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Pitfalls and practical suggestions for using local field potential recordings in DBS clinical practice and research

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Abstract

Objective: Local field potential (LFP) recordings using chronically implanted sensing-enabled stimulators are a powerful tool for indexing symptom presence and severity in neurological and neuropsychiatric disorders, and for enhancing our neurophysiological understanding of brain processes. LFPs have gained interest as input signals for closed-loop deep brain stimulation (DBS) and can be used to inform DBS parameter selection. LFP recordings using chronically implanted sensing-enabled stimulators have various implementational challenges.

Approach: Here we describe our collective experience using BrainSense (Medtronic®) for clinical and research work. We aim to provide insightful tips and practical advice to empower readers with the knowledge needed to navigate the intricacies of the device and make the most out of its features.

Main results: The central issues that apply to several BrainSense features encompass restricted compatibility of stimulation configuration with sensing, differences in electrophysiological signal properties between 'stimulation OFF' and 'stimulation ON at 0.0 mA', and challenges associated with the internal clock of the neurostimulator. In addition, since recordings are obtained from bipolar and not monopolar channels, spatial certainty regarding the distribution of LFPs around the DBS electrode is limited. Several options exist to synchronize LFP time series with external data streams, but standardization and generalization are lacking. The use of at-home chronic LFP recording is limited by a low temporal and spectral resolution. Regarding at-home LFP snapshots, LFP time series are not stored, parts of the power spectrum are censored when stimulating at high or low frequencies, and the stimulation amplitude is not readily available.

Significance: We discussed practical applications, implementation, system limitations, and pitfalls with the aim that sensing can be better applied for clinical practice and research.

Introduction

Deep brain stimulation (DBS) is an effective therapy to improve symptoms in a variety of neurological and psychiatric disorders. It is currently in regular clinical use for movement disorders, epilepsy, and obsessive-compulsive disorder.[1–3] The recent advent of bidirectional neurostimulators that can stimulate and simultaneously record subcortical neural activity has provided a valuable tool for clinical practice and research.[4] The electrical activity of the local neuronal population at the DBS target site – called 'local field potentials (LFPs)' – has been demonstrated to harbor valuable neurophysiological symptom biomarkers ('physiomarkers'). For example, beta frequency activity in the subthalamic nucleus or internal pallidum positively correlates with rigidity and bradykinesia in Parkinson's disease (PD).[5] LFP recordings may allow the indexing of symptom presence and severity, may inform stimulation parameter selection, and may improve our neurophysiological understanding of brain processes.[4, 6] Bidirectional neurostimulators allow the assessment of subcortical neural activity in chronically implanted patients, in an at-home naturalistic environment, and with stimulation enabled. Whereas the use of earlier generations of sensing-enabled devices was limited to research, several recent devices, like Percept PC and RC (Medtronic®), AlphaDBS (Newronika®), and G102RS (PINS Medical®), can be used in standard clinical practice and are widely implemented for that purpose.[4]

In this review, we share our experience as clinicians and researchers with Medtronic® Percept PC and RC devices harboring BrainSense technology.[7, 8] We highlight the options and possibilities of BrainSense but also delineate its limitations. Based on hands-on experience, we indicate pitfalls and provide practical tips to mitigate them. This knowledge may be helpful to accurately estimate the feasibility of a study involving BrainSense, or the clinical adoption of this technology. Altogether, we aim to support the use of BrainSense in the Percept PC and RC neurostimulators empowering clinicians and researchers with the knowledge needed for successful implementations in research and clinical practice. This article further builds on previous literature describing the use of BrainSense technology.[7–10]

Methods

The insights provided in this review are based on the authors' clinical and investigational experiences with BrainSense, the manufacturer's manual for the use of BrainSense ('BrainSense white paper'), and the exploration of BrainSense modalities in the clinician programmer's ('tablet') demo mode. Exemplary illustrations are generated from JavaScript Object Notation (JSON) files of research participants in studies approved by the Institutional Review Board of the University of California, San Francisco (UCSF) – study numbers 10-02130 and 20-31239 – or Institutional Review Board of Amsterdam UMC – study numbers 2022.0368 and 2020.0164. All patients provided written informed consent for participation in the respective studies. These studies were conducted in accordance with the principles embodied in the Declaration of Helsinki and in accordance with local statutory requirements. These examples concern recordings obtained in people with PD but most concepts in this paper can be applied to any other clinical indication using Percept PC or RC. Figures were generated using functions implemented in MATLAB R2023b (Mathworks, Natick, MA). For the BrainSense Survey display items, we used the 'fitting oscillations and one over f' (FOOOF) algorithm (described in Donoghue et al.[11], code available at https://github.com/fooof-tools/fooof) and monopolar estimation calculations (described in Strelow et al.[12]). Medtronic® was not involved in the conceptualization or execution of this work.

Results

General

BrainSense offers four modalities to perform LFP recordings; 1) Survey: in-hospital brief recordings of all possible channels at once with stimulation off, 2) Streaming: in-hospital recordings of one selected channel with stimulation off or on, 3) Timeline: at-home chronic passive LFP power tracking of a selected narrow frequency band, and 4) Events: at-home patient-triggered snapshots of the full LFP power spectrum. Some practical/technical aspects apply to several of these BrainSense modalities, and are discussed here before going into modality-specific aspects in the next sections.

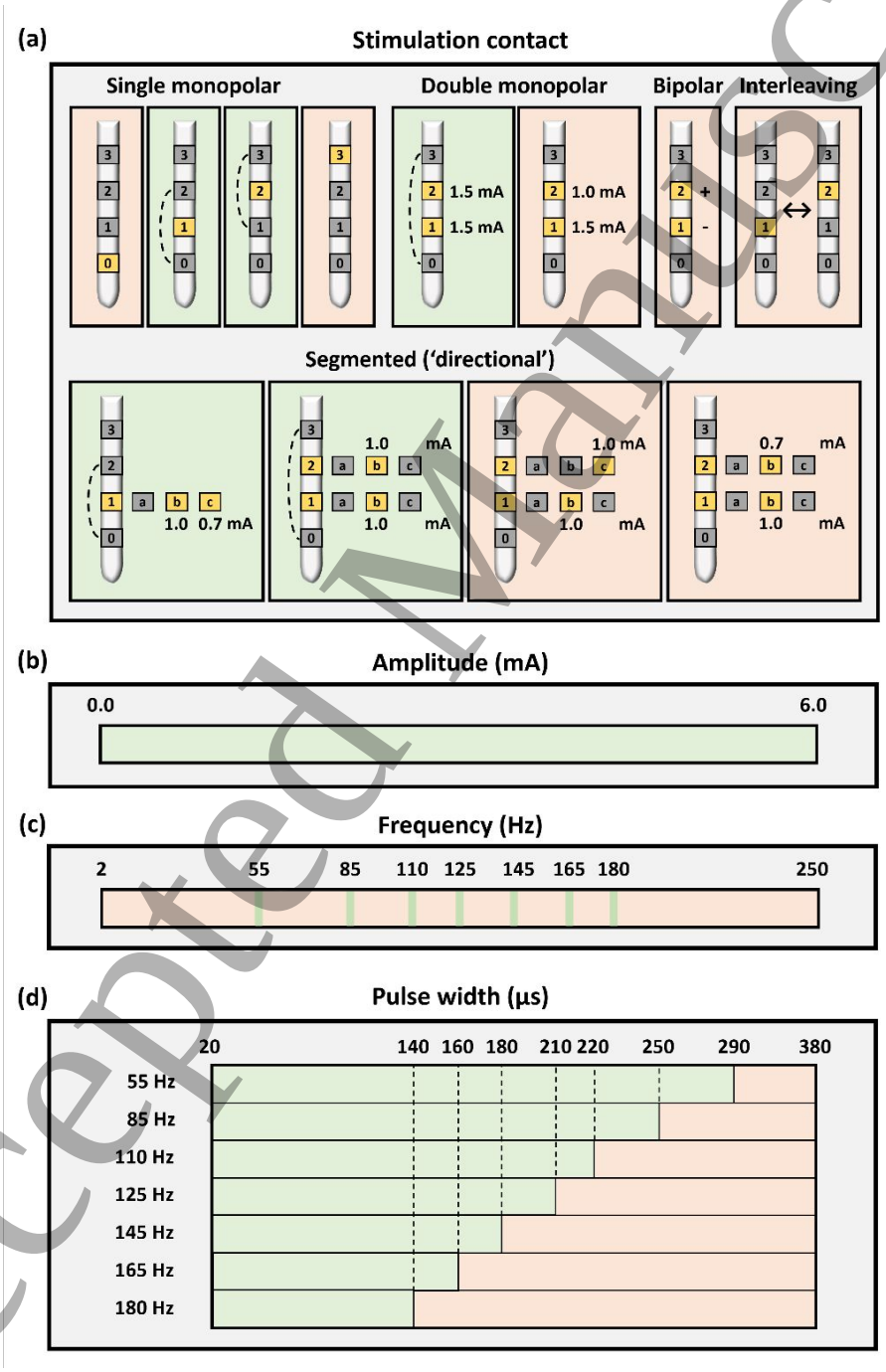

Figure 1. Compatibility between stimulation configurations and BrainSense. This figure illustrates which stimulation parameters are compatible with BrainSense. Background color indicates stimulation configurations that are compatible (green) or incompatible (orange) with BrainSense. This figure only applies to the use of SenSight (segmented) leads; differences with Legacy (non-segmented) leads are discussed in Supplementary Table 2. **(a)** Simultaneous stimulation and LFP recording is not possible with monopolar (or multipolar) stimulation at the most ventral or most dorsal contact, vertically asymmetrical double monopolar stimulation at the two middle contacts, bipolar stimulation, and interleaving stimulation. When using segmented (directional) stimulation, the electrical field of the stimulation needs to be vertically symmetric (i.e. along the longitudinal axis of the lead) to allow simultaneous sensing. Curved dashed lines indicate compatible sensing channels. **(b)** No limitations are imposed concerning stimulation amplitude. **(c)** When using BrainSense, only seven predefined stimulation frequencies can be implemented. Note that stimulation at low frequencies (e.g. theta 4-8 Hz or alpha 8-12 Hz) does not allow simultaneous LFP recording. **(d)** The upper limit of sensing-compatible pulse widths is determined by the stimulation frequency. Note that commonly used pulse widths for movement disorders (i.e. 20 to 120 μs) are always compatible with sensing.

(i) Compatibility between stimulation configuration and sensing: stimulating with simultaneous LFP recording adds constraints to various aspects of the stimulation, including contact configuration, frequency, and pulse width (Figure 1). The electrical fields induced by the stimulation are several orders of magnitude higher than the LFPs generated by neural tissue. So, to measure LFPs while stimulating, stimulation artifacts need to be mitigated by various methods. With BrainSense, this is accomplished by only allowing recording between two contacts surrounding the contact(s) used for stimulation – often called a 'sandwiched montage'. In this way, electrical fields induced by the stimulation are canceled out because they are equally present in both recording contacts – often called 'common mode rejection'. While very effective, this method imposes two important constraints on the stimulation configuration. First, stimulating at the most ventral or most dorsal contact is not compatible with sensing since 'sandwiched montages' are not available for these contacts (Figure 1a). Second, many stimulation configurations inducing asymmetrical electrical fields, like bipolar stimulation or complex directional stimulation, do not allow sensing since the requirements for common mode rejection are not met (Figure 1a). In order to mitigate stimulation artifacts, there are also constraints regarding stimulation frequencies (Figure 1c) and pulse widths (Figure 1d). For example, the most commonly used stimulation frequency (130 Hz) is incompatible with sensing. Altogether, a patient's clinically defined most optimal stimulation configuration may not be compatible with BrainSense. Searching for alternative, equally effective, but sensing-compatible stimulation settings could mitigate the issue. While this may be straightforward for some parameters, like stimulating at 125 Hz instead of 130 Hz (Figure 1c), this may be a challenge for other parameters and may not always be possible.

(ii) Differences between stimulation 'off' and '0.0 mA': LFP recordings with 'stimulation off' are not equivalent to 'stimulation at 0.0 mA'. This is due to differences in the electrical circuitry when enabled or disabled. In general, artifact susceptibility (such as electrocardiography) is higher with stimulation at 0.0 mA than with stimulation off.[13, 14] Even advanced signal processing techniques are limited in removing these artifacts altogether, making comparisons of LFP data across the two conditions problematic. This issue applies to Streaming, Timeline, and Events (Table 1 – see example in Figure 3d). A way to avoid differential contribution of artifacts between recordings is to remain in one of the conditions ('off' or '0.0 mA') throughout the entire data collection. Similarly, to assess the effect of stimulation on LFPs it is advisable to compare 'stimulation at a given mA' with 'stimulation at 0.0 mA', and not 'stimulation off'.

(iii) Timing aspects: for JSON file analyses of Timeline and Event data, timestamps associated with the data are in Universal Time Coordinated (UTC). This is a standard used to set all time zones around the world, which can differ substantially from the patient's time zone (e.g. 7 to 8 hours difference in California). This is critical because: 1) neural activity exhibits diurnal and daytime patterns – for example sleep-wake differences and medication-induced beta fluctuations in PD, and 2) sometimes these LFP data are combined with externally collected data (e.g. wearables or ecological momentary assessments). This issue can be mitigated easily by correcting the timestamps for the UTC offset, taking into account daylight saving time transitioning during the period of recording (Table 1). Relatedly, the neurostimulator's clock can come out of sync with actual real-world time by several minutes over weeks to months. Thus, it is advisable to update the clock (located in 'About' in the drop-down menu next to 'Home' on the tablet's start screen) before starting a clinical or investigational BrainSense period (Table 1).

(iv) Impact of different hardware components on LFP recordings: recently, the rechargeable Percept RC has been implemented in clinical practice. Although sensing features are largely similar to Percept PC, some differences could be relevant for research or clinical use (Supplementary Table 1). These include a more limited memory capacity of Timeline and Events data compared to Percept PC, and advantageous (e.g. battery recharging offering virtually unlimited sensing time) and disadvantageous (e.g. suspension of sensing during recharging) effects of battery recharging on the use of BrainSense. Similarly, there are considerable technical differences between using BrainSense in a neurostimulator connected to Legacy ('quadripolar') compared to SenSight ('octopolar'/'directional'/'segmented') leads (Supplementary Table 2). SenSight leads have lower artifact susceptibility and allow directional sensing. However, they do not allow at-home chronic sensing below 7.81 Hz (i.e. the delta and low-theta range) and have more restrictions with regard to stimulation frequency.

(v) Patient burden and battery usage: First, in-hospital (Survey and Streaming) and at-home (Timeline and Events) LFP measurements require time investment from the patient. In addition, while recording with stimulation disabled (e.g. Streaming at 0.0mA or Survey), PD symptoms may temporarily worsen, which can be troublesome for some patients. The second issue is battery drainage (see Supplementary Table 1), which is especially prominent with Streaming. Extensive BrainSense use may lead to expedited neurostimulator replacement for Percept PC, and more frequent recharging for Percept RC. Therefore, one should be cognizant of battery use when using BrainSense. Whenever BrainSense is not required anymore, it is recommended to disable at-home BrainSense Timeline recordings or to instruct patients to switch to an identical but sensing-disabled group. The increased patient burden and battery issues need to be balanced against the potential benefits of expedited DBS programming and/or improved DBS effectiveness. Potentially, this burden could be outweighed when using BrainSense to replace the burdensome traditional monopolar review for initial DBS programming.

	Data collection	Analysis
General	• Charge batteries upfront (patient programmer & communicator, clinician programmer & communicator, Percept RC neurostimulator). • Update IPG device time before data collection. • Select sensing-compatible stimulation configuration (Fig. 1).	• Correct timestamps for UTC offset.
Survey	• Needs to be executed separately per hemisphere, and per mode (ring-level vs directional). • Warn patient that stimulation will be off for about a minute. To wash out the effect of DBS on LFPs, it is	• Stimulation is switched off (≠ 0.0 mA), therefore less susceptible to artifacts. • Bipolar recordings are obtained. Therefore, there are several methods and challenges concerning beta-based contact selection (Fig. 2).

	recommended to switch off stimulation already a few minutes before Survey. • To minimize artifacts, instruct the patient to relax, and to not move or speak.	
Streaming	• Start with a BrainSense Setup (including a Signal Test) for both hemispheres separately. • When Streaming at 0.0 mA, set amplitude at 0.0 mA before starting the streaming and wait a few seconds to avoid y-axis misscaling. Also, don't switch between 'stimulation off' and 'stimulation 0.0 mA' during Streaming (Fig. 3d). • Can be performed bilaterally simultaneously (requires bilateral Signal Test). Switching between hemispheres is allowed during streaming. • The following actions lead to a pause in the data acquisition: (i) 10 min of inactivity on the physician programmer (recommended to tap on the screen regularly), (ii) switching stimulation frequency or pulse width, and (iii) tapping the 'lead' button. Data after the pause are stored separately in the same JSON file. • Clinician communicator battery drains fast. • There are several methods for synchronization with external data streams (see Fig. 3a,b,c and text). • With 'Indefinite Streaming' (located in the 'Survey' interface), LFP recording of all three stimulation-compatible channels is performed with 'stimulation off'. Data are not displayed on the tablet in real-time.	• Be aware of possible data package losses (Fig. 3c). For long recordings encompassing multiple assessments (e.g. several motor or behavioral tasks), it may be recommended to start a new Streaming session before each assessment. • Sampling frequency (250 Hz) does not allow analysis of high (> 125 Hz) frequencies. • Tablet only shows the power of the selected frequency. For other frequencies: (i) redo Streaming with other selected frequency, or (ii) offline JSON file analysis. • With 'Indefinite Streaming', LFPs are less susceptible to artifacts since stimulation is switched off (≠ 0.0 mA).
Timeline	• To save battery, let patients switch to an identical but sensing-disabled group whenever possible. • If patients switch between sensing-enable groups, harmonize the sensing settings (Fig. 4a). • When selecting a tracking frequency, the surrounding 5 Hz is tracked – beware of crossing boundaries between canonical frequency bands (Fig. 4b). • With SenSight leads, the lowest tracking frequency is 7.81 Hz – delta frequencies cannot be tracked (Fig. 4b). • Sensing characteristics are different between 'stimulation OFF' and 'stimulation at 0.0 mA'. • Storage is limited to 60 days of BrainSense Timeline recording (35 days in Percept RC), beyond that, data is overwritten.	• By default, only the Timeline data since the previous session are downloaded. To download data from previous sessions as well, tap the button 'Read all events'. • Y-axis on tablet can be out of scale due to extreme outliers in LFP data (due to artifacts) (Fig. 4e,f). Perform offline analysis to mitigate. • LFP units are patient-specific, across-patient analyses need normalization. • Resolution of LFP and stimulation amplitude data is limited to 10-min averages (Fig. 5f-i). • Timestamps associated with these 10-min averages relate to the beginning of the 10-min window (Fig. 5f-i). • Correct for UTC offset to get data in the participant's time zone (Fig. 4c,d). Beware of UTC offset changes with daylight saving time transitions.
Events	• Storage is limited to 400 (Percept PC) and 200 (Percept RC) events with LFP capture (limit rarely reached). • Only 4 event types can be enabled across all stimulation groups. • When setting up the events, LFP capture needs to be enabled actively. • LFP is not recorded if patient switched to sensing-disabled group. • Imposes (time) burden on patient, as patient needs to connect IPG with patient programmer. • Instruct patient to relax, to not move, and to not speak for 30 sec after triggering an event – to reduce artifacts.	• Raw LFP time series are not stored. Spectral data obtained via on-board FFT are stored. • Frequency resolution is low (0.98 Hz), and it is limited to the range between 0 and 96.68 Hz. • Depending on the stimulation frequency, power above certain frequencies is censored (Fig. 5a-e). • Censoring also takes place if the respective group history is not present anymore on the IPG, which can be the case for old events. • LFP units are patient-specific, and therefore, across-patient analyses need normalization.

	• When stimulation is switched off, LFP can still be captured, but signal characteristics are different from stimulation at 0.0 mA.	• Stimulation amplitude at the moment of an event is not stored, but can be estimated via Timeline (Fig. 5f-i). • Timestamps are retrogradely updated when updating the IPG clock. Be aware of possible event duplication when using 'Read all events' in successive sessions.

Table 1. Using BrainSense for research purposes: pitfalls and suggestions

Survey

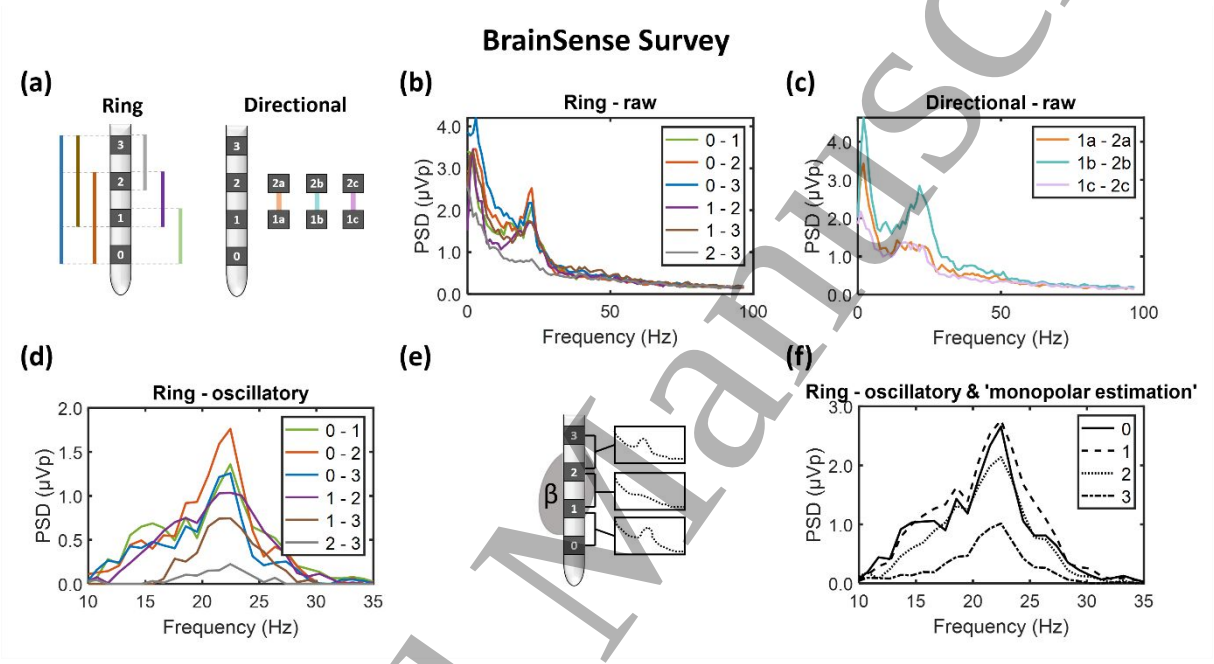

Figure 2. BrainSense Survey. This figure illustrates the challenges and uncertainties when using BrainSense Survey to determine the stimulation contact(s) with the highest beta power peak. An example is given for recordings through a right GPi SenSight lead in a Parkinson's disease patient. **(a)** Visual color-coded representation of the different ring-level (left) and segment-level (right) recording channels to aid the interpretation of panels b, c, and d. **(b)** Power-spectral densities (PSD) of ring-level recordings obtained via BrainSense Survey as provided by the software on board Percept PC. Note that beta peak power is highest in channel 0-2, and that non-oscillatory (1/f) activity differs substantially between channels, most prominently in the low frequencies. **(c)** Power spectral density of selected segment-level BrainSense Survey as provided by the software on board Percept PC. Note that beta peak power is highest in channel 1b-2b. **(d)** Removing non-oscillatory activity via offline postprocessing depicts a clearer picture of the beta peak activity in the different channels. Again, beta peak power is highest in channel 0-2. **(e)** Illustration of the challenge/uncertainty of using bipolar channel recordings to determine the location of highest beta peak power on the single contact level: Beta power is inferred to be low when both sensing contacts are within the beta-generating region. Alternatively, in this example the same recordings might be observed with two focal sources of beta power located near contact 0 and contact 3, respectively. **(f)** To overcome the interpretational limitations of bipolar recording channels, weighted monopolar distributions can be constructed (see Strelow et al.[12]). Note that with this approach contacts 0 and 1 display a virtually similar highest beta peak power. **(b,c,d,f)** Altogether, in this hemisphere, segment 1b could be suspected to be closest to the beta-generating region.

BrainSense Survey aims to assess the spatial distribution of LFPs around the DBS electrode. During the recordings, stimulation is switched off automatically to prevent stimulation artifact and ECG artifact (Table 1). To reduce movement artifacts, patients should be instructed to relax, not move, and not speak, and simultaneous tasks or evaluations should be avoided during recordings.[15] For quadripolar (Legacy) electrodes, recordings are obtained from all six possible bipolar channels involving the four ring-level electrodes (Figure 2a,b). For octopolar (SenSight) electrodes, these are supplemented with recordings from nine bipolar channels involving the six segment contacts – three across the two segmented levels and three within each segmented level (Figure 2a,c). This is often called 'directional sensing'.

Currently, Survey is mainly used to determine the stimulation contact with the highest beta (13-30 Hz) power, which is posited to be the most effective contact for motor symptom control in PD.[16–20] There are a few important challenges when leveraging Survey for this purpose.

First, in the spectral domain, LFPs comprise an aperiodic (1/f) and an oscillatory component.[11] The pathological beta activity in PD constitutes an oscillatory activity.[21] Hence, when using Survey to locate the contact with the highest beta activity, only the oscillatory component of the power spectral density (PSD) should be taken into account. However, this may be challenging because the tablet's interface only provides the full PSD (aperiodic + oscillatory) and because the aperiodic component can differ substantially across recording channels (see examples in Figure 2b,c). This challenge could be addressed with offline analysis. Isolating the oscillatory activity (Figure 2d – e.g. using the FOOOF[11] or IRASA[22] algorithms) may facilitate and improve beta-based contact selection.

Second, since recordings are bipolar, and not monopolar, the contact with the highest beta power can at best be guessed from visually comparing different bipolar recordings, much like localizing epileptic discharges on scalp EEG (Figure 2e). Although this limitation is not specific to BrainSense, it does interfere with the purpose of the Survey, which is to guide contact selection. Offline processing approaches could be followed to potentially improve contact selection. Strelow et al.[12] proposed using an average of power spectral densities across all bipolar recording configurations weighted by the distance between contacts as a proxy for 'monopolar' activity (Figure 2f). Such an approach is necessary to account for the bias in signal amplitude introduced by differences in distance between recording electrodes.

Third, beta peak presence is rated in a binary way ('present' or 'absent') which oftentimes may be a challenge because of the absence of criteria defining a beta peak. Especially beta peaks with a small magnitude may have an artifactual origin. Therefore, the following may be helpful; (1) the tablet indicates if a potential artifact has been detected in which case PSDs are only displayed upon manual overrule, (2) as per BrainSense manual it is suggested that beta peaks below a magnitude of 1.2 µVp should be interpreted with caution, (3) reduction of beta peak power upon stimulation or dopaminergic medication suggests that the beta peak is not an artifact, and (4) in case of doubt offline visual inspection of the raw LFP time series should be conducted to assess the presence of artifacts. Implementing a cut-off of 1.2 µVp, a beta peak was present in 100 out of 118 hemispheres in the ADAPT-PD trial.[23]

Fourth, some hemispheres display two discernable beta peaks, mostly one within the low-beta (12-21 Hz) and the other within the high-beta (22-32 Hz) frequency range. In those instances, it is unclear which peak should be used for the various BrainSense features. Arguably, the peak with the low-beta range may be preferable because (i) dopaminergic medication mostly suppresses low-beta activity [20, 24, 25] and (ii) stimulation-induced suppression of low-beta (and not high-beta) activity has been demonstrated to aid contact selection.[26]

Streaming

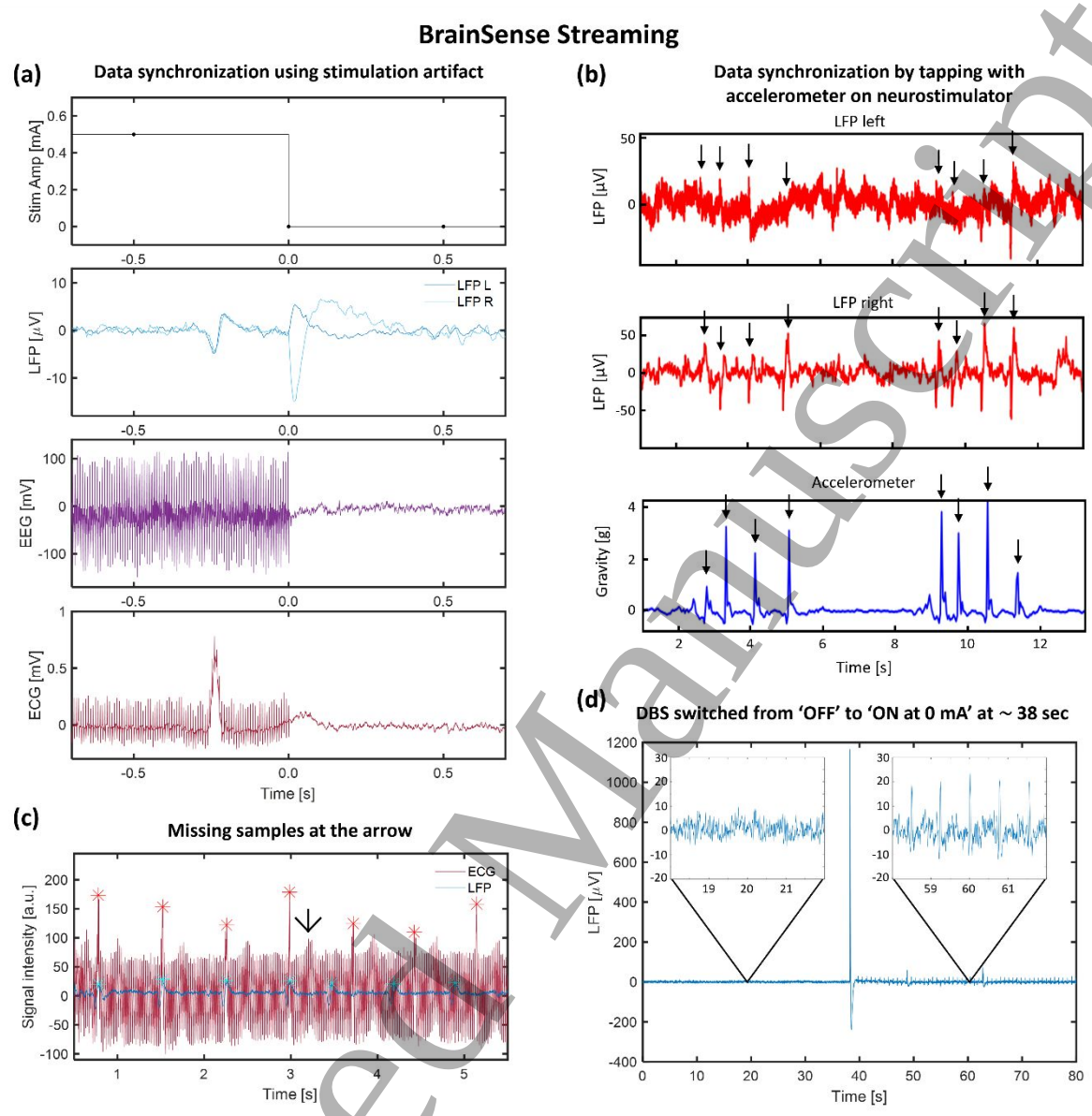

Figure 3. BrainSense Streaming. (a) LFPs can be synchronized with externally recorded EEG signals using stimulation artifacts. Stimulation is ramped up to 0.5 mA and switched to 0.0 mA acutely (upper panel). This sudden drop creates a large artifact in the LFP time series (second panel). Likewise, this sudden stimulation discontinuation is reflected as a sudden discontinuation of stimulation artifact in for example EEG (third panel) and ECG (bottom panel) recordings. This allows to temporally align these data streams. **(b)** To synchronize LFP time series with external data streams (such as accelerometry), artifacts can be induced by semi-rhythmic tapping on the neurostimulator while the accelerometer is held in or attached to the tapping hand. Vertical arrows indicate the taps – in this case two rounds of four semi-rhythmic taps. **(c)** During offline analysis of BrainSense Streaming data, sudden misalignment of the ECG R-peaks in the LFP (stars in blue line) and the ECG (stars in red line) time series is an indication of missing samples ('data package loss'). **(d)** LFP characteristics of streaming with stimulation switched off (from 0 to 38 sec) are different from streaming with stimulation switched on at 0.0 mA (from 38 to 80 sec). In the latter, susceptibility to ECG (and other) artifacts is much higher.

BrainSense Streaming has two main applications: (i) to observe the effect of stimulation on LFPs, and (ii) to relate temporal LFP dynamics to other real-time metrics like clinical, behavioral, kinematic, or electrophysiological measurements – mostly in a research setting. A clinical application of the former is to assess whether stimulation at a certain location induces suppression of pathological beta activity and at which stimulation amplitude this occurs, allowing to inform the selection of stimulation contact and amplitude, respectively.[27, 28] With Streaming, continuous LFP time series from a bipolar channel surrounding one or both middle stimulation contacts are obtained with the option to modulate the stimulation amplitude simultaneously. The tablet's interface only displays the real-time LFP power in a preselected frequency band (5 Hz bandwidth). To appreciate the full frequency spectrum, offline JSON file analysis is required.

A particular challenge in research involving BrainSense Streaming is the proper synchronization of the LFP time series with external data streams (e.g. EEG, ECG, electromyography, and accelerometry). Several synchronization methods can be used (Table 1 and Figure 3a,b,c), with the overarching principle that a transient distinct artifact is introduced in multiple data streams. Commonly used methods of artifact induction include DBS stimulation artifact (Figure 3a), physical tapping on the neurostimulator (Figure 3b) and other recording devices, aligning ECG artifacts (Figure 3c), and transcutaneous electrical neurostimulation (TENS).[9] Some of these methods have recently been explained extensively elsewhere.[9, 29] Currently, these synchronization methods lack standardization and generalization across data streams and settings.

When collecting BrainSense Streaming data, a few practical insights may be helpful (Table 1). First, streaming sessions can be time-consuming and burdensome to patients, especially when several recordings are performed successively with stimulation off. One way to reduce patient burden is to conduct Streaming in both hemispheres simultaneously instead of consecutively. Second, as already outlined above, there are considerable recording differences between 'stimulation off' and 'stimulation at 0.0 mA' (Figure 3d). Therefore, it is recommended to remain in only one mode. Third, sudden large amplitude reductions can induce very large artifacts inflating the y-axis on the tablet interface. Therefore, it is recommended to reduce the stimulation amplitude to 0.0 mA at least a few seconds before starting Streaming.

When analyzing BrainSense Streaming data, solid data preprocessing is valuable to increase the signal-to-noise ratio, and encompasses, amongst others, synchronization (see above) and ECG artifact removal.[13, 30] Details about the latter are not described in this paper but are exhaustively addressed in Stam et al.[13] It is advisable to check the raw LFP time series for (i) data package losses (Figure 3c) and (ii) artifacts. Even though commonly used MATLAB toolboxes for the analysis of Percept data automatically correct for data package losses (e.g. https://github.com/YohannThenaisie/PerceptToolbox and https://github.com/neuromodulation/perceive)[9, 14], it is advisable to document for each experiment whether data is missing, which may impact the reliability and usability of an experiment. Fortunately, when ensuring a sound connection between the tablet and neurostimulator [9], data package losses occur infrequently. Visual inspection of raw LFP time series allows the detection of sudden large amplitude artifacts, for instance induced by movements of the subject. Such motion artifacts (e.g. induced by movements of the neck or arm, or standing up) have been reported to induce broad-band artifacts, especially within the alpha and beta frequency bands.[31] Compared to cortical recordings (EEG), subcortical LFP measurements may be more prone to certain artifacts because of the significantly lower magnitude of the neurophysiological signal (1 - 10 µV compared to 10 - 100 µV).

A limitation of BrainSense Streaming is that the recording is spatially limited to only one channel per hemisphere at once. To overcome this limitation, BrainSense also allows to perform 'Indefinite

Streaming'. This option can be located from the BrainSense Survey window in the programming interface. With Indefinite Streaming, LFPs of all three stimulation-compatible channels are recorded from both hemispheres with 'stimulation off'. Data are not displayed on the tablet in real time but can be downloaded from the JSON file after the recording. Notably, stimulation cannot be enabled during Indefinite Streaming.

Timeline

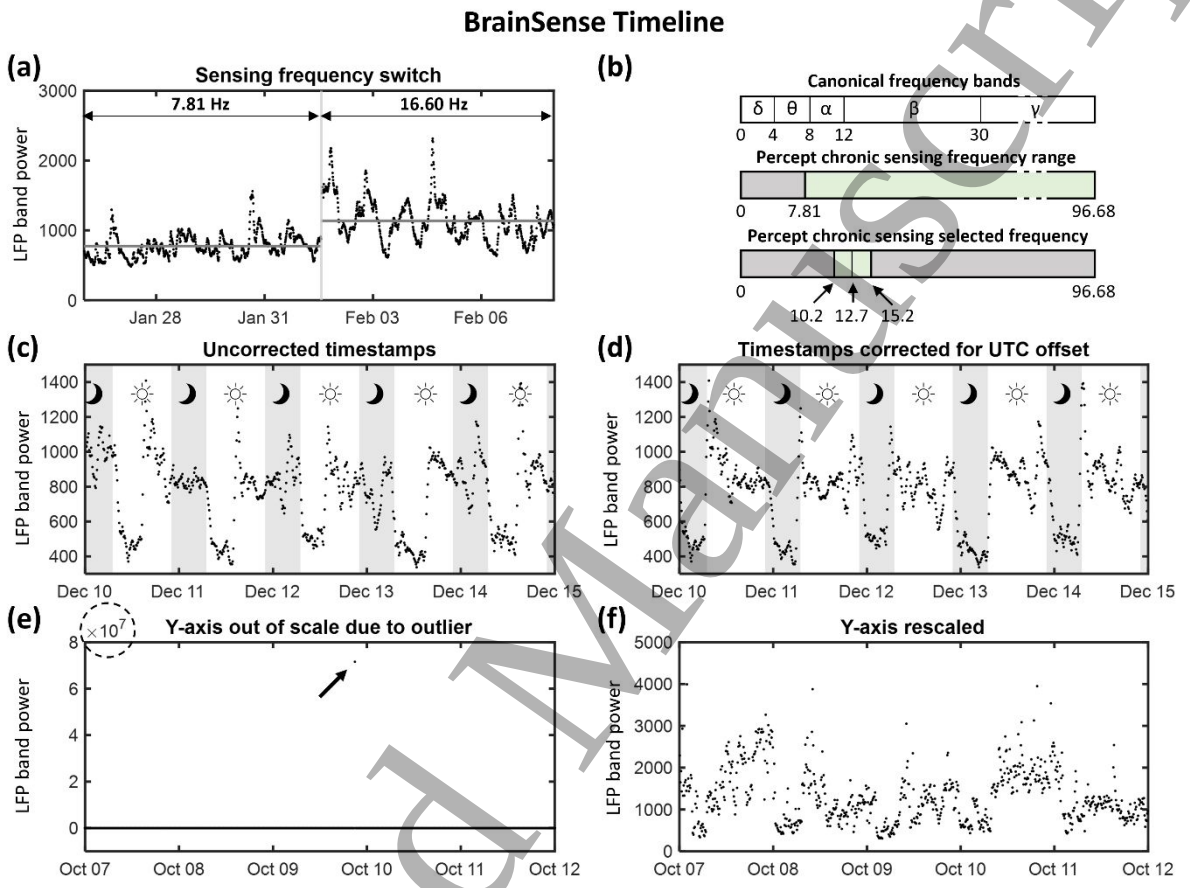

Figure 4. BrainSense Timeline. Illustration of a few pitfalls associated with the use of BrainSense Timeline. **(a)** Timeline data obtained via a right GPi Legacy lead in a PD patient. At first sight, a sudden increase in LFP power seems to occur in the middle of the period (vertical gray line). This pattern of LFP power is due to the patient switching from a DBS group with a sensing frequency of 7.81 Hz to another DBS group with a sensing frequency of 16.60 Hz (using the patient programmer). **(b)** Using SenSight leads, the lower limit of the chronic sensing frequency is 7.81 Hz (middle bar). Note that frequencies in the delta (0-4 Hz) or low-theta (4-6 Hz) range cannot be tracked chronically. For a given selected frequency for chronic sensing, a 5 Hz band around this frequency is tracked (lower bar). In the example depicted here, the selected frequency (12.7 Hz) leads to tracking the power of two canonical frequency bands (alpha, 8-12 Hz and beta, 13-30 Hz). **(c,d)**: Timeline data obtained via a left STN SenSight lead in a PD patient with a sensing frequency at 12.7 Hz. In the JSON file, timestamps associated with the timeline LFP data are in UTC. (c) uncorrected offset of the patient's location time zone may give rise to an incorrect appearance of day-night beta power fluctuations. (d) After UTC offset correction. **(e,f)**: Timeline data obtained via a right GPi SenSight lead in a Parkinson's patient with a sensing frequency at 17.58 Hz. Artefactual LFP outliers can complicate the interpretability of Timeline data. (e) An example for a single LFP outlier of extreme magnitude (arrow) inflating the y-axis scale with a factor x10^4 (dashed circle). On the tablet, this leads to the appearance of LFPs being zero throughout the entire period. (f) Rescaling the y-axis with offline JSON file analysis,

however, allows the visual restoration of beta power time dynamics. Note that rescaling the y-axis is not possible in real-time on the clinician's programmer interface.

The goal of BrainSense Timeline is to obtain insights into the time dynamics of LFP power in the patient's naturalistic environment. For each hemisphere, the stimulation amplitude and LFP power are tracked continuously with relatively low temporal (10-minute averages) and spectral (average power within a 5 Hz band centered around the frequency previously selected in clinic) resolutions. Clinically, this feature is mainly used to track daytime medication-induced beta fluctuations – indexing motor fluctuations – and their response to stimulation changes, often in conjunction with BrainSense Events.

When planning to use BrainSense Timeline, one needs to be aware of a few practicalities. First, in order to activate Timeline and Events, BrainSense needs to be configured in clinic. This involves, amongst others, the performance of a 'signal test' and the selection of a frequency band for at-home tracking in each hemisphere. When several groups are present on the neurostimulator, this needs to be done for all groups. Second, storage of Timeline data on the Percept PC is limited to 60 days (35 days for Percept RC – Supplementary Table 1). Any data acquired earlier than the previous 2 months is overwritten. Third, if patients switch between groups using their programmer, it sometimes causes false trends in LFP behavior if for instance the tracked frequency differs between groups (Figure 4a). Therefore, it is recommended to enable sensing in all groups and align the sensing features across these groups. Fourth, with SenSight leads, chronic sensing is not possible for frequencies below 7.81 Hz (i.e. delta and theta ranges - Figure 4f and Supplementary Table 2). Fifth, when selecting a frequency for chronic sensing, the average power within a 5 Hz band around this selected frequency is tracked. This is important to consider because, if the selected frequency is near the boundaries between two canonical frequency bands, both bands contribute to the tracked power (Figure 4b). For example, a selected frequency of 12.7 Hz would encompass power from alpha (8-12 Hz) and beta (13-30 Hz) canonical bands.

Evaluation of BrainSense Timeline data can be done in real-time on the tablet and/or offline through JSON file analysis. In the JSON file, the timestamps associated with the timeline data are in UTC. So, to perform offline analyses in the patient's time zone, timestamps need to be corrected for the UTC offset and daylight saving time switches (Figure 4c,d). High-magnitude artifactual LFP outliers can complicate the interpretability of timeline data on the tablet by inflating the y-axis scale, leading to the appearance of LFPs being zero throughout the entire period (Figure 4e). Rescaling the y-axis with offline JSON file analysis is needed to visually restore the LFP dynamics (Figure 4f). This is not possible in real-time on the tablet.

Events

BrainSense Events allows to obtain full-spectrum LFP snapshots on moments that are relevant to the patient – e.g. the presence or severity of a symptom are noticeable by the patient. Whereas BrainSense Timeline requires no patient effort at all, BrainSense Event recording is not possible without patient input. Upon triggering an event via the patient programmer, a 30-second LFP recording is obtained. Storage is limited to 400 (Percept PC) and 200 (Percept RC) events with LFP capture.

A few practical and technical notes could be important when considering use of BrainSense Events (Table 1). First, whereas clinicians/researchers can freely choose the name of event types (e.g. 'Dancing movements' or 'Tremor in the left foot'), one is limited to only four event types per patient. Second, analogous to BrainSense Timeline, when patients switch between groups, it is recommended to enable

sensing in all groups. LFPs would not be recorded if a patient has switched to a sensing-disabled group. Third, it is important to realize that the 30-second LFP time-series are not stored on the neurostimulator. Instead, a PSD is obtained via a fast Fourier transform over 1-second time windows within the entire 30-second time series with a frequency resolution of 0.98 Hz. These PSDs are stored on the device. Fourth, depending on the stimulation frequency, power values above a certain frequency are automatically censored on-board the neurostimulator (Figure 5a,b,c,d,e). This may especially complicate research into gamma oscillations (e.g. entrained gamma) when stimulating at low (≤ 85 Hz) or high (≥ 180 Hz) frequencies.[32–34] Fifth, when analyzing Events in two subsequent JSON files at once, it is important to consider that Events may be duplicated if the time of the device has been updated in between the two files. For example, an Event may be logged in the first JSON file on 12-APR-2024 12:11, however, when the time of the device is then updated by for instance 1 minute, the Event may be duplicated and shown in the second JSON file on 12-APR-2024 12:12.

For the analysis of BrainSense Event data, a limitation of the device is that the stimulation amplitude at the moment an Event was triggered by the patient is not recorded in the JSON file Event data structure. Instead, it can be deducted from the BrainSense Timeline data. However, there are two important constraints in using Timeline data to estimate the stimulation amplitudes corresponding to Events: 1) estimation is challenging when a patient changed the stimulation amplitude around the time of the Event (Figure 5f,g,h,i), and 2) Timeline data may not be available anymore for events recorded more than 60 days before.

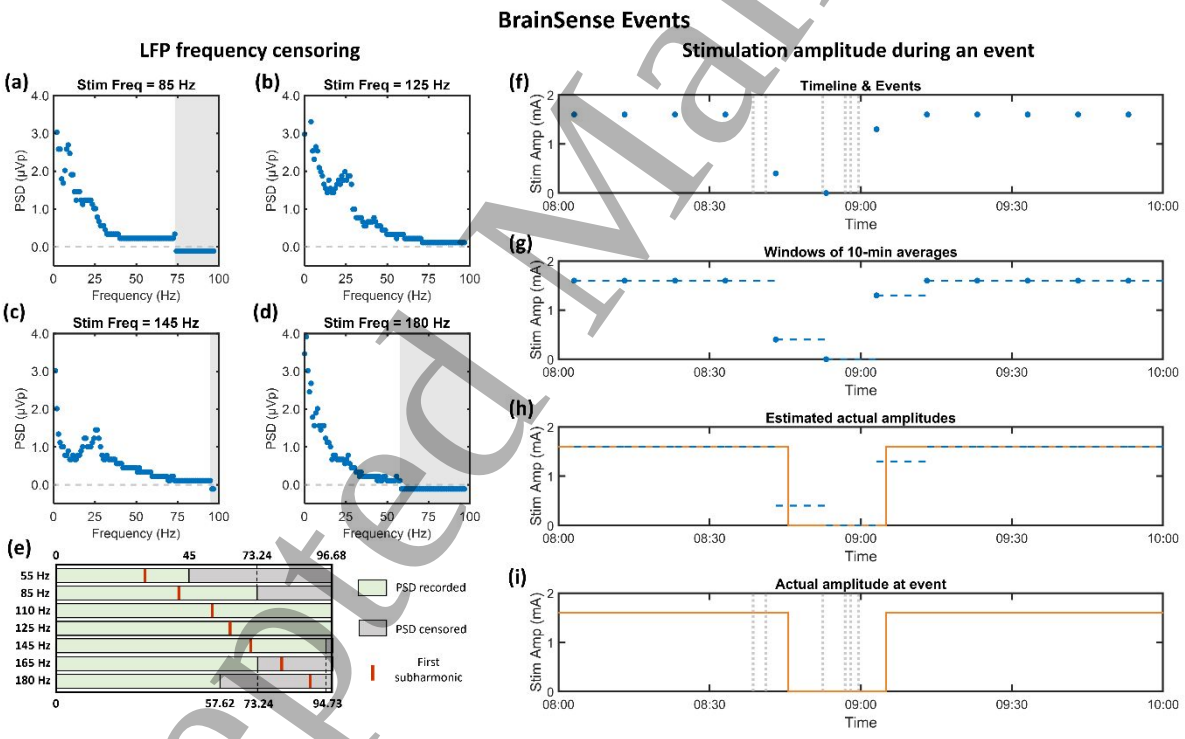

Figure 5. BrainSense Events. (a,b,c,d,e) Depending on the stimulation frequency, power values above a certain frequency in an Event recording are automatically censored on-board Percept PC. (a,b,c,d) Examples of Event power-frequency data for four different hemispheres, each stimulated at a different frequency. Gray zones indicate censored power values. Whereas no data is censored when stimulating at 125 Hz (b), increasing parts of the power spectral density are censored when stimulating at 145 Hz (c), 85 Hz (a), or 180 Hz (d). Note that 'censored' data are not represented as 'NaN' values but as negative values. (e) Illustration of the frequency ranges with censored LFP data (gray), according to stimulation frequency. The first subharmonic frequencies are indicated by vertical red lines. Note that, when stimulating at 165 or 180 Hz, LFP data of the first subharmonic frequencies (82.5 and 90 Hz) are censored. **(f,g,h,i)** Challenges and mitigations for the estimation of the

stimulation amplitude at the moment of a patient-triggered Event recording. Timeline data obtained via a left STN SenSight lead in a Parkinson's disease patient who was instructed to trigger a few Events with stimulation at 1.6 mA and a few Events with stimulation at 0.0 mA. (f) Timeline amplitude data. The stimulation amplitude at the moment an Event recording was triggered (vertical gray dashed lines) is not readily apparent from this data and is not recorded in the JSON file event data structure. (g) The first step in determining the actual amplitude during the Event is the notion that the Timeline amplitude (and LFP) data constitute a 10-min average amplitude value in the ensuing 10-min window. (h) With this knowledge, an estimate of the actual amplitude curve can be reconstructed. (i) Realigning the Event times onto the actual amplitude curve allows the determination of the actual stimulation amplitude at the moment each Event was triggered.

Discussion

In the last years, real-time LFP recording with BrainSense has been increasingly implemented in clinical practice and research involving DBS. It has shown promise for clinical use in movement disorders (1) guiding initial DBS programming replacing the labor-intensive monopolar review [35], (2) optimizing long-term DBS programming [6, 36], and (3) improving DBS effectiveness and tolerability through adaptive DBS (aDBS).[23, 37] Some important investigational implementations have been to (1) understand neurophysiological processes involving DBS target nuclei (e.g. encoding of gait [38] and passive cycling [39] in STN), and (2) to establish physiomarkers of motor (e.g. bradykinesia in PD [28] or severity of dystonia [40]) and non-motor (e.g. anxiety in PD [41]) symptoms.

To further propel BrainSense's clinical usefulness, appropriate knowledge of the possibilities, drawbacks, and challenges of this technology is required. For instance, BrainSense is not possible with several stimulation configurations, excluding a considerable portion of patients from this technology. Although the user-friendly tablet interface of this advanced technology is an important strength and facilitates its clinical implementation, there are several limitations associated with this interface. For instance, offline data analysis - which is not readily implementable in most clinical practices - is often required. Similarly, assessing Timeline and Event data on the interface may be a challenge in case of abundant data, but can be facilitated via open-source online tools like the BRAVO platform.[42] Finally, the temporal-spectral resolution (i.e. 10-minute average of a narrow 5 Hz frequency band) of BrainSense Timeline may be too limited for certain paroxysmal symptoms like freezing-of-gait, and storage capacity (i.e. 35 days for Percept RC) may not suffice to address certain long-term clinical problems - especially in remote areas.

Some practical restrictions regarding BrainSense may impede certain research strategies. First, assessing the effect of theta frequency stimulation[43] is not possible since sensing cannot be enabled when stimulating at a theta-band frequency. Second, evaluating subcortical LFP dynamics upon nigral stimulation[44] is challenging since stimulation at the most ventral contact is not compatible with sensing. Third, research into other frequency bands than beta may be a challenge because of various reasons; tracking of delta and theta power is not possible in Timeline when using SenSight leads, considerable portions of spectral power within the gamma frequency range in Events are censored depending on the stimulation frequency, and the low sampling frequency (250Hz) does not allow to assess frequencies above 125 Hz, including high-frequency activity (> 200 Hz).[45, 46] Fourth, the spatial uncertainty when trying to localize the origin of the neural signals based on bipolar recordings is challenging, for instance to determine the stimulation contact with the highest beta power. Fifth, although BrainSense allows LFP recording in chronically implanted patients, the modalities for in-hospital use (i.e. Survey and Streaming) are more advanced than those in the at-home naturalistic setting (i.e. Timeline and Events).

Regardless of these limitations, BrainSense remains a powerful tool which has the potential to greatly expand our understanding of physiological and pathological brain processes, and to significantly

improve the effectiveness and safety of neuromodulation for neurological and psychiatric disorders. A good understanding of its capabilities and limitations is crucial to advance research and clinical practice with this novel technology.

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