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Deep Brain Recordings

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Depth recordings from human subcortical structures have improved our knowledge of human brain circuitries and provided better understanding of the effects and mechanism of action of deep brain stimulation. Two types of signals can be recorded: single unit spikes and local field potentials (LFP). The basal ganglia (BG) are particularly well suited for deep brain recordings and here we review how the oscillatory activities recorded in these structures helped improve our understanding of the sensorimotor brain functions in particular, along with cognitive and emotional-motivational. The oscillations may be classified by frequency into bands at < 8, 8–30 and > 60 Hz. The best characterized band is the 8–30 Hz and existing evidence suggests that it is antikinetic and inversely related to motor processing. On the other hand, accumulating evidence suggests that the > 60 Hz band may be related to normal function.

K e y w o r d s: Deep Brain Stimulation, basal ganglia, Local Field Potential, electrophysiology, neurophysiology

1. Introduction

Deep brain stimulation (DBS) is not a new technique; the possibility was proposed in the 1930s. It gained popularity in the 1980s [1, 2] after neurosurgeons, who used lesioning of brain structures to alleviate symptoms, observed that chronic electrical stimulation produced similar effects. Although the mechanism of action is not yet fully understood, DBS has become a standard treatment for movement disorders such as Parkinson's disease (PD), dystonia and tremor that are refractory to medical treatment. Because of its success with movement disorders, it is also being investigated in other neurological diseases such as epilepsy and cluster headache, [3] and in selected psychiatric disorders such as depression [4]. DBS differs from functional electrical stimulation and sensory prosthetics (e.g., cochlear implants) in that DBS

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does not act as a substitute for affected tissues or organs. DBS targets specific brain nuclei or pathways and influences brain function and behavior (movements, sensations, thoughts and feelings), thus relieving symptoms and improving the overall functioning of the patient. Depending on the disorder, target location in the brain and stimulation parameters, DBS may exert excitatory or inhibitory effects. Stereotaxic implantation of DBS electrodes in the brain offers unique opportunities for neurophysiological studies on neural structures and pathways near the DBS target that are not accessible to non-invasive studies. For example, the activities of deep brain target structures and nuclei can be recorded in different conditions with or without the application of external electrical stimulation through the implanted electrode. This type of study has improved our knowledge of human brain circuitries and provided further understanding of the effects of DBS.

2. Basal Ganglia and DBS

Basal ganglia (BG) are frequently used for recording and stimulation because DBS of the basal ganglia is an accepted treatment for movement disorders such as PD and dystonia. The commonest targets are the subthalamic nucleus (STN) or the globus pallidus pars interna (GPi). Either single unit recordings can be made intraoperatively through microelectrodes or local field potentials (LFP) can be recorded from the DBS electrode with externalized leads in the days following electrode implantation, before connection to the pulse generator.

It is known that the basal ganglia are involved in motor control, but their roles remain poorly defined [5]. Hypothesized functions of the BG include movement planning and initiation [6, 7], automatic execution of routine movements [8], and selection or inhibition of competing motor programs [9]. Movement preparation is impaired in PD and this may be related to akinesia. PD patients have a greater impairment of self-paced than externally triggered movements, as evidenced by their improved movements with external cues.

2.1. The Classical Rate Model of the Basal Ganglia

Among the many techniques used to investigate BG physiology and pathophysiology, extracellular single unit recordings is particularly important. Microelectrode recordings are used by many surgical teams to determine the precise location of the target (Vim, GPi, GPe or STN). Accurate detection is based on the firing properties of the BG structures. The BG neurons can be phasically active in the striatum and tonically active in the other structures, exhibiting three different patterns: irregular firing with random distribution, regular firing, and bursting firing (Fig.1 from Hutchison et al., 1998, [10]; Fig. 2 from Lozano et al., 1996, [11]).

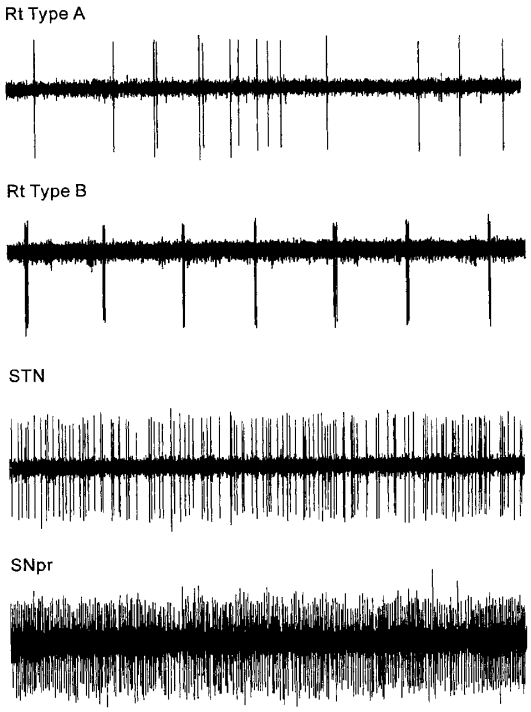

Fig. 1. Spontaneous ongoing discharge of typical neurons recorded in trajectories targeting the subthalamic nucleus. (Top to bottom) Single unit recordings from thalamic reticular (Rt) neurons of the A and B types described by Raeva (see text), subthalamic nucleus, and substantia nigra pars reticulata. Each trace is 2 seconds long. (from Hutchison et al., 1998 [10] by permission of John Wiley and Sons)

Even though the terms spike and burst have been used for a long time, there is still no clear definition for them. Only recently has this notion received more attention [12, 13] because it became apparent that in addition to the spike firing frequency, the firing pattern is as important in neurophysiologic processes [14].

The pathophysiological rate model of the BG, developed in the late 1980s [15], had a great impact on the understanding of BG physiology and their alterations in pathological conditions. This influential model explains the pathophysiology of Parkinson's disease (PD) by modifications in neuronal firing rate in different basal ganglia nuclei, which has led to extensive use of stereotactic surgery for PD. However, it is now clear that the rate model is inadequate for observations such as amelioration of dyskinesia, and cannot account for the absence of obvious motor deficits following GPi or thalamic lesion [8]. One explanation may be that the pattern of basal ganglia activity is important and pallidotomy or DBS disrupts the aberrant, noisy signals. Attempts have been made to improve the rate model, for example, by incorporating a center-surround mechanism [9].

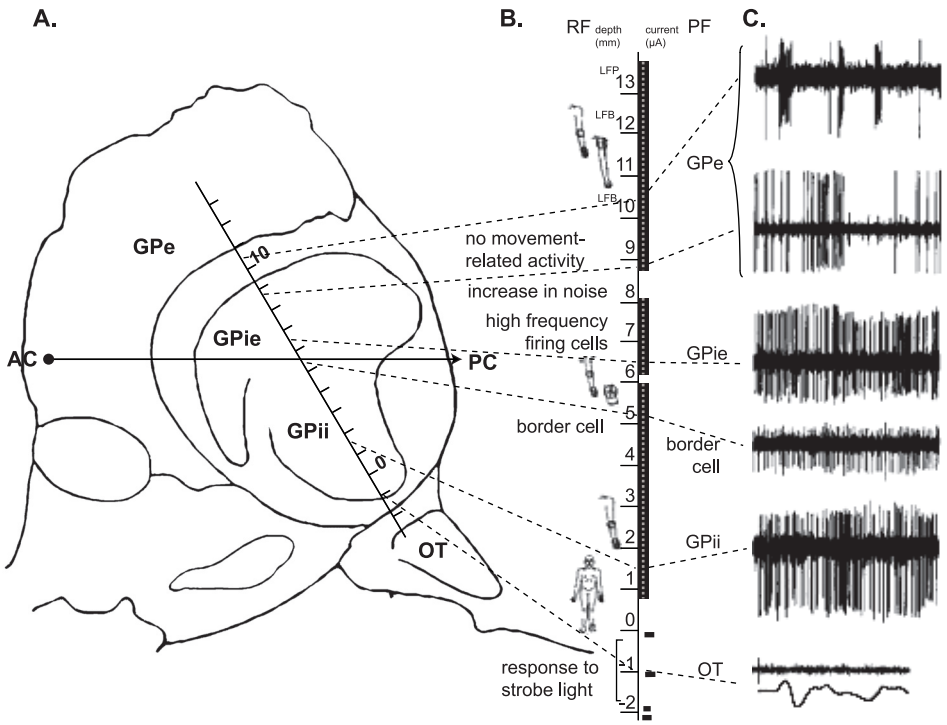

Fig. 2. A: Physiological data obtained from one trajectory through the globus pallidus and optic tract (OT), plotted on the 20-mm sagittal map from the Schaltenbrand and Wahren stereotactic atlas. B: The locations of neurons and their responses as well as intraoperative observations of the characteristics of recordings can be seen. C: Oscilloscope traces of representative examples of the neuronal types described in text. At the bottom is a single sweep of the filtered trace for which the optic tract field potential to visual stimuli was heard but not readily seen. With appropriate filter settings for visual evoked potential measurement from the optic tract, the visual evoked potential can be seen, as illustrated below (the smooth trace). LFB, low-frequency burst neuron; RF, receptive field; PF, projected field; AC, anterior commissure; PC, posterior commissure; GPii, internal segment of GPi; GPie, external segment of GPi. For other abbreviations, see legend to Figure 1. (from Lozano et al.1996 [11], by permission of the American Association of Neurological Surgeons)

2.2. The Oscillation Model of the Basal Ganglia

Several authors have suggested that synchronized activity is pathological and likely to result in less efficient coding of information by the basal ganglia or loss of neuronal selectivity, leading to the movement impairments characteristic of PD [16, 17]. Brown and colleagues [18, 19] proposed that θ and β oscillations are antikinetic rhythms whereas the γ band is a prokinetic rhythm in the basal ganglia. Therefore PD would be due to excessive antikinetic β rhythm and deficiency of the prokinetic γ rhythm. This will be termed the oscillation model of the basal ganglia. They suggested that

the synchronized 8–30 Hz (θ and β) activity antagonizes novel motor processing by disturbing rate coding necessary for voluntary movement.

2.3. The Nature, Functions and Changes of Brain Oscillations in PD

Oscillation is a fundamental feature of the brain and results from the dynamic interplay between intrinsic cellular and circuit properties of neural networks. It can be observed in single neurons, small groups of neurons, as well as between distant brain areas [20]. Oscillations allow activated groups of neurons in distant brain regions with sparse interconnections to become temporally linked and to activate specific downstream targets. Abnormal oscillatory activity may play an important role in neurological diseases [16].

Whether basal ganglia LFPs represent the synchronized activity of local neuronal populations is still debated, as is the relationship between the LFPs and neuronal spikes. It is established that oscillations in the cortical EEG are generated by synchronous changes in large numbers of cortical pyramidal neurons [21, 22]. BG nuclei do not have the laminar architecture of the cerebral cortex. Cytoarchitectural studies in the monkey and rat suggest that, despite minor inter-species variations in arborisation, STN contains tightly packed principal neurons with elliptic dendritic fields, aligned along the primary nuclear axis [23, 24, 25]. Similar studies in the pallidum also demonstrate elliptic field morphology but with the dendritic fields parallel to the lateral body of the nucleus [26]. Some studies suggest that LFPs recorded in BG nuclei may reflect synchronous changes in large populations of neurons. In healthy primates [27] and alert PD patients [28] there are synchronous oscillations across large areas in the BG and between BG and the cortex, supporting the view that the oscillations are generated in the entire cortex-BG-thalamus circuit rather than solely in internal BG circuits. In addition, in vivo recordings from rat nucleus accumbens demonstrated that changes in LFP activity are due to synchronous membrane potential fluctuations [29]. Recordings from the rat STN showed correspondence between LFP and synchronized neuronal activity following cortical stimulation [30]. LFP oscillations are also synchronized with neuronal activity in the STN of anaesthetized rats [31].

Brain oscillations are named according to the frequency bands. These include δ-oscillation (delta, 1–4 Hz), θ-oscillation (theta, 4–10 Hz), β (beta, 10–30 Hz) and γ-oscillation (gamma, 30–80 Hz). They can also be classified by division into frequency bands of < 8, 8–30 and > 60 Hz. In the basal ganglia, the best characterized is the 8–30 Hz frequency band, which has been recorded from the human STN, GPi and the striatum.

LFP recordings showed prominent 14–30 Hz oscillations in both the GPi and STN of PD patients following medication withdrawal [32]. There is temporal coupling between STN and GPi and also between these nuclei and the cortical EEG in the 8–30 Hz band. Administration of levodopa leads to reduction in β oscillations

[19]. However this frequency band may be too wide to be treated as a whole. Recent findings suggest that narrower bands may have a different topography with respect to reactivity to dopamine and phase relationship with cortical rhythms [33].

A study by Kühn et al. [34] found good concordance between elevated levels of LFP activities in the beta-frequency band and electrode contact positions within the STN according to both the surgical coordinates and the characteristics of single- and multi-unit discharge. This result supports the notion that the beta LFP activity recorded in the human STN is generated within STN, although it may be due to intrinsic network properties or driven by afferent inputs. This focal topography does not appear to be shared by LFP activity in the 4–11 Hz range, which had a more distributed topography. The study reveals another important feature: the relatively dorsal distribution of beta LFP oscillations within STN. This deserves further investigation for several reasons: anatomical and electrophysiological studies in monkeys suggest that the primary motor cortex projects to the dorso-lateral STN [35, 36], while projections from the premotor and supplementary motor areas synapse mainly in the dorsal part of motor STN [37]. In addition, neurons responsive to passive and active movement occur in the same region in monkey and human [38, 39]. Thus, the beta LFP activity could be higher in the dorsal STN, which is the region most likely to be related to the development of the cardinal motor features of PD [39]. Furthermore, the medial and ventral parts of STN have connections with the associative cortical regions [40].

Processing of information in the cortico-subcortical pathways may involve oscillatory processes and neuronal synchronization at the network level [41]. Neurophysiological studies in PD patients showed that STN oscillations contribute to both motor and non-motor information processing across the cortico-basal-ganglia--thalamo-cortical loop, being associated with movement preparation and execution, motor imagery, and emotional processing [28, 42, 43, 44]. STN oscillations in the beta range are involved in linking external stimuli to movement planning and execution [45, 46]. These ideas are supported by data showing the contribution of STN beta-oscillations to frequency-specific patterns of synchronization [47], frequency modulation [48] and interaction [49].

In a recent paper [50] STN oscillations were recorded through DBS electrodes in patients with PD during observation of actions. The authors found selective action-related oscillatory modulations in two separate beta bands: low-beta oscillations (10–18 Hz), which selectively desynchronized during observation of action, and high-beta oscillations (20–30 Hz), which synchronized during the observation of both action and action-related objects. The low-beta band was more specific to action observation and the high-beta band was related to observing the action scene. The suggested hypothesis is that STN oscillations could encode information related to the understanding of action, especially for the context-related optimization of action observation.

Even though tremor is a cardinal symptom of PD, how it is generated is not well understood. The frequency of tremor in different extremity muscles is often

similar, yet coherence analysis has demonstrated that tremor in different extremities is almost never coherent. Studies of correlations between single cells spikes or LFPs and tremor-EMG signals showed synchronised tremor-related activity in the STN [28], the ventrolateral thalamus [51] and the GPi [52]. These findings have led to different hypotheses regarding tremor mechanism: that tremor is sustained by different oscillators [53]; that transmitter systems other than the dopaminergic system might be involved; or that circuits other than basal ganglia may play important roles [54]. Reck et al. [55] made simultaneous STN LFP and EMG recordings from patients with tremor-dominant PD. The coherence between tremor EMGs and STN LFPs showed significant tremor-associated coupling at single-tremor and double-tremor frequencies. Also, the EMG–LFP coherences showed differences between antagonistic muscles (flexor, extensor), and in the spatial distribution of LFPs within the STN. These findings suggest the existence and distribution of muscle-specific tremor-associated LFP activity at different tremor frequencies and an organization of tremor-related sub loops within the STN.

Recordings in the 60–90 Hz band have been obtained during many but not all human studies [19]; however, they seem to be more prominent in PD patients after dopaminergic treatment. This inconsistency in LFP spectral peak at 60–90 Hz among patients and studies has several explanations: the band is critically dependent on a good clinical response to levodopa [18], which is not always achieved in postoperative levodopa challenges; in general, high frequency activity tends to be more focal than low frequency activity [20], thus the recording of 60–90 Hz band may depend more on the localization of the contacts than does the recording of lower frequencies, although this awaits confirmation; synchronized activities in the 60–90 Hz band sufficient to be recorded with the DBS electrode may only occur in patients with prominent levodopa-induced dyskinesias [5].

An interesting hypothesis considers that certain gamma activities may be related to normal function. The band under consideration most often appears as a sharply tuned peak between 60 and 95 Hz [32, 56, 57]. This gamma band is higher than the most commonly reported gamma band in recordings involving the sensory cerebral cortex (40–60 Hz) [58]. It is interesting to point out that the sharp ~70 Hz activity is evident in records made at rest and during movement [59], whereas broad gamma band changes are only evident as spectral features in averages time-locked to movement [57, 60]. These findings suggest that the sharply tuned gamma activity may be more relevant for arousal-related processes, even though they do not exclude the possibility that oscillatory activity over a broader gamma band may be more specifically related to the coding of movement-related parameters [18, 19]. The subcortical gamma activity is phase coupled with the gamma activity recorded over motor cortical areas [61, 62] and both increase with voluntary movement [57]. In PD patients, BG gamma activity is increased by dopaminergic therapy simultaneously with improvement in motor performance [32, 59]. These observations support the idea that synchronization of BG nuclei in the gamma band may facilitate motor

processing [19]. The possible distinction between finely tuned gamma activity and broad band gamma event-related synchronization deserves further investigation.

Much higher frequencies of around 300 Hz have also been reported in the STN in PD patients following treatment with levodopa.

3. Involvement of BG in Movement Preparation

Since PD patients usually have difficulty in initiating movement, the BG may be involved in movement preparation. STN is particularly well suited to play a role in movement preparation because it receives direct input from the supplementary motor area (SMA) through the cortico-subthalamic pathway.

Paradiso et al. [63] examined the role of STN in movement preparation and initiation by simultaneously recording from DBS electrodes implanted in the STN and from the scalp electrodes (EEG) while patients were performing self-paced wrist extension movements. The recordings consisted of movement-related potentials (MRP), which in scalp EEG presents as a slow negative deflection starting 1–3 s

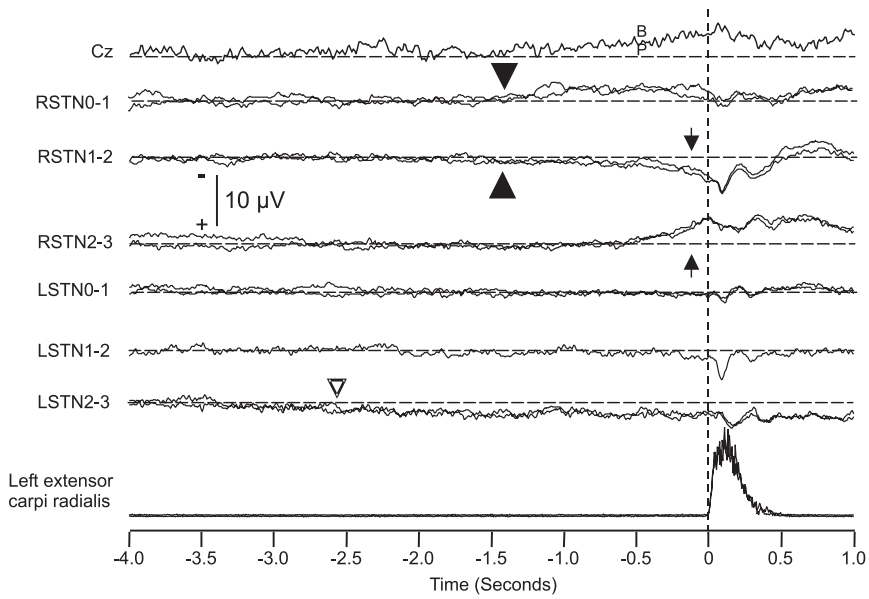

Fig. 3. Bipolar scalp and STN movement related potential recordings. Averaged responses of 42 self paced L-wrist extensions in one patient. Even and odd epochs were averaged separately and superimposed. R refers to right and L refers to left. Traces represent recordings from respective bipolar DBS electrodes, Cz is the vertex scalp EEG and the lower trace identifies the averaged EMG activity of the left extensor carpi radialis. The filled arrowheads indicate the contralateral STN MRP onset while the open arrowhead indicates the ipsilateral STN MRP. The vertical marker was aligned at the onset of movement activity (from Paradiso et al., 2003 [63], by permission of Wolters Kluwer Health)

before the onset of self-paced movements and probably reflect cortical movement preparation and initiation [7]. The study found a cortical negative MRP with onset at 1690±336 ms before EMG onset. STN pre-movement MRP was observed in 11 of the 13 patients (Fig. 3, from Paradiso et al., [63]). The STN activity occurred with both ipsilateral and contralateral hand movement. The onset of the STN MRP was 2095±1005 ms (ipsilateral) and 2020±920 ms (contralateral) and these potentials were not significantly different from the cortical MRP. The study concluded that the STN or nearby structures are active before self-paced movements in humans.

Paradiso et al. [64] also studied the role of the thalamus in the preparation of the self-paced movement in tremor and myoclonus dystonia patients. Recordings were made simultaneously from the scalp and from the DBS electrode placed in the ventrolateral (VL) nucleus of the thalamus while the patients were making self-paced wrist extension movements. Scalp recordings showed a slow negative pre-movement MRP in all patients (onset 1846±189 ms prior to EMG onset). Thalamic MRP preceded both contralateral and ipsilateral movements, and there was no significant difference between the onsets of thalamic or cortical MRP. The contacts with maximum MRP amplitude from scalp and thalamus showed two narrow frequency bands in α (mean peak 9 Hz) and β (mean peak 17 Hz) bands. Both bands showed pre-movement event- related desynchronization (ERD) with α and β ERD from the scalp and the β ERD from the thalamus beginning 2.5–2.8 s prior to movement onset.

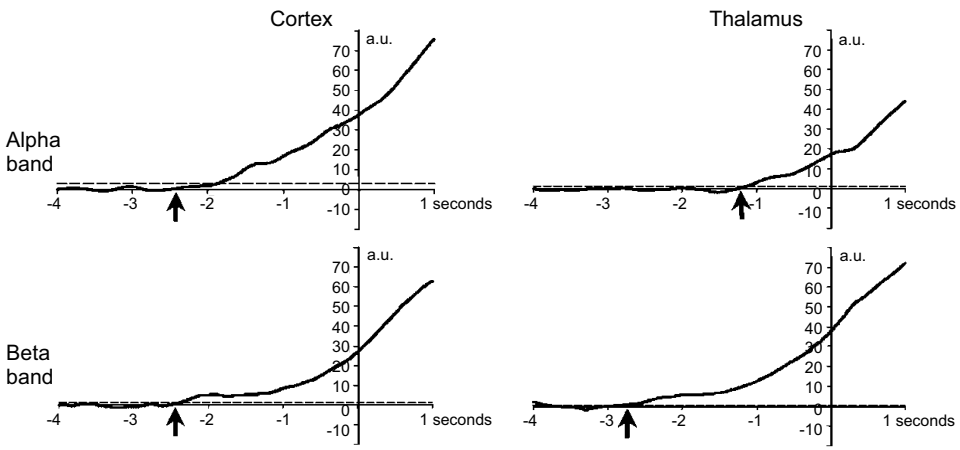

Fig. 4. Cusums of cortical and thalamic ERD in one patient. This figure represents the cusums of the ERD. Cortex refers to mid frontocentral contacts, and thalamus to contacts 1–2 of the quadripolar electrode implanted on the left side. The patient performed right wrist extensions. The abscissa denotes time in seconds, where 0 represents movement onset, and the ordinate denotes ERD cusum in arbitrary units (a.u). The dotted lines correspond to 3 SD of the reference interval. The arrows show the onset time of ERD. In the cortex, alpha and beta ERD start 2.5 s prior to movement. In the thalamus, the onset time of alpha ERD is 1.8 s and of beta ERD is 2.0 s before movement initiation (from Paradiso et al., 2004 [64], by permission of Oxford University Press)

However, the thalamic α ERD began later at about 1.2 s before EMG onset (Fig. 4, from Paradiso et al., [64]).

The cortical and thalamic oscillations were coherent in the β band in the resting baseline period until about 0.5 s before EMG onset, while there was no cortico--thalamic coherence in the α band (Fig. 5, from Paradiso et al. 2004, [64]).

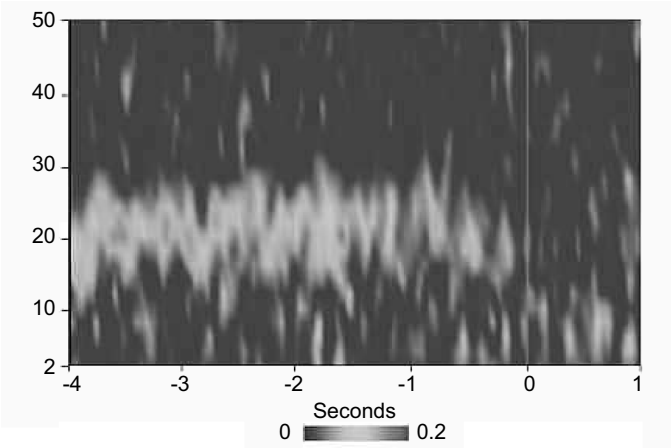

Fig. 5. Temporal representation of the coherence grand average between cortex and thalamus in five patients. This figure represents coherence analysis between scalp mid frontocentral contacts and the thalamic pair of contacts of the quadripolar electrode with maximum MRP amplitude. Electrodes were implanted in either the right or left side and the patients performed contralateral wrist extensions. The abscissa denotes time in seconds, where the vertical marker at 0 represents movement onset, and the ordinate denotes frequency. The gray scale (originally in colour) represents coherence values. Coherence in the beta range, centered at 20 Hz, was present from the start of the epoch and diminished 0.5 s before the movement onset. There was no coherence in the alpha frequency band (from Paradiso et al., 2004 [64], by permission of Oxford University Press)

These results suggest that the cerebellar thalamus is involved early in the process of movement preparation and that different cortico-subcortical circuits may mediate α and β oscillations. Movement preparation is associated with a change in the interactions between motor thalamus and cortical motor areas in the β band.

STN and VL nucleus of the thalamus belong to different pathways involved in movement preparation. Purzner et al. [65] studied the involvement of STN and VL in the preparation of various types of movements. The patients performed two different tasks: self paced and externally cued. Their results suggest that the cortico-BG-thalamocortical circuit (STN) is involved in the preparation of both self-paced and externally cued movements, while the cerebello-dentato-thalamocortical pathway (VL) seems to be involved mostly in self-paced but not in externally cued movements. Nevertheless, the latter pathway may still be involved in the execution of externally cued movements.

The BG can be functionally subdivided into motor, oculo-motor, associative, limbic and orbitofrontal loops according to the main cortical projection area. This organization supports the involvement of BG in functions as diverse as attention, explicit and implicit learning, reward-related behavior and habit formation. This complex organization has changed the traditional view that BG are mainly motor centers. It appears that BG has been designed to provide stability to the network underlying and operating movement control. Under normal conditions, neighboring basal ganglia neurons fire in an uncorrelated fashion [66]. In the dopamine-depleted state, however, the synchrony between neighboring basal ganglia cells, and even between nuclei, is significantly increased, usually together with the emergence of oscillatory activity [67]. It is still not clear why the circuitry involved in the generation of the LFP signals preferentially produces beta-band oscillations and not oscillations in other frequency ranges.

4. Conclusions

While deep brain stimulation is an effective treatment of the motor symptoms of movement disorders, there is still room for significant improvements and this will likely come from a better understanding of the mechanism of action of DBS. In light of recent results, it seems likely that neither single unit recordings nor LFP recordings alone will be able to entirely explain the mechanisms of DBS. We need to better understand how and to what extent spikes are involved in the generation of LFP, and also how LFPs can influence the function of distant and seemingly unconnected neuronal populations. New findings unrelated to the beta band or high frequency stimulation may shed light on the pathophysiological mechanisms of DBS. For example, gamma frequencies have been reported to play a role in physiological conditions.

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