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Short communication

Outcomes, management, and potential mechanisms of interleaving deep brain stimulation settings

Svjetlana Miocinovic [a, *], Pravin Khemani [a], Rebecca Whiddon [a], Pam Zeilman [b], Daniel Martinez-Ramirez [b], Michael S. Okun [b], Shilpa Chitnis [a]

[a] Department of Neurology and Neurotherapeutics, University of Texas Southwestern, 5323 Harry Hines Blvd., Dallas, TX 75390, USA
[b] Department of Neurology, Center for Movement Disorders and Neurorestoration, University of Florida, 3450 Hull Road, Gainesville, FL 32607, USA

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ABSTRACT

Introduction: DBS is a therapeutic option for patients with Parkinson disease (PD), tremor and dystonia. In patients who experience suboptimal clinical results with conventional programming (monopolar, double monopolar or bipolar settings), interleaved pulses can sometimes be used to provide differential therapeutic benefits with the possibility of fewer side effects. Interleaving allows a clinician to define two "programs" that automatically alternate. The goal of this paper is to 1) present clinical scenarios where DBS interleaving was used across two clinics to provide improved symptom control in three patients with suboptimal results from conventional programming; 2) address the potential mechanisms of interleaving; and 3) provide practical tips on the use of interleaving.
Methods: Three patients were formally compared for therapeutic benefit on interleaved and conventional parameter settings.
Results: Interleaving is most likely to be useful in two clinical scenarios: 1) different contacts are beneficial for specific symptoms, but each at a different stimulation amplitude; or 2) symptoms are resolved incompletely, and further voltage increase is limited by side effects. The factors underpinning the differences in outcomes with interleaving are unknown but may be highly dependent on specific symptoms and to electrode positioning. Interleaving is a relatively new programming platform and there is no data to demonstrate long-term benefits.
Conclusions: Interleaving is a tool that may augment outcomes, and possibly obviate the need for surgical revisions, although in our experience across two large centers it has been effective for only a small number of patients.

1. Introduction

Chronic deep brain stimulation (DBS) therapy emerged in the late 1980's for the treatment of tremor and in the early 1990's for advanced Parkinson disease (PD). Although DBS technology has not changed fundamentally since its inception, the latest commercially available neurostimulator upgrades of Activa PC, Activa RC and Activa SC (Medtronic, Inc., Minneapolis, MN) offer increased programming functionality with an interleaving feature.

Interleaving refers to activating two stimulation programs that rapidly alternate from pulse to pulse between each other (Fig. 1). Each of the two interleaving programs can specify the active electrode contact(s), pulse width and pulse amplitude. The frequency for each program must be the same and it is limited by the device up to 125 Hz. One or both electrodes can be interleaved, but no more than two programs can be used for each electrode [1].

Interleaving has been suggested as a strategy when conventional programming techniques fail to achieve desired results. Undesirable results may or may not be due to factors such as suboptimal positioning of the lead. When clinicians struggle to program a DBS device they often employ various additional techniques including bipolar settings, double monopolar or tripolar settings, and alternative pulse widths and frequencies to manipulate the electrical field. Interleaving provides an alternative method to alter the shape of the electrical fields, and possibly maximize benefits. The purpose of this paper is to explain the concept of interleaving, hypothesize on mechanism(s) of action, illustrate its use in three patients, and offer practical tips for its use.

* Corresponding author. Present address: University of California, San Francisco, Department of Neurology, 505 Parnassus Avenue, Box 0114, Room M-798, San Francisco, CA 94143-0114, USA. Tel.: +1 415 476 9202; fax: +1 415 476 3428.
E-mail address: svjetlana.miocinovic@ucsf.edu (S. Miocinovic).

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2. Methods

Three patients with PD were implanted with bilateral subthalamic (STN) DBS electrodes at two expert DBS institutions. All three patients underwent standard clinical programming, but achieved suboptimal results with conventional techniques. They maintained stable clinical benefit for at least 3 months on the interleaved settings. In all patients, interleaving was used in only one hemisphere. UPDRS examination (off medications) was performed for seven stimulation conditions detailed in Table 1, in a single session, in a non-blinded, non-randomized manner, allowing at least 5 min for each stimulation setting to take effect and 30 min for the initial stimulation washout. The aim was to compare stimulation effects using the same parameters, but different electrode configurations.

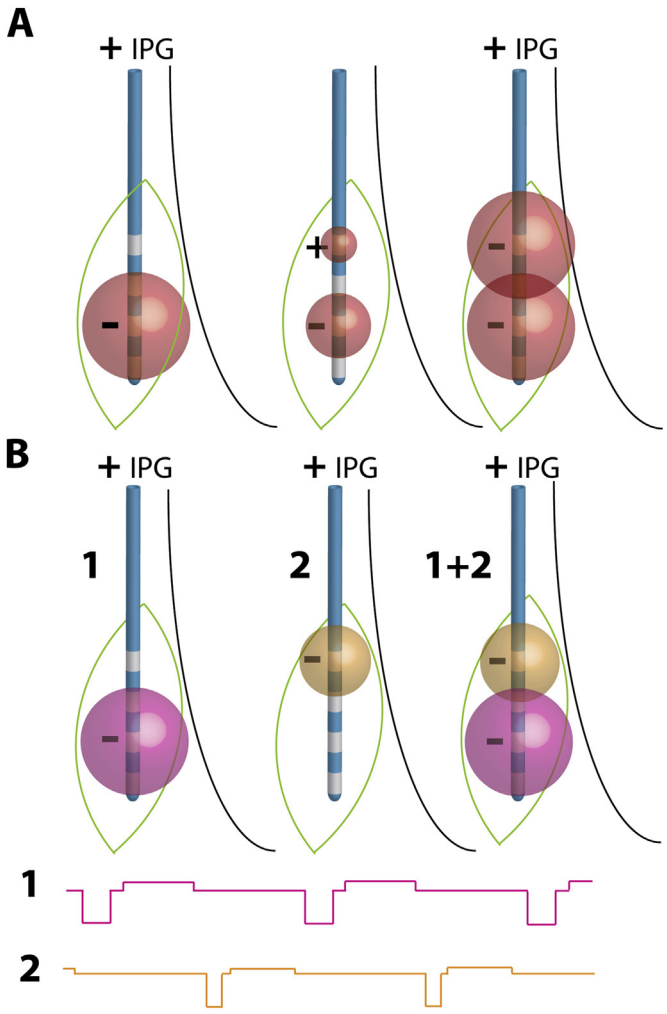


Fig. 1. Graphical representation of the hypothesized mechanisms of interleaving. Spheres represent estimated volume of tissue activated during various DBS programming settings [8]. In this example green outline represents subthalamic nucleus (STN) and black curve is the corticospinal tract. Top section (A) demonstrates conventional settings: monopolar stimulation at contact 1 (left) does not stimulate sufficiently large area of the nucleus and does not provide complete resolution of symptoms. Changing to bipolar setting (middle) provides some additional activation around contact 3, but it is overall insufficient because bipolar stimulation results in a narrower field. Double monopolar (right) provides sufficient coverage of the nucleus but also stimulates corticospinal tract causing side effects. Bottom section (B) illustrates interleaved programming: user specifies two programs which are applied interchangeably. Bottom tracings show shape and timing of the stimulation pulses applied to each contact (large negative pulse activates neurons, while small positive afterpulse recovers charge). For each program, user defines specific contacts, amplitude and pulse width, although frequency is limited up to 125 Hz by the device. This allows greater freedom in selecting different stimulation settings for the two contacts while still benefiting from monopolar field. In this example, interleaving provides sufficient stimulation of the nucleus while avoiding the corticospinal tract. Small overlap area experiences stimulation at twice the frequency since it is seeing pulses from both programs, but clinical utility of this phenomenon is unknown [2].

3. Results

3.1. Case 1

A 61 year-old man with tremor-predominant PD for 11 years suffered from dyskinesia and motor fluctuations with off periods characterized by tremor, marked deterioration of speech and slowing of gait. Bilateral STN DBS was performed with resultant suboptimal tremor control despite multiple programming sessions. On the post-operative MRI, the left electrode was found to be medial to the STN (contact 2 was 7 mm lateral, 1 mm posterior and 1 mm ventral to the midcommisural point (MCP)). The left STN single monopolar setting only partially improved the tremor. Double monopolar setting at the amplitude and pulse width necessary to control tremor could not be tolerated due to diplopia. Interleaving allowed a dorsal contact to be set to higher amplitude and pulse width, while the contact below was set to a tolerable lower amplitude and pulse width. Together, the two contacts provided complete tremor resolution without side effects.

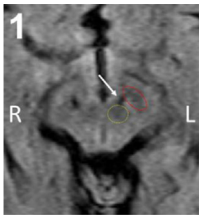
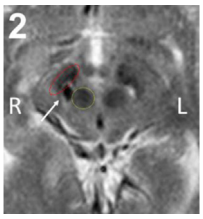
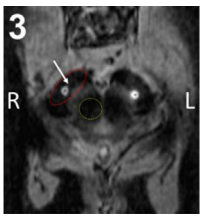
3.2. Case 2

A 65 year-old man with PD for 11 years had tremor, rigidity and bradykinesia that was significantly worse on the left side. He was implanted with bilateral STN DBS due to frequent wearing off and tremor that did not completely respond to high doses of levodopa. On post-operative MRI, his right DBS lead was medial and posterior to the optimal target in the STN (contact 10 was 10.5 mm lateral, 4.5 mm posterior and 4 mm ventral to the MCP). The right STN single monopolar stimulation did not provide sufficient tremor and/or bradykinesia improvement. Double monopolar settings at 90 μs resulted in diplopia and paresthesias which limited further increases in parameters. A double monopolar setting at 60 μs and a slightly higher amplitude improved tremor, but did not further improve bradykinesia. Interleaved settings with similar amplitude and pulse width at the two contacts improved both tremor and bradykinesia, in a seemingly synergistic manner beyond what either double monopolar setting could achieve. The patient did well on this setting for 4 months, but later reported dysarthria which resolved when switched off the interleaved setting, and he therefore was programmed back to a double monopolar setting at 3.0 V and 60 μs which improved his speech but worsened other symptoms. The patient had also been receiving vocal fold injection augmentation for dysphonia, and his last injection was 9 months prior to the reemergence of dysarthria which may have biased his overall outcome.

3.3. Case 3

A 58 year-old man with PD for 16 years had symptoms including stiffness, dystonia and tremor. Over time he developed dyskinesia, wearing off and frequent levodopa dose failures. He underwent staged bilateral STN DBS. On post-operative CT/MRI fusion, his right DBS lead was well placed in the STN (contact 2 was 13 mm lateral, 0 mm posterior and 1 mm ventral to the MCP). The right STN single monopolar programming at contact 2 improved tremor and caused only rare dyskinesias, but worsened nighttime rigidity, which resulted in a reported sleep quality deterioration. Single monopolar DBS at contact 1 improved sleep by decreasing stiffness, but increased daytime dyskinesia. Dyskinesias were present even with elimination of entacapone and controlled release levodopa. Interleaved settings using contacts 1 and 2 decreased daytime dyskinesias and improved nighttime mobility and sleep by patient report. Clinically, contact 2 had an antidykinetic effect even though it was not located in the zona incerta where this can be expected.

Table 1
Electrode locations and clinical scores on conventional and interleaved settings. On post-operative imaging white arrow indicates electrode artifact, yellow dotted line indicates the red nucleus and dashed red line indicates the STN/SNr region (for patient 3 pre-operative MRI was merged with post-operative CT; all images are axial slices at the level of red nucleus, 3–4 mm below the MCP). Total UPDRS part III scores and selected items reported for contralateral side to the interleaved lead using various stimulation settings. T = arm tremor, R = arm rigidity, B = finger taps/hand opening–closing/wrist turning, S = speech. Stimulation frequency was 125 Hz for all settings.

Electrode location	DBS OFF	Single monopolar I	Single monopolar II	Double monopolar I	Double monopolar II	Bipolar I	Bipolar II	Interleaved
		C+2-/3.2/90	C+3-/4.2/120	C+2-3-/3.2/90	C+2-3-/4.2/120	3+2-/3.2/90	2+3-/4.2/120	C+2-/3.2/90 C+3-/4.2/120
	UPDRS: 34	**UPDRS: 20**	**UPDRS: 21**	**UPDRS: 23**	**UPDRS: 21**	**UPDRS: 21**	**UPDRS: 26**	**UPDRS: 12**
	T 3	T 1	T 1	T 1	T 0	T 1	T 2	T 0
	R 2	R 0	R 0	R 0	R 0	R 0	R 0	R 0
	B 2/2/3	B 1/1/2	B 1/2/2	B 1/2/3	B 1/1/3	B 1/1/2	B 1/1/3	B 0/0/1
	S 1	S 1	S 2	S 2 Confusion	S 2 Diplopia	S2	S 2	S 1
		C+10-/3.1/90	C+11-/3.2/60	C+10-11-/3.1/90	C+10-11-/3.2/60	11+10-/3.1/90	10+11-/3.2/60	C+10-/3.1/90 C+11-/3.2/60
	UPDRS: 62	**UPDRS: 32**	**UPDRS: 32**	**UPDRS: 29**	**UPDRS: 28**	**UPDRS: 55**	**UPDRS: 46**	**UPDRS: 21**
	T 3	T 2	T 2	T 2	T 1	T 3	T 3	T 1
	R 3	R 2	R 2	R 1	R 1	R 3	R 3	R 1
	B 4/4/4	B 2/3/3	B 2/2/3	B 2/2/3	B 2/2/3	B 4/4/4	B 4/4/4	B 2/1/2
	S 2	S 2	S 1	S 2 Tingling	S 2	S 2	S 1	S 1
		C+1-/2.0/90	C+2-/1.5/90	C+1-2-/2.0/90	C+1-2-/2.0/90	2+1-/2.0/90	1+2-/1.5/90	C+1-/2.0/90 C+2-/1.5V/90
	UPDRS: 39	**UPDRS: 22**	**UPDRS: 19**	**UPDRS: 20**	**UPDRS: 21**	**UPDRS: 24**	**UPDRS: 27**	**UPDRS: 18**
	T 1	T 1	T 1	T 1	T 1	T 1	T 1	T 1
	R 1	R 1	R 0	R 0	R 1	R 1	R 1	R 0
	B 1/1/1	B 1/1/1	B 0/1/0	B 0/0/1	B 1/1/1	B 1/1/1	B 1/1/1	B 0/0/0
	S 1	S 1 Dyskinesia[a]	S 1 Stiffness[a]	S 1	S 1	S 1	S 1	S 1

[a] Side effects reported by the patient at home, while on typical medication regimen.

The patient remains on interleaved settings for 23 months and reports continued and sustained benefit.

4. Discussion

Interleaving is a programming technique available in new generation DBS neurostimulators which allows two sets of stimulation parameters to be applied interchangeably (on a millisecond level). We present three PD patients where interleaving was employed because conventional programming did not achieve sufficient therapeutic benefit, or was limited by side effects. In two patients, electrode placement was suboptimal, but the lead was well placed in the third. Interleaving proved beneficial in all three cases, though was unsustained in one.

The most important feature of interleaving is that it enables the use of multiple negative (cathodal) contacts, but at different amplitudes (Fig. 1B). The standard double monopolar setting (two negative contacts with the IPG set as case positive or anodal) forces both contacts on the DBS lead to be set at the same amplitude (and pulse width), which can result in adverse reactions, as frequently both contacts cannot be programmed at high settings (Fig. 1A, right). One may also set a double monopolar amplitude below the side effect thresholds for both contacts, or a programmer may alternatively choose a single monopolar or bipolar setting. These approaches however, may not in all cases provide sufficient spread of current for an optimal therapeutic response (Fig. 1A, left and middle). Even though pulses from the two programs are offset from each other, they are potentially creating an effective electrical field that is a result of the combination of the two individual fields [2].

Several published reports on interleaving have employed the technique as a means to use different amplitudes at two negative contacts. Wojtecki et al. recently published a case report of a PD patient whose rigidity and bradykinesia responded to STN stimulation at contact 1 at 3.9 V, however the tremor responded best to stimulation at contact 3 at 1.5 V [3]. Double monopolar stimulation at 3 V or higher resulted in unacceptable dysarthria, so an interleaving strategy was employed. Kovacs et al. similarly reported a case series of 4 dystonia patients where interleaving was more beneficial than monopolar (either single or double) stimulation. In this series the authors argued that the use of different voltages at each contact maximized the amount of current necessary to control dystonia [4]. Weiss et al. recently used interleaving in a study of gait and balance in PD patients with STN DBS and the strategy employed was to simultaneously stimulate STN and SNr [5]. Interleaving was used so that both nuclei could be stimulated together, however higher current was delivered to the contact in the STN, and lower voltages were programmed for the SNr. Another use of interleaving was demonstrated by Barbe et al. who used Vim DBS to suppress tremor while at the same time directing more current to the dorsal contact in an attempt to lessen dysarthria [6].

It is unknown if interleaving provides any additional advantage over simply allowing use of different amplitudes at different contacts, which is not an option available on FDA approved DBS devices. Interleaved settings with identical amplitudes and pulse widths at two different contacts would be similar to double monopolar settings however, pulses at each contact would be offset by 4 ms (125 Hz equals 8 ms interpulse interval). We do not know if the effect of the two programs in an interleave is simply the sum of the effects of the individual fields, or if the phase delay may provide an enhanced, synergistic outcome [2]. In our case 2, double monopolar settings even though tolerated, did not provide the same beneficial outcome as the interleaved setting. However, and

notably the benefits of interleaving were short lived in this patient, and in the end, interleaving may have caused side effects which were not present at a similar double monopolar setting. Similarly, Baumann et al. used interleaving in one patient with ET and PD to stimulate STN and Vim [7]. Interestingly, the authors reported that single monopolar stimulation was effective for relieving ET when the active contact was the most dorsal, in the Vim. Single monopolar stimulation was effective against PD when the active contact was the most ventral, in the STN. In this case, double monopolar settings using both contacts did not alleviate either symptom, but also did not evoke side effects. The authors proposed that "the importance of pulse timing (simultaneous vs interleaving) may be related to temporal integration in the receiving brain areas". Because single monopolar DBS was therapeutic for each individual symptom, this would imply that the double monopolar setting was causing some sort of undesirable interference. This presumed interference would likely be at downstream targets because the volumes of stimulation from two distal contacts could not overlap except at higher voltages (even with narrow spacing 3389 electrode). As a result, interleaving potentially could be argued to have synergistic effects that may be either clinically beneficial or deleterious.

The potential synergistic effect of interleaving (either positive or negative) may in part be due to the area of overlap between the two electric fields that is intentionally created by the interleaved programs. If active contacts are sufficiently close together, and amplitudes sufficiently large, there will be a volume of tissue that will be exposed to pulses from both programs, and effectively be stimulated at double the interleaved frequency. In our case 2, the patient eventually developed dysarthria on an interleaved setting but not on a similar double monopolar setting, and we hypothesize that this was due to the long-term effects of being stimulated at 250 Hz, though this notion is highly speculative. The device manufacturer has set the maximum interleaving frequency to 125 Hz, so the maximum frequency that neuronal elements in the overlapped area can be stimulated would be 250 Hz. Although such frequencies are unlikely to be harmful to neurons, there is a potential concern that additive charge density at high frequencies and high pulse widths may exceed safety limits [2].

In clinical practice, interleaving is most likely to be useful in two scenarios: 1) different contacts are beneficial for specific symptoms, but each is beneficial at different stimulation amplitude and one contact may have side effects at higher amplitude; or 2) symptoms are resolved incompletely and further voltage increase is limited by side effects. There are also potential drawbacks to interleaving; in some cases it may drain the neurostimulator battery faster than the conventional settings and it limits frequency to 125 Hz which may be suboptimal for tremor control. Interleaving may be most beneficial in cases where there is a suboptimal lead placement, however long-term interleaving settings may not always hold benefit. Interleaving should be thought of as one more tool that may augment outcomes, and possibly obviate the need for surgical revisions.

Financial disclosure/Conflict of interest

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