sTMS Blocks Cortical Spreading Depression by Suppressing Cortical Neuronal Firing and by Increasing the Threshold of Activation of the Occipital Cortex

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Introduction

- Single pulse transcranial magnetic stimulation (sTMS) is a non-invasive, neuromodulation treatment for migraine with minimal side effects
- sTMS induces an electrical charge in the underlying cortex by electromagnetic induction
- Excitation of the visual cortex is found to be involved both at the pre-ictal and ictal phase
- sTMS was previously shown to affect trigeminothalamic activity through corticothalamic inhibition. However, the actual effects of sTMS within the cortex have not been studied

Methods

Animals: All procedures were performed in accordance to a UK Home Office approved project licence. Experiments were performed in anaesthetised Male Sprague-Dawley rats (250 – 350g).

sTMS: A bespoke coil of 11 mm diameter was used to deliver sTMS pulses with rise time of 170 µs and intensity ranging from 100-600µV (0.1-1.1 T) (figure 1)

A. Investigations of sTMS effects on Spontaneous Neuronal Activity

- A tungsten recording electrode was utilised to record spontaneous neuronal activity within the visual cortex (figure 2a)
- Upon establishment of baseline recordings, two sTMS pulses (100-600µV, 0.1-1.1T) were applied at the ipsilateral visual cortex
- Spontaneous neuronal activity was recorded for up to 90 min post-sTMS application

B. sTMS effects on Glutamate Induced Neuronal Activity Experiment

- Neurons responding to microiontophoresis of L-glutamate (40-90 nA) were recorded from the visual cortex, using a combined recording/microiontophoretic electrode
- Upon establishment of baseline L-glutamate epochs, two sTMS pulses of 600 µV (1.1 T) were applied to the ipsilateral visual cortex (figure 2b)
- L-glutamate induced neuronal activity was recorded for 30 min post-sTMS application

C. sTMS effects on Electrically Induced CSD Experiment

- A concentric stimulating electrode was utilised to induce a CSD in the visual cortex. Stimulating current and pulse width were gradually increased until a CSD was induced (CSD induction threshold)
- An Ag/AgCl electrode into parietal cortex was utilised to record the DC-shift activity of a travelling CSD (figure 2c)
- Two 600 µV (1.1 T) sTMS pulses were applied to the ipsilateral visual cortex, and induction of CSD was repeated every 30 min for 120 min, with the stimulating parameters increased until a CSD was induced
- In an independent animal group CSD induction threshold was assessed following pre-treatment with two pulses of sTMS at 600 µV (1.1 T)

Figure 1: Custom made 11mm rodent sTMS coil

A. sTMS effect on spontaneous neuronal activity of the visual cortex

- A tungsten recording electrode was utilised to record spontaneous neuronal activity within the visual cortex (figure 2a)
- Upon establishment of baseline recordings, two sTMS pulses (100-600µV, 0.1-1.1T) were applied at the ipsilateral visual cortex
- Spontaneous neuronal activity was recorded for up to 90 min post-sTMS application

B. Glutamate Induced Neuronal Activity Experiment

- Neurons responding to microiontophoresis of L-glutamate (40-90 nA) were recorded from the visual cortex, using a combined recording/microiontophoretic electrode
- Upon establishment of baseline L-glutamate epochs, two sTMS pulses of 600 µV (1.1 T) were applied to the ipsilateral visual cortex (figure 2b)
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C. Electrically Induced CSD Experiment

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- In an independent animal group CSD induction threshold was assessed following pre-treatment with two pulses of sTMS at 600 µV (1.1 T)

Figure 2: Experimental setup

A. sTMS effect on spontaneous neuronal activity of the visual cortex

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- Upon establishment of baseline recordings, two sTMS pulses (100-600µV, 0.1-1.1T) were applied at the ipsilateral visual cortex
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B. Glutamate Induced Neuronal Activity Experiment

- Neurons responding to microiontophoresis of L-glutamate (40-90 nA) were recorded from the visual cortex, using a combined recording/microiontophoretic electrode
- Upon establishment of baseline L-glutamate epochs, two sTMS pulses of 600 µV (1.1 T) were applied to the ipsilateral visual cortex (figure 2b)
- L-glutamate induced neuronal activity was recorded for 30 min post-sTMS application

C. Electrically Induced CSD Experiment

- A concentric stimulating electrode was utilised to induce a CSD in the visual cortex. Stimulating current and pulse width were gradually increased until a CSD was induced (CSD induction threshold)
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- In an independent animal group CSD induction threshold was assessed following pre-treatment with two pulses of sTMS at 600 µV (1.1 T)

Figure 3: sTMS reduces spontaneous neuronal activity of the visual cortex

- A. sTMS reduces spontaneous neuronal activity of the visual cortex
- B. sTMS reduces glutamate induced neuronal activity
- C. sTMS blocks electrically induced CSD

Figure 4: sTMS reduces glutamate induced neuronal activity

- A. Example of peri-stimulus histogram demonstrating reduction in cortical spontaneous neuronal activity post-sTMS. B. Spontaneous neuronal activity was significantly reduced following 2x 500 and 600 µV (~0.9 T) sTMS pulses (P < 0.05). There was no reduction in spontaneous neuronal activity following 2x 100-400 µV (~0.7 T) sTMS pulses. *, P < 0.05

Figure 5: sTMS blocks electrically induced CSD

- A. sTMS reduces spontaneous neuronal activity of the visual cortex
- B. sTMS reduces glutamate induced neuronal activity
- C. sTMS blocks electrically induced CSD

Conclusions

Our data show that sTMS, when applied at intensities below the motor activation threshold suppresses spontaneous and glutamate-induced neuronal activity at the visual cortex and increases the electrical threshold required for a CSD induction. Collectively, these findings suggest that sTMS reduces cortical excitability by increasing the threshold of activation of cortical neurons.

Acknowledgements

References