



Thalamic deep brain stimulation decelerates automatic lexical activation



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ABSTRACT

Background: Deep Brain Stimulation (DBS) of the thalamic ventral intermediate nucleus (VIM) is a therapeutic option for patients with essential tremor. Despite a generally low risk of side effects, declines in verbal fluency (VF) have previously been reported.

Objectives: We aimed to specify effects of VIM-DBS on major cognitive operations needed for VF task performance, represented by clusters and switches. Clusters are word production spurts, thought to arise from automatic activation of associated information pertaining to a given lexical field. Switches are slow word-to-word transitions, presumed to indicate controlled operations for stepping from one lexical field to another.

Patients & methods: Thirteen essential tremor patients with VIM-DBS performed verbal fluency tasks in their VIM-DBS ON and OFF conditions. Clusters and switches were formally defined by mathematical criteria. All results were compared to those of fifteen healthy control subjects, and significant OFF-ON-change scores were correlated to stimulation parameters.

Results: Patients produced fewer words than healthy controls. DBS ON compared to DBS OFF aggravated this deficit by prolonging the intervals between words within clusters, whereas switches remained unaffected. This stimulation effect correlated with more anterior electrode positions.

Conclusion: VIM-DBS seems to influence word output dynamics during verbal fluency tasks on the level of word clustering. This suggests a perturbation of automatic lexical co-activation by thalamic stimulation, particularly if delivered relatively anteriorly. The findings are discussed in the context of the hypothesized role of the thalamus in lexical processing.

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1. Introduction

Over the last decades, Deep Brain Stimulation (DBS) of the thalamic ventral intermediate nucleus (VIM) has become an established therapeutic option for patients suffering from disabling essential tremor (ET) (Koller, Lyons, Wilkinson, & Pahwa, 1999; Obwegeser, Uitti, Turk, Strongosky, & Wharen, 2000; Pahwa et al., 2006; Sydow, Thobois, Alesch, & Speelman, 2003; Zhang et al., 2010; for a review see Chopra, Klassen, & Stead, 2013). Although various studies have shown a low risk of side-effects (e.g., Borretzen et al., 2014; Kalia, Sankar, & Lozano, 2013;

Troster et al., 1999), the question of whether VIM-DBS may induce subtle cognitive impairments is still under debate: Whereas post-operatively only minor and mostly positive effects on general cognitive scores have been described (Benabid et al., 1996; Fields et al., 2003; Schuurman, Bruins, Merkus, Bosch, & Speelman, 2002; Troster, Fields, et al., 1998; Troster et al., 1999; Woods et al., 2001), deteriorations in verbal fluency (VF) have frequently been reported (Benabid et al., 1996; Fields et al., 2003; Schuurman et al., 2002; Troster et al., 1999; cf. Troster, Wilkinson, Fields, Miyawaki, & Koller, 1998; Woods et al., 2001). Next to brain microlesioning by DBS surgery, VIM stimulation itself appears to decelerate word output (Ehlen, Schoenecker, Kühn, & Klostermann, 2014). However, which particular VF-related operations are influenced by the thalamic stimulation has not been studied so far.

This conceptual point can be addressed by ‘temporal cluster analysis’. In this approach, the dynamics of word output from

Abbreviations: DBS, Deep Brain Stimulation; ET, essential tremor; FBF, fused Bousfieldian function; STN, subthalamic nucleus; TEED, total electrical energy delivered; VF, verbal fluency; VIM, ventral intermediate nucleus.

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individual VF performances are subjected to mathematical curve fitting. In doing so, intervals with higher versus lower than predicted production velocity are distinguished and categorized as clusters and switches, respectively. Since the relatedness is higher within than between clusters (Vonberg, Ehlen, Fromm, & Klostermann, 2014), automatic activation spread over strongly connected ‘association nodes’ within the underlying neuronal network is thought to facilitate the comparably fast word output during clusters (Collins & Loftus, 1975; Fitzgerald, 1983; Graesser & Mandler, 1978; Gruenewald & Lockhead, 1980; Pollio, 1964; Roelofs, 1992; Troster, Fields, et al., 1998; Troyer, Moscovitch, & Winocur, 1997; Vonberg et al., 2014). Switches, in turn, are considered to reflect the transition from one lexical field to another, implying attention-demanding, non-automatic frontal lobe operations (Troyer et al., 1997).

In patients with Parkinson’s disease, we recently found that DBS of the subthalamic nucleus (STN) increased switches, but left cluster-related word production unaffected, suggesting stimulation-related improvement of basal ganglia functions for lexical field transitions (Vonberg, Ehlen, Fromm, Kuhn, & Klostermann, 2016). Such an exclusive effect of VIM-DBS on the executive part of word production seems unlikely from a model perspective. Different clinical and research findings support the assumption that the flexible coupling of cortical areas is mediated by thalamic nuclei, which thus become part of cognitive networks depending on ongoing behavioral demands (Ahrens et al., 2015; Bradfield, Hart, & Balleine, 2013; Crosson, 2013; Crosson, Benjamin, & Levy, 2007; Fama & Sullivan, 2015; Ferguson & Gao, 2015; Funahashi, 2013; Hart et al., 2013; Ketz, Jensen, & O’Reilly, 2015; Klostermann et al., 2006, 2009; Marzinzik et al., 2008; Mitchell et al., 2014; Nikulin et al., 2008; Pinault, 2004; Pulvermuller, 1999; Saalman & Kastner, 2015; Schmahmann & Pandya, 2008; Sherman, 2005; Tiedt et al., 2016). Accordingly, VIM-DBS could induce a decline of cluster-related word production by thalamocortical network perturbation and the consequent reduction of automatic lexical activation spread (Collins & Loftus, 1975). Concerning lexical switching, the impact of VIM-DBS might be relatively smaller, since underlying operations do not only depend on the state of network connectivity, but additionally on active basal ganglia processing (Vonberg et al., 2016). Thus, the hypothesis of a VIM-DBS induced decline of word production within clusters shall be tested against the alternative possibility of an unspecific stimulation effect, impairing cluster and switch-related word processing to the same extent.

Therefore, word output under VF tasks from patients with active (ON) versus inactivated (OFF) DBS was subjected to temporal cluster analysis. Identified changes were correlated with DBS parameters and, for orientation purposes beyond DBS effects, the results were compared to those of healthy controls.

2. Participants and methods

2.1. Participants

Thirteen patients (eight female/five male) diagnosed with ET and treated bilaterally with VIM-DBS as well as fifteen (seven female/eight male) age and education matched healthy controls participated in the study.

All participants were native German-speakers and had no previous or current history of brain disease apart from ET (in case of patients), including all psychiatric disorders, such as depression, psychosis or apathy (according to the criteria of the German Manual for Psychopathological Diagnosis; AMDP, 2007). An overview over the participants’ demographic and baseline data is provided in Table 1A. The examinations were carried out both in OFF and

ON DBS conditions with a two-month interval in between (at a randomized order of the DBS condition). The ON condition was defined as the active therapeutic stimulation with stable parameters for at least two months. For the DBS OFF condition, DBS was switched off at least thirty minutes before the testing session. Medication – if applicable – remained unchanged. All participants had been recruited from the Outpatient Clinic for Movement Disorders of the Charité. They gave written informed consent to the study protocol approved by the ethics committee of the Charité (protocol number EA2/047/10).

2.2. Electrode localization

Electrode targets were defined preoperatively based on individual stereotactic MRIs in twelve out of the thirteen patients. To refine electrode placement, multiunit activity (MUA) was recorded intraoperatively from microelectrodes along 2–4 parallel trajectories. At the ventral border of the VIM a drop of background activity was expected. From there slightly further down the stereotactic trajectory, cell clusters discharging at the peripheral tremor frequency were identified in most patients, indicative of tremor-driving nuclear areas (Brodkey et al., 2004). At respective sites, macrostimulation was performed to estimate the clinical efficacy of the given electrode placement. Postoperatively, T2w-MRI data served to determine the exact electrode localizations per hemisphere: Data were first normalized in the standard Montreal Neurological Institute (MNI) stereotactic space (Horn & Kuhn, 2014; Schonecker, Kupsch, Kuhn, Schneider, & Hoffmann, 2009). Afterwards, MNI-localizations were detected for each active electrode contact by the center of the susceptibility artefact elicited by the DBS platinum-iridium contacts (Pollo et al., 2004). The geometrical centers of active electrode contacts were determined along the MNI-X (medio-lateral), MNI-Y (antero-posterior), and MNI-Z axis (rostro-caudal). The electrode contacts were then visualized in synopsis with a version of the Morel atlas (Morel, 2013) which had been digitized (Krauth et al., 2010) and normalized into MNI space (Jakab, Blanc, Berenyi, & Szekely, 2012) before. Based on stimulation parameters applied in the clinical setting, the electric field around the active electrodes induced by DBS was estimated using a finite electrode method (FEM) based approach as implemented in SimBio (Wolters, Seok, Macleod, & Hämmäläinen, 2010) and FieldTrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) toolboxes. This forward-modeling approach originally designed for EEG field-modeling was adapted for the case of DBS inside Lead-DBS. The volume of activated tissue (VAT) was determined by thresholding the E-Field gradient vectors at a value of 0.05 V/mm². An overview of the electrode localizations and VAT calculations is given in Fig. 4. The stimulation parameters are provided in Table 1B.

2.3. Baseline data

To assess cognitive functions such as working memory and executive functions, the Parkinson Neuropsychometric Dementia Assessment (PANDA) (Kalbe et al., 2008) was used. This comprehensive test was originally designed for assessing the cognitive state of patients with Parkinson’s disease and was shown to be superior to common short scales (Gasser, Calabrese, Kalbe, Kessler, & Rossier, 2016). It was used here because our study was embedded in a larger context of DBS investigations including patients with Parkinson’s disease and ET. Since the PANDA contains a VF test, this subtest was subtracted from the result, providing the *netPANDA* (maximum 23 points).

Tremor was quantified as the sum (maximum 32 points) of the following tremor scores, each ranging from 0 (no tremor) to 4 (maximum tremor): Upper limbs (right and left; postural and action), lower limbs (right and left), axial and voice tremor.

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