Functional MRI and deep-brain stimulation: Impact from distortion artifacts

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Target audience: Neuroscientists, neurologists and psychiatrists investigating mechanisms behind deep-brain stimulation; Researchers interested in fMRI and resting-state fMRI.

Purpose: Deep-brain stimulation (DBS) is a rapidly evolving neurosurgical strategy used to treat various debilitating neurological and psychiatric conditions; with continually emerging applications and novel stimulation targets.[1] The striking therapeutic benefit of DBS therapy has been nevertheless established more or less empirically. This has opened entirely new horizons for further basic research and investigations. Several successful attempts to study neural circuitry of patients with fully implanted and active DBS hardware evidence experimental feasibility of functional MRI (fMRI) under strictly controlled safety standards.[2-3] Here, we show that rigorous data analysis standards also need to be adhered to and highlight the associated caveats. In particular, we demonstrate that utmost caution should be exercised when analyzing fMRI data in the vicinity of the DBS electrode, due to severe geometric distortions and signal intensity drops, which may eventually culminate in false-positive findings.

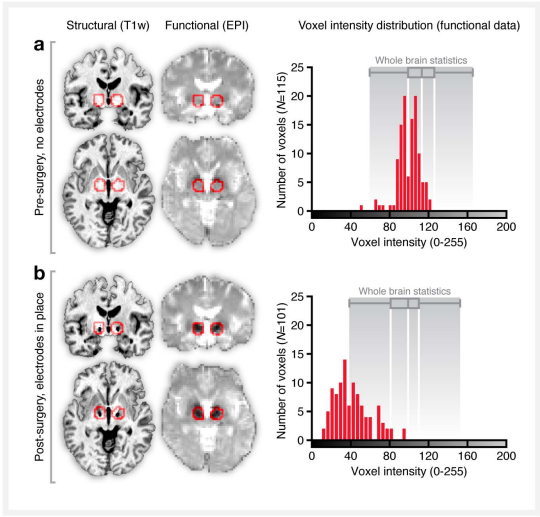

Figure 1. Effect of DBS electrodes targeted at STN in a patient suffering from PD. **(a)** Patient pre- implantation and **(b)** post- implantation, with DBS off. Left panel: MRI images with outlined ROIs. Right panel: histogram of voxel intensities extracted from the ROIs (functional data), leaving out voxels exhibiting drops in structural scans; gray box-plot shows whole-brain statistics from respective functional scan (median, first/third quartile, lower/upper adjacent). The change in intensity distribution post-implantation in the ROI compared to whole-brain intensity distribution and spatially larger signal drops in functional data compared to structural data are particularly noteworthy.

Methods: Images were acquired at 1.5T on a MAGNETOM Symphony scanner (Siemens, Erlangen, Germany). Experiments included T_1-weighted (T1w) and resting-state fMRI (rs-fMRI) scans: 200 volumes of T_2*-weighted functional whole-brain data were collected using a gradient-echo echo-planar imaging (EPI) sequence (*TR/TE/FA* = 3000/51 ms/90°), consisting of 31 axial, 3 mm thick slices with a nominal in-place resolution of 3×3 mm^2. Participants were instructed to follow a fixation-cross on a projector screen while remaining still in a supine position. T1w structural data were measured using a magnetization-prepared rapid acquisition gradient-echo (MP-RAGE; *TR/TI/TE/FA* = 2140/1100/3.93 ms/15°). Functional images were realigned, co-registered with the structural images and resampled to 3×3×3 mm^3. Both anatomical and functional data were normalized to the MNI template. In MR data shown in **Figure 1**, no spatial smoothing and no filtering were performed. The data were randomly selected from a patient with Parkinson's disease (PD) pre- and post-implantation of DBS electrodes targeted at the subthalamic nucleus (STN). Spherical region of interest (ROI) with a 14 mm diameter was formed around the electrode tips (STN) bilaterally. ROI's voxel-value histograms were computed from temporally-averaged functional data. In addition, distributions of whole-brain voxel intensities were calculated. To emphasize the risk of potential false-positive results, rs-fMRI data from the same patient cohort were analyzed in various stages of their transition from levodopa (24 patients) to DBS treatment (13 patients). Pre-processing included spatially smoothing the functional data using an 8 mm full-width-at-half-maximum Gaussian kernel and filtering the fMRI time-courses using a band-pass filter (1/50 Hz-1/8 Hz). Left ROI from **Figure 1** was used as a seed-region for correlation analysis. Finally, a paired *t*-test was performed between the normalized correlation maps of patients in particular treatment states, to observe the response to respective treatment (**Fig. 2**; **a**, **b**). Resulting maps were corrected for multiple-tests using a family-wise error correction at p_{FWE}<0.05. In both analyses (**Fig. 1**, **Fig. 2**), all voxels exhibiting signal drops in T1w scans were excluded from the ROI.

Results: Increased sensitivity of the fMRI signal to artifacts caused by the DBS leads is clearly visible post-implantation (**Fig. 1**). The intensity distribution within the ROI is broadened, with the majority of values shifted to the outlier range. In pre-surgery sessions (without electrodes), paired t-tests (dopaminergic medication on vs. off) revealed changes in functional connectivity of STN with thalamus and cerebellum (**Fig. 2**; **a**). Equivalent analysis (DBS on vs. off) of post-surgery sessions (electrodes in place) still yielded significant, yet ambivalent functional connectivity changes (**Fig. 2**; **b**; in particular cluster 2).

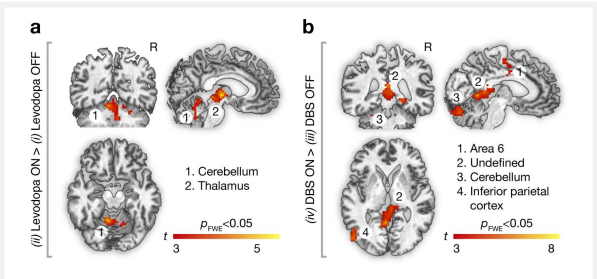

Figure 2. Significant correlation differences between seed-ROI and multiple target regions in a sample of PD patients between particular treatments states: **(a)** 24 PD patients withdrawn from levodopa medication *(i)* and after a dose of levodopa treatment *(ii)*, in agreement with literature. **(b)** Subset of 13 PD patients not treated at all *(iii)* and treated with unilateral left DBS *(iv)*, indicating a mixture of 'true' and false-positive results.

Discussion & Conclusion: Aforementioned artifacts are caused by the low bandwidth in phase-encoding direction of echo planar imaging (EPI) employed for fMRI.[4] It is evident that extracting data from a structure around the electrode tip, despite adjusting the ROI using T1w data, can easily compromise consequent analysis. Functional connectivity changes in cerebellum and thalamus – regions involved in PD pathophysiology[5-6] – were detected in response of patients to levodopa (without electrodes). In contrast, equivocal functional connectivity changes post-implantation in response to DBS (electrodes in place) demonstrate a possibility of obtaining a combination of false-positive and true effects, when selecting seed regions carelessly. Presented work suggests particularly cautious means of analyzing fMRI of patients with implanted DBS electrodes, and/or extremely careful interpretation of obtained results. We advocate excluding all fMRI voxels exhibiting signal drops from the analyses, until conclusive investigations quantifying the impact of aforementioned artifacts on the fMRI signal will be reported.

References:

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