Abstract — Deep Brain Stimulation (DBS) is a promising therapy for neurological and psychiatric disorders. However, the underlying mechanism of action of DBS remains unknown. The effect of DBS in the brain has been studied primarily by direct neural recording and neurotransmitter release studies, which lack the ability to elucidate DBS responses on a whole-brain scale. Functional imaging studies, such as 18F-FDG-PET, reflect changes in neural activity throughout the entire brain volume and thus may provide a unique window to better understand the in vivo mechanism of action of DBS. In order to rule out the underlying neuropathophysiology in human studies of DBS as a confounder, it is necessary to investigate the effect of DBS in the healthy brain. To our knowledge, no DBS 18F-FDG-PET studies have been done in the healthy rat brain. So we decided to investigate the effect of hippocampal DBS (hDBS) on regional cerebral glucose utilization throughout the entire brain volume in healthy rats. Five rats were implanted with a quadripolar DBS-electrode in the right hippocampus and injected with 28.1±1.8 MBq of 18F-FDG to measure regional cerebral glucose utilization during on and off bipolar Poisson distributed hDBS. Additionally, continuous depth-EEG was measured throughout the delivery of stimulation to verify whether EEG abnormalities occurred during DBS. Each rat underwent three PET-scans: (1) before surgery, (2) after surgery, and (3) during hDBS; and one MR-scan for anatomical correlation and electrode position verification. All PET-datasets were co-registered onto the first animal scanned using a mutual information algorithm with Powell's convergence optimization method implemented within the PMOD software. All data from each timepoint were grouped and a template was generated for each group, by calculating voxel-by-voxel the mean value and the standard deviation. Statistical analysis between groups, using a voxelwise two-sample t-test, reveals significant \( p_{corr} < 0.05 \) decreases in the cerebral regional glucose utilization due to hDBS, both in the ipsi- and contralateral hippocampus as well as in other limbic structures, compared to baseline scans acquired before and after electrode implantation. This indicates that hDBS interacts with brain regions spatially remote from the targeted brain structure, due to neuroanatomical connections between limbic structures and interhemispheric commissures.

We conclude that group-analysis of 18F-FDG-PET data is a valuable strategy to investigate both whole-brain response to DBS and connectivity of the targeted structure, as opposed to a region-of-interest oriented analysis strategy. Consequently, 18F-FDG-PET neuroimaging studies have the potential to provide better insight into the mechanism of action of DBS by simultaneously observing activity at multiple sites in the brain and may be a valuable tool to visualize and evaluate its therapeutic effect, and the effect of various stimulation paradigms and target areas for DBS.

**Keywords** — deep brain stimulation; hippocampus; 18F-FDG-PET