Peaks in the beta band of the human subthalamic nucleus: a case for low beta and high beta activity

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OBJECTIVE Peaks in the beta band of local field potentials (LFPs) may serve as a biological feedback signal for closed-loop deep brain stimulation (DBS) in Parkinson’s disease (PD). However, the specific frequency of such peaks and their response to DBS and to different types of movement remains uncertain. In the present study, the authors examined the abundance of discernible peaks in the beta band and the effect of different types of movement and DBS on these peaks.

METHODS Subthalamic nucleus LFPs were analyzed from 38 patients with PD in a frequency range between 10 and 35 Hz, as well as the impact of movement (gait, hand movements) and electrical stimulation on these peaks. The position of the electrode segments from which LFPs were recorded was computed.

RESULTS The authors found a bimodal distribution of peaks in the beta band with discernible high- (27 Hz) and low-frequency (15 Hz) peaks. Movement of either hand had no significant effect on these peaks, whereas walking significantly reduced high-frequency beta peaks but not the peaks in the low beta band. Stimulation caused an amplitude-dependent suppression of both peaks.

CONCLUSIONS DBS suppresses LFP beta peaks of different frequencies, whereas beta suppression caused by movement is dependent on the type of movement and frequency of the peak. These results will support the investigation of distinct LFP spectra for the application of closed-loop DBS.

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KEYWORDS Parkinson’s disease; subthalamic nucleus; local field potentials; beta band; deep brain stimulation; functional neurosurgery

Local field potentials (LFPs) of the subthalamic nucleus (STN) have been analyzed to gain insight into the function of the basal ganglia and as biomarkers for monitoring clinical symptoms. In Parkinson’s disease (PD), increased synchrony of neuronal networks has been associated with reduced segregation of parallel processes, leading to reduced specificity of motor programs.1,2 Increased synchrony has been observed in the beta band (13–35 Hz) of the LFPs of the human STN in the form of spectral peaks. The amplitude of such peaks has been shown to correlate with symptom severity in akinetic/mixed patients,3,4 and is reduced by dopaminergic medication5 and by deep brain stimulation (DBS).6,7 When investigating signals in the beta band as potential biomarkers for closed-loop stimulation, it must be taken into account that beta peaks are reduced by movement itself.8 This reduction has been shown for alternating hand and finger movements,9,10 and leg movements.11,12 During movement, suppression of beta activity is not always complete and persistent.9 Beta suppression during self-paced finger movements was prominent at the beginning of the recording but progressively decreased over the course of the recording.13 The influence of gait on the amplitude of beta peaks was reported to be nonsignificant in one study,14 but high beta (20–30 Hz) was significantly reduced during gait in another study.15 Several authors have subdivided the beta band into a low (13–20 Hz) and a high (20–35 Hz) band. Whether this distinction reflects two different physiological processes has not yet been clarified, however, some observations favor this hypothesis. In subjects with gait freezing, activity in the low beta band was suggested to correlate with this symptom.11,16,17 Low beta peaks are attenuated by levodopa more than high beta peaks.18 Hand and leg movements cause beta suppression in a slightly different pattern, i.e., leg movements cause more suppression in the high beta band as compared to hand movements.15 In one study, low-beta
peak amplitude correlated better with bradykinesia scores as compared to high beta amplitude. The latter authors reported a clear bimodal distribution of peaks in the beta band, with maxima at 17 and 25 Hz. When investigating the effect of levodopa on beta peaks, Kühn et al. surprisingly found that in individual subjects beta peaks considerably changed their frequency in the on/off condition and even could be larger in the on-condition. However, low and high beta peaks were equally reactive to the levodopa challenge and the frequency distribution of peaks in the beta range represented a normal distribution. In another study of the same group, a frequency segment at 11 Hz showed the highest correlation with parkinsonian symptoms.

In this study, we investigated the abundance of beta peaks in the STN of a large cohort and examined the effect of movement and stimulation on high and low beta band peaks. We investigated different stimulation amplitudes and two distinct movement types (hand movement and gait) while using a strict criterion for the definition of a “peak.” The present study aims to clarify which peaks are suitable as biomarkers and how those peaks react in the course of different manipulations mentioned above.

Methods

Patients and Operation

Thirty-eight patients with PD participated (Table 1). The approval of the ethics committee of Ludwig-Maximilian University and written consent from each patient was obtained, and the study was conducted in accordance with the Declaration of Helsinki. Electrodes were implanted into the STN in awake patients according to our standard procedure: the target point (14 mm lateral, 3 mm behind, 3 mm below the anterior commissure–posterior commissure [AC-PC] midpoint) was confirmed or modified according to the visible dorsolateral STN on T2-weighted MR images. During the operation, microelectrode recordings (1–3 tracks, Inomed, Medizintechnik GmbH) confirmed the position within the STN, with characteristic extracellular STN activity in all cases for a length of 4–6 mm. Intraregistered macrostimulation confirmed reduction of rigidity and bradykinesia and caused dyskinesia in some cases. The implanted leads were connected to an externalized extension lead. The stimulator was implanted on the third postoperative day. We used Medtronic leads (model no. 3389) and implantable neurostimulators (INSs: Activa PC, 18 patients; ACTIVA PC+S, 10 patients), Boston Scientific devices in 7 patients (INSs: Percive PC and Gevia, Percive Cartesia Directional Lead), and Abbot devices in 3 patients (INS: Infinity 7; lead: directional lead STJ 6146–61499). The Medtronic ACTIVA PC+S INS, which was implanted in 10 patients, can record LFPs during and without stimulation. The position of the tip of each lead within the AC-PC coordinate system was determined on the postoperative CT scans, which had been aligned with the preoperative MR images. The distance between the tip and the actual two contacts from which LFPs were recorded from this individual lead was determined and the position of the recording site was computed (MATLAB; MathWorks), taking into account the lateral and anterior angle of the lead. All positions were projected on the right side.

Recordings

Recordings were conducted via externalized leads in all 38 patients on the first or second postoperative day. Patients were off-medication for at least 24 hours (levodopa) and had taken the last dopamine agonists at least 4 days prior to the study visit. Three recordings were obtained with each patient in a recumbent position during rest (awake, eyes open) for 2–5 minutes and during right- and subsequent left-hand opening and closing (frequency 2/ second, 2–5 minutes). Hand movements were monitored by an observer but not mechanically recorded. LFPs were amplified and recorded with BrainAmp amplifiers (Brain Products) and digitally stored (resolution 0.1 µV, sampling rate 2000 Hz, filter 0.1–500 Hz). The uppermost contact of the left electrode was used as reference. All further processing was done using MATLAB. Data were digitally referenced so that three bipolar recordings were obtained from each lead. In multisegmented electrodes, mean data from three segments of one ring were treated as data from that ring to obtain three bipolar recordings from each lead.

Additional recordings during different stimulation strengths and during walking (two gait speeds) were obtained with an implanted Medtronic ACTIVA PC+S INS in 10 of the 38 patients. These patients have been reported previously in another study. LFP recordings were obtained with a bipolar setup between contacts 0–2 or 1–3 on the left side and 8–10 or 9–11 on the right side. The electrode in between these contacts was used for stimulation (130 Hz, 60 µsec). The gain factor was 2000, the sampling rate 422 Hz, and LFPs were filtered (0.5–100 Hz). After each recording, data were streamed telemetrically to a host computer. For evaluation, recordings of the same day were taken. Recordings with ACTIVA PC+S INS were obtained 6–12 weeks after the operation subsequent to a levodopa washout period of 6–12 hours, and the last dopamine agonists had been taken on the day before the recording. To study the effect of clinically efficient stimulation on beta peaks, three recordings (duration of 3–5 minutes each) were taken during sitting: stimulation off, and bilateral stimulation at 50% and 100% of the usual voltage of the patient. The effect of gait was assessed during three tests without stimulation: standing for 3–5 minutes, and slow and fast walking for 30 minutes. Patients were instructed to walk either slower or faster than their preferred walking speed. Gait performance was

<table>
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<tr>
<td>Mean disease duration (range)</td>
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<td>Motor subtypes of PD (E/T/AR)</td>
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<tr>
<td>DBS device (M/B/S)</td>
<td>28/7/3</td>
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Motor subtype: E = equivalent, T = tremor-dominant, AR = akinetic-rigid.
DBS device: M = Medtronic, B = Boston Scientific, S = St. Jude Medical.
registered with inertial sensors on shanks, thighs, forearms, and chest at 200 Hz. These recordings were fused by Kalman filtering and the trajectory of the feet, step length, and cadence were reconstructed using a 4-segment leg model with inverse kinematics. Then, gait epochs were semi-automatically defined (according to a quotient step-length/cadence) to exclude phases of standing, gait freezing, or turning from the analysis. Only LFPs obtained during “normal walking” (see Results) were evaluated.

Data Evaluation

The raw data obtained from external leads were high-pass filtered (third-order Butterworth, 1 Hz) and resampled to a sampling frequency of 422 Hz (sampling frequency in the Medtronic ACTIVA PC+S device). To compute the frequency spectrum of all data, we applied the fast Fourier algorithm of MATLAB and averaged the resulting spectra. The fast Fourier transform (FFT) window was 512 data points with an overlap of 256 points. No windowing (Hamming or Hanning window) was used because several tests had shown that low-frequency distortions of the ACTIVA PC+S device were negligible and low-frequency components of the data obtained from external leads had been removed. This resulted in spectrum values representing µV/frequency. The spectral resolution was 0.8242 Hz. No normalization of the spectra was applied. We searched for peaks in the frequency range between 10 and 35 Hz. A peak was defined by the software as the point at which the mean amplitude of either 4 or 6 adjacent data points was at least 20% larger than the mean amplitude of the 8 or 12 data points surrounding the “peak” (Fig. 1A). A visual inspection of the peaks was carried out afterward to verify the identity of the peaks. This method conforms to a previously described procedure. All peak amplitudes were measured in percentages. From each electrode, the one bipolar recording with the highest beta peak was chosen for evaluation. Statistical comparisons were performed with the nonparametric 2-sample Kolmogorov-Smirnov test (MATLAB). A test of normal distribution was made with the Kolmogorov-Smirnov test for normal distribution (MATLAB).

Results

Recordings With Externalized Leads

When analyzing all postoperative recordings (38 patients × 2 sides × 3 tests = 228 spectra), we identified 176 peaks that fulfilled the above-listed criteria. Peaks were clustered around 15 and 27 Hz (Fig. 1C and D). Because this clustering was suggestive of a bimodal distribution, we performed a statistical test of normal distribution (Kolmogorov-Smirnov test) demonstrating that a normal distribution was not present (p < 0.0001). The median frequency of all evaluated peaks in the 10–35 Hz band was 20.2 Hz, and therefore this value was used to separate “low” and “high” beta peaks for further evaluations. Ninety-six of these peaks were below 20.2 Hz (mean 15.5 Hz, mean amplitude 69%) and 80 were above 20.2 Hz (mean 27 Hz, mean amplitude 47.3%). The amplitudes of low and high beta peaks were significantly different (Kolmogorov-Smirnov test, p = 0.0001). The overall frequency of occurrence of peaks in the beta band of our cohort was determined by analyzing only the traces obtained during rest: 68 (87%) of 78 STNs showed at least one peak, 35 (92%) of 38 subjects had at least one peak on either side (Table 2), and two peaks were found in 16 (22%) of 76 nuclei.

To assess the effect of hand movements, we plotted the three traces of every STN (rest, and right- and left-hand movements) and evaluated any set of FFT spectra in which at least one peak was detected according to the definition (Fig. 2). Only reproducible peaks were evaluated. The frequency of peaks was determined manually and the amplitude of all three spectra at this frequency recorded (in percentages, as defined above). During hand movements, no significant suppression of peaks in the beta range was observed (Fig. 1E). The mean level of the beta band was similar for the conditions of rest, right-hand movements, and left-hand movements (ANOVA for repeated measures).

To determine whether contacts showing low and high beta frequencies have different locations, leads were grouped into four categories: low beta only, high beta only, low and high beta, and no beta (in these cases the “recording site” was set to be in between the two middle contacts of the lead). The position of the recording sites of the grouped electrodes was calculated and displayed (Supplemental Fig. 1). The z-values seemed to indicate that low-beta recording sites were deeper than high-beta recording sites (Table 3). However, a 1-way ANOVA comparing the z-values of low, high, and low and high beta contacts showed no significant differences (p = 0.14).

Recordings With and Without Stimulation (ACTIVA PC+S INS)

LFP traces were recorded with and without concurrent DBS in 10 patients with an implanted stimulator (ACTIVA PC+S). The mean amplitude of the beta band was compared in response to setting stimulation to “off,” or to 50% or 100% of the clinical settings. The mean beta levels were 1.16 µV, 1.06 µV, and 1.04 µV, respectively. A statistical comparison (ANOVA for repeated measures) revealed no significant differences.

During off-stimulation, we found 26 peaks according to the above definition in the beta band in 20 STNs; 2 peaks were present in 7 of 20 STNs. Nineteen of 20 STNs showed at least 1 peak. Peak height was not significantly correlated with Unified Parkinson’s Disease Rating Scale (UPDRS) scores (Fig. 1B). Representative curves of 3 subjects during off-stimulation, 50% stimulation, and 100% stimulation are shown in Fig. 3. Stimulation caused a reduction or disappearance of most but not all peaks and the suppression depended on the stimulation amplitude. The effect of stimulation on peak height was statistically evaluated for peaks below and above 20.2 Hz (low and high beta range; Fig. 4A and B). We found a significant suppression of low beta peaks for full stimulation only (p = 0.0116, Fig. 4A), whereas high beta peaks were significantly suppressed by half stimulation (p = 0.007) as well as by full stimulation (p = 0.007, Fig. 4B).

Recordings While the Patient Was Standing or Walking

After aligning the traces of the inertial sensors with the LFP traces and subsequent to defining distinct gait phases...
Plate et al. (Fig. 5), LFP data obtained during “normal walking” were transformed into the frequency domain and peaks were examined (as described above). We found a striking difference between the reaction of low and high beta peaks: whereas walking (slow and fast) caused a significant reduction of high beta peaks of about 50% (p < 0.02), low beta peaks were not reduced (p > 0.7; Fig. 4C and D).

Discussion

In this study we show that stimulation and movement exhibit a differential effect on the STN’s low and high beta activity in PD. Whereas continuous hand movements showed no significant influence on beta peaks, gait reduced high beta peaks, but had no effect on low beta peaks. Conversely, DBS reduced both beta peaks. Our results will support the use of the STN’s LFPs as a biological feedback signal for closed-loop DBS.
Study Limitations

Due to the outpatient setting of this study, where it was not feasible to withdraw dopamine agonists and/or levodopa for longer periods, patients were not completely off-medication during gait recordings because the last intake of dopamine agonists was not more than 12 hours in some patients (the effect of dopamine agonists may last longer than 6 hours). However, comparing distinct experimental variables (movement, stimulation) in the same group of patients allows for a valid internal control permitting us to neutralize the confounding effect of dopaminergic drugs. In this study, data were obtained from leads of different manufacturers. Because every patient served as his/her own control, we do not assume that this fact has a relevant impact on the results.

One Beta Peak or Two?

In our group of 38 patients, 87% of all nuclei (n = 76) showed at least one peak fulfilling the criteria, only 3 subjects showed no beta peak, and 11 subjects showed such a peak on one side only; thus, the majority of subjects (n = 24) had such peaks on both sides. The reason for the absence of such peaks in some patients/nuclei is likely associated with the position of the electrode, although we cannot exclude the possibility that a patient has no beta activity (possibly on one side). The percentage of patients who exhibited beta peak activity and may thus be eligible for closed-loop stimulation was reported to be greater than 95% in a meta-analysis, in which 20 studies, reporting on between 4 and 52 nuclei, were summarized.\textsuperscript{23} Most of these studies reported that 100% of recordings showed such a peak, but this notion must be critically questioned because the methods used to define a peak were not reported. Our findings show that 22% of nuclei had two peaks in the beta range, thus favoring two separate “information channels” within the beta band. Accordingly, we detected a clear bimodal frequency distribution of peaks in the beta band, namely a cluster around 15 and another around 27 Hz. The absence of a normal distribution was confirmed with a high probability. These findings corroborate the re-

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<td>8</td>
<td>13.59</td>
<td>-2.17</td>
<td>-2.22</td>
</tr>
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</table>

All mean values are in millimeters.
FIG. 3. Representative data of 3 subjects (columns) during off-stimulation (upper row), stimulation at 50\% (middle row), and 100\% stimulation (lower row). All results were reproduced at least once. In the left column, a beta peak at 25 Hz is fully suppressed by stimulation. In the middle column, the degree of suppression depends on the stimulation strength. In the right column, the beta peak at 15 Hz does not react to stimulation. Peaks fulfilling the definition explained above are marked with a circle. At 140 Hz, a stimulation artifact can be seen. El. = electrode; E0, E1, E2, E3 = electrode segments; Stim = stimulation. Figure is available in color online only.

FIG. 4. Impact of stimulation (A and B) and gait (C and D) on beta peaks. Peaks between 10 and 33 Hz were evaluated while stimulation was either off or set to 50\% or 100\% of the clinically determined voltage. A: Peaks in the low beta range (10–20.2 Hz) were significantly reduced by stimulation at 100\% only (p = 0.0116). B: Peaks in the high beta range (above 20.2 Hz) were significantly reduced when stimulation strength was 50\% (p = 0.0069) and 100\% (0.0069). C and D: Effect of walking (stimulation off) on beta peaks. Low beta peaks were not significantly reduced by walking (C), whereas high beta peaks (D) were significantly reduced during slow and fast walking.
Sustained high beta activity was either suppressed or not, suggesting that the STN and its connections to cortico-striatal pathways are differentially affected by stimulation. The bimodal distribution of beta activity observed in our study could be explained by the differential effects of high-frequency stimulation on high and low beta peaks. The observed suppression of beta activity during movement, particularly high beta activity, is consistent with previous reports and further supports the idea that beta activity is a marker of neuronal activity and connectivity in the basal ganglia [20].

**Stimulation**

We found that the impact of stimulation was significant as compared to the impact of hand movements, with stimulation reducing low (half and full stimulation) and high beta peaks (full stimulation only). The pathophysiology of LFP suppression caused by high-frequency stimulation is most likely explained by stimulus strength-dependent silencing of neuronal activity as a consequence of synaptic depression. LFPs can be suppressed for up to 60 seconds even after cessation of stimulation, which corresponds well with the gradual onset of rigidity after cessation of stimulation in a clinical setting. Studies reporting the differential effect of stimulation on high and low beta peaks...
are rare because concurrent stimulation and recording of LFPs can only be achieved with experimental devices.

In a study of simultaneous stimulation and LFP recordings, a progressive suppression of peaks of the LFP activity at frequencies between 11 and 30 Hz was seen as the voltage was increased significantly beyond a stimulation threshold of 1.5 V. The latter authors studied 19 nuclei with 44 peaks in the beta band (86 in the low and 58 in the high beta range) and demonstrated a decrease in both frequency spectra. Another study reported data of 13 nuclei. These authors found 7 significant suppressed beta peaks in the low beta range (8–20 Hz), but obviously no beta peaks of higher frequency were found. The authors suggested that the low beta rhythm might be considered as a marker of pathology, whereas the high beta rhythm could be essentially a physiological rhythm.

During intraoperative stimulation and LFP recording, Whitmer et al. found a suppression of beta activity between 15 and 35 Hz (maximum at 18 Hz within the STN and 13 Hz dorsal at the STN), but the report did not specify whether individual peaks in the low or high beta band were seen in the 13 nuclei. Summing up the available literature and our results, clinically efficient stimulation reduces beta peaks in the low and high range by approximately 50%, although individual differences must be taken into account.

**Walking**

Low and high beta peaks clearly reacted differently with regard to walking: only high-frequency peaks (above 20.2 Hz) were significantly reduced by gait, whereas peaks below this frequency remained at the baseline amplitude. This striking difference was also seen in our earlier study with 5 subjects, 3 of whom had gait freezing and showed elevated low beta amplitudes. Low beta elevation in patients with gait freezing has also been reported by two other groups. In our previous report, we analyzed the overall beta level (separate peaks were not analyzed) during gait in the same 10 patients as reported here and found a suppression of the high-frequency fraction of the spectrum. Tinkhauser et al. found that foot movements preferentially suppressed beta in the high-frequency band, although these studies are difficult to compare to our own results because our patients were walking whereas their patients made foot movements intraoperatively. With the same recording equipment as reported in this study, another group investigated gait-related beta activity and found no significant impact of gait on the beta frequencies in 12 patients (24 nuclei), when the absolute power between 13 and 30 Hz was analyzed. Also, when the same group analyzed beta activity during gait in individual patient-specific frequency bands, a different shape of the frequency pattern was reported, but a statistical difference of the beta peak between gait and rest was not evaluated because the focus was on the analysis of beta burst duration. The authors made no distinction between low and high beta, but instead evaluated the frequency band that was prominent in the individual patient. However, from their work one may conclude that the exaggerated beta bursts in patients with gait freezing may be prominent in the low beta range but not in the high beta range.

A third group using Medtronic ACTIVA PC+S INSs found no specific changes in subthalamic power spectral densities but a different beta phase modulation during gait and standing. The two latter groups found no significant beta suppression during gait without explicitly mentioning whether their patients had peaklike activity in the beta band. As shown in this report, beta peaks were present in our data and this may be a prerequisite for detecting a clear suppression of beta activity during walking. Furthermore, we could show in this report that such suppression is limited to beta activity above 20 Hz, which may preclude significant effects when the whole beta band is analyzed.

**Conclusions**

When using the beta band amplitude as a biomarker for closed-loop stimulation, one may choose either individual peaks (if present) or the whole beta band. At least two criteria should be met for biosignals considered for closed-loop stimulation. First, such signals must correlate with clinical symptoms. This condition is met for peaks in the low and high beta band and symptoms of bradykinesia and rigidity. As a second criterion, the signal should not be influenced by ongoing activities of the patient. According to the present study, this criterion applies to low beta peaks only, which are on average not significantly reduced by hand movements and remain stable during gait as compared to high beta peaks. Based on our current results, we therefore suggest using peak activity in the low beta band as a feedback signal. Another reason for choosing them is their apparent enhancement in gait freezing as some above-cited studies suggest. Our findings that certain beta peaks show significant changes during stimulation and movement, but the beta level itself does not, support the conclusion of not using the entire beta band as a feedback signal for closed-loop stimulation.

**Highlights**

- Continuous hand movements did not reduce the amplitude of beta peaks.
- Walking caused a reduction of high beta peaks but not low beta peaks.
- Peaks in the low beta range are not reduced by ongoing movement and therefore should be chosen as a biomarker for closed-loop DBS.

**Acknowledgments**

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**References**


Disclosures

For this study, 10 ACTIVA PC+S DBS systems were supplied by Medtronic at no cost. The study was reviewed and approved by the Medtronic DBS external research board but fully conceived and conducted without the influence of the company. No financial support or honoraria were paid for this study. For the overall evaluation of the performance of the implanted neurostimulators, Medtronic obtained descriptive and imaging data of 9 patients and paid the researchers for these data. K.B. received speaker’s honoraria from Medtronic, J.H.M. received speaker’s honoraria from Medtronic, Abbott, Boston Scientific, and Brainlab. A.B. and S.S. are paid Medtronic employees; in reviewing the manuscript, they contributed to technical accuracy, but did not influence the results or the content of the manuscript.

Author Contributions

Conception and design: Plate, Mehrkens, Bötzel. Acquisition of data: all authors. Analysis and interpretation of data: Plate, Koeglsperger, Bötzel. Drafting the article: Plate, Koeglsperger, Bovet, Stanslaski, Bötzel. Critically revising the article: Plate, Bötzel. Reviewed submitted version of manuscript: Plate, Bötzel. Approved the final version of the manuscript on behalf of all authors: Plate. Statistical analysis: Plate, Bötzel. Study supervision: Bötzel.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Figure 1. [https://thejns.org/doi/suppl/10.3171/2021.3.JNS204113](https://thejns.org/doi/suppl/10.3171/2021.3.JNS204113).

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