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Worsening of Verbal Fluency After Deep Brain Stimulation in Parkinson's Disease: A Focused Review

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ABSTRACT

Worsening of verbal fluency after treatment with deep brain stimulation in Parkinson's disease patients is one of the most often reported cognitive adverse effect. The underlying mechanisms of this decline are not well understood. The present focused review assesses the evidence for the reliability of the often-reported decline of verbal fluency, as well as the evidence for the suggested mechanisms including disease progression, reduced medication levels, electrode positions, and stimulation effect vs. surgical effects. Finally, we highlight the need for more systematic investigations of the large degree of heterogeneity in the prevalence of verbal fluency worsening after DBS, as well as provide suggestions for future research.

1. Introduction

This focused review was invited as a result of the II. International Conference on Deep Brain Stimulation (Düsseldorf, March 2016), and it aims to provide an up-to-date status on the incidence and potential explanations for the often-reported verbal fluency (VF) decline after deep brain stimulation (DBS) in Parkinson's disease (PD), as well as a set of pointers for future research. Several explanations have been proposed including disease progression, reduced medication levels, microlesions, as well as electrode location and stimulation itself, but with no clear conclusions drawn so far. Advancing our understanding of this aspect of DBS contributes to the continued improvement of the DBS treatment, as well as to our understanding of the effect mechanisms behind DBS.

The timeliness of this focused review has allowed us to include three recently published meta-analyses on neuropsychological adverse effects (including VF worsening) after DBS in PD [12,80,81]. As revealed by Combs et al. [12], there are relatively few studies assessing VF declines after DBS in the internal globus pallidus (GPi) compared to DBS in subthalamic nucleus (STN), which is also mirrored in this review. This underrepresentation of GPi studies is reflective of a general tendency in the field to prefer STN to GPi as target for DBS in PD [63], as well as of potential differences in cognitive adverse effects between the two targets [12].

The structure of this review centers around two overarching questions:

1. What is the evidence for verbal fluency (VF) worsening after DBS-treatment in PD?
2. What are the possible mechanisms underlying such a decline?

In response to 1, we will review the evidence for the commonly reported VF decline in relation to pre- and post-surgery evaluations for both STN- and GPi-DBS, as well as highlight the large degree of heterogeneity in the incidence of VF worsening following DBS, which has not been investigated systematically yet.

In response to 2, we will review the literature in relation to suggested explanations such as disease progression, reduced medication levels, electrode positions, and stimulation vs. lesion effects.

2. Background

PD is a progressive neurodegenerative disease characterized by the motor symptoms rest tremor, postural instability, rigidity and bradykinesia (slowness of movement) and a variety of non-motor symptoms including cognitive decline and worsening of VF [53,86].

DBS in STN and GPi has been shown to effectively alleviate PD patients' motor symptoms when medication is no longer a viable treatment [17,21,32,36,46,87,88]. However, the effects of DBS on cognition are still not well understood [79]. And as already mentioned, one of the most consistently reported detrimental effects of DBS in PD is a worsening of VF [12,48,69,79–81]. VF deficits are also part of the PD symptomatology prior to DBS surgery [24], but the underlying cause of the worsening after DBS is still an open question.

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Verbal fluency is tested with a task requesting the patient, within a minute, to name as many words as possible starting with a specific letter (e.g., F, A, or S; known as phonemic or letter fluency) or stemming from a given category (e.g., animals; known as semantic or category fluency) [8,35]. Deficits in verbal fluency may thus come about from both linguistic and executive dysfunctions as it involves a multitude of cognitive processes including lexical search, memory retrieval, executive functioning, and response monitoring, inhibition, and selection [35,59].

3. Evidence for Worsening of Verbal Fluency After DBS

When assessing the evidence for VF worsening after DBS, it is important to note the point raised by Woods et al. [78] that far from all studies reporting on cognitive sequelae of DBS include the sufficient sample sizes to detect even large effect sizes. In fact, in their sample of 30 published studies between 1997 and 2004, only two studies did. This urges caution in interpreting the results of most individual studies on this topic and places a strong emphasis on the results of carefully conducted meta-analyses, and in the absence of such on the results from well-powered randomized control trial (RCT) studies.

Fortunately, in relation to the evidence for VF worsening after DBS, two meta-analyses have aptly summed up the available literature on pre- and post-surgery evaluations of the cognitive sequelae of DBS at least three months after surgery.

Parsons et al. [48] conducted a meta-analysis on 28 studies from 1990 to 2006 on STN-DBS meeting inclusion criteria which included reporting of change scores and neuropsychological evaluations at baseline and follow-up. Among the 28 studies, 16 reported data for phonemic VF (355 patients), and 16 reported data for semantic VF (337 patients), summing up to 21 studies in total reporting on phonemic and/or semantic VF. On the basis of this, they found average effect sizes of moderate size (0.51 and 0.73) for both phonemic and semantic VF declines.

Combs et al. [12] extended Parsons et al.'s [48] meta-analysis from 2006 by analyzing studies with baseline and follow-up neuropsychological evaluations from both STN- and/or GPi-DBS treatments in PD. These meta-analyses revealed that both targets resulted in moderate effect size declines in both phonemic and semantic VF. However, the available evidence for the effects of GPi-DBS on VF are still relatively sparse, and therefore the observed slight disadvantage for STN is inconclusive. In their meta-analyses on STN-DBS and GPi-DBS, there are, however, a few inconsistencies. First, there are overlapping study cohorts (Ardouin et al. [5] and Pillon et al. [50]; as well as Daniels et al. [15] and Witt et al. [74]). Second, the reported total number of studies included vs. those listed in the overview table do not exactly match ([12], Table 1). And third, the total numbers of patients reported for the phonemic VF task for both STN-DBS and GPi-DBS exceed the total sums of included study patients in the overview table ([12], Tables 1–3). Nonetheless, these inconsistencies are minor, and we deem the reported results credible.

There is thus reliable evidence for a worsening of moderate effect size in both phonemic and semantic VF after STN-DBS. The evidence for a similar decline in GPi-DBS is still too sparse to be considered reliable, but there are subtle tendencies suggesting a slight disadvantage for STN (when considering other cognitive adverse effects, as well).

Following the publication of the results from the large RCT study on STN- and GPi-DBS by the CSP-468 Study Group ([21,55,70,71], the debate on which target – STN or GPi – to select for DBS in PD has received renewed attention [42,73].

4. Suggested Causes of Worsening of Verbal Fluency

4.1. Disease Progression

In order to assess the continued disease progression as a potential explanation of the reported VF declines, studies are needed which include a matched PD control group on best medical treatment (BMT) with VF testing at similar baseline and follow-up intervals as the DBS group. Very recently, two meta-analyses were conducted on such studies comparing VF declines in STN-DBS PD patients and in PD patients on BMT [80,81]. Both meta-analyses seem to confirm that PD patients after STN-DBS treatment experience VF worsening to a larger extent (i.e., moderate to small effect sizes) than matched PD patients on BMT. However, these results should be interpreted with considerable caution due to substantial methodological issues in both meta-analyses.

First, Wyman-Chick [80] included eligible studies published between 2000 and June 2014, but only 9 out of 140 identified studies met the study's inclusion criteria for phonemic VF and also only 9 for semantic VF (i.e., in total, 10 studies were included: 8 with both phonemic and semantic, 1 with only phonemic, and 1 with only semantic VF data). Furthermore, the author relied on comparisons of the two groups' VF scores only at the follow-up evaluation (and not the groups' change scores). But a difference in follow-up scores is not necessarily reflective of a difference in change scores. Both Marshall et al. [38] and Zangaglia et al. [85] are examples of this discrepancy. In Marshall et al. [38] neither phonemic nor semantic VF changes were significantly different between the DBS-treated and BMT groups ($p = 0.41$ and $p = 0.60$, respectively). However, when only the follow-up values were included in Wyman-Chick's [80] meta-analysis, the differences between the two groups were assigned adjusted effects sizes of −0.33 and −0.21 for phonemic and semantic VF, respectively, denoting small, but substantial, differences between the two groups at follow-up. Zangaglia et al. [85] reported a significant difference in phonemic VF scores between the two groups at the 36-month-follow-up. However, there was already a noticeable difference between the two groups at the baseline, albeit non-significant, and the STN-DBS PD group's phonemic VF scores did not change significantly between baseline and follow-up ($p = 0.164$). Hence, none of the included differences in follow-up VF scores from the two studies adequately reflect a reduction in VF scores due to the DBS treatment compared to BMT.

Second, Xie et al. [81] included studies published until June 2015 and focused on potential differences in the two groups' change scores. For the VF deficits, this meant that only 6 and 4 out of 172 identified articles were included for phonemic and semantic VF, respectively (these numbers are available in the article's supplementary material). Unfortunately, the authors included both Witt et al. [75] and Daniels et al. [15] as separate studies, yet these are overlapping cohorts (Witt et al. [75] analyzed a subset of the patients in Daniels et al. [15]). Furthermore, it seems the authors selected the wrong standard deviation (SD) values from the study by Castelli et al. [9] and Rothlind et al. [55]. They wrongfully interpreted the SD values of the mean values at the follow-up evaluations as belonging directly to the change scores. Castelli et al. [9] is also included in Wyman-Chick's [80] meta-analysis where she has interpreted exactly the same SD values as belonging to the mean values at the follow-up evaluation. Furthermore, it is not clear why only the phonemic (and not also semantic) VF values were included from Cilia et al. [11], Merola et al. [40], and Rothlind et al. [55] (where semantic VF values are listed under “Processing speed” in Table 3), and vice-versa for the semantic (but not phonemic) VF values from Williams et al. [72], when both sets of VF values were readily available in all four studies. Including these values could have increased the number of properly included studies for both VF scores to six (when also accounting for the overlap between Witt et al. [75] and Daniels et al. [15]).

Hence, both meta-analyses suffer from relatively low power ([81], in particular), as well as from substantial methodological issues. We therefore consider their combined evidence relatively inconclusive.

However, if we focus on the two RCT studies included in the meta-analyses, i.e., Witt et al. [74] and Rothlind et al. [55], they both provide evidence in the form of well-powered direct comparisons of the change scores of both DBS and BMT groups. Both report significant worsening of both phonemic and semantic VF in the DBS groups compared to the BMT group between baseline and after 6 months. In fact, Rothlind et al. [55] included both an STN- and a GPi-DBS group, and both groups showed very similar declines in VF after DBS compared to the BMT