Chronic Deep Brain Stimulation-Induced Plasticity in the Rat Basal Ganglia

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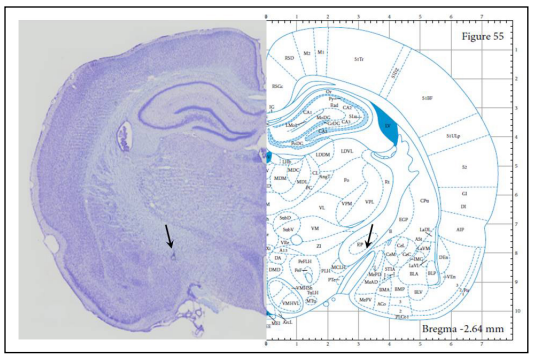
Introduction

- High frequency GPi-DBS durably improves both generalized and cervical dystonia (1).
- The clinical benefits of GPi-DBS occur over weeks to months, implicating changes in gene expression and structural morphology.
- In a pilot study, the expression of PSA-NCAM, a developmental protein regulating synaptogenesis, cell migration and axonal sprouting was observed in animals following 7 days of EP (rat GPi) DBS, and was associated with improved motor coordination and more spontaneous locomotion (2).
- Therefore, we measured the time course of behavioural changes, immunochemical markers of plasticity (PSA-NCAM) and other cellular markers resulting from chronic EP-DBS in rats.



Methods

- Adult male SD rats (290-350 g) were assigned to 3 groups: 1) 4 hrs, 2) 7 d and 3) 28 d (N=8 each).
- PlasticsOne 0.005" one-channel stainless steel stimulating electrodes were implanted in the left EP (AP: +1 mm, ML: +2.90 mm, DV: +8.01 mm; Figure 1) at an angle of 24.3 degrees anterior to bregma. A cranial cap was fitted and rats were allowed to move freely in their cages.
- Only data from animals in which electrodes were confirmed in the EP were further analyzed (4 hrs (N=4), 7 and 28 d (N=6 each)). The unimplanted side served as an internal control.
- Of the implanted rats, we used a ratio of 2:1 stimulated to sham; DBS was applied after 1 week. All rats were scored on the open field, cylinder and horizontal ladder tests pre-op, on POD 4 and weekly. Brains were fixed in 4% PFA, cryosectioned at 40 um, stained for Nissl, PSA-NCAM, NF200 and GFAP, and examined by fluorescence microscopy.

Results

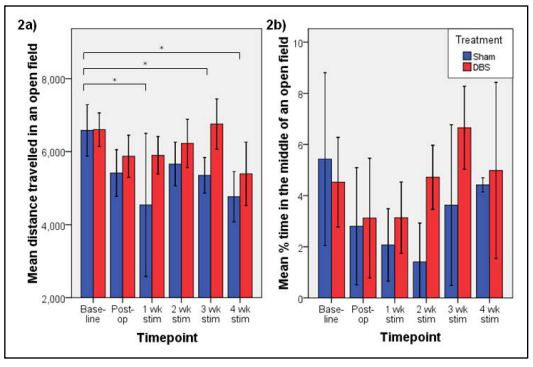
Behaviour

Locomotor activity

- DBS rats travelled further than sham-stimulated animals irrespective of time (F=5.840, p=0.031, Figure 2a). Distances travelled at 1 (t=-4.015, p=0.007), 2 (t=-3.418, p=0.031) and 4 (t=-4.068, p=0.007) weeks were reduced vs. baseline, irrespective of treatment (F=10.242, p=0.002). There was an interaction of treatment and time (F=16.394, p<0.001); DBS- travelled further than sham-stimulated animals at 3 weeks (t=4.012, p=0.002), while sham-stimulated animals traveled less after 1 (t=-3.487, p=0.020), 3 (t=-3.577, p=0.020) and 4 weeks (t=-3.145, p=0.041) vs. baseline.

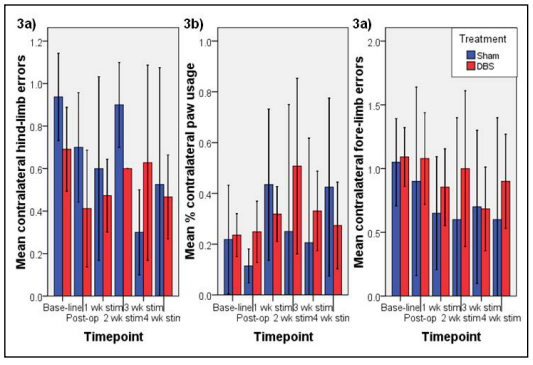
Exploratory behaviour

- There was no interaction between treatment and time (Figure 2b). There was an effect of time (F=15.994, p<0.001), however post-hoc tests did not identify any group differences.



Limb use asymmetry

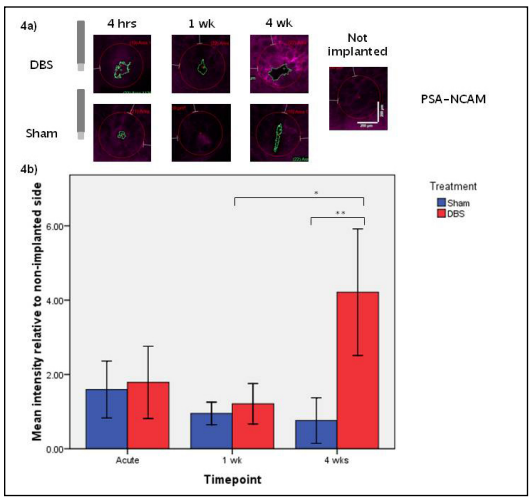
- There were no effects of treatment or time, and no interaction of treatment and time in contralateral limb use in the cylinder task (Figure 3a).
- DBS did not influence the number of contralateral hind- or fore-limb errors in the horizontal ladder task (Figures 3a and 3b); there was no interaction of treatment and time, and no effects of treatment or time were observed for either limb.
- Ipsilateral limb errors were also unaffected (not shown).



Immunohistochemistry

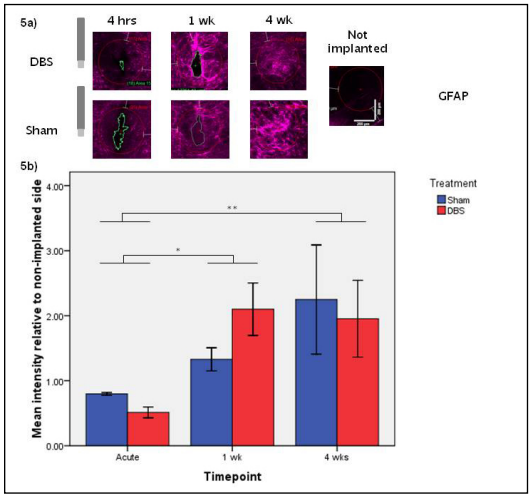
PSA-NCAM

- Irrespective of time, DBS- had increased EP PSA-NCAM relative to sham-stimulated controls (F=5.756, p=0.037). We saw no effect of time (F=2.501, p=0.132), but there was an interaction of treatment and time (F=4.167, p=0.048); increased PSA-NCAM was seen after 4 vs. 1 week (t=4.126, p=0.033) in DBS animals, and between DBS- and sham-stimulated animals at 4 weeks (t=-3.877, p=0.003).



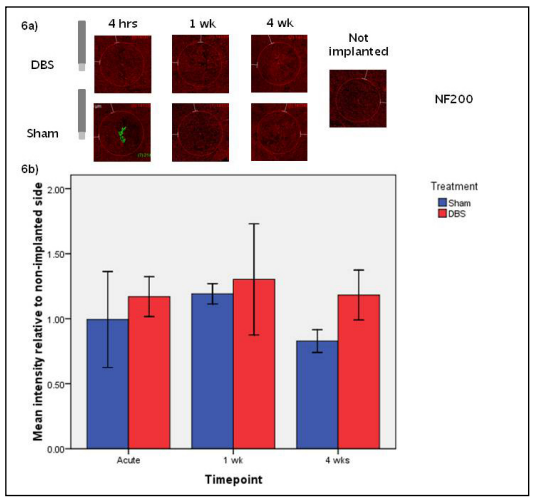
GFAP

- GFAP expression was not influenced by treatment (F=0.076, p=0.789), and we saw no interaction of treatment and time (F=2.517, p=0.130; Figure 3b). However, there was a significant effect of time (F=13.048, p=0.02); GFAP was increased with 1 (t=-3.668, p=0.013) and 4 weeks (t=-5.003, p=0.002) vs. 4 hrs of stimulation regardless of treatment.



NF200

- Neither treatment (F =2.201, p=0.169) nor time (F=1.086, p=0.374), nor the interaction of these terms (F=0.280, p=0.762), was associated with a significant change in the NF200 expression (Figure 3c)..



Conclusions

- Chronic stimulation of the rat GPi-equivalent leads to robust expression of PSA-NCAM, a molecule implicated in neurogenesis, cellular migration, neurite outgrowth, and synaptic remodeling, without changes in the expression of NF200.
- Increased GFAP expression is seen in both DBS
- and sham-stimulated animals, which likely reflects local inflammation secondary to electrode implantation and/or its presence over time.
- While sham-stimulated animals did exhibit deleterious behavioural sequelae, including decreased locomotor activity, DBS may be protective against these effects. As such, this study supports a role for neuroplasticity in the mechanism of action of DBS.

Learning Objectives

Readers should be able to appreciate the evidence underpining a role for plasticity in DBS for dystonia, and understand the experimental processes for elucidating this role in vivo.

References

1. Kiss ZHT, Doig-Beyaert K, Eliasziw M et al. (2007) Canadian multicentre trial of bilateral pallidal DBS for cervical dystonia. Brain 130:2879-2886
2. Inan SY, Dyck R, Kiss ZHT. (2010) Chronic high-frequency stimulation in the rat basal ganglia: behaviour and histology. Soc. Neurosci. Abstr. Program No. 755.12