Chronic high frequency deep brain stimulation of the nucleus accumbens drives time dependent changes in functional connectivity in the rodent limbic system

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INTRODUCTION

Deep brain stimulation (DBS) of the nucleus accumbens is an effective treatment for patients with treatment refactory obsessive-compulsive disorder (OCD) [1]. Stimulation of this region has also demonstrated benefit in patients with treatment resistant depression [2,3] and has been proposed for the treatment of the positive symptoms associated with schizophrenia [4]. Despite its increasing application in the clinic, the mechanism by which DBS of the nucleus accumbens effects its therapeutic benefit remains poorly understood. Using combined stimulation and recording techniques, we examined how chronic (5 days) DBS affected rhythmic brain activity in freely moving rats.

DBS of AcbC yields time dependent increases in local gamma activity

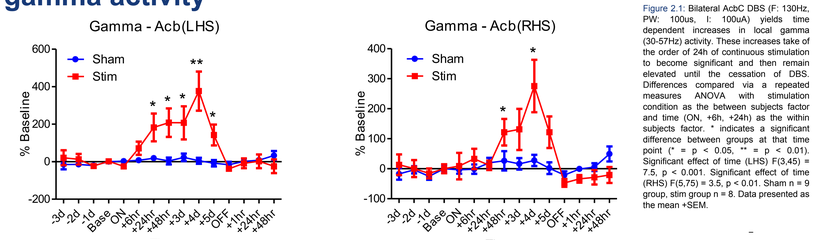

Figure 2.1: Bilateral AcbC DBS (F: 130Hz, PW: 100us, I: 100uA) yields time dependent increases in local gamma (30-57Hz) activity. These increases take of the order of 24h of continuous stimulation to become significant and then remain elevated until the cessation of DBS. Differences compared via a repeated measures ANOVA with stimulation condition as the between subjects factor and time (ON, +6h, +24h) as the within subjects factor. * indicates a significant difference between groups at that time point (* = p < 0.05, ** = p < 0.01). Significant effect of time (LHS) F(3,45) = 7.5, p < 0.001. Significant effect of time (RHS) F(5,75) = 3.5, p < 0.01. Sham n = 9 group, stim group n = 8. Data presented as the mean +SEM.

MATERIALS & METHODS

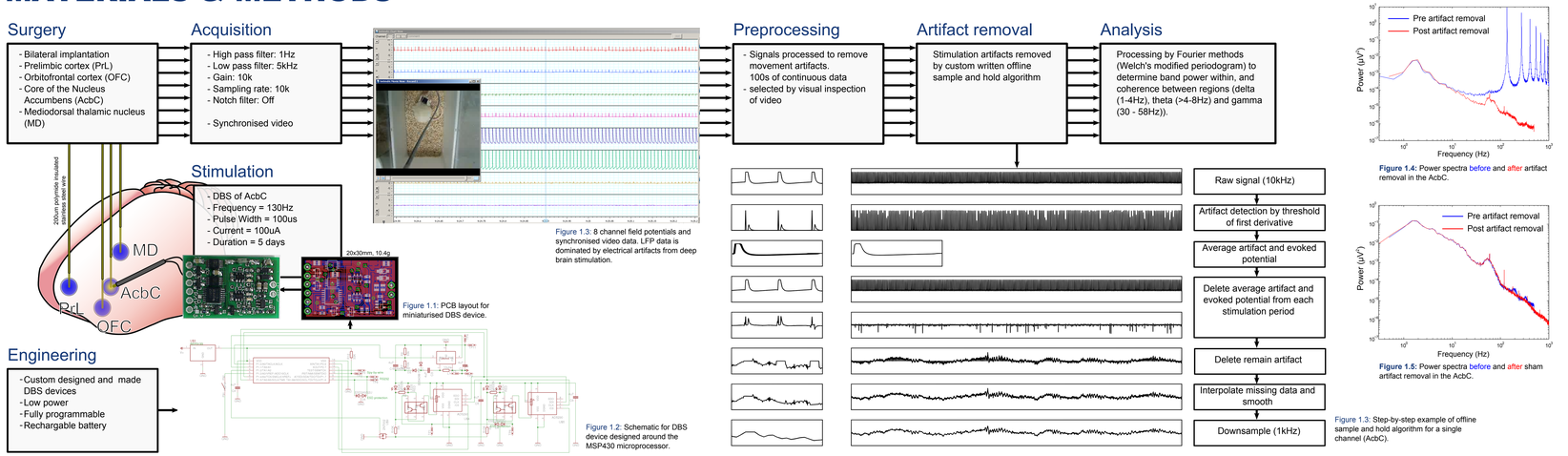

Figure 1.1: PCB layout for miniaturised DBS device.

Figure 1.2: Schematic for DBS device designed around the MSP430 microprocessor.

Figure 1.3: 8 channel field potentials and synchronised video data. LFP data is dominated by electrical artifacts from deep brain stimulation.

Figure 1.3: Step-by-step example of offline sample and hold algorithm for a single channel (AcbC).

Figure 1.4: Power spectra before and after artifact removal in the AcbC.

Figure 1.5: Power spectra before and after sham artifact removal in the AcbC.

DBS of AcbC yields time, frequency and region dependent changes in coherence between connected nodes of the limbic system

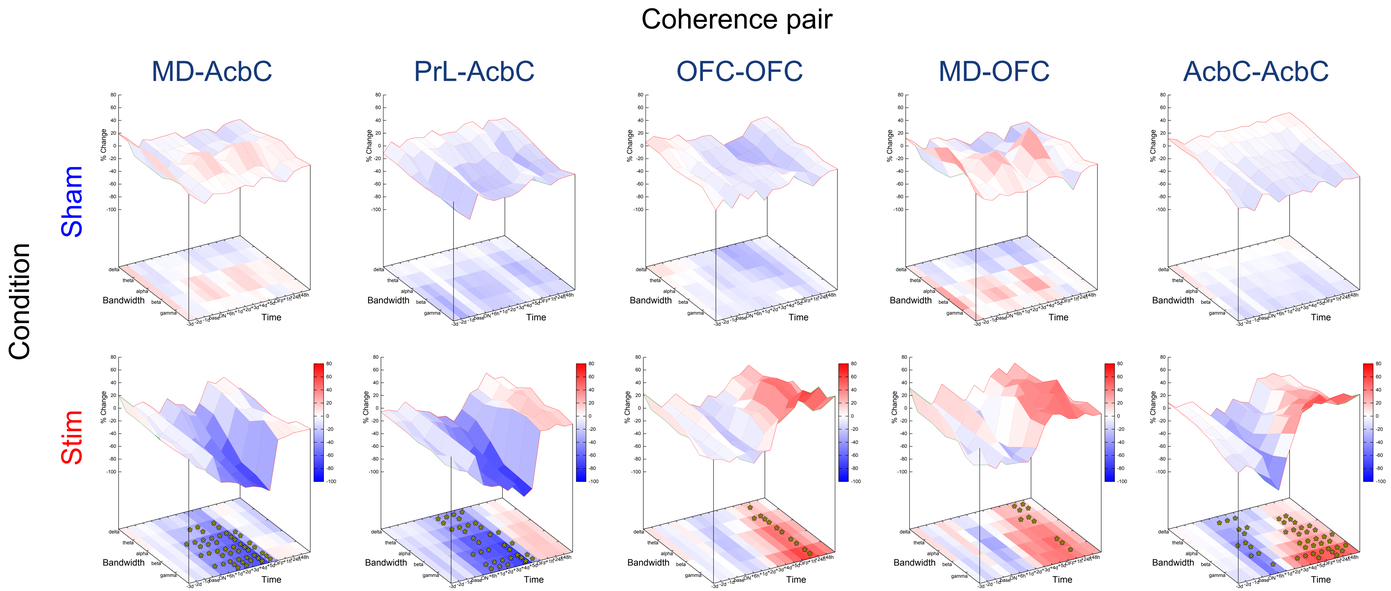

Figure 3: Bilateral AcbC DBS (F: 130Hz, PW: 100us, I: 100uA) yields time, frequency and region dependent changes in coherence, a putative measure of functional connectivity between pairs of connected nodes in the rodent limbic system. Sham stimulation demonstrated consistent functional connectivity between all regions tested over the 10 days of recording (3 days pre-sham stimulation, 5 days sham stimulation and 2 days washout).

MD-AcbC: Bilateral AcbC DBS yielded a timed dependent decrease in functional connectivity between the MD and the AcbC. This decrease is seen in the theta, alpha and beta bands. Any apparent reduction in delta coherence is not statistically significant. The greatest changes are seen at the highest frequencies. This reduction in coherence is seen immediately following the start of DBS (ON) and continues to decrease with sustained DBS, returning to baseline levels following the cessation of DBS (OFF).

PrL-AcbC: Similarly, bilateral AcbC DBS yielded a timed dependent decrease in functional connectivity between the PrL and the AcbC. This decrease is seen across all wavebands and requires in excess of 6 hours of sustained DBS to become apparent. The greatest decrease in coherence is seen after continued DBS and returns to baseline levels following the cessation of DBS.

OFC-OFC: Bilateral AcbC DBS yielded little change in coherence between left and right OFC during DBS. However there is a significant difference between the stim and sham conditions across all wavebands 1h following the cessation of DBS. It is not clear whether this is a rebound effect or whether the system was approaching this state.

MD-OFC: Similarly, bilateral AcbC DBS yielded little change in coherence between the MD and the OFC. However there is a significant difference between the stim and sham conditions across all wavebands barring alpha 1h following the cessation of DBS. Again, it is not clear whether this is a rebound effect or whether the system was approaching this state.

AcbC-AcbC: Interestingly bilateral AcbC DBS yielded an initial decrease in bilateral coherence between the left and right AcbC, followed by a recovery and finally an increase in coherence between these regions. Again these effects were most pronounced at the highest frequencies.

All data shown is for LHS. Similar effects were seen in each hemisphere (data not shown). Additional comparisons yielded no effects (data not shown).

Sham n = 9 group, stim group n = 8. (* = p < 0.05, ** = p < 0.01, *** = p < 0.001).

DISCUSSION & IMPLICATIONS

These data suggest that chronic high frequency stimulation of the core of the nucleus accumbens leads to an increase in gamma activity in the stimulated region. These changes appear to take a long time to manifest yet disappear rapidly following the cessation of stimulation. In addition this stimulation paradigm yields marked changes in coherence, a putative measure of functional connectivity, between multiple nodes of the limbic system. These changes in coherence occur over similar timescales as the changes in power seen within the stimulated nucleus, arguably indicating that changes within the stimulated region may drive changes in connectivity between regions linked with the stimulation target. Whilst some of these changes (MD-AcbC, PrL-AcbC) disappear rapidly following the cessation of stimulation some persist well into the post-stimulation period (OFC-OFC, MD-MD, AcbC-AcbC) indicating a role for long term, plastic changes in the affected system. Moreover the changes in AcbC-AcbC coherence display complicated temporal dynamics furthering the implication that DBS plays a complex role in long term plastic changes in the stimulated network.

The time periods required to generate observable changes in oscillatory power within regions and coherence between regions highlights the necessity of studying DBS chronically. This mirrors the clinical experience, certainly in psychiatric disorders, where therapeutic effects may vary with time and take many weeks to become apparent.

REFERENCES & ACKNOWLEDGEMENTS

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Support: NIH/NIMH (MH086400)
Thanks to Dr. Bernd Porr

Conte Center for Research in OCD
Elucidating the neurocircuitry of deep brain stimulation for obsessive compulsive disorder