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Introduction

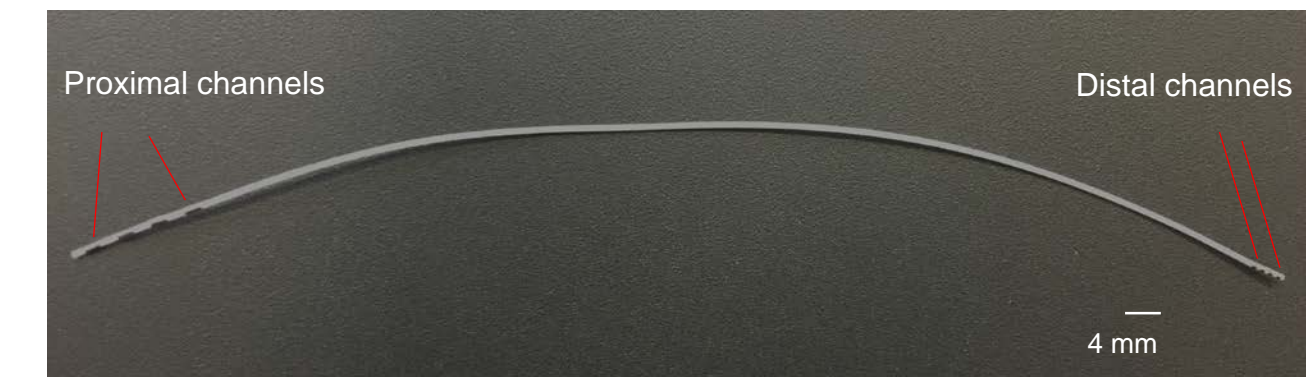
Deep brain stimulation (DBS) is a surgical procedure during which a specific medical device called neurostimulator is implanted. This one sends via implanted leads electrical impulses to specific targets in the brain for treatment of movement and neuropsychiatric disorder (e.g. Dandekar et al., 2018; Grassi et al., 2018). The neural mechanisms are not yet fully understood but this procedure is a therapy approved for Parkinson's disease, essential tremor and dystonia, developed in the early 1990ies thanks to translational models in non-human primates (NHPs).

The aim here is to refine the stereotaxic approach to facilitate translational research for novel DBS indications to enable mechanistic investigations in models of mental disorders, specially on NHPs (e.g. Li et al., 2013).

Development & Design

To achieve our goal, diverse technical developments have been necessary (Lanz et al., in preparation).

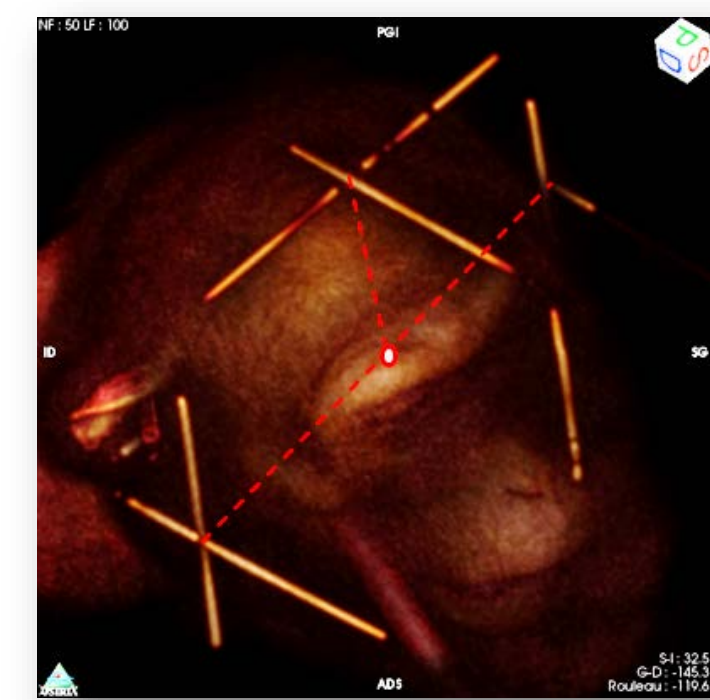
- The first necessary and essential step was the purchase of the correct DBS lead. For that we used similar **DBS lead** than for human application, however all the dimensions were adjusted according to our model's size.
- The second one consists of enhancing the accuracy of DBS electrodes implantation in the region of interest; the nucleus accumbens (NAc). Akin to the surgical procedure used in humans, a **MRI-localizer** was developed which was then combined with a MRI-compatible stereotaxic frame for NHPs. The approach allowed to define a working volume within the brain, based on individual reference coordinates.
- To be as least invasive as possible, some improvements on the surgical equipment have been performed, specifically on the **micro-manipulator**, which greatly enhanced the ease and accuracy of electrode placement even when using an angular approach. An additional rotator adaptor, on which we attached a vernier and a stereotaxic holder were manufactured and placed on this manipulator in order to reach the targeted brain region.
- To confirm the correct electrode positioning and the same depth of bilateral electrodes, a series of radiographies (**X-Rays**) was performed during the surgery.
- To verify the position post-implantation and before beginning behavioural sessions, a **CT-scan** was performed and merged with the preoperative MRI acquisitions. With these obtained **fusions** (n=3) we are able now to double check, in vivo, the accuracy of the electrode implantation without waiting for post-mortem histological confirmation.



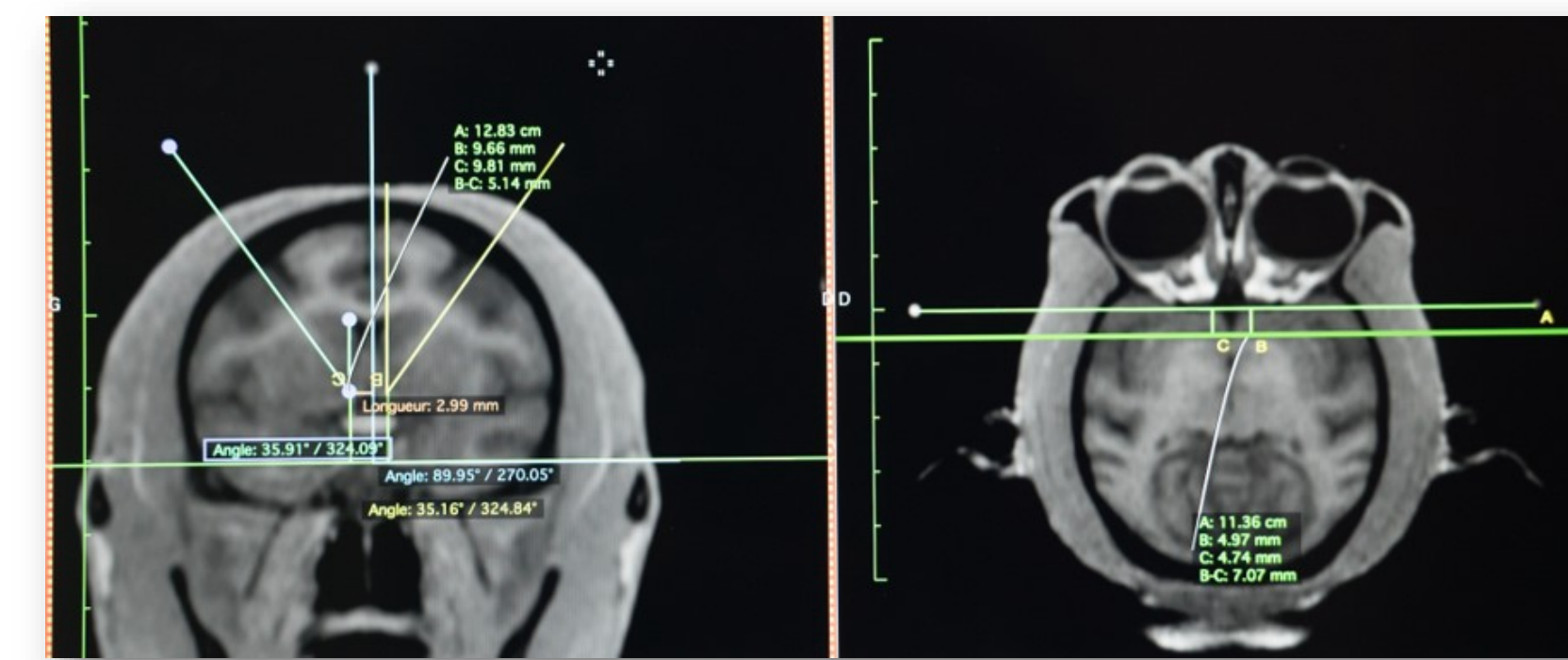
Representation of the type of **DBS lead** used. University of Fribourg (2016)



Developed **MRI-localizer** attached to a standard stereotaxic frame. University of Fribourg (2016)



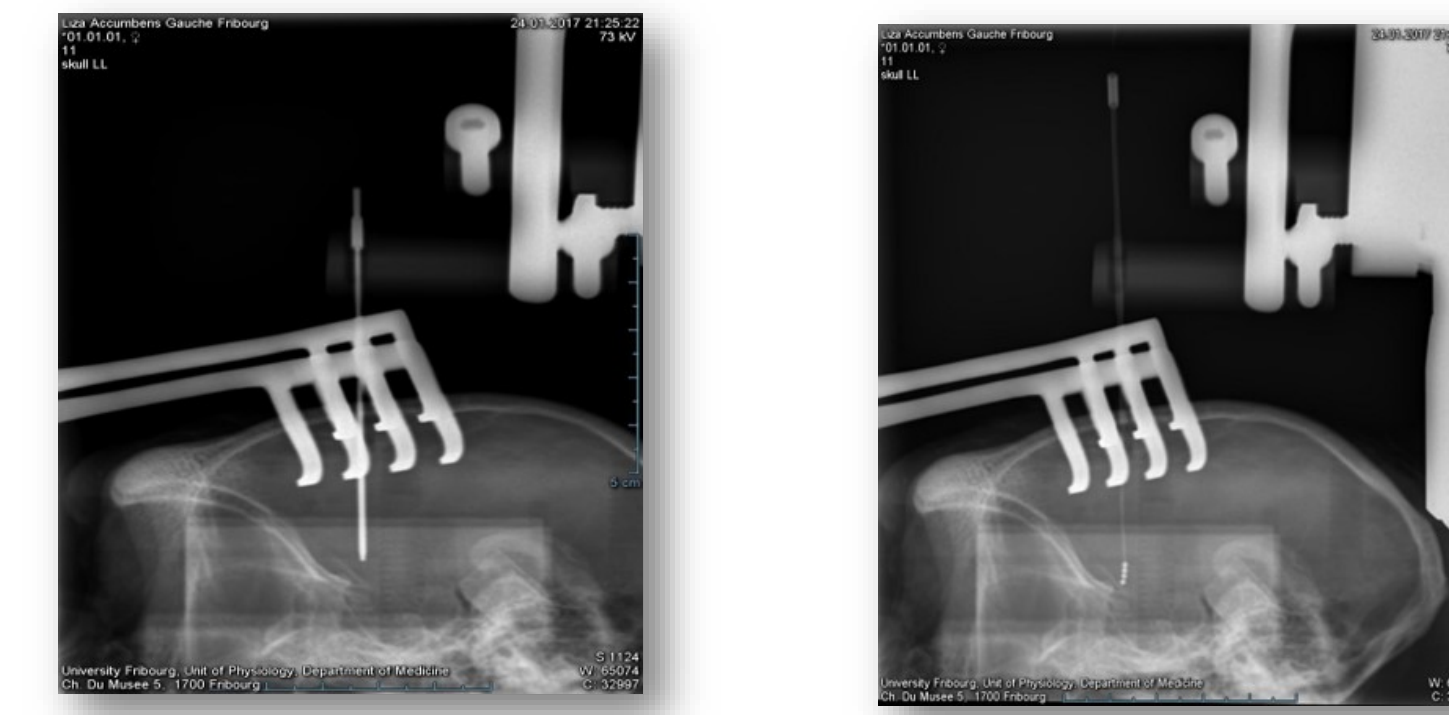
3D reconstruction of the animal's head and the MRI-localizer. University of Fribourg (2017)



Print screen of the region of interest determined from calculated coordinates with Osirix software and displayed on a coronal (left) and axial (right) views. University of Fribourg (2017)



Pictures of the **micro-manipulator** with different additional pieces (Rotator adaptor and vernier). University of Fribourg (2017)



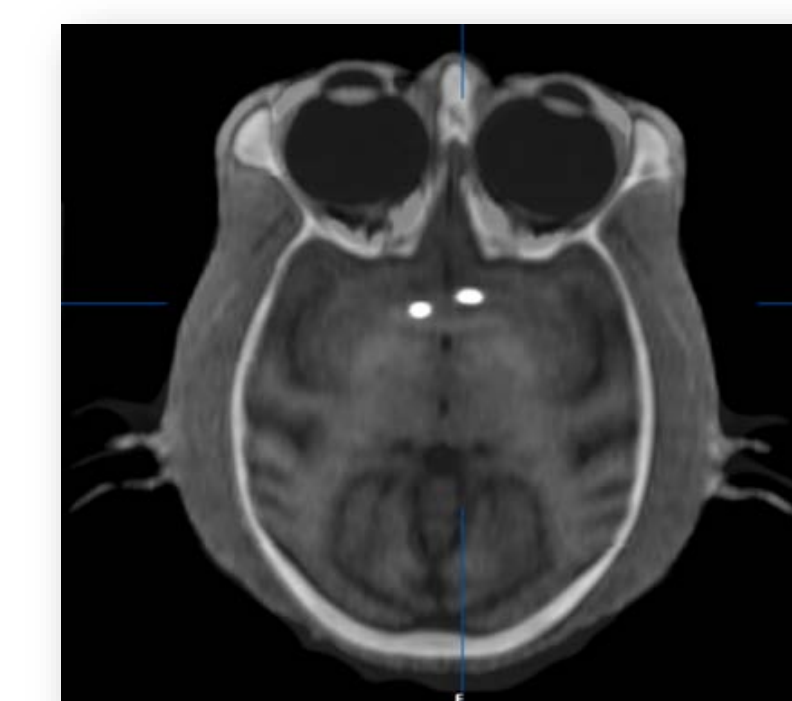
Left: X-Ray of the cannula positioning (according the region of interest). **Right:** X-Ray of the electrode positioning. University of Fribourg (2017)



CT-Scan display of one animal demonstrating electrode alignment. University of Fribourg (2017)



Left: Coronal view of CT-scan and MRI **fusion** display in an animal demonstrating electrode accuracy in the region of interest. **Right:** Axial view of the **fusion** display in the same animal. University of Fribourg (2017)



Highlights

The electrode implantation technique is similar to the one used in humans (e.g. Parkinson's disease).

At that step (n=3), the obtained fusions demonstrate that the technique is accurate and reproducible (in vivo).

Having no MRI at the university's site, the approach developed (standard stereotaxic frame, MRI-localizer, etc.) allows us to transport the animal from the Fribourg Hospital (HFR) to the surgery room following the MRI acquisitions. This by keeping the animal in the frame to calculate the correct coordinates.

In conclusion, our refined stereotaxic approach enables a translational DBS research with standards similar to the implantations in humans.

Perspectives:

In order to improve and facilitate the fusion step, a second localizer (identical to the one used for MRI) will be used for CT-scan acquisition.

Development of a universal connector (neurostimulator), adaptable to all skull morphologies. Currently, the connectors are individually manufactured according to the morphology of each animal.

Literatures:

[1] Dandekar MP, Fenoy AJ, Carvalho AF, Soares JC, Quevedo J. Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications. *Mol Psychiatry*. 2018 May;23(5):1094-1112. doi: 10.1038/mp.2018.2. Epub 2018 Feb 27.

[2] Grassi G, Figeo M, Ooms P, Righi L, Nakamae T, Pallanti S, Schuurman R, Denys D. Impulsivity and decision-making in obsessive-compulsive disorder after effective deep brain stimulation or treatment as usual. *CNS Spectr*. 2018 Jun 4;1-7. doi: 10.1017/S1092852918000846.

[3] Lanz F, Rouiller E.M., Lüscher C., Momjian S.: Development and design of a stereotaxic device for DBS electrode implantation in non-human primates. In preparation.

[4] Li N, Gao L, Wang XL, Chen L, Fang W, Ge SN, Gao GD. Deep brain stimulation of the bilateral nucleus accumbens in normal rhesus monkey. *Neuroreport*. 2013 Jan 9;24(1):30-5. doi: 10.1097/WNR.0b013e32835c16e7.

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