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EEG and MEG primers for tracking DBS network effects

Vladimir Litvak[a], Esther Florin[b], Gertrúd Tamás[c], Sergiu Groppa[d,1,*], Muthuraman Muthuraman[d,1,*]

[a] The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK
[b] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany
[c] Department of Neurology, Semmelweis University, Budapest, Hungary
[d] Movement disorders and Neurostimulation, Biomedical Statistics and Multimodal Signal Processing Unit, Department of Neurology, University Medical Center of the Johannes Gutenberg University, Langenbeckstrasse 1, 55131 Mainz, Germany

A B S T R A C T

Deep brain stimulation (DBS) is an effective treatment method for a range of neurological and psychiatric disorders. It involves implantation of stimulating electrodes in a precisely guided fashion into subcortical structures and, at a later stage, chronic stimulation of these structures with an implantable pulse generator. While the DBS surgery makes it possible to both record brain activity and stimulate parts of the brain that are difficult to reach with non-invasive techniques, electroencephalography (EEG) and magnetoencephalography (MEG) provide complementary information from other brain areas, which can be used to characterize brain networks targeted through DBS. This requires, however, the careful consideration of different types of artifacts in the data acquisition and the subsequent analyses. Here, we review both the technical issues associated with EEG/MEG recordings in DBS patients and the experimental findings to date. One major line of research is simultaneous recording of local field potentials (LFPs) from DBS targets and EEG/MEG. These studies revealed a set of cortico-subcortical coherent networks functioning at distinguishable physiological frequencies. Specific network responses were linked to clinical state, task or stimulation parameters. Another experimental approach is mapping of DBS-targeted networks in chronically implanted patients by recording EEG/MEG responses during stimulation. One can track responses evoked by single stimulation pulses or bursts as well as brain state shifts caused by DBS. These studies have the potential to provide biomarkers for network responses that can be adapted to guide stereotactic implantation or optimization of stimulation parameters. This is especially important for diseases where the clinical effect of DBS is delayed or develops slowly over time. The same biomarkers could also potentially be utilized for the online control of DBS network effects in the new generation of closed-loop stimulators that are currently entering clinical use. Through future studies, the use of network biomarkers may facilitate the integration of circuit physiology into clinical decision making.

Introduction

The mechanism of action of deep brain stimulation (DBS) is still questioned. However, the hypothesis of modulation of disease- or symptom-related oscillatory networks has been intensively debated in the last years (Boon et al., 2020; de Hemptinne et al., 2015; Muthuraman et al., 2018a). Electroencephalography (EEG) and magnetoencephalography (MEG) are capable of exploring the dynamic oscillations in the sensorimotor system and the associated functional networks. By analysis of EEG and MEG data one can identify distinct regional activity and also measure the strength of the correlation, also known as coherence, between central signals (Lalo et al., 2008) or central and peripheral signals e.g., electromyography (EMG) (Airaksinen et al., 2015) in the frequency domain. In addition, they can be used to estimate the direction of information flows in specific frequency bands (Muthuraman et al., 2014; Williams, 2002) or to capture cross-frequency coupling (López-Azcárate et al., 2010). Accordingly, these methods can also provide information about the disease-related alterations in neuropsychiatric diseases (Pfurtscheller et al., 1998; Timmermann et al., 2003). A tremendous amount of research has been obtained from patients with movement disorders such as tremor, Parkinson's disease (PD) and dystonia; therefore we link DBS effects, simultaneous local field potentials (LFP) recordings through implanted electrodes and EEG/MEG studies.

Comparing the EEG and the MEG, their possible temporal resolution range is identical (Hari et al., 2018). MEG has the strength of precise source localization capability due to the higher signal-to-noise ratio for its primary target, the post-synaptic currents in the brain (Baillet, 2017). However, MEG is less sensitive than EEG in detecting deep sub-cortical sources since radial current flow only induces weak MEG signals (Ahlfors et al., 2010; Baillet, 2017). Combining MEG and EEG is, therefore, a promising approach for obtaining more reliable estimates of both cortical and subcortical activities (Hari et al., 2018; Muthuraman et al., 2014).

Measurements from patients with implanted DBS provide the opportunity to study not only cortical but parallel subcortical target activities with a high signal-to-noise ratio (Williams, 2002), to analyze potentials evoked by DBS in the cortex (Ashby et al., 2001) as well as to explore the restoration process caused by DBS therapy in pathological oscillations (Kühn et al., 2008). The investigation of the overlap of the symptom-

* Corresponding author.
E-mail address: mmuthura@uni-mainz.de (M. Muthuraman).
[1] Both the authors have equal contribution to this work.

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related and DBS-targeted networks (Heinrichs-Graham et al., 2014) and (Devos, 2004; Schnitzler et al., 2009; Walker et al., 2012) has shown Fig. 2 immense potential for discovering new stimulation paradigms or sensing target locations.

Networks involved in physiological rhythmic movements and bradykinesia

EEG studies identified the primary sensorimotor cortex (Muthukumaraswamy, 2010), the supplementary motor area (SMA) involved in the generation of voluntary upper (Muthuraman et al., 2012) and lower limb (Raethjen et al., 2008) movements; in addition the dorsolateral prefrontal cortex, the thalamus, and the cerebellum were active during voluntary hand movements (Tamás et al., 2018). In a study combining MEG and EEG, the activity of deep sources (thalamus and cerebellum) was more robustly identifiable with the addition of MEG than with EEG recording alone (Muthuraman et al., 2014). In Parkinson's disease, alterations of the above-mentioned cortical regions were widely examined and associated with bradykinesia using EEG (Brown and Marsden, 1999; Pfurtscheller et al., 1998; Wang et al., 1999) and MEG (Heinrichs-Graham et al., 2014; Pollok et al., 2012; Vardy et al., 2011).

Pathological networks identified with EEG and MEG recordings

Based on EEG (Hellwig et al., 2001; Muthuraman et al., 2012; Muthuraman et al., 2018b) and MEG (Pollok et al., 2008; Schnitzler et al., 2009; Timmermann et al., 2003) measurements, the cortico-thalamo-cerebellar loops play a pivotal role in Parkinsonian and essential tremor (ET) as well as in voluntary rhythmic movement mimicking tremor. EEG pointed out altered connectivity in the primary sensorimotor cortex and the premotor (PM)/prefrontal cortex and parietal cortex in the generation of resting tremor in PD, ET (Roy et al., 2019), and voluntary movements mimicking tremor (Muthuraman et al., 2012; Muthuraman et al., 2018b). MEG confirmed the role of the primary sensorimotor cortex and cingulate/SMA and PM cortex in the generation of Parkinsonian resting tremor (Timmermann et al., 2003); additional tremor sources were found in the secondary sensory cortex (S2), posterior parietal cortex (PPC) and the ipsilateral cerebellum (Pollok et al., 2008). MEG recordings localized the synchronized sources of ET in the primary motor, PM cortex, the thalamus, brainstem, and ipsilateral cerebellum (Schnitzler et al., 2009). In dystonia, MEG/EEG recordings described an abnormal synchronization in the cortico-striato-pallido-thalamo-cortical circuits and cerebello-thalamo-cortical pathways that play an important role for the generation of dystonic movements and impairment in motor control (Lehéricy et al., 2013; Neychev et al., 2008). MEG identified altered connectivity in the primary sensorimotor cortex, PM and PPC cortex areas, the thalamus, and the cerebellum in patients with writer's cramp; the network being driven by altered interconnection compared to controls (Butz et al., 2006). MEG detected altered connectivity between the primary sensory and motor cortex in patients with focal hand dystonia (Melgari et al., 2013). Earlier studies with EEG or MEG found pathophysiological alterations in the sensory cortices in dystonia patients (Dolberg et al., 2011; Hinkley et al., 2012) in addition to the primary sensorimotor cortex and the SMA (Deuschl et al., 1995; Tecchio et al., 2008).

In the next sections, we summarize first how the activity of the distinct symptom-related oscillatory networks change with DBS as detected by EEG, MEG, and deep brain LFP recordings. Further, we also outline the technical details and difficulties associated with such recordings and highlight the future perspective on how to employ these functional modalities to optimize DBS procedures. Here, the careful removal of the artifacts due to DBS is critical.

DBS artifacts in EEG and MEG recordings

When obtaining EEG or MEG in DBS-treated patients several different types of artifacts can be observed. MEG is sensitive to the presence of any ferromagnetic metal components, particularly moving ones. Therefore, even when a stimulator is turned off, its movement as a result of breathing, heartbeat and fidgeting can severely contaminate the MEG signals, particularly at the low frequencies. Furthermore, ferromagnetic wires and other components (e.g., screws) can generate severe artifacts even in patients without implanted stimulators (Litvak et al., 2010a). The artifacts have been shown to be partially locked to heart beat, likely because of slight movements of the metal parts due to pulsation of blood vessels and they have complex, 'rotating' topography which makes them difficult to remove by topography-based methods such as Independent Component Analysis (ICA) or signal space projection (SSP) (Uusitalo and Ilmoniemi, 1997). There are several ways of handling these artifacts that have shown to be effective. First, the actual wires can be modified to remove the ferromagnetic components to make them more MEG-compatible. In the case of the Medtronic DBS electrode, the most problematic component was the externalization lead, a stainless steel component temporarily connected to the DBS electrode to enable recording and stimulation. The company made a non-ferromagnetic version of these leads which were used in several studies (Hirschmann et al., 2011, 2013b). Other manufacturers, such as Boston Scientific and Abbott (St. Jude Medical), made their externalization kits non-ferromagnetic by default. An effective strategy first suggested by Litvak et al. (2010) was the use of beamforming, a common MEG source analysis method. Beamforming by definition effectively suppresses sources of no interest including artifacts; its regularization parameter can be tuned to ensure effective suppression of wire artifacts while preserving physiological signals of interest. Finally, Signal Space Separation (SSS) (Taulu et al., 2004) and its temporal extension (tSSS) (Taulu and Hari, 2009) have been shown to effectively remove metal and stimulation artifacts and enable, for instance, comparison of sensory evoked responses both during on and off DBS (Airaksinen et al., 2010).

The stimulation itself generates very strong spectral peaks at the stimulation frequency (which can vary from 60 to 180Hz) and its harmonics (Allen et al., 2010). These peaks can be narrow band, but there are also some cases where the spectral components leak into neighboring frequency bins (Santillán-Guzmán et al., 2013a). In addition, due to aliasing effects lower frequency bands like the beta (14-30 Hz) and low gamma band (31-49 Hz) can also be affected. On the other hand, in the time domain they appear as periodic sharp peaks, completely obscuring the physiological EEG/MEG signals. In **Fig. 1A** we show three seconds of an EEG and MEG signal when DBS is ON. The corresponding power spectra are also shown. The stimulation frequency for this case is 130 Hz. This recording corresponds to resting state, i.e. no task was performed. There are two modes of DBS that differ significantly in the severity of artifacts they generate. In the 'bipolar' mode, the current passes between two (or more) contacts on the same electrode. In the 'monopolar' mode, the current flows between the electrode and the stimulator case located in the patient's chest. While for the bipolar mode the current loop is enclosed inside the stimulated brain structure and therefore the currents and associated magnetic fields are weak outside the skull, in the monopolar mode the current flows between the head and the chest thus creating much greater electric potential differences between EEG electrodes and also much stronger magnetic field changes. Nevertheless, some EEG and MEG studies use the monopolar mode either because it is more common in clinical programming or because it is the only way to record from the stimulation site during DBS (Oswal et al., 2016a; Oswal et al., 2016b).

Numerous methods have been proposed for suppressing the DBS artifacts (Allen et al., 2010; Frysinger et al., 2006; Jech et al., 2006b; Kühn et al., 2008). Initially it was proposed to switch off the stimulation for a few seconds in order to record the true EEG/MEG signals. However, it might also be necessary to analyze the signals when the

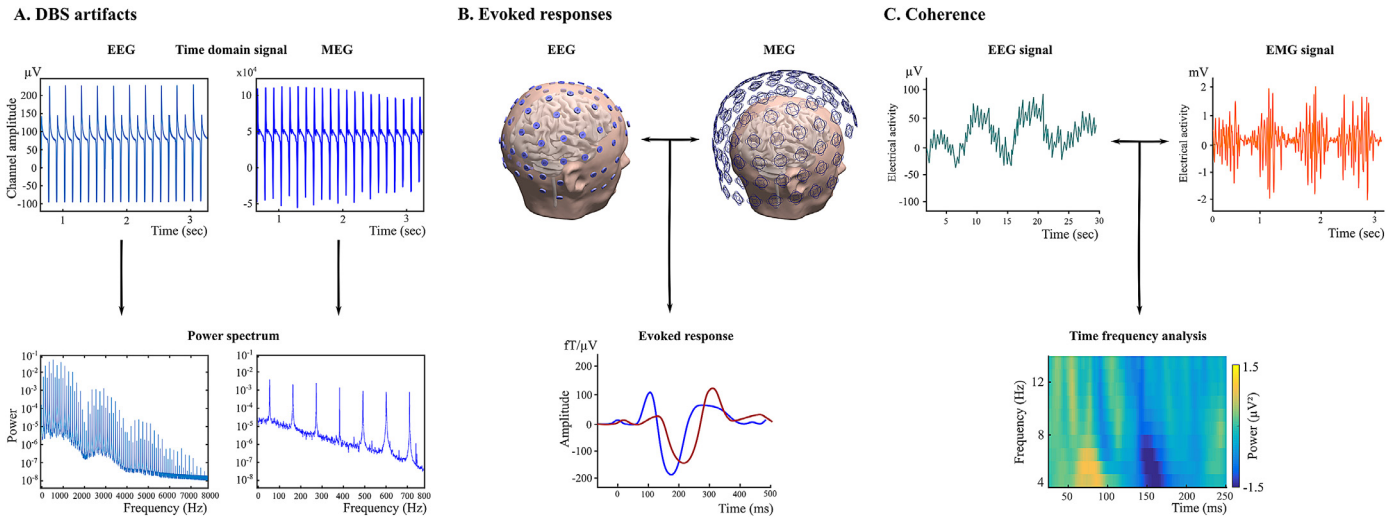

Fig. 1. Representative figures of a single subject showing DBS artifacts, evoked responses and corticomuscular coherence. A) The time domain signal of electroencephalography (EEG) and magnetoencephalography (MEG) from a single channel/sensor of a unipolar stimulation in the first row. The corresponding power spectrums are shown in the second row separately for EEG and MEG. B) Head models with the EEG electrodes and MEG coils in blue overlaid on the scalp in the first row. Representative task/stimuli evoked responses in the second row: the blue line indicates the P100 and N200 evoked responses (represent visually evoked potentials) and the red line indicates the P300 (represents auditory evoked potential). C) shows the EEG and electromyography (EMG) signal in the first row and the corresponding coherence in the second row with time and frequency information.

stimulation is ON. In this case, filtering techniques are needed for suppressing the DBS artifact. The easiest solution would be to use low-pass and notch filters (Jech et al., 2006a). However, if the stimulation peaks overlap many frequency bins or broadening occurs, then these filters cannot suppress them efficiently. A filtering method based on the Hampel identifier, which treats artifacts as outliers in the frequency domain and replaces them with interpolated values, was introduced to remove the DBS artifacts but retain the spectral and temporal fidelity of the EEG (Allen et al., 2010). One drawback is that the Hampel filter modifies the phase of interference frequencies, which is an issue for both resting and task based EEG signals (Allen et al., 2010). In addition, this method cannot adequately handle physiological artifact sources such as head motion, which are common in movement disorder patients. A new approach called the spectral signal space projection was developed, in which time-frequency (TF)-specific spatial projectors are designed and applied to the noisy TF-transformed data and whitened source estimation is performed in the TF domain. It is suited for removal of several types of artifacts produced by DBS, related to both stimulation and physical movement of the head (Ramírez et al., 2011).

In a further study, unlike the above discussed approaches for filtering, special emphasis was placed on optimal phase reconstruction (Santillán-Guzmán et al., 2013b). This method showed a high flexibility for eliminating undesired signals, however depending on the length of the data, the optimization step can be very time consuming (Santillán-Guzmán et al., 2013a). In order to circumvent this, an approach was proposed which uses well-approximated sinusoidal components or natural harmonics as integer multiples of the stimulation frequency. In addition, the aliased frequency components were determined based on the sampling frequency using integer multiples. Here, it is necessary to run simulation tests with the chosen setup parameters to determine how to optimize the filtering approach (Sun et al., 2014).

A purely data-driven method was proposed especially for MEG data using a four step approach involving independent component analyses and mutual information (Abbasi et al., 2016). The first step decomposes MEG data to independent components (ICs). Second, mutual information (MI) between stimulation signal and all ICs is calculated. Third, artifactual ICs are identified by means of an MI threshold and finally the MEG signal is reconstructed using only non-artifactual ICs. The major difference to the previous proposed methods is that the actual stimulation signal is used as the reference signal (Abbasi et al., 2016).

For correcting artifacts from LFPs a new approach was proposed based on template subtraction (Qian et al., 2016). This method involves detrending the raw data, followed by empirical mode decomposition, peak detection, building a template and then subtracting it from the original data to obtain the clean signal.

Two recent reviews provide more detail on the topic of DBS artifact correction. One (Kibleur and David, 2018) focusses on EEG evoked potentials acquired during DBS. The other (Lio et al., 2018), also discussing EEG, concentrates on combining techniques such as oversampling, antialiasing analog filtering and digital low-pass filtering, which are necessary but typically not sufficient to fully remove DBS artifacts when used in isolation. In addition, Lio et al. also summarize more advanced methods, including techniques tracking outliers in the frequency-domain, which can be effective, but are rarely used. They also provided an open source toolbox, which can be accessed at (https://github.com/guillaumelio/DBSFILT/releases), that contains most of the discussed artifact removal methods.

Regardless of the method applied, sufficient validation approaches are necessary to assess their ability to suppress only the artifact signals without removing any physiological information. In this direction, an interesting validation approach was proposed using machine learning to check spatiotemporal patterns of neural activity recorded during stimulation and compare to those recorded when stimulation is off (Boring et al., 2019). The authors checked every step in the artifact correction, followed it with accuracy estimation and indicated that all the steps are important and increase the accuracy. One more validation method used a phantom setup to characterize precisely the MEG artifacts that occur during DBS at clinical settings (Oswal et al., 2016b). Kandemir at al. recently compared the performance of several of the methods described above for removal of both stimulation and movement artifacts in a phantom. The ICA method performed best for sensor-level analysis and tSSS method for beamforming source analysis (Kandemir et al., 2020).

To facilitate successful post-hoc processing in both the EEG and MEG during DBS some important parameters that should be kept in mind to enable neural activity to be captured are summarized here. In EEG, the

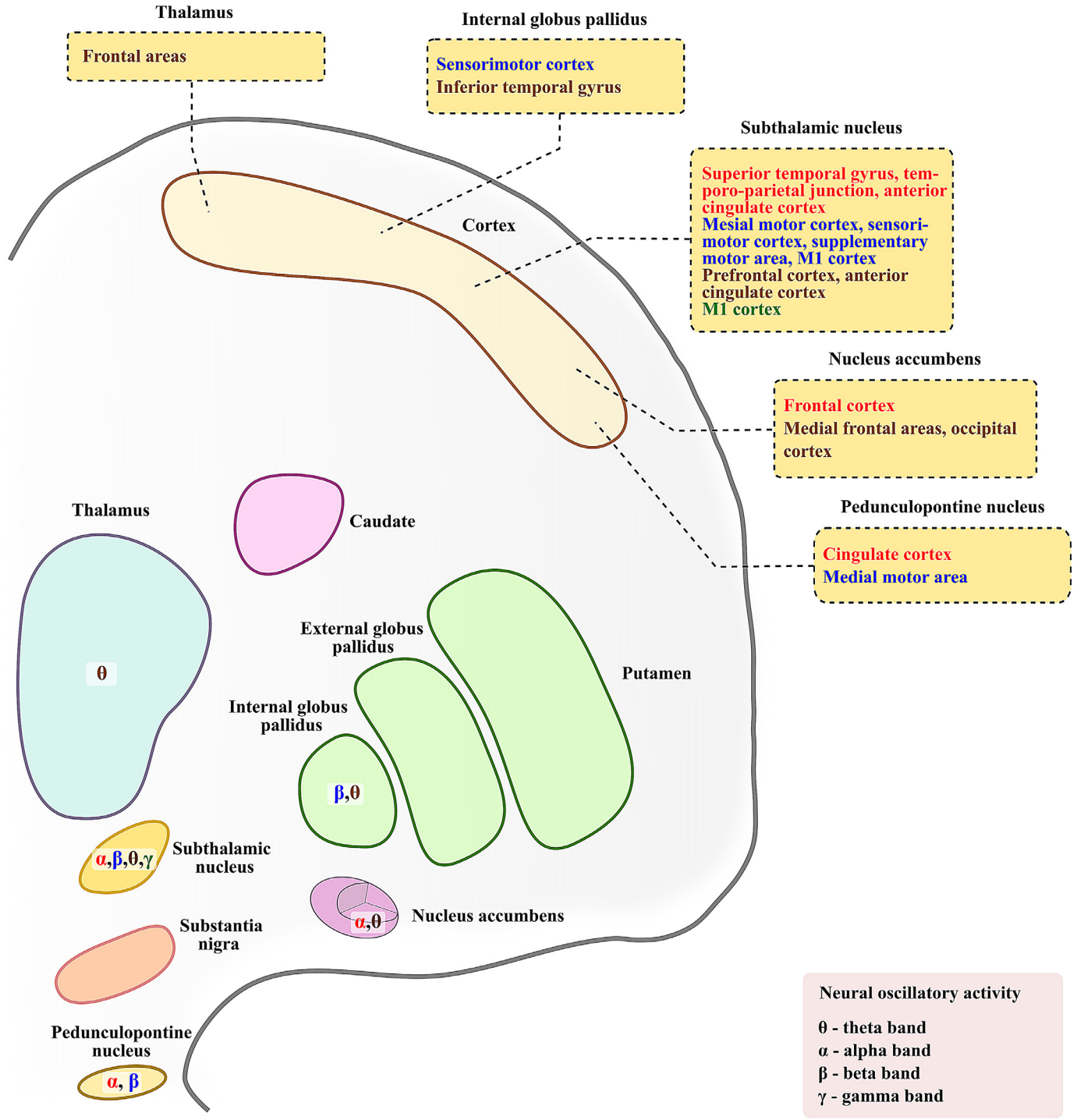

Fig. 2. Topography of observed oscillatory activity within subcortical targets of deep brain stimulation (DBS). Representation of oscillatory activity observed in a given neurological condition is based on the evidence from combined studies of local field potential (LFP) recordings from the DBS electrodes and electroencephalography (EEG) or magnetoencephalography (MEG). Each sub-cortical structure and their corresponding cortical connections (presented in panels) is color-coded correspondingly to symbols of neural oscillations (presented in the subcortical target) that was observed in specific frequency bands.

sampling frequency of the recordings needs to be at least 1000 Hz and preferably above 5000 Hz to remove aliasing artifacts from the stimulation frequency. To avoid saturation of EEG amplifiers due to slow drifts, a maximum recording duration of 5 minutes is recommended. It is good practice to always perform baseline (Stimulation OFF) recordings of rest or task with the same patient and monopolar and bipolar recordings with the same stimulation parameters. In MEG, in addition to the above points, collecting phantom measurements to test the setup for each study and empty room recordings prior to each recording session are recommended.

Parallel detection of intracranial LFP and EEG, MEG recordings

Simultaneous recording of intracranial LFP from DBS electrodes and surface EEG or MEG is of considerable interest because it makes it possible to examine the interactions of DBS targets with the rest of the brain,

particularly the cortex, which contributes strongly to the non-invasive recordings. There are several ways to do this, each with its own advantages and limitations.

Recordings during surgery

The first possibility is to record intraoperatively during the DBS implantation surgery. Here, in many cases research can build on existing clinical procedures where single unit recordings or online analysis of LFP are used for surgical targeting (Kinfe and Vesper, 2013). One advantage of this approach is the potential to record from any patient undergoing surgery without special arrangements such as externalization of DBS leads, which will be discussed below. The second advantage is the ability to record from many sites along the implantation trajectory (van Wijk et al., 2017b) and in areas targeted by exploratory microelectrodes around it and not only from the final implantation site. The third advantage is the possibility to record single units or multiunit activity in addition to LFP, EEG and in some cases electrocorticography (ECoG). This provides a richer set of signals and one can then study the relation between a single neuron and the activity of large neural populations both local and remote.

However, the intraoperative approach also has significant limitations. First, the possibility to perform these recordings depends on the preference of the neurosurgeon and the specifics of their implantation technique. While some surgeons find intraoperative electrophysiological recordings helpful, others rely solely on MRI-guided implantation, which is normally done under general anesthesia (Foltynie et al., 2010; Kochanski and Sani, 2018). Although intraoperative LFP recordings could also be done in this case, most researchers do not find them informative because of suppression of brain rhythms induced by the anesthetic (Malekmohammadi et al., 2018b) and the inability to study waking behavior. In cases of surgery under local anesthesia when recordings are possible, they are always severely limited in time and the patients might be experiencing considerable stress and discomfort making it difficult for them to focus on performing experimental tasks. Second, although EEG recordings can be done during surgery, it is difficult to achieve coverage of the whole head with a sufficient number of electrodes to allow source localization (but see (Belardinelli et al., 2019)).

Recording from externalized leads with staged surgery

An alternative way to record LFP in DBS patients is via lead externalization before implantation of the stimulator in the chest. As this is the most common way of combining invasive and non-invasive recordings, we will, only introduce it here; and examples of specific studies will be provided in the following sections.

The clinical motivation for separating the electrode implantation from stimulator implantation can be twofold. For surgery done under local anesthesia, the patient could be stressed and fatigued at the stage when general anesthesia is required for stimulator implantation. Therefore, some neurosurgeons consider it safer to separate the two surgeries and perform them on different days. One more reason is that externalized leads allow test stimulation to be performed checking whether DBS is effective and thus ensuring that electrode repositioning is not required before the procedure is finalized by implanting the stimulator. Since the patients with externalized leads are normally required to stay hospitalized, a staged surgery incurs higher costs and for this reason, it is practically never done in the US. The externalization procedure requires a special kit provided by the electrode manufacturers containing externalization leads. These leads are connected to the DBS leads under the skin and their other end is externalized via an incision. Often a long free end of the electrode is coiled somewhere under the skin to be used later for connecting to the stimulator. This has two consequences important for our discussion here. First, the scalp of a patient with externalized leads has several injured and sensitive areas: the stitches above the burr holes, the incisions where the leads come out, the areas under which there are wires and the scars left by the stereotactic frame screws. Therefore, also in this category of patients, whole head coverage by EEG electrodes is difficult to achieve, especially with a cap. Second, there are several possible sources of ferromagnetic metal such as the externalization wires, connectors and screws located in different places under the scalp, depending on the surgeon's considerations. These metal parts are the source of severe artifacts in MEG as discussed previously. An additional feature of DBS patients in the first few days after implantation that should be kept in mind is the so called 'stun effect' (Eusebio and Brown, 2009). The essence of this effect is that the injury, tissue displacement and edema resulting from electrode insertion often affect the symptom severity as well as LFP activity (Chen et al., 2006). Therefore, recordings done at this stage might be representative of neither the state prior to the surgery nor the chronic post-implantation state. The duration of the externalization stage is normally between two days and a week. On the day immediately following the surgery, many patients experience fatigue and post-operative confusion. Therefore, with very short externalizations LFP recordings might be challenging. In our own research, recordings are normally done between 1 and 5 days post-implantation. The main advantage of this recording type is the fact that the patients can be fully awake and capable of performing relatively complex tasks with relatively long recording sessions. The exact details of what is achievable depend on the disease, symptom severity and the patient's recovery. In addition, several recording sessions could be done in the same patient allowing, for example, drug studies or paradigms examining learning over time. If precautions are taken to avoid contamination of the surgical wounds, patients with externalized leads can be taken outside the hospital ward, which makes it possible to record MEG. Most centers where such recordings have been done have the MEG in or close to the hospital but in some cases patients were even recorded at a different site in the same city.

Recordings during battery replacement surgery

A further possibility to record LFP from DBS electrodes arises during battery replacement surgery. This surgery, which can be done under local anesthesia, is performed approximately every 3-5 years unless the stimulators can be externally charged. This setting is particularly useful for studies of closed-loop DBS because there is no stun effect and the optimal stimulation parameters have been established. Since the surgery does not involve the head, in principle whole head EEG could be done with a cap. The recording duration is still limited and the location is restricted to the operating theatre but since this surgery is less stressful for the patient and the clinical team, it could be a good opportunity for research that is perhaps underused at the moment with only a few studies published to date (Giannicola et al., 2012; Piña-Fuentes et al., 2017; Swan et al., 2014), none of them involving EEG.

Recordings from chronically implanted sensing stimulators

Finally, a novel opportunity has arisen in recent years with the appearance of more sophisticated stimulators (such as Activa PC+S (Swann et al., 2018a) and more recently Percept™ PC and Summit™ RC+S devices by Medtronic (Stanslaski et al., 2018)) allowing LFP to be recorded and streamed online to an external device. Here, the recordings do not have to be scheduled around a surgery, stun effect does not pose a problem and multiple recording sessions can be done with the same patient allowing longitudinal studies. Moreover, a combination with whole head EEG is possible. However, synchronization is required between the LFP and EEG recordings. This can be achieved by triggering short DBS trains at the beginning and the end of the recording or using a transcutaneous electrical nerve stimulation (TENS) device. Both methods generate simultaneous pulse artifacts in EEG and LFP recordings that can later be used for offline synchronization.

The first generation of stimulators, Activa PC+S, had several limitations compared to recording from externalized leads: recording from

only one channel per hemisphere at a time, limited recording duration and high noise level especially with DBS on. These limitations were reduced in the second generation with the Percept™ PC device offering a sampling rate of 250Hz with six simultaneous recording channels and Summit™ RC+S allowing up to 1000Hz with four simultaneous channels. Moreover, these devices allow for continuous data streaming in laboratory settings and also offer other options for monitoring spectral data features at home, but these are more difficult to combine with EEG. A remaining key issue is that multiple recordings drain the device's battery with a rule of thumb that one hour of continuous streaming is equivalent to one day of stimulation. This is less of an issue with short recordings but e.g., sleep monitoring or recording for extended periods to examine daily activities could be problematic. It is, therefore, important that patients recruited for such studies are well informed about possible implications. Summit™ RC+S is rechargeable, but of this writing is not universally available.

Combined MEG-LFP recordings in patients with externalized leads

Technical issues

While at least a few channels of EEG can be recorded in all of the settings described above, simultaneously recorded MEG and LFP is primarily limited to post-operative lead externalization. In principle, MEG could also be recorded in patients with sensing stimulators, but we are not aware of any studies of this kind and the levels of interference in the MEG generated by this setup have not been characterized. In any case, the motivation to use MEG is not as strong when whole head EEG can be a feasible alternative.

The main advantage of MEG in DBS patients with externalized leads is the ability to record from the whole head while avoiding physical contact with the scalp. An additional advantage is the MEG's superior source localization capabilities, which are not affected by the inhomogeneities in skull conductance around the burr holes. The burr holes, however, pose additional challenges specific to MEG, namely connector and wire artifacts as described above. In addition to these ferromagnetic metal artifacts, there are also issues with optimal positioning of a patient in the MEG helmet. The length of the free end of the externalization leads taken outside the scalp can vary depending on how the surgeons positioned the rest of the wire under the skin. Therefore, often connectors required to link the lead with the recording equipment cannot be taken sufficiently far from the part of head that should be inside the helmet. In this case, it is difficult to insert the head deep in the helmet without pulling on the connectors and the leads, which could be uncomfortable or even dangerous for the patient. In practice, we often position Medtronic connectors, which are particularly problematic in this respect due to their size and shape, horizontally at the nose bridge taking care to not obstruct the patient's vision. Still, in most cases the head of a DBS patient would not be as deep in the helmet as that of a subject without wires.

Additional difficulty specific to MEG is the necessity for the patient to keep still during the recordings. This can be particularly challenging in patients having uncontrollable movements such as tremor or dyskinesia. Parkinson's patients on dopaminergic medication also tend to be restless and fidgety. In these cases, it is important to use continuous head position monitoring. The information about head location and movement can be used to reject part of the data with excessive movement and adjust the forward model to be the most representative of the actual head location during a block. It could also be used for movement compensation as part of the Signal Space Separation (SSS) algorithm available for the Neuromag MEG systems (Taulu and Simola, 2006). Ferromagnetic metal artifacts can interfere with the correct interpretation of the Head Position Indicator (HPI) coil signals resulting in a loss of head tracking for part of the recording. A strategy for dealing with this problem for the case of CTF MEG system was described in detail by Oswal et al. (Oswal et al., 2016b). Briefly, the idea is that for all valid measurements of HPI locations their pairwise distances should be the same within measurement error whereas for invalid measurements this is not the case. One can then compare all the measurements for a recording session to identify the valid segments and interpolate the rest.

An additional technical issue is synchronization of LFP recordings with MEG. Most MEG systems come with a built-in EEG system that is sampled concurrently with MEG. However, these EEG systems are not certified by the manufacturer for intracranial recordings. One solution is to perform safety testing in-house according to the local safety procedures. Alternatively, an external EEG system can be used to record LFP and any electrical signals from the patient's scalp. The use of an EEG system that is battery powered and optically isolated from any equipment connected to the electrical grid is a good way to ensure its safety. Such recordings must be synchronized to MEG during offline processing and would thus require a common synchronization signal such as event triggers recorded on both systems. To ensure precise synchronization we described an algorithm using electronically generated random white noise recorded on both systems (Oswal et al., 2016b). While we do not advocate the use of this particular method for all cases, it is definitely insufficient to only synchronize the onsets of the recording because the clocks on the EEG and MEG systems might run at slightly different speeds resulting in an error that accumulates over the length of a recording block. We would recommend having at least two synchronization signals, at the beginning and the end of a block and interpolating the time axis of one of the recordings to match the other. Note that plugging a synchronization device into both the system connected to DBS leads and MEG can break the optical isolation of the former and therefore has to be done with caution. Two separate concurrently sampled amplifiers optically isolated from each other could be used for an analogue signal or a trigger port optically isolated from the EEG system - for a digital trigger.

Overview of experimental results to date

We will focus on studies combining LFP recordings from DBS electrodes and either EEG or MEG that pertain to the functional connectivity of DBS targets with other parts of the brain, particularly its frequency, directionality and topography Fig. 2.

The subthalamic nucleus (STN)

The first study reporting simultaneous recordings of STN LFP and EEG following DBS surgery was published by Williams et al. (Williams, 2002). Although only a few EEG electrodes were placed on each patient, this early study captured several of the key phenomena that were subsequently studied in greater detail: coherence in the beta band peaking around the mesial motor areas, a separate coherence peak in the alpha band, and narrow-band coherence in the high gamma (60-90 Hz) band that was only present on dopaminergic medication. Williams et al. also assessed the directionality of coupling and found the cortex to lead in the beta and alpha bands and the STN to lead in the gamma band. These findings were further extended in several subsequent LFP-EEG studies (Fogelson et al., 2005; Kato et al., 2015; Lalo et al., 2008) that made further distinctions between theta and alpha coherence and between high- and low- beta coherence suggesting that these could be associated with different functional loops between the cortex and STN.

MEG studies made it possible to localize the cortical areas coherent with the STN and show for the first time that coherences in different frequency bands correspond to topographically distinct networks (Hirschmann et al., 2011; Litvak et al., 2010b). The beta coherence localized to the mesial frontal sensorimotor areas and the alpha coherence to the superior temporal lobe peaking around the temporo-parietal junction with a separate peak in deep brain areas specifically the brainstem. Two more recent single case MEG studies in non-Parkinsonian patients (Cao et al., 2019; Wojtecki et al., 2017) showed that beta coherence

is also present in these cases although whether its magnitude is different from the PD group is not clear. In addition, both of these studies reported coherence in the alpha-theta band with the anterior cingulate cortex (ACC). It is not presently clear whether the differences in the topography of the alpha-theta coherence between PD and non-PD are due to some of these coherences being a disease feature or due to differences in parts of the STN being targeted in the different disease groups. Previous anatomical studies suggested that limbic areas of the prefrontal cortex including ACC have direct connections with the limbic part of the STN (Haynes and Haber, 2013).

Of special interest is the recent study of Belardinelli et al. (Belardinelli et al., 2019) in which the authors managed to achieve more extensive EEG coverage during DBS surgery than any of the previous studies, although the coverage was still sparse over the frontal and parietal cortex. The authors localized both the mesial motor beta and prefrontal theta coherent networks but not the temporo-parietal alpha network. Although only three patients were included in the report, this study shows that it could be practical to use coherence as a marker for surgical targeting. Such an application would not necessarily require complete EEG coverage because there is no need to localize the cortical networks in every patient, but rather to determine the subcortical location displaying the highest coherence with a particular network. Thus, only a few electrodes optimally placed to be sensitive to the network of interest would be sufficient to guide implantation in real time.

The main obstacle to such practical use is that it has not been shown to date that coherence is superior to other neurophysiological markers for any of the DBS targets. The only published study looking at coherence distribution across contacts (Hirschmann et al., 2011) found evidence that beta coherence is more focal than alpha across the STN contacs. However, as of yet, there is no evidence to date that coherence is more informative than STN beta power or intraoperative single cell recordings with respect to the optimal stimulation target. With the development of more precise tools for anatomical analysis of DBS lead placement (Horn et al., 2019), this issue is likely to be revisited in the next few years.

While the topography of beta coherence is in excellent agreement with the known anatomy of the hyperdirect cortico-STN pathway in humans (Lambert et al., 2012) and also with intraoperative recordings (Whitmer et al., 2012), the anatomical substrates of the temporo-parietal alpha network and the STN-ACC network are not as clear. It might be the case that these polysynaptic pathways sustain these networks. Alpha coherence between the STN and the brainstem is plausible in light of the fact that the STN and the pedunculo-pontine nucleus (PPN) are likely to be reciprocally connected because stimulation of one affects the other (Neagu et al., 2013; Stefani et al., 2019) and also alpha was shown to be a dominant frequency in the PPN (Thevathasan et al., 2012).

An open question is whether there is only one cortico-subthalamic beta network or two. From anatomical studies it is known that the motor part of the STN receives input from the cortex via the hyperdirect pathway originating primarily in the mesial Supplementary Motor Area (SMA) as well from the indirect pathway via the striatum and the external Globus Pallidus (GPe) (Lambert et al., 2012; Wichmann and DeLong, 1996). The origins of the indirect pathway appear to be more diffuse across the whole motor strip and unlike the hyper direct pathway it is mediated by three synapses, two of which are inhibitory. It is, therefore, less likely that such an indirect connection is associated with detectable coherence. On the other hand, there is some evidence for the existence of distinct low beta coherence from a stimulation study of Oswal et al. (Oswal et al., 2016a) as well as some evidence for coherence in the low beta band from intraoperative recordings (de Hemptinne et al., 2015; Lipski et al., 2017) as well as earlier LFP-EEG studies (Fogelson et al., 2005; Lalo et al., 2008).

A possibly related open question is about the connection between the cortico-subthalamic coherence and the exaggerated beta activity in the STN that is a clear hallmark of Parkinsonian impairment, particularly bradykinesia and rigidity (Eusebio and Brown, 2009; Weinberger et al., 2009). The study of Litvak et al. (Litvak et al., 2012) showed that the frequency of the coherence was higher than that of pathological STN beta and unlike STN beta, coherence was not strongly affected by dopamine. Hirschmann et al. (Hirschmann et al., 2013b) did find significant suppression of coherence by levodopa and a correlation of coherence magnitude with clinical impairment in the unmedicated state. However, this latter correlation was negative, meaning that the most impaired state was associated with high STN beta power but low STN-M1 coherence. Therefore, it could be the case that the two phenomena are completely unrelated or that there exists a more complex nonlinear relation between them (Marceglia et al., 2006). It could also be possible that weaker low-frequency cortico-subthalamic coherence mediated by the indirect pathway is more closely related to the pathological beta but is difficult to detect with MEG in the presence of much stronger high-beta coherence mediated by the hyper direct pathway. A recent study (Tinkhauser et al., 2018) demonstrated stronger cortico-STN phase coupling during prolonged STN beta bursts which were previously shown to underpin the exaggerated low beta. However, as this study did not distinguish between high- and low- beta coupling, it is not clear which of the interpretations it supports. Following the characterization of resting coherent networks, more recent studies examined how these networks are modulated by clinical conditions and cognitive tasks. Several studies looked at the modulation of the cortico-subthalamic coherence by movement (Hirschmann et al., 2013a; Imbach et al., 2015; Litvak et al., 2012; Oswal et al., 2013). A brief increase of high gamma (60-90Hz) coherence was shown around the time of finger movements and this effect was increased by dopaminergic medication and correlated with clinical improvement (Litvak et al., 2012). This phenomenon is likely to be related to the narrow-band gamma coherence described originally by Williams et al. (Williams, 2002) and more recently by Swann et al. (Swann et al., 2016; Swann et al., 2018b). These more recent studies make the connection between narrow-band gamma and dopamine-induced dyskinesia in PD. Conversely, alpha coherence with the temporo-parietal areas decreases during movement; this effect is enhanced by dopamine and correlates with clinical improvement (Oswal et al., 2013). The study of Hirschmann et al. (Hirschmann et al., 2013b) did not show significant modulation of the alpha coherence by movement, but in that study the movement was repetitive finger flexion rather than discrete button presses which could possibly explain the difference. Beta coherence between the STN and the motor areas seems to follow the changes in power i.e. decrease with movement (Hirschmann et al., 2013b; Imbach et al., 2015) and overshoot the baseline after movement termination (Litvak et al., 2012). However, one should be cautious when interpreting these effects as they could well be driven by the power confound, artifactual co-modulation of power and coherence due to changes in the signal to noise ratio (Muthukumaraswamy and Singh, 2011), which is very difficult to factor out in this case.

STN-cortical communication was also implicated in tremor (Hirschmann et al., 2013a) with increase in coherence at the tremor frequency associated with spontaneous resting tremor episodes and in gait freezing with freezing episodes associated with a decrease in the STN-cortical coupling in the 4-13Hz band (Pozzi et al., 2019). Since the latter study was performed with combined telemetric stimulator (Activa PC+S) and EEG recordings, there was full coverage of the scalp. However, no source localization was done and it is, therefore, impossible to say whether these effects involve the same resting low-frequency network that was found in MEG studies.

Additional series of studies examined the role of cortico-subthalamic communication in motor learning and error monitoring. Bidirectional communication between the STN and the motor cortex increased during the post-movement beta rebound but the component from the STN to cortex specifically communicated task-relevant movement errors and was correlated with the degree of adaption achieved across subjects (Tan et al., 2014). Phase coupling in the beta band between EEG and LFP in both the STN and internal Globus Pallidus (GPi) was shown to

be modulated during force adjustment in a force matching task but only on dopaminergic medication (Fischer et al., 2019).

Finally, STN was also shown to be involved in conflict detection and adjustment of the threshold for decision making in evidence accumulation paradigms. This involved communication in the theta band between the medial frontal cortex, an area known to be involved in conflict detection (Cohen, 2014), and the STN. The increase in theta coherence was specific to trials involving presentation of conflicting sensory evidence (Zavala et al., 2016a; Zavala et al., 2016b; Zavala et al., 2014). Both the theta band coherence between the STN and prefrontal cortex and beta band coherence between the STN and the motor cortex were affected by speed vs. accuracy task instructions (Herz et al., 2017) and changes in STN-frontal coherence predicted the ability of subjects to adjust their decision thresholds between tasks (Herz et al., 2016).

Globus pallidus

Internal globus pallidus (GPi) is a further common DBS target for PD, dystonia and Tourette syndrome (Lee et al., 2019). GPi receives direct excitatory projection from the STN and, therefore, there are commonalities between the two structures in terms of their oscillatory activity and connectivity. DBS electrodes targeting the GPi often also have their top contacts in the adjacent external globus pallidus (GPe) making it possible to also record from this structure. A comprehensive MEG study of resting cortico-pallidal networks in dystonia was presented by Neumann et al. (Neumann et al., 2015). Three frequency-specific networks were described: beta network with the ipsilateral sensorimotor cortex, theta network with the inferior temporal lobe and alpha network with the cerebellum Fig. 2. The coherence magnitude in the latter network negatively correlated with clinical impairment, albeit in a rather small patient sample. These results (with the exception of GPi-cerebellar alpha coherence) have recently been reproduced in a study focusing on the border between GPi and its neighboring structure – the Nucleus Basalis of Meynert (NBM) (Gratwicke et al., 2020). This later study also showed differences in GPi-cortical beta coherence between two very similar disorders, Parkinson's disease dementia and dementia with Lewy bodies. However, a small sample size and systematic differences in lead placement strategies between the two groups do not allow making a definite conclusion that coherence could be a disease biomarker in this case and this question requires further study.

Although cortico-GPi coherence encompassed both high- and low-beta ranges, movement-related coherence decrease was limited to the low beta range (van Wijk et al., 2017a). Greater decrease was associated with faster reaction times across subjects. Movement-related coherence decrease was also found in an EEG-LFP study (Talakoub et al., 2016). Based on combined intraoperative ECoG and GPi-LFP recordings Xiao et al. (Xiao et al., 2019) recently performed a complex network analysis taking into account both phase-amplitude coupling and coherence in both cortex and GPi and in different frequency bands. This analysis confirmed the key role of beta activity in this circuit and found that movement-related changes in network features correlated with hemibody UPDRS scores.

A further study study found a relation between cortico-pallidal coherence patterns and the type of dystonic symptoms (Yokochi et al., 2018). In patients with phasic symptoms, an alpha peak appeared on both GPi power and cortico-pallidal coherence. In patients with tonic symptoms, a delta power peak was more prominent but there was no delta coherence with the cortex.

The effects of DBS on pallido-cortical coherence were different for different disorders. In PD, DBS was found to specifically reduce high beta coherence between GPi and the motor cortex in an intraoperative study by Malekmohammadi et al (Malekmohammadi et al., 2018a). However, in dystonia where oscillatory pathological activity suppressed by DBS was found in the theta/alpha (4-12Hz) band, cortico-GPi coherence was also suppressed in the same band (Barow et al., 2014). These results suggest that both dystonia and PD might be 'oscillopathies' of different oscillation types (Nimmrich et al., 2015).

Pedunculo-pontine nucleus

Pedunculo-pontine nucleus (PPN) is an area of the brainstem, which is part of the reticular activating system. It was suggested as a DBS target for PD patients with balance and gait problems (Pereira et al., 2008). The first report of simultaneous PPN-LFP and EEG recording was by Androulidakis et al. (Androulidakis et al., 2008). This study found coherence between the EEG and LFP in the alpha band. This coherence appeared to be bi-directional and was increased by dopaminergic medication.

A more detailed mapping of oscillatory networks coherent with the PPN was undertaken in the MEG study by Jha et al. (Jha et al., 2017). This study also found PPN-cortical coherence in the beta band. Interestingly, its topography was different from that described for the STN and GPi and concentrated in the deep medial motor areas which are known to contain the representation of the legs, consistent with the relation of PPN to the walking circuit. Alpha coherence also mapped to brainstem areas surrounding the PPN itself and to the cingulate cortex.

Thalamus

Thalamus is the main gateway for cortical inputs. It consists of many nuclei, each part of a different pathway and therefore, it would probably be too simplistic to try to generalize across different studies unless they targeted the same nucleus.

Theta coherence with predominantly frontal sites was the main feature for thalamic sites in PD (Sarnthein and Jeanmonod, 2007), neurogenic pain (Sarnthein and Jeanmonod, 2008) and chronic disorder of consciousness (Wojtecki et al., 2014). The latter study showed modulation of this coherence in an unconscious patient when hearing familiar voices addressing the patient. In the PD study, beta coherence was also found lateralized to the side of the LFP recording.

Bour et al. (Bour et al., 2015) performed recordings in three patients with Tourette's syndrome implanted in the thalamus. In two patients, they found coherence in the alpha band and in the third patient in the high beta band (peaking around 25 Hz). Thalamocortical coherence increased preceding the onset of tics.

Finally, Malekmohammadi et al. (Malekmohammadi et al., 2015) studied two epilepsy patients with cortical ECoG strips who also had electrodes stereotactically guided to the thalamus as part of a study on seizure propagation. These electrodes, however, were not targeted to any specific thalamic nucleus. The authors showed cortico-thalamic theta coherence with three distinct cortical areas: sensori-motor, anterior inferior temporal and mid-temporal. In all the cases the most coherent ECoG contacts were consistent with diffusion tractography results seeded from the corresponding thalamic contacts. Furthermore, theta coupling was directed from the thalamus to the cortex and also thalamic theta phase was coupled to cortical beta amplitude. These results are consistent with the fact that cortico-thalamic loops exist for most of cortical areas. In combination with results from other studies mentioned above, these findings suggest that theta coupling might be a universal mode of thalamo-cortical communication. However, more studies are necessary to generalize this idea to all thalamo-cortical loops.

Nucleus accumbens

Nucleus Accumbens (NAc) belongs to the ventral striatum, which is believed to be part of the circuit performing action selection based on anticipated rewards. It receives input mainly from temporal and prefrontal cortical areas and projects back to the prefrontal cortex and parietal cortex via the GP, STN and the thalamus (Haber, 2003; Haber and Knutson, 2010). NAc-DBS was tested for several different indications including drug addiction, depression, obsessive-compulsive disorder (OCD)

and epilepsy. No concurrent NAc-LFP and MEG studies have been performed to date, but several of the EEG studies had good scalp coverage.

Cohen et al. (Cohen et al., 2011) performed simultaneous NAc-LFP and EEG recordings in OCD patients while they performed a simple reward motivation task previously shown to activate the ventral striatum. They found directed functional connectivity from the cortex to NAc in the theta band peaking over medial frontal sites and increased by reward anticipation.

In a different study (Horschig et al., 2015), the patients had diverse diagnoses including addiction, depression and OCD. They performed a covert visual attention task. Cortex and NAc were found to be coherent in both theta and alpha bands. The theta coherence was modulated by the task and did not have clear directionality whereas the alpha coherence was primarily from the cortex to NAc. Whereas the theta coherence was strong in both frontal and occipital channels, for alpha coherence this was only true in frontal channels suggesting that they correspond - at least partially - to different cortical sources.

In the study of Stenner et al. (Stenner et al., 2015) epilepsy patients with NAc electrodes were recorded at rest and while performing a standard economic decision-making task. There was only one EEG electrode common to all patients, located at the vertex (Cz). All patients showed significant coherence between LFP and EEG at delta and low theta frequencies. The directionality was not consistent at rest but during the action selection phase of the task the cortex was clearly driving NAc.

Finally, Smith et al. (Smith et al., 2020) recently showed that that oscillatory connectivity between frontal cortex and NAc region in the delta (1-4Hz) band correlates with OCD impairment such that stronger connectivity predicted more OCD symptoms.

Summary

The picture emerging from these studies is that cortico-subcortical coherent networks are a ubiquitous phenomenon and can be found for all the major DBS targets tested and for different clinical conditions. This makes them unlikely to be solely a feature of disease, although their modulation by pathological processes cannot be ruled out. An interesting question is how many different coherent networks there are and whether the subcortical nuclei that display similar coherence topographies with the cortex are also coherent with each other. This question is difficult to address with studies of DBS patients alone because DBS implantations in multiple subcortical targets are extremely rare. Perhaps LFP recordings in non-human primates provide insight. Other key questions for the coming years are what role if any these networks play in healthy cortico-subcortical communication and in mediating the effects of DBS. The advent of telemetric stimulators such as Percept PC^{TM} as the default option for many clinical sites will make combining high-quality LFP recordings with whole head EEG straightforward. This is expected to revolutionize the field and drastically increase the available research opportunities. We are, therefore, hopeful that these and many other questions will be addressed in the coming years both inside the lab and in real-life environments.

DBS-related cortical responses and network effects

As outlined in the previous chapter one can either simultaneously record LFPs with EEG/MEG in the short time window after electrode implantation but before stimulator implantation or record in the post-operative phase once the stimulation is in chronic use. Within this section, the focus will be on the cortical effects of DBS once the stimulator is in chronic use. In this case one can either investigate the fields and potentials evoked by DBS during a paradigm (see Fig. 1B) or focus on oscillatory network changes due to DBS.

While nowadays DBS is used to treat several neurological and psychiatric diseases, most studies combining DBS with EEG or MEG have investigated the effect of DBS in Parkinson's disease, where DBS treatment is most frequently used. Therefore, the focus in the following will be mainly on Parkinson's disease. Moreover, we will not survey studies investigating the effects of DBS during a particular paradigm, but will examine studies investigating the effect of DBS on cortical activation and potential mechanisms of DBS.

Evoked Fields and Potentials

One of the first studies to investigate the motor cortical evoked responses due to STN stimulation was by Ashby and colleagues. Combining EEG with DBS stimulation turned on, motor cortical responses were found with short latencies of 1, 3, 5, 8, and 22 ms (Ashby et al., 2001; Baker et al., 2002; Walker et al., 2012). Moreover, the peak amplitude of the short latency response was dependent on the stimulation intensity (Walker et al., 2012). To further investigate the interaction between motor-cortex and STN, (Kuriakose et al., 2009) combined TMS over the motor cortex with DBS. Here, the most consistently evoked cortical response was around 22.2 ms. If a TMS pulse was applied ~22 ms and ~4 ms after the DBS pulse, the motor-evoked potential amplitudes measured at the contralateral first dorsal interosseous increased. Based on this finding, they concluded that short latency STN-DBS evoked responses are a result of antidromic stimulation, while the longer latency responses are mediated via polysynaptic transmission through the basal-ganglia-thalamo-cortical circuit. The later global evoked responses (45-80 ms) due to TMS were also enhanced by STN-DBS while levodopa did not have an influence on these responses, but only on those at around 80-130ms (Casula et al., 2017). Thus, the combination of both STN-DBS and levodopa therapy seems to have an influence on the motor cortex.

To investigate whether the evoked responses are related to the clinical efficacy of DBS, (Romeo et al., 2019) investigated the evoked potentials to 20 Hz STN stimulation with EEG during the implantation of the STN-DBS electrode. Interestingly, a large amplitude of the evoked high frequency response around 20 ms was predictive of motor side effects during postoperative therapeutic 130 Hz STN-DBS. Furthermore, it has been posited that STN-DBS is mainly clinically effective due to antidromic activation of the motor cortex (Gradinaru et al., 2009; Kuriakose et al., 2010; Walker et al., 2012). However, a recent study with non-human primates indicated that antridromic activation of M1 due to STN stimulation diminishes under chronic stimulation (Johnson et al., 2020). In addition, pallidal stimulation without any antidromic activation of M1 leads to similar clinical effects. Thus, antidromic activation due to STN stimulation might play a role for the efficacy of STN-DBS, but may not be the main factor.

Using MEG, (Hartmann et al., 2018) investigated evoked responses due to STN-stimulation in Parkinson patients and due to stimulation of the thalamic ventral intermediate nucleus (VIM) in essential tremor patients. Patients were measured in the MEG on the day after surgery while 5 Hz stimulation was applied on the side contralateral to the more affected body side. Consistent with EEG studies (Walker et al., 2012), evoked responses due to STN-stimulation in PD patients were observed in ipsilateral sensorimotor MEG sensors as early as 1 ms after stimulation. Through dipole fitting the location for the evoked fields was determined to be in most cases in the pre- or post-central gyrus. This study proved both the feasibility of recording evoked fields from STN-DBS within MEG and the possibility of localizing the evoked fields through source reconstruction. To differentiate the effect of stimulating within different areas of the STN (Chen et al., 2020) investigated the cortical responses of ventral STN stimulation with EGoG recordings. They identified short latency responses within the inferior frontal gyrus in line with a hyperdirect connection between STN and IFG.

A recent modeling study has examined in detail the conduction delays of cortical evoked potentials due to STN stimulation (Gunalan and McIntyre, 2020). These findings suggest that evoked potentials due to antidromic activation of the hyperdirect pathway occur after 1.5ms. Thus, very early responses could rather be due to volume conduction (Maling et al., 2018). Moreover, these early responses could also be generated by activation of the fibers passing the internal capsule. Thus,

when considering the clinical effects of evoked potentials and their potential for improved stimulation protocols, it is key to i) differentiate between responses due to stimulation of the internal capsule vs. the hyperdirect pathway and ii) to exclude responses only due to volume conduction.

Concerning VIM stimulation in ET patients, Hartmann and colleagues identified event related fields (ERFs) within the central sulcus at latencies as early as 1 ms after the DBS pulse. Long latency cortical responses following VIM DBS consisted of peaks at 13, 40, 77, and 116 ms. Similar early responses have been determined with EEG: VIM stimulation generated evoked responses in the ipsilateral motor cortex at latencies of 0.9, 5.6, and 13.9 ms. Interestingly, the early peak at 0.9 ms was related to the tremor suppression in ET (Walker et al., 2012).

A further DBS target is the GPi in dystonia patients. When stimulating within the GPi, the cortically-evoked responses measured with EEG showed two peaks around 10 and 25 ms after the stimulation within the motor cortical area (Ni et al., 2018; Tisch et al., 2007). Stimulating the GPe led to a smaller evoked response with similar latencies. Of note here is that the low-frequency stimulation used in the study actually displayed adverse effects in dystonia. Still, the results may provide insights into the pathways involved in GP stimulation. (Tisch et al., 2007) suggest that GPi stimulation leads to an activation of pallidothalamic neurons, which project to the sensorimotor cortex. Contrary to VIM and STN stimulation, there seems to be no antidromic activation due to GP stimulation. When investigating the clinical relevance of the cortically-evoked responses in children due to GPi stimulation, (Bhanpuri et al., 2014) found that the clinically chosen contact led to higher evoked potentials in the ipsilateral sensorimotor areas. This finding might help clinicians choose the best contact, because the clinical benefits in dystonia often only occur after 6 months of chronic stimulation, which makes finding the optimal stimulator settings difficult. In a more recent study the latency of the motor evoked responses with a peak around 25 ms was confirmed (Ni et al., 2018). In addition, a negative evoked potential around 10 ms after the GPi pulse was found. Using TMS it was described that the later evoked response around 25 ms corresponds to an inhibitory GPi input to the primary motor cortex. Around 10 ms after the stimulus, the GPi exhibits an excitatory input to the primary motor cortex (Ni et al., 2018).

Oscillatory networks

We focus now on oscillatory network changes mainly derived from studies in Parkinson patients, which recorded EEG/MEG during DBS stimulation. Recordings from externalized DBS electrodes in the immediate post-operative phase from only the STN have demonstrated that STN-DBS in Parkinson's disease, similar to dopaminergic medication, reduces pathologically elevated beta activity within the STN, which in turn correlates with reduced akinesia and rigidity (Kühn et al., 2008). Based on the previously reviewed literature, the expectation concerning STN-DBS would be that it reduces the pathological oscillations in Parkinson's disease within the motor network. The first studies looking into the cortical effects of DBS utilized EEG since the DBS stimulation artifact is not that pronounced in EEG recordings. During self-paced movements, DBS stimulation increased beta oscillations on the contralateral sensorimotor and primary motor cortex (Devos et al., 2003). Post-movement beta desynchronization was enhanced, with DBS seemingly promoting normal function (Devos et al., 2003). Furthermore, the mu rhythm over the primary sensorimotor cortex was increased during preparation of movement and actual movement. This increase correlated with the improvement in bradykinesia due to DBS (Devos, 2004). Considering cortical changes across the whole brain and across all frequencies, STN-DBS was associated with an increase in peak alpha frequency and reduced power (Jech et al., 2006a). Concerning cortical-cortical interactions, EEG coherence in the range from 10-35 Hz is reduced due to STN-DBS and is correlated with clinical improvement (Silberstein et al., 2005). Using dynamic imaging of coherent sources (DICS) Muthuraman and colleagues (2012) investigated the network effect based on the actual DBS stimulation frequency. Based on this frequency they identified a network comprising primary sensory motor cortex, supplementary motor area, prefrontal cortex, diencephalon, cerebellum and brainstem.

The feasibility of investigating DBS effects within the MEG was demonstrated by (Mäkelä et al., 2007). To remove the DBS artifact from the MEG recordings, they used tSSS. They found in one patient a decrease in 3-20 Hz activity over the sensorimotor cortex. In a larger group of patients, it was shown that the N100 amplitude of auditory evoked fields is increased due to DBS, while DBS did not induce significant changes for the somatosensory evoked response (Airaksinen et al., 2010).

The same group then investigated the effect of STN-DBS on oscillatory activity, finding a relation to the clinical symptoms: UPDRS action tremor scores correlated with peri-central oscillations in the alpha (6-10 Hz) and beta range (21-30 Hz). Moreover, the occipital alpha rhythm correlated negatively with rigidity and motor impairment in general (Airaksinen et al., 2012). In a subsequent study, (Luoma et al., 2018) showed that 5-25 Hz activity was suppressed in fronto-parietal regions due to DBS. However, this change in oscillatory activity was not associated with clinical improvement. The suppression of widespread cortical alpha/beta power seems to be rather robust, because in a further study it could be shown that widespread cortical alpha/beta power was reduced and that this reduction was most prominent over the sensorimotor cortex (Abbasi et al., 2018). When investigating whole-brain oscillatory activity in the range from 1-48 Hz, Cao and colleagues demonstrated that improved symptoms of PD due to STN-DBS correlated with alpha power in temporal, occipital, and parietal areas (Cao et al., 2015). In addition, the suppression of beta oscillations in the temporal cortex correlated with motor improvement (Cao et al., 2017). This finding is in line with the findings of (Airaksinen et al., 2012). In a further study, the same authors could show that motor symptom improvement due to STN DBS negatively correlated with increased high gamma oscillation in the right frontal cortex (Cao et al., 2017).

Based on both EEG and MEG studies, STN-DBS primarily alters alpha and beta oscillations. Moreover, the decrease in beta oscillations is correlated with improved rigidity and bradykinesia. This finding conforms to the hypothesis that beta activity is pathologically increased in Parkinson's disease. Concerning tremor most changes due STN-DBS were detected in the alpha range, but also within high-gamma oscillations. Unfortunately, those studies did not clarify whether the alpha-frequency range was at twice the tremor frequency. Nevertheless, the predicted relation between gamma oscillations and tremor was detected (Beudel et al., 2015).

Several studies have investigated the cortico-muscular coherence (CMC) in order to directly analyze the relation between cortical activity and tremor. Beta cortico-muscular coherence during tremor episodes was increased when the stimulator was on, compared to the stimulator being turned off. (Park et al., 2009) suggested that this increased cortico-muscular coherence when the stimulator is on is related to improved motor performance. However, (Airaksinen et al., 2015) did not find a relationship between CMC and motor symptoms, even though they found cortico-muscular coherence to be altered by DBS. During postural tremor in both ET and PD patients, the peak amplitude of the postural tremor frequency was reduced due to STN-DBS. However, this study did not investigate a direct relation to postural tremor (Connolly et al., 2012). On the other hand, (Kern et al., 2016) found a clear relation between CMC and DBS effects in one patient. One study also investigated the CMC in orthostatic tremor (Gilmore et al., 2019). Zona incerta stimulation led to a decrease in CMC at the tremor frequency and patients reporting improved symptoms. Considering these conflicting results –in particular for PD-, further studies clarifying the effect of CMC and its relation to DBS and improved motor symptoms are needed.

To investigate the direct effects of STN-DBS on the interaction between STN and motor cortical regions, (Oswal et al., 2016a) and colleagues investigated coherence between STN and cortical regions

with and without STN-DBS. They reported decreased coupling in beta-frequencies between motor-cortex and STN during DBS. However, only the change in strength of local STN oscillations correlated with the clinical improvement by DBS. This raises the question whether beta activity is the only pathological oscillation in Parkinson's disease and what role whole brain network alterations play.

Concerning DBS stimulation for dystonia, we could only identify one study that investigated oscillatory activity during stimulation with EEG (Miocinovic et al., 2018). Within their dystonic patient cohort, seven were implanted within the GP and five within the STN. Still, across all patients they found a normalizing effect of DBS on the alpha power in motor cortex, while alpha power was decreased without stimulation.

Summary and future perspectives for DBS

For the majority of DBS targets, significant coherence was observed with non-invasive EEG or MEG recordings. In most cases, this coherence was not due to picking up the signals from the DBS target directly (with the exception of possibly the PPN), but due to recording from other brain structures, primarily parts of the cortex that were coherent with the DBS targets. Cortico-subcortical coherence is typically narrow-band and can be assigned to one of the 'classical' EEG bands (with some flexibility in how these bands are defined in different studies). Typically, coherence is observed below 35 Hz with the exception of high-gamma cortico-STN coherence, which is likely a pathological feature related to dyskinesia.

There are some recurrent motives when comparing the findings for different subcortical structures. Beta coherence seems to be specific to the sensorimotor regions, while theta coherence pertains to frontal and temporal areas. Alpha was less specific and encompassed temporal and frontal regions as well as the brainstem, the cerebellum and cingulate cortex.

In addition to coherence, another way to understand the mechanism of DBS is investigating the evoked responses due to DBS itself. In this approach, the precise timing information allows inference about the existing connection between subcortical and cortical structures. Even though DBS stimulation is specific to certain sub-cortical structures, the network effects were evident with their connections to cortical structures.

The question remains whether frequency-specific oscillatory coherent networks exist that link several subcortical structures with specific parts of the cortex and if so, what is their function. This question is difficult to answer in humans because DBS implantations in more than one target in the same hemisphere are rare. Comparing human and animal data could be a possible way forward (see e.g. (West et al., 2018)). However, the details of organization of these networks in animals, especially rodents might be different from the human case.

Despite the technical and conceptual challenges, combined LFP and EEG/MEG recordings in DBS patients present a unique opportunity to study physiological connectivity in behaving humans. Compared to purely non-invasive studies, the main advantage of the DBS setup is that the connectivity is strong, clearly seen in single subjects and reproducible across patients. In addition, at least on the invasive side, the structures participating in the communication are clearly identified. Compared to recordings in epilepsy patients with electrocorticography or stereotactic EEG, the advantage of DBS is in precise and consistent placement of electrodes that affords group studies. The wearable MEG technology (Boto et al., 2018) that is currently being developed holds the potential for enabling recording for longer time periods with less discomfort and more naturalistic tasks. Moreover, the future generations of more sophisticated stimulators will afford high-quality LFP recordings without the need for externalization. These developments are expected to expand the field and lead to new exciting discoveries. Their role in the future adaptive or closed-loop DBS therapy should be found in a multilevel functional neuroimaging screening. Their combination with anatomical connectivity modalities such as diffusion tractography or fMRI would improve the precision of identification of target networks and determine optimal location of sensing and stimulating electrodes. The innovation of segmented DBS leads with several contacts and the possibility of various shaping of the stimulation field need extra time and effort from the clinical care. Together with the estimation of volume of tissue activated, the information provided by EEG or MEG by frequency related network response characterization could definitively assist advanced programming approaches (Ramirez-Zamora et al., 2019).

Data and Code Availability Statement

All data generated during the writing of the current review is included in the manuscript.

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