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

JO Lloyd[1], BN Okine[1], MG Jones[2,3], A AL-Kaisy[4], G Lambru[1,5], SB McMahon[2], AP Andreou[1,5]

1. Headache Research-Wolfson CARD, King's College London (KCL), London, UK, 2. Neurorestoration Department, Wolfson CARD, KCL, London, UK, 3. Zenith Neuroteck Ltd, London, UK, 4. Pain Management and Neuromodulation Centre, Guy's and St Thomas's NHS Trust, King's Health Partners, London, UK, 5. Headache Centre, Guy's and St Thomas's NHS Trust & Wolfson CARD, KCL, King's Health Partners, London, UK

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

Objectives

This study aims to investigate the cortical actions of sTMS in a migraine model

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 um and intensity ranging from 100-600V (0.1-1.1 T) (figure 1)

Figure 1: *Custom made 11mm rodent sTMS coil*

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 (100-600V; 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-glutame epocks, two sTMS pulses of 600 V (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 V (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 600V (1.1 T)

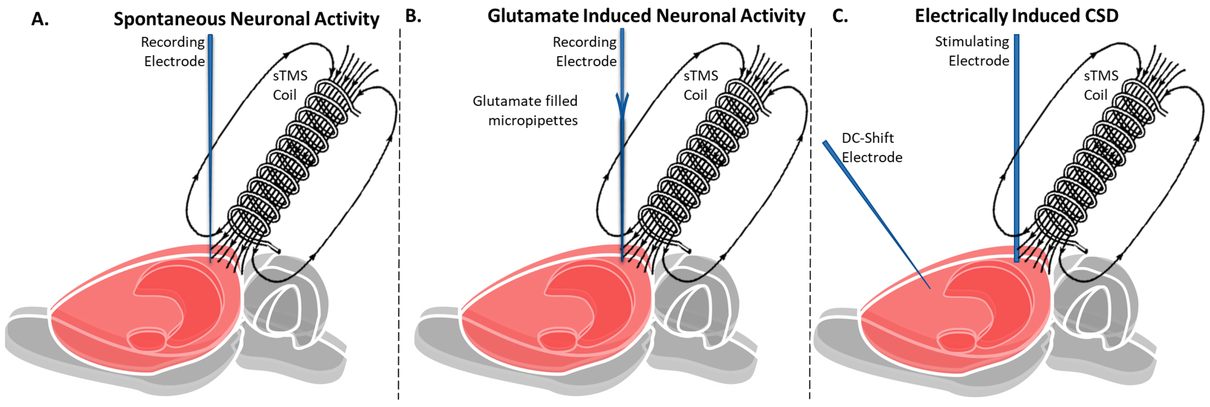

Figure 2: Experimental setup; *A.* *sTMS effect on spontaneous neuronal activity of the visual cortex experiment* ***B.*** *sTMS effect on glutamate induced neuronal activity of the visual cortex* ***C.*** *sTMS effect on electrically induced CSD*

Results

A. sTMS reduces spontaneous neuronal activity of the visual cortex

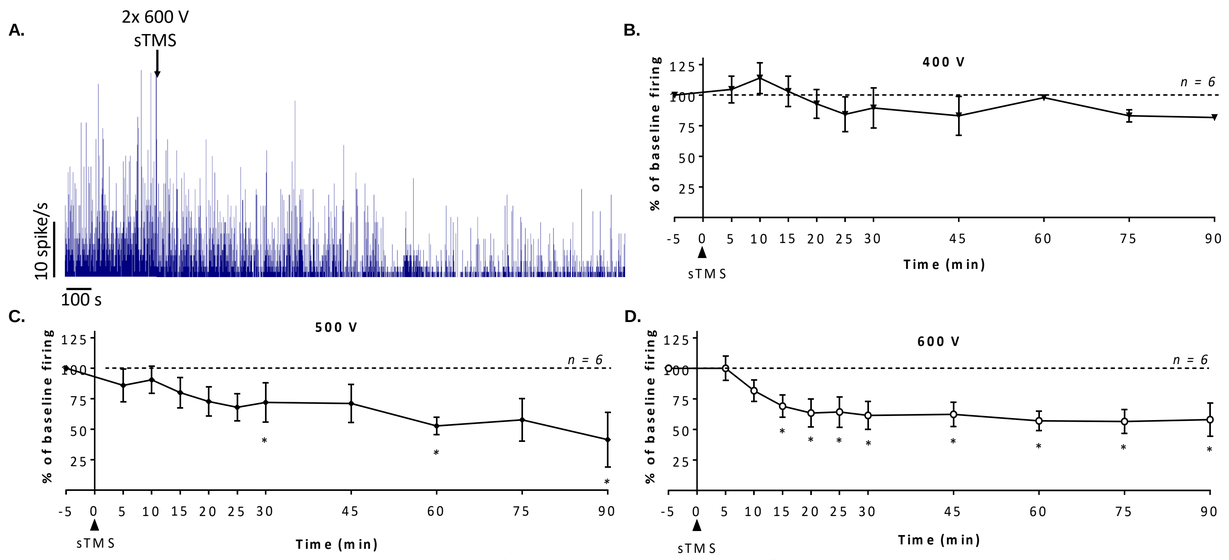

Figure 3: sTMS reduces spontaneous neuronal activity — *A.* *Example of peri-stimulus histogram demonstrating reduction in cortical spontaneous neuronal activity post-sTMS.* ***B. S****pontaneous neuronal activity was significantly reduced following 2x 500 and 600 V (~0.9 T-1.1 T; P < 0.05). There was no reduction in spontaneous neuronal activity following 2x 100-400 V (~0.1-0.7 T) sTMS pulses. *, P < 0.05*

B. sTMS reduces glutamate induced neuronal activity

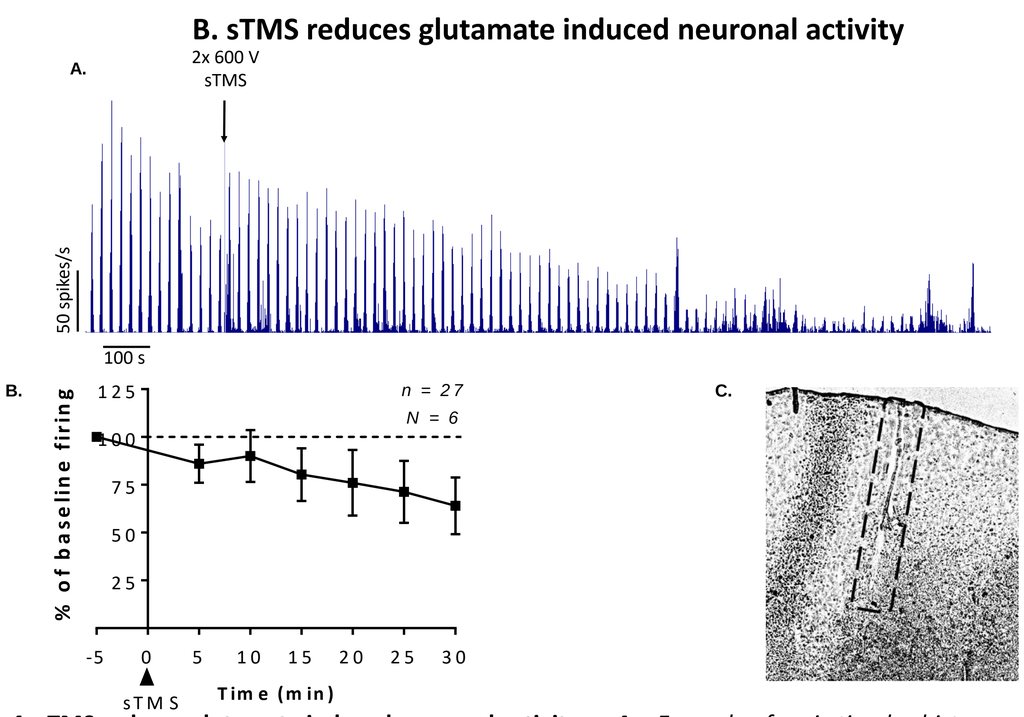

Figure 4: sTMS reduces glutamate induced neuronal activity — *A.* . *Example of peri-stimulus histogram demonstrating reduction in glutamate induced neuronal activity,* ***B.*** *Glutamate induced neuronal activity was significantly reduced following 2x 600 V (1.1 T) sTMS pulses (P < 0.0001).* ***C.*** *Example of a recording site in the occipital cortex, demonstrating the electrode trace. *, P < 0.05*

C. sTMS blocks electrically induced CSD

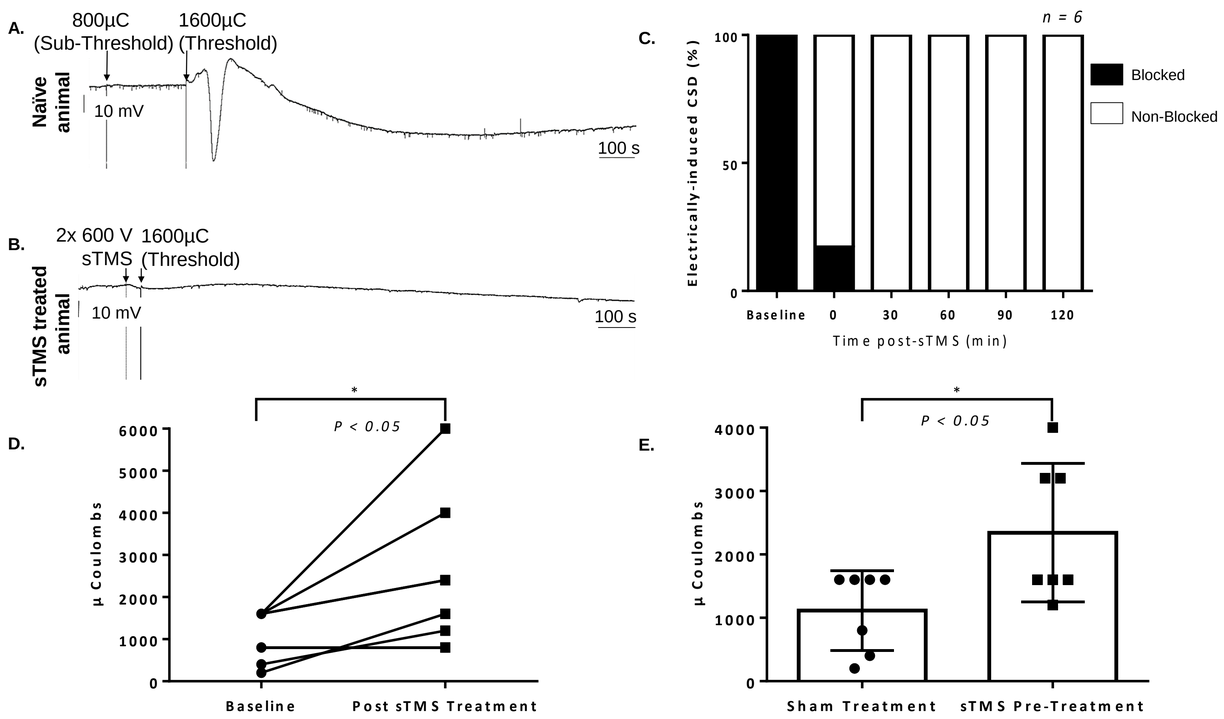

Figure 5: sTMS blocks electrically induced CSD — *A.* *A trace demonstrating a DC-shift in response to an induction of CSD following electrical stimulation of the occipital cortex with 1600 µC (CSD induction threshold), but not with 800 µC.* ***B.*** *DC trace from the same animal, demonstrating the lack of a CSD with 1600 µC (CSD induction threshold) following 2 sTMS pulses (600 V).* ***C.*** *sTMS treatment significantly blocked induction of a CSD using the stimulating parameters identified as the CSD induction threshold (P < 0.0001)* ***D.*** *sTMS treatment significantly increased the CSD induction threshold (P < 0.05).* ***E.*** *CSD induction threshold is significantly higher in animals pre-treated with two pulses of sTMS (600 V), compared to sham treated animals.*

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.

References

1. Lipton *et al. Lancet Neurol,2010; 9*(4): 373-380. **2.** Schulte & May. *Brain,* 2016; 139: 1987–1993. **3.** Mainera et al., *Ann Neurol,* 2011; 70(5): 838–845. **4.** Andreou et al, *Brain*, 2016; 139(7): 2002–2014

Acknowledgements

the migraine trust