Brain & Language 134 (2014) 23–33

Contents lists available at ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Differential effects of deep brain stimulation on verbal fluency

Felicitas Ehlen [a], Thomas Schoenecker [b], Andrea A. Kühn [b,c], Fabian Klostermann [a,c,*]

[a] Charité, University Medicine Berlin, Dept. of Neurology, Motor and Cognition Group, Campus Benjamin Franklin, Germany
[b] Charité, University Medicine Berlin, Dept. of Neurology, Motor Neuroscience Group, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany
[c] Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Unter den Linden 6, 10099 Berlin, Germany

ARTICLE INFO

Article history:
Accepted 7 April 2014
Available online 9 May 2014

Keywords:
Parkinson's disease
Essential tremor
DBS
Localization
Verbal fluency

ABSTRACT

We aimed at gaining insights into principles of subcortical lexical processing. Therefore, effects of deep brain stimulation (DBS) in different target structures on verbal fluency (VF) were tested.

VF was assessed with active vs. inactivated DBS in 13 and 14 patients with DBS in the vicinity of the thalamic ventral intermediate nucleus (VIM) and, respectively, of the subthalamic nucleus (STN). Results were correlated to electrode localizations in postoperative MRI, and compared to those of 12 age-matched healthy controls.

Patients' VF performance was generally below normal. However, while activation of DBS in the vicinity of VIM provoked marked VF decline, it induced subtle phonemic VF enhancement in the vicinity of STN. The effects correlated with electrode localizations in left hemispheric stimulation sites.

The results show distinct dependencies of VF on DBS in the vicinity of VIM vs. STN. Particular risks for deterioration occur in patients with relatively ventromedial thalamic electrodes.

1. Introduction

Impaired verbal fluency (VF) has been repeatedly reported in the context of deep brain stimulation (DBS), particularly for DBS targeting the subthalamic nucleus (STN) in Parkinson's disease (PD) patients (Ardouin et al., 1999; Cilia et al., 2007; De Gaspari et al., 2006; Funkiewiez et al., 2004; Gironell et al., 2003; Lefaucheur et al., 2012; Mikos et al., 2011; Moretti et al., 2003; Morrison, 2004; Parsons, Rogers, Braaten, Woods, & Troster, 2006; Pillon et al., 2000; Saez-Zea, Escamilla-Sevilla, Katati, & Minguez-Castellanos, 2012; Saint-Cyr, Trepanier, Kumar, Lozano, & Lang, 2000; Smeding et al., 2006; Witt et al., 2013; Yamanaka et al., 2012; Zangaglia et al., 2009). Corresponding deficits are not easy to categorize, since VF comprises lexical and executive subcomponents, such as word search, access and suppression, set shifting, or rule adherence (Castner, Chenery, et al., 2007; Castner, Copland, et al., 2007; De Gaspari et al., 2006; Dromey & Bjarnason, 2011; McDonald, Brown, & Gorell, 1996; Saint-Cyr et al., 2000; Zec et al., 1999) and involves cortical, thalamic and basal ganglia (BG) structures (Castner et al., 2008; De Gaspari et al., 2006; Obeso, Casabona, Bringas, Alvarez, & Jahanshahi, 2012; Schroeder et al., 2003). Furthermore, in PD patients, disease related reduction of VF is frequently observed, possibly on the basis of imbalanced selection processes for lexical alternatives (Castner et al., 2008; Obeso et al., 2012). In patients with a history of DBS in the vicinity of STN, VF might additionally be hampered by an impaired ability to switch between word clusters (De Gaspari et al., 2006; Saint-Cyr et al., 2000).

As a neuroanatomical basis of DBS-induced VF declines, lesions from the stereotactic trajectory to the STN have been proposed, e.g. affecting the prefrontal cortex (Halpern, Rick, Danish, Grossman, & Baltuch, 2009; Lefaucheur et al., 2012; Mikos et al., 2011; Morrison, 2004; Okun et al., 2009; Pillon et al., 2000; Witt et al., 2008) or the head of the caudate nucleus (Witt et al., 2013). Further, the stimulation per se has been reported to subtly influence VF (Dromey & Bjarnason, 2011; Pillon et al., 2000), depending on the particular tissue volumes affected by DBS current spread in and outside the STN (Mikos et al., 2011; Okun et al., 2009; York, Wilde, Simpson, & Jankovic, 2009).

It is worthwhile to note that although postoperative VF decline is known also in DBS targeting the ventral intermediate nucleus (VIM) within the ventrolateral thalamus for patients with essential tremor (ET) (Benabid et al., 1996; Fields et al., 2003; Schuurman, Bruins, Merkus, Bosch, & Speelman, 2002; Troster, Wilkinson, Fields, Miyawaki, & Koller, 1998; Troster et al., 1999; Woods, Fields, Lyons, Pahwa, & Troster, 2003; Woods et al., 2001), systematic investigations on the actual stimulation effects of this DBS approach are scarce (Heber et al., 2013; Loher et al., 2003).

* Corresponding author at: Charité, University Medicine Berlin, Dept. of Neurology, Motor and Cognition Group, Campus Benjamin Franklin, Germany.
E-mail addresses: felicitas.ehlen@charite.de (F. Ehlen), thomas.schoenecker@charite.de (T. Schoenecker), andrea.kuehn@charite.de (A.A. Kühn), fabian.klostermann@charite.de (F. Klostermann).

http://dx.doi.org/10.1016/j.bandl.2014.04.002
0093-934X/

Further investigation of this issue appears promising, given that clinical and experimental observations range from lexical abnormalities in thalamic surgery, over complex aphasic syndromes in thalamic stroke, to the identification of language-related thalamic potentials in recordings from the ventrolateral thalamus – compatible with an involvement of thalamic nuclei in diverse language functions (Bogousslavsky, Regli, & Uske, 1988; Glenberg et al., 2008; Graff-Radford, Damasio, Yamada, Eslinger, & Damasio, 1985; Hebb & Ojemann, 2012; Hermann et al., 2008; Johnson & Ojemann, 2000; Karussis, Leker, & Abramsky, 2000; Lakoff & Johnson, 1980; Mateer & Ojemann, 1983; Repovs & Baddeley, 2006; Wahl et al., 2008; Wilson & Gibbs, 2007; for a review see Schmahmann, 2003). Accordingly, the assessment of topographical stimulation effects on VF pursues two aims, first, to collect clinically relevant information for the optimization of electrode targeting, and second to collect data which might be of interest with respect to the subcortical network involved in lexical processing. In the latter regard, different models have been formulated. One of the prevailing views is that cortico-thalamic operations underlie language-related capacities, whereby the thalamus is conceived as a kind of monitor to 'selectively engage' and connect regionally distributed cortices relevant for the ongoing linguistic demand (Mateer & Ojemann, 1983; Nadeau & Crosson, 1997; Skinner & Yingling, 1977; Tettamanti et al., 2005; Wahl et al., 2008; cf Alm, 2004). Other positions are that linguistic information is processed through cortico-basal-ganglia-thalamo-cortical loops, with the BG supporting the selection of competing lexical input from the cortex and the thalamus facilitating the release of chosen word representations (Crosson, 1985, 1992; Wallesch & Papagno, 1988), or that the basal ganglia (BG) serve the 'attentional engagement of semantic networks' (Copland, 2003). Further, it has been posited that the BG are merely involved in procedural, particularly inhibitory aspects of lexical processing (Castner et al., 2008; Longworth, Keenan, Barker, Marslen-Wilson, & Tyler, 2005).

Based on the above said, we presumed that, in general, patients with a history of DBS surgery would show VF deficits. With respect to DBS in the vicinity of VIM, we posited negative stimulation effects on VF via current spread into nuclei involved in lexico-phonemic and semantic processing, irrespective of alternating task demands. Regarding DBS in the vicinity of the subthalamic nucleus, we presumed a modulation of procedural rather than lexico-specific aspects of task performance. Such could become overt as changed performance in alternating VF conditions or in phonemic subtasks in which the use of combinatorial sound rules may be pivotal (Ullman, 2006).

Against this background, 13 vs. 14 patients with DBS in the vicinity of VIM and, respectively, of STN performed VF tasks ON as well as OFF stimulation, their regular drug treatment remaining unchanged. The subjects had to produce as many words as possible, belonging to predefined semantic or phonemic categories comprising both alternating and non-alternating task conditions. This permitted analysis of whether potential DBS effects reflected interactions with domain-specific word processing related to semantic vs. phonemic tasks or with other, e.g., frontal type functions, such as set shifting required in the alternating condition. Finally, specific correlations of obtained effects with spatial and dynamic stimulation parameters were calculated. All results were compared to those of healthy controls.

2. Subjects and methods

2.1. Participants

38 subjects participated in the study, 13 with ET, 14 with PD and 12 healthy controls. All ET patients were treated by DBS in the vicinity of VIM (VIM being the target electrode position), all PD patients with DBS in the vicinity of STN (STN being the target electrode position; for details see Tables 1a and 1b). Part of the results from the current PD group have been reported in a previous study (Ehlen et al., 2013).

All patients performed the experiments twice, i.e., ON vs. OFF DBS under continued drug treatment. The interval between the two sessions was about two months. The DBS OFF condition was defined as at least 30 min of DBS inactivation prior to experiment onset and the ON state as continuous stimulation with therapeutic stimulation parameters. The order of examinations in the ON vs. OFF states was randomized.

Participants were excluded if they scored below 15 points in the Parkinson Neuropsychometric Dementia Assessment (PANDA) or if they were diagnosed with brain diseases other than PD including all psychiatric disorders, such as depression, psychosis or apathy (according to the criteria of the German Manual for Psychopathological Diagnosis, AMDP, 2007). All participants were native German speakers. The groups were matched for age, years of education, PANDA, and disease duration.

Patients were clinically assessed using the motor section of the Unified Parkinson Disease Rating Scale (UPDRS, part III) and the PANDA. We defined tremor intensity as the sum-score of UPDRS subitems 20 and 21 (tremor at rest, action and postural).

The study participants were recruited from the Outpatient Clinic for Movement Disorders of the Charité. All subjects gave written informed consent to the study protocol approved by the local ethics committee.

2.2. Electrode localization

Target points had been calculated based on individual preoperative stereotactic MRIs. Intraoperatively, they were confirmed by the typical firing patterns in microelectrode recordings. The clinical efficacy of electrode targeting was intraoperatively assessed by test macrostimulations.

Table 1a
Baseline characteristics.

Characteristics	DBS patients		Controls	*p*-Values		
	VIM *n* = 13 *M* (±SD)	STN *n* = 14 *M* (±SD)	 *n* = 12 *M* (±SD)	Controls vs. VIM	Controls vs. STN	VIM vs. STN
Age (years)	69.38 (±9.43)	63.43 (±8.31)	66.17 (±7.37)	.12	.96	.09
Educ. (years)	9.54 (±1.76)	10.36 (±1.45)	9.33 (±0.98)	.96	.15	.20
Gender (f/m)	7/6	3/11	5/7	.70	.41	.23
Handedness (r/l)	12/1	13/1	10/2	.59	.22	1.00
PANDA (points)	22.00 (±5.34)	22.29 (±22.29)	25.75 (±2.63)	.14	.10	.88
Disease duration (years)	15.77 (±13.50)	13.79 (±5.03)				.61
DBS duration (years)	3.02 (±2.83)	3.43 (±2.03)				.67

This table provides an overview of baseline characteristics of both patient groups and healthy controls (Cntr).