Thalamo-cortical responses to deep brain stimulation of the posterior hypothalamic nucleus in rats-an fMRI study of neuroconnectivity

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INTRODUCTION: Deep brain stimulation (DBS) is the only available treatment for advanced Parkinson's disease (PD) after medications fail. Recent studies have shown the stimulation of other non-basal ganglia nuclei such as the pedunculopontine tegmental nucleus can also ameliorate certain symptoms of PD[1]. One such novel site for DBS is the posterior hypothalamic nucleus (PH), which has been shown to reverse haloperidol and 6-OHDA lesion–induced akinesia in different behavioural paradigms[2, 3]. In order to determine functional connectivity, we used fMRI to study activation caused by stimulation of the PH. Stimulation was done using a novel implantable electrode which we developed and which is suitable for stimulation and recording within a 9.4T MRI[4].

METHODS: Carbon fibres (~200 µm) were implanted in the PH of 5 male Long-Evans rats with ketamine/xylazine anaesthesia. Animals were allowed at least a week to recover and screened for no stereotypical or unilateral behaviour before imaging. During the fMRI session, the animals were anaesthetized with isoflurane and placed in the 9.4T MRI. The fMRI experiment consisted of a set of images acquired using a fast spin echo sequence (TR/TE = 3000/60 ms, 64 echoes per TR, FOV = 3 cm^2, matrix size= 128x128, slice thickness 1.5 mm). After collecting 2 minutes of baseline, images were acquired during two 1 min periods of stimulation of the PH (0.1 s pulse width, 100 Hz monophasic square waves) interrupted by 3 min rest periods. Voxels of activation were analyzed using a fuzzy clustering based analysis with significance set at $p < .0005$ [5].

RESULTS: In general, BOLD responses were elicited bilaterally (Fig 1a,c). The total number of activated voxels was not significantly different on the ipsi and contralateral sides of the brain from the site of stimulation (Fig 1c). Multiple large regions of cortex, thalamus, and hippocampus were activated. The striatum showed significant, but small amounts of activation.

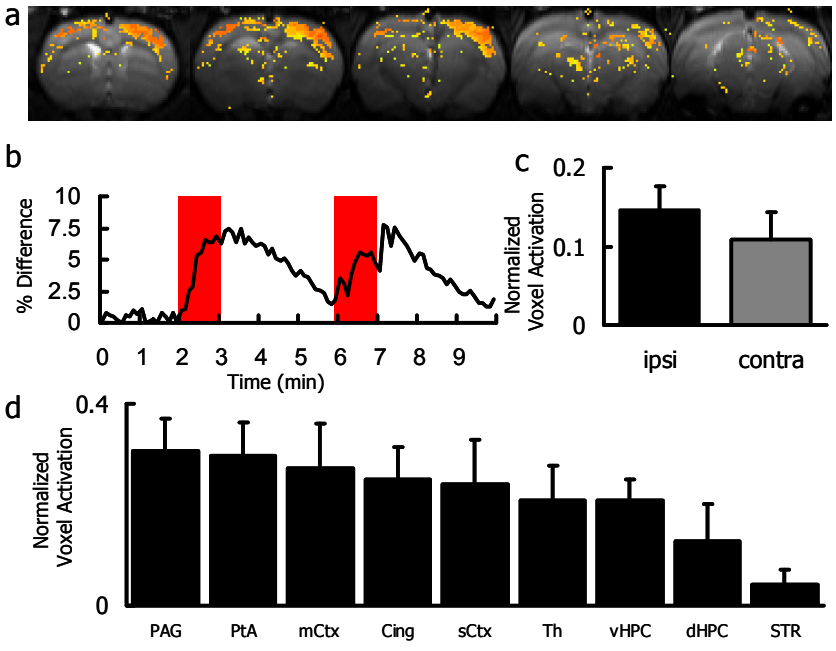

Figure 1. Regional response to stimulation of the posterior hypothalamic nucleus (PH). a) Representative multislice fMRI images in one subject b) Average time course of response in one subject as a percent difference to baseline. Vertical red bars refer to PH stimulation. (c) Relative numbers of activated voxels in the ipsi and contralateral sides with respect to the side of PH stimulation (d) The proportional number of voxels activated by PH stimulation ranked in different brain regions. (mean±SD). Abbreviations from left to right are: PAG: periaqueductal gray matter; PtA: parietal cortex; mCtx: motor cortex; Cing: cingulate cortex; sCtx: somatosensory cortex; Th: thalamic nuclei; vHPC: ventral hippocampus; dHPC: dorsal hippocampus; STR: striatum.

DISCUSSION: fMRI shows that there is significant functional connectivity between the PH and large regions of cortex and hippocampus. These functional connections will impact on the response to DBS within the PH, and so may provide therapeutic effects to experimentally induced akinesia.

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