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Title:

Differential outcomes of rTMS and anesthesia effects on functional connectivity in the rat brain

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Abstract: (Your abstract must use **Normal style** and must fit in this box. Your abstract should be no longer than 300 words. The box will 'expand' over 2 pages as you add text/diagrams into it.)

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique routinely used in humans in their awake state. In contrast, rTMS experiments in rodents are often executed under anesthesia to allow for reproducible and focal stimulation. Effects of rTMS on neural networks are, however, reliant on underlying brain activity at the time of stimulation, and may therefore be significantly affected by the anesthetic state. Using low-frequency rTMS, this study tested whether resting-state functional connectivity in stimulated cortical tissue is diversely affected by different anesthetics.

Naïve, male Sprague Dawley rats were divided into three experimental groups. All animals received 20 minutes rTMS (1Hz) for four consecutive days, while anesthetized with either isoflurane (n=5), dexmedetomidine (n=6) or propofol (n=6). Stimulation was applied over the right sensorimotor cortex, using a 25mm figure-of-eight coil (Neurosoft Ltd.). Preceding and following rTMS, functional MRI was performed while animals were anesthetized with separate anesthetics. Spatiotemporal correlations between low-frequency BOLD fluctuations representing functional connectivity, were calculated between primary and secondary motor cortices, primary and secondary somatosensory cortices, thalamus, and caudate putamen. Changes in inter- and intrahemispheric functional connectivity were evaluated with a mixed-design ANOVA (RStudio Inc.v.0.99.903).

There was a significant effect of anesthesia on functional connectivity between different inter- and intrahemispheric regions, with generally higher values in isoflurane-anesthetized animals as compared to dexmedetomidine and propofol anesthesia. In addition, there was a tendency of lower functional connectivity, particularly between sensorimotor cortex and thalamus (Fig.1).

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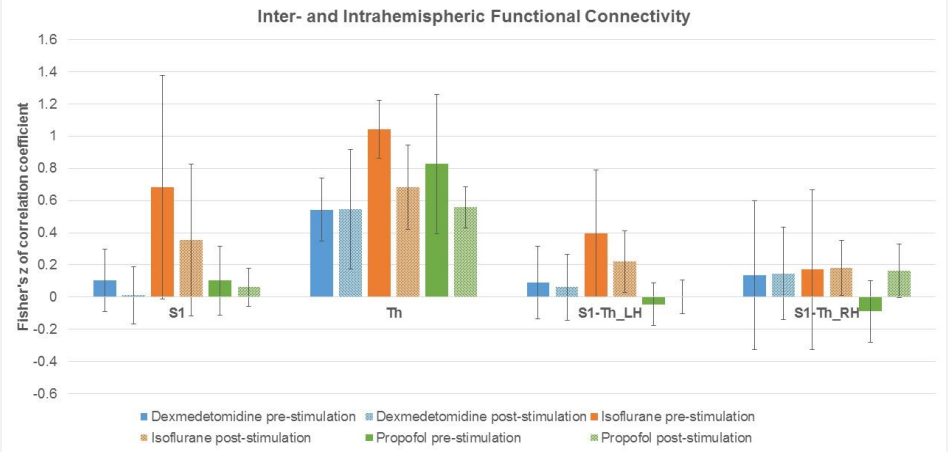

Figure 1: Interhemispheric (S1, Th) and intrahemispheric (S1-Th) functional connectivity (z') between homotopic regions of interest pre- and post-rTMS. The bars represent mean functional connectivity values +/- standard deviation. S1, primary somatosensory cortex; Th, thalamus; LH, left hemisphere; RH, right hemisphere.

Low-frequency rTMS has the ability to reduce cortical excitability, an effect that shares similarities with long-term depression. Consequently, this may lead to significant changes in functional connectivity within the stimulated network. Although we observed tendencies for lowered functional connectivity after low-frequency rTMS, this varied considerably between different anesthetics. Our results emphasize the importance of considering the effect of anesthesia on the outcome of experimental rTMS.