COMPARISON OF THE EFFICACY OF UNIPOLAR AND BIPOLAR ELECTRODE CONFIGURATION DURING SUBTHALAMIC DEEP BRAIN STIMULATION

(Full length article)

Gabriella Deli, MD¹; Istvan Balas MD, PhD²; Ferenc Nagy¹, MD, PhD¹; Eva Balazs, NP¹; Jozsef Janszky¹, MD, PhD¹; Samuel Komoly¹, MD, DSc¹;
Norbert Kovacs¹*, MD, PhD

¹Department of Neurology, University of Pecs, Pecs, Hungary
²Department of Neurosurgery, University of Pecs, Pecs, Hungary

Correspondence to:
Dr. Norbert Kovacs, MD, PhD
University of Pecs
Department of Neurology
H-7623, Pecs, Ret utca 2,
Tel: +36 72 535-900
Fax: +36 72 535911
Email: norbert.kovacs@aok.pte.hu

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Abstract

Deep brain stimulation of the subthalamic nuclei (STN) is a well established treatment in advanced Parkinson’s disease (PD). Based on the clinical efficacy and elicited side-effects, both unipolar and bipolar stimulation modes may be applied. Bipolar stimulation usually produces a more focused and therefore thinner area of tissue activated during stimulation than unipolar stimulation does. The primary aim of our clinical study was to quantify the different clinical efficacy between these two stimulation modes.

Twenty-one patients with PD previously underwent bilateral STN DBS implantation were involved in the study. Approximately three years after the implantation, we evaluated rigidity, tremor and bradykinesia according to the Unified Parkinson’s disease Rating Scale in a practically off condition. Keeping the cathode of the chronic stimulation setting constant, the amplitude of stimulation was changed between 0 and 3.6V by 0.2V steps. Subsequently, the improvements in rigidity, tremor and bradykinesia were compared between unipolar and bipolar modes using 60µs pulse-width and 130Hz frequency.

Within the examined amplitude range, unipolar stimulation usually had a significantly higher efficacy than bipolar stimulation; however, also with a higher rate of side-effects (19% vs. 0%). Depending on the evaluated parkinsonian symptoms, the efficacy of uni- and bipolar stimulation was different. To achieve the same level of improvement during bipolar stimulation, approximately 0.4-0.5V higher amplitude was required than in unipolar mode. However in some cases, the efficacy of bipolar
stimulation was unable the reach that of unipolar stimulation within the examined amplitude-range.

**Abbreviations:** ADL = Activities of Daily Living (Schwab and England Scale); HYS = modified Hoehn Yahr Scale; UPDRS = Unified Parkinson’s Disease Rating Scale, STN = subthalamic nucleus, VTA = volume of tissue activated during stimulation
Introduction

The efficacy of bilateral deep brain stimulation (DBS) of subthalamic nuclei (STN) in the treatment of drug-refractory advanced idiopathic Parkinson’s disease is demonstrated by several randomized, controlled trials[1, 2] and metaanalyses[3]. Based on the clinical situation and elicited side-effects, two types of stimulation modes might be applied for achieving optimal therapeutic improvement: unipolar and bipolar stimulation[4, 5].

In case of unipolar stimulation, one or more of the contacts are programmed to cathode (negative pole) against the case of implantable pulse generator (IPG), whereas in bipolar settings at least two contacts on the electrode are activated, one as cathode and another as anode (positive pole). The current diffusion entirely differs between these modes: Unipolar stimulation provides a roughly radial current diffusion that covers an approximately spherical space around the stimulating electrode with a relatively high volume of tissue activated during stimulation (VTA)[6]. In contrast, bipolar stimulation creates a narrower and more focused current field with a maximal effect near the cathode[7].

From the clinical practice it is generally considered that "monopolar stimulation is usually used because it requires lower stimulation intensity than bipolar stimulation to achieve approximately the same clinical benefit."[5] The aim of this study was to quantify the difference between the uni- and bipolar stimulation and provide a clinically applicable approach how to change between these modes.
Methods

Subjects

Twenty-one patients with idiopathic PD (12 male, age 61.8±7.1 years) were enrolled. All of them fulfilled the UK Brain Bank criteria[8] for PD and underwent bilateral subthalamic DBS implantation 3.3±1.5 years before the examination. (Table 1) Each subject gave written informed consent according to the Regional Ethical Board of University of Pecs. All of the enrolled patients were operated and programmed at University of Pecs according to the previously published protocols.[9] In all cases STN DBS produced a stable and prominent improvement with unchanged stimulation parameters >1 year and a postoperative brain MRI verified the appropriate electrode position. (Supplementary material)

Study procedure

The clinical efficacy of DBS was evaluated in a practically off period, after an overnight (>12 hours) drug withdrawal[10]. Severity of rest tremor, rigidity and bradykinesia was measured on the upper extremities based on the appropriate UPDRS items (20, 22 and 23). At least 30 minutes before starting the investigations, the parameters of stimulation were set to 0 Volts 130 Hz 60 µs on both electrodes allowing chronic stimulation effect to vanish. Subsequently, stimulation with 0V was considered the baseline level.

We started the examination with a randomly assigned order of bipolar or unipolar stimulation of the electrode contralateral to the side with the more prominent parkinsonian symptoms. In case of unipolar settings, the contact with the best therapeutic effect (the cathode during the chronic stimulation) was programmed to cathode and the case of IPG was set to anode; whereas for bipolar stimulation an
adjacent contact (usually the proximal one) was programmed to anode and the cathode remained unchanged.

Subsequently, the amplitude of stimulation was changed between 0 and 3.6 Volts by 0.2V increments while frequency and pulse-width remained constant. After each amplitude increment, we waited for at least 15 seconds before evaluating the parkinsonian symptoms by the means of UPDRS. If persistent and disabling stimulation-related side-effect developed, we had forborne from increasing the Voltage of the stimulation further. After finishing the evaluation of one stimulation mode, the patient had a small break before changing to the other mode. To ensure the reliability of UPDRS measurement, the same examiner (EB) evaluated the efficacy in all patients.

To measure the efficacy of DBS, we compared the appropriate UPDRS values at each amplitude level to the baseline. Subsequently, the effects of uni- and bipolar stimulation modes were contrasted.

**Statistical analysis**

Statistical evaluation was done by using the SPSS software package (version 17, SPSS Inc.). Because none of the obtained data followed the normal distribution, non-parametric Mann-Whitney, Wilcoxon’s and Kruskal-Wallis tests were performed. For correlation analysis, Spearman’s rho was calculated. The level of statistical significance was set at 0.05.

**Results**

**Occurrence of persistent stimulation-related side-effects**

Within the examined stimulation settings, unipolar stimulation produced persistent stimulation-related side-effects more often than bipolar stimulation did \((p<0.05)\). Applying bipolar stimulation, we could increase the amplitude of stimulation up
to 3.6V without eliciting any persistent stimulation-related side-effects. However, using unipolar stimulation four patients experienced severe stimulation-related side-effects (e.g. double-vision or capsular symptoms) before reaching the amplitude of 3.6V. Therefore in these four subjects, we were unable to assess efficacy of unipolar stimulation using amplitudes higher than the thresholds for eliciting side-effects (2.8V, 3.0V, 3.2V, and 3.2V).

Appearances of slight, non-disabling and temporary paraesthesias did not interfere with the evaluation process and were not included in calculation of side-effects.

**Rigidity**

The relation between the severity of rigidity and the amplitude of stimulation is demonstrated by Figure 1. Only amplitude equal to or higher than **1.0V** produced significant improvement in rigidity compared to baseline. Between the severity of rigidity and the applied stimulation amplitude a prominent and significant negative correlation could be demonstrated (**rho=-0.926, p<0.001**).

Uni- and bipolar stimulation had statistically similar efficacy on rigidity while the amplitude of **3.0 V** or less was applied. In the cases where higher Voltage values were used, however, unipolar stimulation turned to be more efficient (**p<0.05, Figure 1**). Interestingly, bipolar stimulation up to 3.6V was unable to reach the therapeutic efficacy of unipolar stimulation with 3.2V.

Comparing amplitude levels requiring improving rigidity from 2-points to 1-point and from 1-point to 0-point, significantly higher Voltages were required in bipolar mode than in unipolar electrode configuration. (**Table 2**)

**Bradykinesia**

Bradykinesia measured by UPDRS item 23 did not demonstrate any statistically significant improvements compared to baseline until **1.4V** was applied in either unipolar
or bipolar mode. The higher the amplitude was the higher improvement in bradykinesia could be observed. Again, a strong and significant negative correlation could be calculated between the amplitudes of stimulation and the level of bradykinesia ($r=\textbf{-0.908}$, $p<0.001$, Figure 2).

Efficacy of bipolar and unipolar stimulation in reducing bradykinesia significantly differed in cases where amplitude of 2.6V or higher were applied ($p<0.05$). Using bipolar stimulation within this amplitude range, approximately 0.3-0.4V higher amplitudes were needed than that of unipolar stimulation to achieve numerically the same therapeutic improvement. Similarly to the case of rigidity, bipolar stimulation with 3.6V was unable to catch-up with the efficacy of unipolar stimulation of 3.0V.

As far as the clinical efficacy was matched, unipolar stimulation required 0.46V less amplitude to improve bradykinesia from the severity of 1-point on UPDRS item 23 to 0 point. (Table 2)

**Rest tremor**

Compared to baseline, there was no statistically significant improvement in rest tremor if amplitude less than 1.4V were applied. Deep brain stimulation with amplitudes of at least 1.4V produced significant tremor reduction, which suggested a strong negative correlation between the amplitude and tremor severity ($r=\textbf{-0.879}$, $p<0.001$, Figure 3).

As far as tremor reduction was concerned, there was no statistically significant difference between the efficacy of uni- and bipolar stimulation modes within the range of 0-2.6V. However, unipolar stimulation significantly better improved rest tremor than bipolar stimulation did using voltages above 2.8V. Interestingly bipolar stimulation in the range of 2.8-3.6V was unable to catch up and reach the therapeutic efficacy of unipolar stimulation with 2.8V.
Discussion

Although several studies evaluated the effects of unipolar STN DBS on various Parkinsonian symptoms[11] and demonstrated that stimulation parameters have a great impact on clinical outcome[4, 5, 11, 12], cognitive performance[13, 14], freezing of gait[15, 16] and apraxia of eyelid opening[17], this is the first systematic comparison between the efficacy of unipolar and bipolar stimulation modes, as far as the authors are aware. In this study we compared the efficacy of uni- and bipolar stimulation on various parkinsonian symptoms as a respect of stimulation amplitude. For chronic stimulation in nearly 80-90% of the cases unipolar stimulation is applied because it requires lower stimulation intensity and therefore allow longer battery life compared to bipolar stimulation[5]. However, in cases where stimulation-related side-effects occur, meaning an unwanted current diffusion to other neuronal networks situated nearby STN, changing from unipolar to bipolar stimulation might be a solution[4, 5].

Fulfilling our expectation, unipolar stimulation was able to improve rest tremor, rigidity and bradykinesia to a larger extent than bipolar stimulation could. Interestingly, the difference between these stimulation modes was statistically insignificant until a certain amplitude level had been reached. The level of this threshold varied depending on the type of examined Parkinsonian symptoms (2.6V for bradykinesia, 2.8V for rest tremor and 3.2V for rigidity).

Besides describing the different therapeutic effects of uni- vs. bipolar stimulation, our primary aim was to provide a clinically well usable rule of thumb to ease switching from one mode to another. Based on our study, we can conclude that there is no universal quotient which could be applied under all possible circumferences. Because up to 2.6V both stimulation modes had similar efficacy, theoretically one can change from one mode to the other by leaving the value of amplitude unchanged. However, in cases
where higher Voltage levels are used, after changing to bipolar mode 0.3-0.5V higher amplitude may be needed to achieve similar symptomatic control. This difference represents approximately a 10-20% increment in the amplitude of unipolar stimulation.

Of note, bipolar stimulation in the range of 2.8-3.6V was unable to achieve the same therapeutic efficacy as unipolar stimulation with the amplitude of 2.8V had on rest tremor. Similar phenomenon could be observed in other parkinsonian symptoms, however, with different threshold levels: Bipolar stimulation up to 3.6V was unable to catch-up with the efficacy of 3.0V unipolar stimulation for bradykinesia and that of 3.2V unipolar stimulation for rigidity. However it remains unknown whether a further increase in the amplitude of bipolar stimulation (to a value of >3.6V) would have improved further its efficacy of bipolar stimulation or not.

The difference in efficacy of bipolar and unipolar stimulation modes is probably due to the divergent current diffusion to the surrounding tissue and the size of VTA. Because the contact with negative pole was kept constant during both stimulation modes and adjacent contacts were used for bipolar stimulation, possibly the difference in VTA may play a major role in the different therapeutic outcome. To minimize a possible error arising from different electrode locations, we exclusively enrolled patients with stable improvement (>3 years) after DBS implantation and good electrode position confirmed by postoperative brain MRI.

One of the limitations of the study is the narrow spectrum of possible stimulation parameter configurations examined. We applied only a constant frequency with 130 Hz and a pulse-width of 60 µs because we took the length of the examination into consideration during planning the present study. In the present protocol we evaluated the efficacy of 36 different stimulation parameters requiring approximately 60-70 minutes depending on the physical status and the compliance of the patient. Therefore we thought that testing other pulse-width or frequency values would have significantly
increased the burden of patients resulting in bias and less reliable data due to fatigue and/or worse compliance.

Another important drawback of our study is the arbitrary cessation of exploration of stimulation amplitudes beyond 3.6V. Because in our cases amplitude levels less than 3.6V were applied for chronic stimulation and including more intensity levels would have increased the burden of the subjects, in the planning phase of the present study we decided to analyze the efficacy of stimulation between 0-3.6V. However, based on our results, the authors are aware of the fact that this approach prevented us to explore the whole therapeutic window. If more latitude was given on voltage and settings, the efficacy of bipolar stimulation could more closely approximate that of unipolar stimulation. Similarly, using bipolar stimulation with larger span of the contacts could have resulted in different, presumably higher, efficacy. Therefore, further studies are required to compare the efficacy of unipolar and bipolar stimulation at various amplitude, frequency or pulse width combinations.
References


Legends

**Figure 1.** The relationship between the amplitude of unipolar (solid line) and bipolar stimulation (dotted line) in Volts and severity of rigidity measured by the UPDRS item 22 is demonstrated (median). Significant improvements compared to the baseline are marked by the appropriate significance levels. Significant differences between the efficacy of uni- and bipolar stimulation are presented by vertical arrows ($p<0.05$).

**Figure 2.** The relationship between the amplitude of unipolar (solid line) and bipolar stimulation (dotted line) in Volts and severity of bradykinesia measured by the UPDRS item 23 is demonstrated (median). Significant improvements compared to the baseline were marked by the appropriate significance levels. Significant differences between the efficacy of uni- and bipolar stimulation are presented by vertical arrows ($p<0.05$).

**Figure 3.** The relationship between the amplitude of unipolar (solid line) and bipolar stimulation (dotted line) in Volts and severity of rest tremor measured by the UPDRS item 20 is demonstrated (median). Significant improvements compared to the baseline are marked by the appropriate significance levels. Significant differences between the efficacy of uni- and bipolar stimulation are presented by arrows ($p<0.05$).
Financial disclosures

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- IB reported no financial disclosures.
- FN was supported by a grant from Norwegian Financial Mechanism (HU00114)
- EB reported no financial disclosures
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- SK was supported by a grant from Norwegian Financial Mechanism (HU00114)
- ZA was supported by a grant from Norwegian Financial Mechanism (HU00114)
- NK was supported by the government-based Bolyai Scholarship of Hungarian Academy of Sciences and the Hungarian Neuroimaging Foundation.

Author roles

1. Research project: A. Conception, B. Organization, C. Execution;
3. Manuscript: A. Writing of the first draft, B. Review and Critique;

GD 1C, 2C, 3B
IB 1B, 2C, 3B
FN 1B, 2C, 3B
EB 1C, 2C, 3B
JJ 1A, 2A, 3B
SK 1B, 2C, 3B
ZA 1B, 2C, 3B
NK 1, 2, 3
### Table 1.

<table>
<thead>
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<th>Characteristics</th>
<th>Value</th>
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<td>Age (years)</td>
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</tr>
<tr>
<td>Type of PD (T/R/M)</td>
<td>2/7/12</td>
</tr>
<tr>
<td>Sex (f/m)</td>
<td>12/9</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>14.8 ± 5.5</td>
</tr>
<tr>
<td>Time between operation and examination (years)</td>
<td>3.3 ± 1.5</td>
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<tr>
<td>ADL (ON medication, ON stimulation)</td>
<td>86.1% ± 7.1%</td>
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<tr>
<td>UPDRS-III (ON medication, ON stimulation)</td>
<td>16.6 ± 6.5</td>
</tr>
<tr>
<td>UPDRS-III (OFF medication, ON stimulation)</td>
<td>25.8 ± 7.7</td>
</tr>
</tbody>
</table>

**Table 1.** Selected descriptive data of the patients with idiopathic Parkinson’s disease (PD) included in the study. Type of PD is described tremor-dominant (T), rigid-akinetic (R) and mixed (M) forms. ADL respects Activities of daily living measured by Schwab and England score, UPDRS-III stands for the motor examination part of Unified Parkinson’s Disease Rating Scale.
<table>
<thead>
<tr>
<th>UPDRS score</th>
<th>Rigidity</th>
<th>Bradykinesia</th>
<th>Rest tremor</th>
</tr>
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<td></td>
<td>Unipolar</td>
<td>Bipolar</td>
<td>Unipolar</td>
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<td>4 → 3</td>
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<td>1.05 ±</td>
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<td>0.47</td>
<td>0.76</td>
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</tr>
<tr>
<td>3 → 2</td>
<td>1.05 ±</td>
<td>1.37 ±</td>
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<td>0.63</td>
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<tr>
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<td>2.43 ±</td>
<td>1.87 ±</td>
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<td>0.60</td>
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<tr>
<td>1 → 0</td>
<td>2.41 ±</td>
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<td>2.67 ±</td>
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<tr>
<td></td>
<td>0.52</td>
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<td>0.45</td>
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Table 2. Demonstration of amplitude levels capable of improving rigidity, bradykinesia and rest tremor by 1-point on UPDRS items 22, 23 and 20, respectively. Amplitude values are given Volts (mean ± standard deviation).

Unipolar and bipolar represent unipolar and bipolar electrode configurations, respectively.

N/A represents conditions where none of the patients had the severity of 4 points at baseline.

* demonstrates significant difference compared to unipolar electrode configuration.
The graph shows the relationship between UPDRS score (item 20) and voltage. The data is divided into two groups: Unipolar (solid red line) and Bipolar (dashed blue line). The significance levels are indicated as follows:

- **p < 0.05** for the overall trend.
- **p < 0.01** for the descending trend.
- **p < 0.001** for the steepest part of the descent.

The voltage is measured on the x-axis, ranging from 0 to 3.6, and the UPDRS score on the y-axis, ranging from 0 to 3.
<table>
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<td>3,1</td>
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Chronic stimulation parameters for the enrolled patients.