Neuropsychologia 89 (2016) 74–82

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Effects of thalamic deep brain stimulation on spontaneous language production

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ARTICLE INFO

Article history:
Received 25 January 2016
Received in revised form
18 April 2016
Accepted 25 May 2016
Available online 4 June 2016

Keywords:
VIM-DBS
Thalamus
Spontaneous language
Syntax

ABSTRACT

The thalamus is thought to contribute to language-related processing, but specifications of this notion remain vague. An assessment of potential effects of thalamic deep brain stimulation (DBS) on spontaneous language may help to delineate respective functions.

For this purpose, we analyzed spontaneous language samples from thirteen (six female / seven male) patients with essential tremor treated with DBS of the thalamic ventral intermediate nucleus (VIM) in their respective ON vs. OFF conditions. Samples were obtained from semi-structured interviews and examined on multidimensional linguistic levels.

In the VIM-DBS ON condition, participants used a significantly higher proportion of paratactic as opposed to hypotactic sentence structures. This increase correlated negatively with the change in the more global cognitive score, which in itself did not change significantly.

In conclusion, VIM-DBS appears to induce the use of a simplified syntactic structure. The findings are discussed in relation to concepts of thalamic roles in language-related cognitive behavior.

1. Introduction

Deep brain stimulation (DBS) is a therapeutic option successfully used for the treatment of patients with different long-term movement disorders (Martinez-Ramirez et al., 2015). Next to the most common application of DBS of the subthalamic nucleus (STN) in patients with Parkinson's disease (PD), DBS of the thalamic ventral intermediate nucleus (VIM) is mainly applied to treat patients with essential tremor (ET) (Koller et al., 1999; Obwegeser et al., 2000; Pahwa et al., 2006; Sydow et al., 2003; Zhang et al., 2010; for a review see Chopra et al., 2013). In this context it appears noteworthy, that the thalamus is thought to be crucially involved in the integration of both sensorimotor and cognitive processes, thus enabling contextually suitable behaviors (Ahrens et al., 2015; Bradfield et al., 2013; Fama and Sullivan, 2015; Ferguson and Gao, 2015; Funahashi, 2013; Ketz et al., 2015; Klostermann, et al., 2006, 2009; Marzinzik et al., 2008; Mitchell et al., 2014; Nikulin et al., 2008; Pinault, 2004; Saalmann and Kastner, 2015; Schmahmann and Pandya, 2008). On the level of language processing, such thalamic function has been conceived as the integration, modulation, and monitoring of cortical language-specific and working memory functions – complemented by the basal ganglia (Crosson, 1985, 1992; Lieberman, 2002; Nadeau and Crosson, 1997; Ullman, 2001, 2004, 2006; Wahl, et al., 2008; for reviews see Barbas et al., 2013; Crosson, 2013; Klostermann et al., 2013; Saur et al., 2008). Particularly ventral, mediodorsal, and intralaminar nuclei (Barbas et al., 2013; Ehlen et al., 2014; Woods et al., 2003) have been proposed as candidate structures for language-relevant functions.

Early conceptions of an integrative thalamic function for language performance came from observations of lexical abnormalities under intraoperative thalamic stimulation (e.g., Hugdahl and Wester, 1997; Ojemann, 1985; Ojemann and Ward, 1971; for a review see Hebb and Ojemann, 2012) and particularly from repeatedly observed "thalamic aphasia" in patients with a history of left hemispheric thalamic stroke. These patients typically suffer from anomia, semantic paraphasia, decreased verbal output and fluency, as well as varying degrees of comprehension deficits (e.g., Bogousslavsky et al., 1986; Carrera and Bogousslavsky, 2006;

Abbreviations: ANOVA, analysis of variance; *DBS*, deep brain stimulation; *ET*, essential tremor; *PANDA*, Parkinson Neuropsychometric Dementia Assessment; *PD*, Parkinson's disease; *STN*, subthalamic nucleus; *VF*, verbal fluency; *VIM*, ventral intermediate nucleus

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http://dx.doi.org/10.1016/j.neuropsychologia.2016.05.028

Crosson, 1984; Kuljic-Obradovic, 2003; Liebermann et al., 2013; Nolte et al., 2011; Pergola et al., 2013; Raymer et al., 1997; for reviews see Crosson, 2013; De Witte et al., 2011; Schmahmann, 2003; Van der Werf et al., 2000). Respective deficits appear to increase as a function of sentence complexity and were proposed to result from a reduced thalamic ability to relate sentence elements to one another (Crosson, 2013). In a similar sense, semantic paraphasia in patients with thalamic lesions was argued to result from impaired semantic feature binding (Crosson, 2013), i.e., a reduced capacity to integrate cortically stored semantic features to create a complete concept of the respective word (Assaf et al., 2006; Crosson, 2013; Hart et al., 2013; Kraut et al., 2002a, 2002b; Nadeau and Crosson, 1997; Stringaris, et al., 2007).

In line with these clinically-motivated findings, an integrative thalamic function was suggested by electrophysiological studies indicating thalamo-cortical co-activity during semantic and syntactic information processing (Hohlefeld et al., 2013; Krugel et al., 2014; Slotnick et al., 2002; Wahl et al., 2008).

However, concrete implications for spontaneous language are difficult to assess systematically. Given that VIM-DBS induces functional state changes well defined with respect to their timing and neuroanatomical point of action in the thalamus, the evaluation of its neuromodulatory effects on language processing may provide further insight into respective functions.

In this regard it is worth noting that reduced word production in verbal fluency (VF) tasks has regularly been found under active VIM-DBS (Benabid et al., 1996; Ehlen et al., 2014; Fields et al., 2003; Schuurman et al., 2002; Troster et al., 1999, 1998; Woods et al., 2001, 2003). However, effects of VIM-DBS on natural language have – to our knowledge – not yet been examined. This seems surprising because, from a practical perspective, the question of whether the mentioned DBS effects on VF indicate impairments also on the level of communication, relates to important aspects of patients' everyday social life. In view of the presumed integrational thalamic function outlined above, VIM-DBS was expected to impact on spoken language primarily on the level of complexity, particularly affecting the hierarchical organization of sentences and possibly word composition or class. However, to gain a broader picture of VIM-DBS effects on natural language beyond these levels, a large number of linguistic measures was additionally investigated.

We therefore comprehensively assessed spontaneous language samples from semi-structured interviews of patients with VIM-DBS in their ON vs. OFF stimulation conditions. The aim of the study was two-fold: conceptually to gain further information about thalamic contributions to biolinguistic functions and clinically to complement the understanding of potential DBS non-motor side effects.

2. Patients and methods

2.1. Patients

Thirteen patients (six female / seven male) diagnosed with ET and treated with VIM-DBS participated in the study, all of whom were right-handed native German-speakers. VIM-DBS had been established for at least one year in all but one patients (who had been treated for six months) and was generally applied bilaterally except for one participant with left-hemispherical DBS only. None of the participants had a previous or current history of brain disease other than ET, 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 data is provided in Table 1. The examinations were carried out in the ON vs. OFF stimulation state within a two-month interval in randomized order. Medication, if applicable, remained unchanged.

Table 1
An overview of the participants' baseline characteristics is given as group mean values and standard deviations (SD) including DBS-related parameters. All data relate to the individual ON-stimulation session.

A. Participants' Baseline Data			
	Mean	SD	Range
Age (years)	70.15	± 9.24	69–75
School education (years)	9.62	± 1.71	13–13
Disease duration (years)	15.38	± 13.57	11–56
DBS duration (years)	3.50	± 3.19	.5–10
B. Stimulation Parameters			
	Right	Left	
	Mean ± SD	Mean ± SD	
Amplitude (V)	3.32 ± 1.46	3.11 ± 1.49	
Pulse width (μs)	60.00 (median)	60.00 (median)	
Frequency (Hz)	152.50 ± 33.27	162.69 ± 48.63	
Polarity (mono / bi)	8 / 4	8 / 5	
Position of center of active contacts			
x (mm)	14.10 ± 1.32	13.91 ± 1.47	
y (mm)	− 15.46 ± 1.36	− 15.47 ± 1.32	
z (mm)	− 1.30 ± 1.89	− 1.33 ± 1.44	

An overview of the participants' baseline characteristics is given as group mean values and standard deviations (SD) including DBS-related parameters. All data relate to the individual ON-stimulation session.

For the DBS OFF condition, stimulation was switched off at least thirty minutes before beginning the interview (in order to attain a situation that was considered a compromise between informative value and strain for the patients). Examinations in the DBS ON condition were carried out under therapeutic stimulation parameters that had been stable for at least two months prior to the assessment.

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 local ethics committee (protocol number EA2/047/10).

2.2. VIM-DBS implantation

Implantation of tetrapolar DBS electrodes (Medtronic®, model 3378) into the VIM had been performed by stereotactic surgery based on preoperative MRIs. Electrode localization had been accomplished using atlas coordinates as well as intraoperative micro-electrode recordings and intraoperative macro-electrode stimulation. They were confirmed by post-operative T2w-MRIs within two days after the implantation. All operations were carried out in the Charité University Hospital Berlin in the Department of Neurosurgery by the same neurosurgeon and his team at the Campus Virchow Klinikum.

2.3. Spontaneous language samples

Spontaneous language samples were acquired from semi-structured interviews conducted by an interviewer trained in psychological interviewing and were digitally recorded (software: Audacity 1.3.13-beta, microphone: the t.bone MB 88U Dual) in a sound-proof chamber within the Charité University at the Campus Virchow Klinikum. Patients were comfortably seated on a chair in an upright position. The microphone (the t.bone MB 88U Dual) was located at a distance of approximately 30 cm from the mouth. The sound quality was checked and adjusted in the beginning of each interview by simultaneously listening to the spoken voice via