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Multisensory stimulation improves functional recovery and resting-state functional connectivity in the mouse brain after stroke

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ABSTRACT

Stroke causes direct structural damage to local brain networks and indirect functional damage to distant brain regions. Neuroplasticity after stroke involves molecular changes within perilesional tissue that can be influenced by regions functionally connected to the site of injury. Spontaneous functional recovery can be enhanced by rehabilitative strategies, which provides experience-driven cell signaling in the brain that enhances plasticity. Functional neuroimaging in humans and rodents has shown that spontaneous recovery of sensorimotor function after stroke is associated with changes in resting-state functional connectivity (RS-FC) within and across brain networks. At the molecular level, GABAergic inhibitory interneurons can modulate brain plasticity in peri-infarct and remote brain regions. Among this cell-type, a decrease in parvalbumin (PV)-immunoreactivity has been associated with improved behavioral outcome. Subjecting rodents to multisensory stimulation through exposure to an enriched environment (EE) enhances brain plasticity and recovery of function after stroke. Yet, how multisensory stimulation relates to RS-FC has not been determined. In this study, we investigated the effect of EE on recovery of RS-FC and behavior in mice after stroke, and if EE-related changes in RS-FC were associated with levels of PV-expressing neurons. Photothrombotic stroke was induced in the sensorimotor cortex. Beginning 2 days after stroke, mice were housed in either standard environment (STD) or EE for 12 days. Housing in EE significantly improved lost tactile-proprioceptive function compared to mice housed in STD environment. RS-FC in the mouse was measured by optical intrinsic signal imaging 14 days after stroke or sham surgery. Stroke induced a marked reduction in RS-FC within several perilesional and remote brain regions. EE partially restored interhemispheric homotopic RS-FC between spared motor regions, particularly posterior secondary motor. Compared to mice housed in STD cages, EE exposure lead to increased RS-FC between posterior secondary motor regions and contralesional posterior parietal and retrosplenial regions. The increased regional RS-FC observed in EE mice after stroke was significantly correlated with decreased PV-immunoreactivity in the contralesional posterior motor region. In conclusion, experimental stroke and subsequent housing in EE induces dynamic changes in RS-FC in the mouse brain. Multisensory stimulation associated with EE enhances RS-FC among distinct brain regions relevant for recovery of sensorimotor function and controlled movements that may involve PV/GABA interneurons. Our results indicate that targeting neural circuitry involving spared motor regions across hemispheres by neuromodulation and multimodal sensory stimulation could improve rehabilitation after stroke.

Abbreviations: RS-FC, resting-state functional connectivity; fcOIS, functional connectivity optical intrinsic signal imaging; GSR, global signal regression; MSR, multiple signal regression; ROI, region of interest; NDi, intrahemispheric node degree; NDc, interhemispheric (contralateral) node degree; STD, standard environment; EE, enriched environment; PV, parvalbumin; M1, primary motor cortex; M2, secondary motor cortex; M2p, posterior secondary motor cortex; SFL, somatosensory forelimb cortex; PP, posterior parietal cortex; RS, retrosplenial cortex; VIS, visual cortex

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1. Introduction

Stroke is a leading cause of death and long term adult disability (Mozaffarian et al., 2016). Following stroke, direct tissue damage and disconnection of remote brain areas causes functional disruption that can span multiple domains (Carter et al., 2010; He et al., 2007; Silasi and Murphy, 2014). Neuroplasticity after stroke involves molecular changes within perilesional and tissue remote from the lesion that can be influenced by distant regions spared from injury (Cramer, 2008). Understanding and influencing the processes of functional neuroplasticity are therefore crucial in providing more effective therapies.

Recovery of sensorimotor function can be enhanced by rehabilitative training of the affected modality (Carey et al., 2011; Wolf et al., 2010). Other complex multimodal training paradigms have also shown efficacy in accelerating rehabilitation outcomes (Bunketorp-Käll et al., 2017). Non-invasive brain stimulation strategies, such as transcranial magnetic stimulation and direct current stimulation, provide support for rehabilitation interventions (Hatem et al., 2016), and mimic aspects of peripheral stimulation that might trigger endogenous plasticity mechanisms of the brain (Carmichael, 2012; Wieloch and Nikolich, 2006). In animal models of stroke, multisensory stimulation can be applied through enriched environments (EE), i.e. cages of 5–10 animals containing multilevel platforms, tubes, chains and toys (Johansson and Ohlsson, 1996). The complex task- and experience-driven stimulation of brain plasticity following exposure to EE affects spine density and size, release of growth factors, and changes in cell signaling in the brain considered to improve sensory, motor, and cognitive function (Nithianantharajah and Hannan, 2006).

At the systems level, functional magnetic resonance imaging (fMRI) has revealed that behavioral recovery is associated with changes in patterns of resting-state functional connectivity (RS-FC) within and across resting-state networks (Carey et al., 2013). FMRI studies in humans shortly after ischemic stroke demonstrated that disruption of interhemispheric homotopic RS-FC predicted poor motor, somatosensory, and attentional recovery (Bannister et al., 2015; Carter et al., 2010). In a mouse model of stroke, functional connectivity optical intrinsic signal imaging (fcOIS) revealed that disruption of homotopic RS-FC correlates with infarct size and acute behavioral deficits (Bauer et al., 2014). A similar fMRI study in rats after stroke revealed that restoration of homotopic RS-FC correlated with spontaneous improvement in chronic sensorimotor function (van Meer et al., 2010).

At the molecular level, multiple mechanisms contribute dynamically to the post stroke recovery process over multiple spatiotemporal scales (Wieloch and Nikolich, 2006). For example, GABAergic inhibitory interneurons modulate brain plasticity in the perilesional and remote brain regions by affecting the balance between excitation and inhibition in the recovery phase after stroke (Clarkson et al., 2010; Witte, 2000). Among the population of GABAergic interneurons, parvalbumin (PV)-immunoreactive cells are of particular importance. These cells are considered gate keepers of excitability of the cortical microcolumns and regulators of cortical gamma oscillations important for cognition and brain plasticity (Freund, 2003; Hensch, 2004). Enriched housing decrease hippocampal PV immunoreactivity in PV/GABA cells, indicating that these cells adopted an early developmental phenotype seen during critical periods of brain development (Donato et al., 2013). After experimental stroke, PV levels are modulated (Alia et al., 2016; Inácio et al., 2011) and a decrease in the levels of PV-immunoreactivity has been associated with improved functional recovery (Zeiler et al., 2013). A large fraction of cortical PV inhibitory neurons have been recently demonstrated to exhibit long-range transcallosal projections interconnecting homotopic cortical regions, supporting a direct role of PV^+ cells on interhemispheric inhibition (Rock et al., 2017), which might also influence recovery after stroke.

Despite the number of studies describing the therapeutic effects of EE on behavioral recovery, information concerning how EE influences systems- and molecular-level changes in the brain remains lacking. We hypothesized that multisensory stimulation of the brain by EE housing after stroke leads to improved functional recovery and RS-FC after stroke. To test this hypothesis, we employed fcOIS to study changes within various functional cortical networks in mice after photothrombotic stroke involving the left sensorimotor cortex. Two days after stroke, mice were moved to EE housing or standard (STD) cages. FcOIS was performed 14 days after stroke or sham surgery, and behavioral outcome was evaluated at 2 and 14 days of recovery. Brains were harvested on day 14 after the final imaging session. To evaluate molecular changes in remodeled cortex, populations of PV-immunoreactive neurons were examined using confocal microscopy.

2. Materials and methods

2.1. Ethical statement

All animal procedures were approved by the Malmö-Lund ethical committee (permit number: M 50-15) and reported according to the ARRIVE guidelines. The mice were housed in STD laboratory cages (2 mice per cage) before stroke or sham surgery, and in STD or EE after stroke (see "Housing conditions" section below for details). The mice were kept in a reverse light-cycle with free access to food and water. Image acquisition and behavioral analysis were performed during the awake periods.

2.2. Surgical procedures

2.2.1. Mounting of glass window

Fifty-two C57bl mice aged 8–10 weeks were included in the study. One week prior to stroke mice were anesthetized with 2% isoflurane and mounted in a stereotactic frame. A midline skin incision was made to expose the skull. A round coverslip glass plate 13 mm in diameter and 0.15 mm in thickness was glued on top of the exposed skull with Super-Bond (L-type Clear, Sun Medical), and the skin was glued at the edges of the glass window to close the incision.

2.2.2. Induction of photothrombosis

For induction of photothrombotic stroke, mice were anesthetized using isoflurane (2% in O_2) and positioned in a stereotaxic frame. Body temperature was maintained with a heating pad set to a target temperature of 37 °C. A bolus of Rose Bengal (0.1 mg/kg, Sigma) was injected in the peritoneal cavity. Ten minutes after the injection, a $4 \times 2\ mm^2$ rectangular area (localized 2.5 to − 1.5 mm from bregma, beginning 0.8 mm to the left of the midline) was illuminated for 20 min with 3100 K light (Schott, KL 1500). Sham surgeries were performed similarly without illumination following injection of Rose Bengal. All mice recovered on a heating pad after the stroke and sham procedures.

2.3. Housing conditions

Two days after stroke and sham surgeries, all mice were sorted in pairs into either STD or EE cages where they were housed for 12 days. A researcher who was not involved in the stroke procedure or behavior assessments performed the sorting. Fifteen mice with stroke and 11 sham mice were housed in STD cages; 15 mice with stroke and 11 mice with sham surgery were housed in EE cages as described previously (Nygren and Wieloch, 2005; Quattromani et al., 2014). Each EE cage measured 40 cm × 40 cm × 35 cm, and contained 5–6 mice. Sham and stroke mice were housed together in EE cages. The EE cages were equipped with tubes, chains, ladders, toys and platforms at different levels. Objects were rearranged twice a week.

2.4. The paw-placement test

At 2 and 14 days of recovery, sensorimotor function of each paw was evaluated by the paw-placement test (De Ryck et al., 1992;