extracellular matrix molecules are also important for callosal development and guidance cues, especially at the level of the midline (Donahoo and Richards, 2009).

The ECM includes chondroitin sulfate proteoglycans (CSPGs) of the lectican family (aggrecan, brevican, neurocan, versican), as well as tenascins. CSPGs and tenascins are components of a specialized form of ECM called perineuronal nets (PNNs) (Celio et al., 1998) which mainly enwrap the neuronal cell body and proximal dendrites of parvalbumin/GABAergic (PV/GABA) inhibitory neurons (Härtig et al., 1994). Recent studies have implicated CSPGs and PNNs in regulating and restricting structural plasticity. Disruption of PNNs by removal of inhibitory CSPGs, neutralization with antibodies or manipulation of PNNs components may allow experience-dependent plasticity (Pizzorusso et al., 2002; Soleman et al., 2012). Recent studies from our group showed degradation and reduction in the number of aggrecan$^+$ PNNs after experimental stroke and concomitant training through an enriched environment (EE). These results were accompanied by better outcome in several behavioral tests in rats (Madinier et al., 2014; Quattromani et al., 2017).

Recovery of brain function lost after stroke is not only a mere consequence of a local structural damage but is also due to an alteration of the physiological state of neural networks connected to the lesion (Corbetta, 2010). This concept also extends to experimental models; implementing comparable functional neuroimaging tools in both rodents and humans is a promising strategy for providing clinical translation. Functional connectivity optical intrinsic signal (fcOIS) has been recently shown to be an optimal tool to address this need (Bauer et al., 2014; White et al., 2011; Hakon et al., 2017). The aim of this study was to further elucidate possible mechanisms of PNN function/disruption after stroke on the molecular and network level. In order to test if the PNNs disruption was responsible for the better functional recovery seen after EE in our previous study (Madinier et al., 2014), we took advantage of a quadruple knock-out mutant mouse model (Q4) which lacks the ECM components brevican, neurocan, tenascin-C and tenascin-R. Q4 mice and relative controls were subjected to photothrombotic stroke (PT) and their neurological deficits assessed at different times during recovery. FcOIS was performed before and 14 days after PT to understand how the lack of specific ECM components affect

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