Deep brain stimulation of the mediodorsal thalamic nucleus and its implications for the treatment of schizophrenia

University of Strathclyde Glasgow

[1]S. G. EWING & [2]J. A. PRATT

[1]Bioengineering & [2]SIPBS, The University of Strathclyde, Glasgow, UK

[1]Corresponding author: Samuel G. Ewing - sge3@pitt.edu

INTRODUCTION

Whilst antipsychotic drugs treat the positive symptoms associated with schizophrenia they have limited effects against the negative symptoms and cognitive deficits. Here a deep brain stimulation (DBS) strategy analogous to that used in Parkinson's disease is proposed. Methods for the validation of this strategy in a phencyclidine (PCP) rat model of schizophrenia are described. Given the weight of evidence implicating disruption of the thalamo-cortical system, particularly the mediodorsal thalamic nucleus (MD) and prefrontal cortex (PFC), studies have focussed on investigation of the consequences of high frequency stimulation of the MD. Results are reported in terms of spectral analysis of the electrocorticogram (ECoG) and the expression of the immediate early genes (IEGs) *zif-268* and *c-fos*.

MATERIALS & METHODS

In the study concerning the expression of IEGs, custom made bipolar stimulating electrodes were implanted bilaterally into the MD of isoflurane anaesthetised rats. Stimulation was delivered unilaterally to either the right or left MD whilst the contralateral hemisphere served as a control. High frequency stimulation stimulation (Frequency, 130Hz; Amplitude, 200µA; Pulse Width, 100µs) was delivered for 3 hours via a custom designed and made deep brain stimulation device. Brains were then removed, sectioned and radio labelled for the immediate early genes *zif-268* and *c-fos* before being exposed to x-ray film for 8 days. The relative optical density of the resultant autoradiograms were analysed with MCID, a computer based optical densitometer.

In the study concerning the spectral analysis of the ECoG, custom made bipolar stimulating electrodes were implanted unilaterally into the left MD of rats treated sub-chronically with PCP (2.6mg/kg for 5 days, 3 day washout) or saline. Animals were anaesthetised with isoflurane and 7 screw electrodes were implanted in the skull overlying the cortex of the left hemisphere and one in the skull overlying the cerebellum. Differential ECoG recordings were made between the 7 cortical electrodes and the cerebellar electrode. Baseline ECoG recordings were made for 30 minutes before delivering high frequency stimulation (Frequency, 130Hz; Amplitude, 200µA; Pulse Width, 100µs) for 1 hour via a custom designed and made deep brain stimulation device. A bipolar montage was derived by subtracting the signals from adjacent electrodes. The power spectra of the derived signals was computed using Fourier methods and the absolute band power computed for the delta (1-4Hz) and theta bands (4-8Hz). In addition the coherence between electrodes was computed in the delta and theta bands.

DBS of the MD yields increases in the expression of *zif-268* but not *c-fos* in the frontal cortices

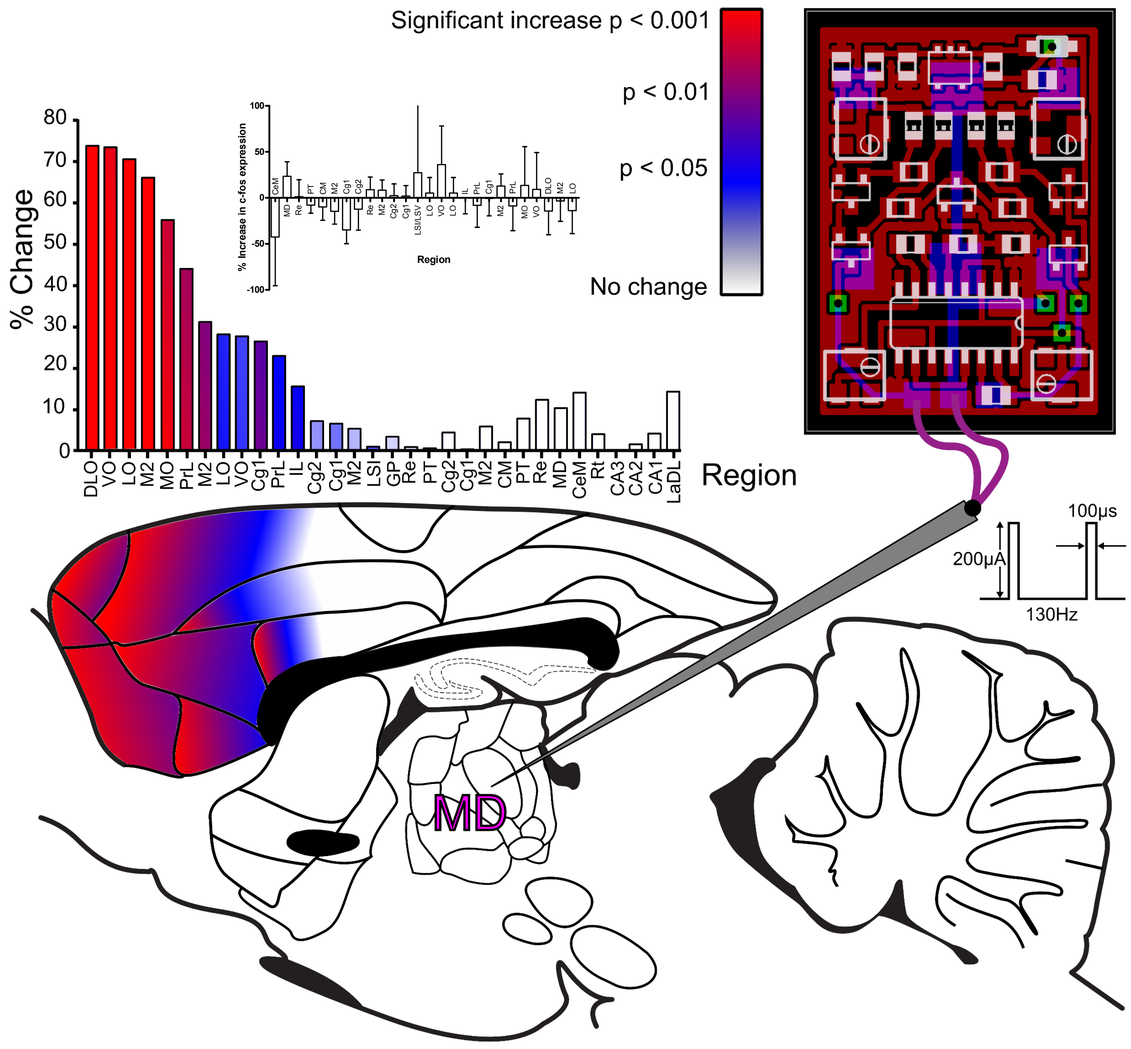

Figure 1: Summary of the changes in the expression of the mRNA encoding the IEGs *zif-268* and *c-fos*. Significant increases in the expression of *zif-268* - but not *c-fos* (inset) - were seen in the frontal regions of the cortex; including the orbital, limbic and frontal motor cortices. These differences are seen to be greatest more rostrally, diminishing in sections taken more caudally and dissappearing altogether beyond the level of the striatum.

PCP treated rats exhibit increased low frequency power which is further augmented by DBS of the MD

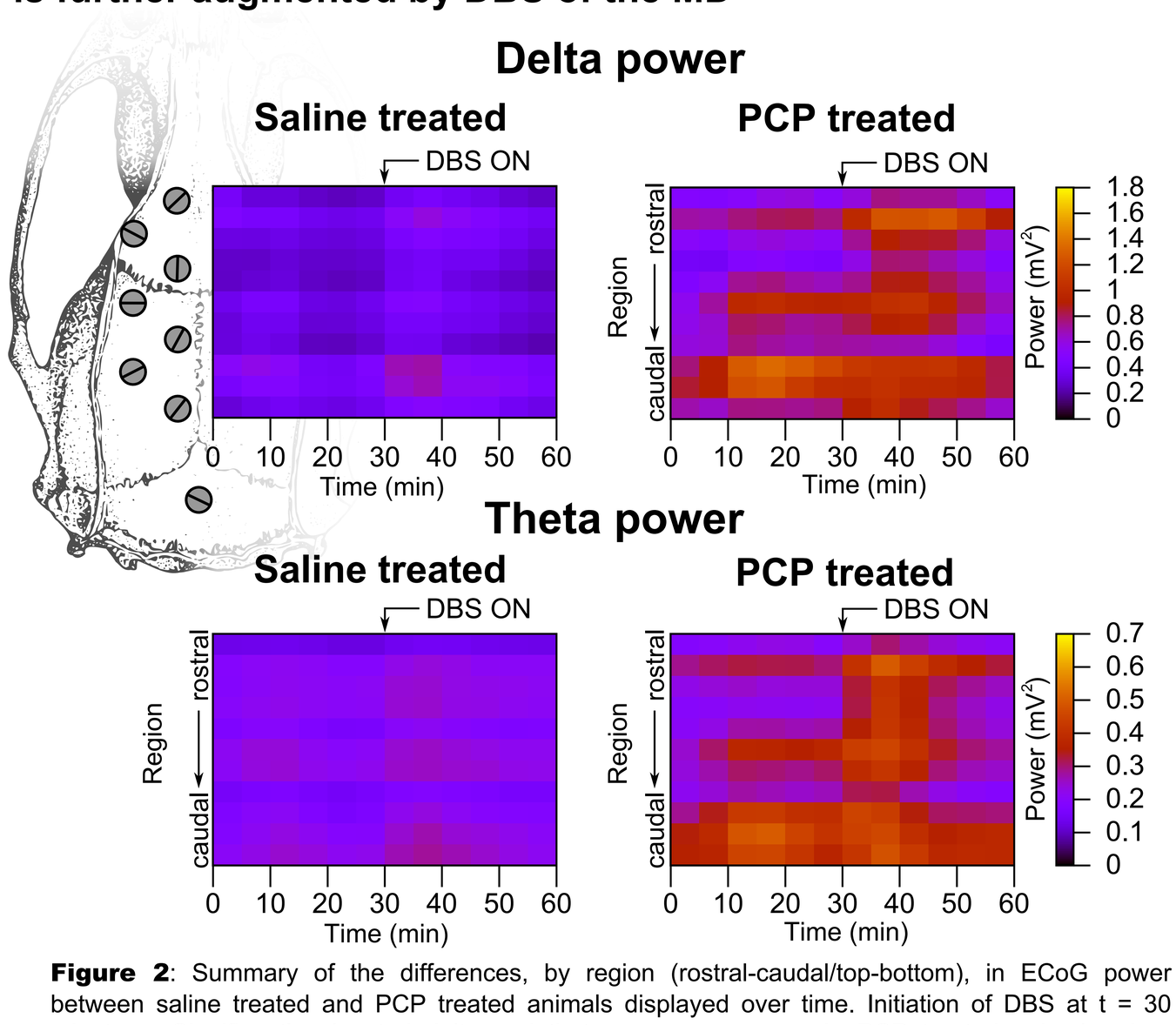

Figure 2: Summary of the differences, by region (rostral-caudal/top-bottom), in ECoG power between saline treated and PCP treated animals displayed over time. Initiation of DBS at t = 30 minutes. Significantly elevated delta and theta power was seen in PCP treated animals when compared with saline treated controls in recordings from electrodes overlying the frontal motor cortex and the parietal cortex. These differences were transiently exacerbated by DBS of the MD.

Discussion

Deep brain stimulation of the MD at frequencies which confer a therapeutic benefit in movement disorders such as Parkinson's disease yield activation of frontal regions of the cortex, as evidenced by increased expression of the IEGs *zif-268*. The differential expression of *zif-268* and *c-fos* is most likely a consequence of the induction dynamics of these IEGs (Zangenehpour & Chaudhuri, 2002) although is also reminiscent of stimuli yielding LTP (Davis et al., 2003).

The ECoG spectral profile of rats treated subchronically with either saline or PCP exhibit anomalies (increases in low frequency power) similar to those reported in schizophrenic patients (Boutros et al., 2008). DBS of the MD transiently augments this increase in PCP treated animals suggesting increased cortical synchronisation in these animals.

Implications

Impairment in the ability to recruit the prefrontal cortex is frequently reported in schizophrenia. The results of these experiments demonstrate activation of frontal cortical regions as a consequence of deep brain stimulation of the MD. Furthermore quantitative analysis of the ECoG demonstrates a spectral profile, in rats treated sub-chronically with PCP, similar to that seen in schizophrenic patients.

References

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