Direct comparison of oscillatory activity in the motor system of Parkinson's disease and dystonia: A review of the literature and meta-analysis

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HIGHLIGHTS

• The distribution of low-frequency (LF) and beta oscillatory power differs between Parkinson’s disease (PD) and dystonia.
• Increased LF power is present in subcortical local field potentials (LFPs) of dystonia when compared to PD.
• Increased beta power is present in subcortical LFPs of PD when compared to dystonia.

ABSTRACT

Objective: To outline the current knowledge of (sub)cortical oscillations in Parkinson’s Disease (PD) and dystonia, and to quantitatively summarize the results of direct comparisons of local oscillatory power between both diseases in the resting state, without medication or stimulation, in both the low-frequency (LF, ±4–12 Hz) and beta (±13 to ±30 Hz) range.

Methods: Eight relevant studies were included. Recordings from 127 dystonia-, and 144 PD-patient hemispheres were analyzed. Ratios of LF and beta power between diseases were obtained.

Results: Beta oscillations in dystonia were lower when compared to beta oscillations in PD, ratio = 0.72, Z = 3.56, p = 0.0004, 95% CI [0.60, 0.86]. Subgroup analyses showed significant differences only in the GPI, whilst conflicting evidence was shown in the STN. LF oscillations in PD were lower when compared to LF oscillations in dystonia, ratio = 0.77, Z = 2.45, p = 0.01, 95% CI [0.63, 0.95]. Subgroup analyses showed significant differences in the GPI and the STN, but not in the M1.

Conclusions: LF and beta oscillations are present in the resting-state motor network of both PD and dystonia patients. However, the power distribution of those oscillations differs between diseases.

Significance: This meta-analysis provides high-level evidence which supports the presence of exaggerated oscillations across the parkinsonian/dystonic motor networks.

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1. Introduction

Parkinson's disease (PD) and dystonia are movement disorders with different phenotypes, showing respectively paucity and an excess of movements. Despite these clinical differences, deep brain stimulation (DBS) is an effective treatment for both disorders (Vidalhlet et al., 2005; Kupsch et al., 2006; Odekerken et al., 2013).

The preferred target for DBS is the internal globus pallidus (GPI) in dystonia, and the subthalamic nucleus (STN) in PD. However, recent studies have demonstrated that a similar symptomatic improvement can be obtained either when the GPI is the target chosen for DBS in PD (Mansouri et al., 2018), or the STN in dystonia (Ostrem et al., 2017), using roughly similar stimulation parameters when comparing nuclei of the same disease. Currently, the exact
mechanisms behind this duality on stimulation targets are not fully understood.

1.1. Pathological oscillations model

An emerging theory that provides some insight to this target duality phenomenon is the presence of pathological oscillatory patterns extended throughout the cortico-basal ganglia-thalamocortical (CBGTC) network of PD and dystonia patients (Guridi and Alegre 2017). This (pathological) local oscillatory activity in the CBGTC network can be explored by means of recordings of grouped neuronal activity obtained either from the same electrodes used for stimulation (local field potentials, LFPs), or from electrodes placed on cortical areas (electrocorticography, ECoG). In animal research, the GPi-LFPs of non-human primate PD models have shown exaggerated oscillations in the beta range (13 to ~30 Hz) compared to healthy animal controls (Leblois et al., 2007). On the other hand, none of the current dystonia animal models available (Chaniary et al., 2008; Ip et al., 2016) have been yet employed for such comparison; only non-human primate data of parkinsonian animals has been compared with human dystonia and PD data (Starr et al., 2005). In human PD subjects, prominent beta oscillatory activity has been found in the rest OFF medication state, in both the GPi and the STN (Brown et al., 2001). This cortical beta activity decreases both after the application of DBS (Eusebio et al., 2011; Wang et al., 2018) and administration of levodopa (Kuhn et al., 2006). Similarly, prominent low-frequency (LF; 4–12 Hz) activity has been described in the GPi of dystonia patients (Chen et al., 2006), which is regulated after the application of DBS (Barow et al., 2014). In the motor cortex (M1), the interaction of beta oscillations with other frequency bands (beta-broadband phase-amplitude coupling (de Hemptinne et al., 2013, 2015)), or with signals from subcortical regions (beta coherence (Hirschmann et al., 2013, Wang et al., 2018)), rather than the oscillatory power, has been shown to be altered in PD, and regulated after the application of DBS, in both the STN and the GPi. In the aforementioned study, the LF cortical-GPi rest coherence of dystonia patients was also increased.

1.2. Limitations of studies of pathological oscillatory activity

It is well known that oscillations play a role in physiological functions in the nervous system. For that reason, the detection of prominent oscillatory activity in a determined neuronal structure, does not necessary imply that such activity is exaggerated. Only a comparison with a healthy structure could determine whether oscillations detected on the affected network are pathologically increased. However, unlike animal research, studies that investigate local oscillatory activity in PD or dystonia patients usually cannot be contrasted with healthy human subjects, due to the invasive nature of (sub)cortical electrode placements. Occasional invasive recordings carried out on patients with functional movement disorders (Kobayashi et al., 2011; Ramos et al., 2015) or epilepsy (Aulicka et al., 2014; Kondylis et al., 2016) have demonstrated that certain neurophysiological features, previously only demonstrated on PD or dystonia, are not restricted to such organic movement disorders. Recently, prominent beta oscillations were described in the dorso-lateral STN of patients with obsessive compulsive disorder (Wojtecki et al., 2017; Rappel et al., 2018). For those reasons, while experiments that compare either PD or dystonia patients before and after treatment are helpful to explore the effect of treatment on LF and beta oscillations on the parkinsonian/dystonic CBGTC network, they cannot determine whether such oscillations were increased on the first place. Given the lack of healthy controls as reference, the modulatory effect of both DBS and medication on the oscillatory activity could be interpreted as either a suppression of aberrantly increased oscillations, or a compensatory mechanism, in which physiological activity is suppressed, in order to counterbalance disturbances located elsewhere in the network. Therefore, there is a theoretical possibility that prominent oscillatory activity would also be present in healthy control subjects, and that either DBS or medication could induce a similar desynchronization on both the healthy and parkinsonian/dystonic CBGTC network.

1.3. Comparison of oscillatory patterns between dystonia and PD

A feasible alternative for the lack of healthy controls in CBGTC oscillation research is the use of diseases with different phenotypes as controls. Thanks to the target duality mentioned before, dystonia and PD patients seem to be the best control for each other, since it is possible to perform invasive recordings from the same target for both diseases and under similar conditions. Although the comparison of oscillatory activity between two different diseases cannot reveal whether prominent oscillations are pathological, the presence of increased LF or beta activity in only one of the diseases, when all the other factors are similar, could indicate that such oscillations are indeed exaggerated in patients with that disease. This knowledge, together with the modulation caused by treatment, could provide a better estimation to determine in which degree the presence of an increment in the LF or beta oscillatory activity is considered to be pathological.

1.4. Limitations of comparison studies

A modest number of studies have directly compared CBGTC structures between PD and dystonia patients. However, numerous factors considerably limit the generalizability of the findings encountered on individual articles. One of the major constrains regarding neurophysiological studies comparing PD and dystonia, is the small number of subjects included on each study (Table 1). This low number of subjects could be explained by the fact that the preferred DBS targets in PD and dystonia are different. This preference makes it difficult to plan prospective studies in which PD and dystonia are implanted in the same structure. Next to this, neurophysiological changes can be studied at different spatiotemporal levels. Besides the recording of synchronous populations of neurons by means of LFPs or ECoG, neuronal activity can be explore using micro-electrode recordings (MER), which collect spiking activity of single neurons. Furthermore, from these two signal-types, a plethora of neurophysiological characteristics can be studied in which the spike rate for the MER and power spectral density (PSD) estimates for LFP or ECoG recordings are the most well studied. In order to address more widespread variations in CBGTC loops, simultaneous or additional cortical recordings can be made invasively (de Hemptinne et al., 2015) or non-invasively (Oswal et al., 2016). From an analysis perspective, local activity in interaction with other regions in the CBGTC network can be studied, using coherence analyses or phase-amplitude coupling (PAC, (de Hemptinne et al., 2015)), among others. The pipelines to analyze LFPs can vary at different levels of the procedure, from one of the many elements of preprocessing (filtering, standardizing) to the methods of performing the frequency analysis and post-processing techniques to specifically analyze the frequency bands of interest and their characteristics, together with the units in which the results are expressed (normalized units, log-power, etc.). This interaction of parameters can contribute to a greater or lesser extent to the divergence of results. Moreover, neurophysiological changes can be studied in different experimental conditions; examples of these are rest, tonic contraction, pinch and start-stop paradigms, all requiring different motor programs. Given these various approaches at different stages of the scientific pro-
cess, the a priori chance of two studies using a similar approach is rather low, which makes it difficult to replicate findings (Errington et al., 2014).

In summary, information regarding the comparison of the oscillatory activity in dystonia and PD patients is scarce, and it is difficult to draw general conclusion from individual articles, due to all the constrains aforementioned. For that reason, the objective of the following meta-analysis is to quantitatively summarize the findings of articles that compared the oscillatory activity in dystonia and PD patients, in the LF and beta range, while taking into account the constrains aforementioned. For that reason, the objective of the following meta-analysis is to quantitatively summarize the findings of articles that compared the oscillatory activity in dystonia and PD patients, in the LF and beta range, while taking into account the limiting factors mentioned above in the analysis, in order to provide high-level evidence that could help to determine whether LF and beta oscillations are increased in the dystonic and parkinsonian CBGTC networks, respectively. We aimed to control for all the factors mentioned above with our inclusion criteria and methods mentioned on the next section.

2. Methods


2.1. Our inclusion criteria were:

- Articles directly comparing oscillatory activity in PD and dystonia from the same anatomical structure. By including PD and dystonia recordings coming from the same center, we ensured that both data were subjected to the same techniques used for data acquisition and signal (pre)processing.
- Articles including recordings from the GPi, STN or M1. N.B.: studies comparing other CBGTC structures are seldom reported.
- Articles reporting oscillatory activity in the rest state and without medication nor stimulation. This condition is the most common for all the recordings. Other conditions often diverge across studies.

2.2. Our exclusion criterium was:

- Articles not reporting sufficient information to perform the meta-analysis (e.g. not reporting measures of dispersion or results not divided into LF and beta frequencies).

Our search resulted in 32 articles from 2003 to 2018, from which twelve studies met the inclusion criteria. (Silberstein et al., 2003; Starr et al., 2005; Tang et al., 2007; Crowell et al., 2012; Weinberger et al., 2012; Neumann et al., 2012; Miocinovic et al., 2015; Wang et al., 2018, 2016; Geng et al., 2017; Lofredi et al., 2018; Piña-Fuentes et al., 2019) Of these twelve studies, two studies met the exclusion criteria and therefore were not included in the analysis (Table 1). Of these 10 studies, 2 studies only reported MER data. As MER data uses a different outcome measure (count of single-unit peaks), we will focus this meta-analysis on local oscillatory power (LFPs or ECoG), in order to harmonize the results. A small analysis of MER data can be found in Supplementary Figs. 1–2. Therefore, eight studies were used to perform the meta-analysis. Recordings from 127 dystonia- and 144 PD-patient hemispheres were included in the meta-analysis. Spectral power was reported at different structures: the STN (n = 2 articles), the GPi (n = 4 articles) and the M1 (n = 3 articles).

2.3. Data approximation

Data reported in the articles, as either power spectral density (PSD) estimates or box plots/scatter plots, were approximated, using a reverse engineering software (WebPlotDigitizer, Texas, USA (Rohatgi (2011))). This allowed us to determine the mean/median power across the LF-beta range and a measure of dispersion (e.g. standard deviation (SD), standard error of the mean (SEM) or interquartile range (IQR) and minimum and maximum) from the plots presented. All subsequent calculations were performed in MATLAB (ver. 2018a, Mathworks, Inc. Natick, 151 Massachusetts, USA). Data obtained from the approximation of each PSD estimate were interpolated, in order to obtain the values for

Table 1
Summary of articles directly comparing patients with Parkinson’s disease (PD) and dystonia using invasive recordings. GPi = internal part of the globus pallidus, M1 = primary motor cortex, STN = subthalamic nucleus, LFP = local field potential, MER = micro electrode recording, ECoG = electrocorticography, N = number.

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year of Publication</th>
<th>Recording Site</th>
<th>Method</th>
<th>N hemispheres PD</th>
<th>N hemispheres dystonia</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silberstein et al.</td>
<td>2003</td>
<td>GPi</td>
<td>LFP</td>
<td>19</td>
<td>17</td>
<td>Included</td>
</tr>
<tr>
<td>Crowell et al.</td>
<td>2012</td>
<td>M1</td>
<td>ECoG</td>
<td>10</td>
<td>10</td>
<td>Included</td>
</tr>
<tr>
<td>Neumann et al.</td>
<td>2012</td>
<td>STN</td>
<td>LFP</td>
<td>10?</td>
<td>2</td>
<td>Included</td>
</tr>
<tr>
<td>Miocinovic et al.</td>
<td>2015</td>
<td>M1</td>
<td>ECoG</td>
<td>14</td>
<td>22 (8 ARM Dys)</td>
<td>Included</td>
</tr>
<tr>
<td>Geng et al.</td>
<td>2017</td>
<td>STN</td>
<td>LFP</td>
<td>22</td>
<td>16</td>
<td>Included</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2016</td>
<td>STN</td>
<td>LFP</td>
<td>28</td>
<td>12</td>
<td>Included</td>
</tr>
<tr>
<td>Wang et al.</td>
<td>2018</td>
<td>GPi</td>
<td>LFP</td>
<td>20</td>
<td>14</td>
<td>Included</td>
</tr>
<tr>
<td>Piña-Fuentes et al.</td>
<td>2018</td>
<td>GPi</td>
<td>LFP</td>
<td>8</td>
<td>14</td>
<td>Included</td>
</tr>
<tr>
<td>Lofredi et al.</td>
<td>2018</td>
<td>GPi</td>
<td>LFP</td>
<td>10</td>
<td>10</td>
<td>Included</td>
</tr>
<tr>
<td>Starr et al.</td>
<td>2005</td>
<td>GPi</td>
<td>MER</td>
<td>101</td>
<td>302</td>
<td>Included in MER analysis.</td>
</tr>
<tr>
<td>Tang et al.</td>
<td>2007</td>
<td>GPi</td>
<td>MER</td>
<td>168</td>
<td>173</td>
<td>Included in MER analysis.</td>
</tr>
<tr>
<td>Weinberger et al.</td>
<td>2012</td>
<td>GPi</td>
<td>LFP + MER</td>
<td>94</td>
<td>273</td>
<td>Excluded. Peaks were not divided into LF or beta; mean LFP-PSD estimates not reported.</td>
</tr>
</tbody>
</table>

N.B.: Articles not reporting sufficient information to perform the meta-analysis (e.g. not reporting measures of dispersion or results not divided into LF and beta frequencies).
the mean power ± SD/SEM in the range of 4–30 Hz, in frequency bins of 0.25 Hz, for both conditions. SEM were transformed to SD by multiplying the SEM by the square root of the sample size. Data expressed as mean ± SD of log-transformed units (mean[Log] and SD[Log]) were transformed back to their raw scales by using the estimation methods proposed by Higgins et al. (Higgins et al., 2008). If PSD estimates were approximated, the average mean power for the LF and beta band was obtained; average SDs were obtained by calculating the square root of the averaged variance (SD²). When box plots were employed in the articles, means and SD were approximated using the sample size, median, IQR, and minimum and maximum reported, according to the methods developed by Wan et al. (Wan et al., 2014). When power data reported was divided into frequency bands, the mean ± SD LF power was obtained by averaging the mean ± SD power of theta and alpha bands, weighted according to the number of Hz included on each band; a similar procedure was performed to calculate the mean ± SD beta power from both low and high mean ± SD beta power.

2.4. Statistical analysis

Means of individual studies could not be grouped, since each article used different units to express PSD values, e.g. percentage of total power, normalized power (arbitrary units, a.u.), or log power (μV²/Hz). For this reason, values of average LF power in the different studies in PD were expressed as a fraction relative to dystonia (e.g. an average LF value of 2.2 a.u. in dystonia and 1.5 in PD would give a ratio of 0.68). Similarly, this was performed for average beta power in dystonia relative to PD (e.g. an average beta value of 1.2 a.u. in PD and 0.7 a.u. in dystonia would give a ratio of 0.58). Ratios can be grouped, since they are unitless, while keeping the proportion of power between PD and dystonia constant. Ratios were Log-transformed (LogRatio) for further statistical analysis. The variance of LogRatios was approximated by using the delta method described by Friedrich et al. (Friedrich et al., 2008). Statistical analysis was performed using RevMan (v 5.3, Copenhagen, Denmark (The Nordic Cochrane Centre (2014))). An overall estimate using LogRatios was calculated through the generic inverse variance method with a random effects model. The weight of each study was calculated according to the formula (1/variance of the effect estimate). Outcomes were divided in subgroups according to the localization of the recording. Ratios were transformed back to raw scales after the analysis.

3. Results

3.1. LF ratios

The overall ratio was 0.77 for LF oscillations in PD compared to dystonia, Z = 2.45, p = 0.01, 95% CI [0.63, 0.95] (Fig. 1). Subgroup analyses revealed a strong effect of subcortical structures: GPi LF ratio = 0.61, Z = 4.96, p = 0.00001, 95% CI [0.50, 0.74]; STN LF ratio 0.67, Z = 2.09, p = 0.04, 95% CI [0.46, 0.98]. No differences in cortical ratios were found, M1 LF ratio 1.02, Z = 0.51, p = 0.61, 95% CI [0.94, 1.11]. The concordance of results within subgroups was high, with $I^2 = 0%$ for all structures.

3.2. Beta ratios

The overall ratio was 0.72 for beta oscillations in dystonia compared to PD, Z = 3.56, p = 0.0004, 95% CI [0.60, 0.86] (Fig. 2). Subgroup analyses revealed a strong effect in the GPi: beta ratio = 0.62, Z = 7.26, p < 0.00001, 95% CI [0.55, 0.71], which showed a high concordance within subgroup studies, $I^2 = 0%$. Beta ratio effects in the STN and M1 were not significant, STN beta ratio 0.63, Z = 0.97, p = 0.33, 95% CI [0.24, 1.61]; M1 beta ratio 0.82, Z = 1.65, p = 0.10, 95% CI [0.65, 1.04]. The concordance of results within STN and M1 subgroups was low, STN $I^2 = 87%$, M1 $I^2 = 79%$.

4. Discussion

Based on the findings of the articles included in this meta-analysis, the distribution of local oscillatory power, observed in the LF-beta range of the CBGTC network, differs between PD and dystonia patients in the resting state, without medication nor stimulation. Resting-state LF oscillatory activity in dystonia patients is increased when compared to PD patients. On the contrary, resting-state beta oscillatory activity is increased in PD patients, when compared to dystonia patients. Subgroup analyses revealed primarily a subcortical predominance of such distribution (GPi and STN).

4.1. Significance of LF oscillations

In this meta-analysis, the presence of LF oscillations was increased in both the resting-state GPi and STN of dystonia patients when compared to PD patients, while the LF oscillatory power in the resting-state M1 was virtually similar between diseases. The high degree of concordance within articles supports a selective role for exaggerated subcortical LF activity in dystonia. However, the functional significance of increased LF oscillations is up to now a topic for debate. Nevertheless, increasing evidence points out toward their relation with a hyperkinetic state. It has been proposed that exaggerated LF oscillations carry a dystonic drive with them, as suggested by studies showing an increased coherence in the LF range between GPi and electromyography (EMG) of dystonic muscles (Sharott et al., 2008), or between dystonic muscles (EMG-EMG) (Tijssen et al., 2000). Next to this, such oscillations are increased in both the GPi and STN during the performance of ballistic movements (Singh et al., 2011). While LF oscillations in the dystonic M1 seem not to be exaggerated, an increased coherence in the LF range between the M1 and subcortical structures, such as the GPi (Wang et al., 2018) or the cerebellum (Neumann et al., 2015), possibly indicates that an abnormal regulation of downstream flow of prokinetic oscillatory information is present in dystonia. Notwithstanding the evidence accumulated, certain difficulties need to be addressed in order to unify this theory. Firstly, it is important to point out that a potential confounding factor is the fact that diverse forms of dystonia (e.g. postural deformities, OFF-dystonia, striatal toe, torticollis, among others) could be present in the phenotype of unmedicated PD patients (Doherty et al., 2011), potentially incrementing the LF power in PD, if present at the moment of the recordings. This is relevant when using PD as a control for comparisons with dystonia recordings, since these features might be not actively investigated during the clinical examination and possibly not reported on the information of the patients that were included on the studies. However, even with this confounding factor against them, subcortical LF oscillations were found to be more prominent in dystonia. Second, the range of LF oscillations (4–12 Hz) does not coincide with those of the typical frequency bands used in electroencephalography (EEG), which divides LF into theta and alpha activity. This could lead to heterogeneity when reporting findings on the LF range. Whether there is a relevant functional division between theta and alpha bands in dystonia is yet unknown. Lastly, the exact role of LF oscillations on each dystonia subtype is still unclear. This is especially important as dystonia is an etiologically heterogeneous disorder in which various (genetic) types respond differently to DBS (Fox and Alterman 2015). It was not possible to control for
Fig. 1. Forest plot summarizing the ratios of low-frequency power in Parkinson’s disease in relation to dystonia across the different articles included. LF = low-frequency, GPi = internal part of the globus pallidus, M1 = primary motor cortex, STN = subthalamic nucleus, PD = Parkinson’s disease, Dys = Dystonia, SE = standard error, CI = confidence interval.

Fig. 2. Forest plot summarizing the ratios of beta power in dystonia in relation to Parkinson’s disease across the different articles included. GPI = internal part of the globus pallidus, M1 = primary motor cortex, STN = subthalamic nucleus, PD = Parkinson’s disease, Dys = Dystonia, SE = standard error, CI = confidence interval.
mixed types of dystonia in the studies approached.

4.2. Significance of beta oscillations

An overall agreement across studies included in this meta-analysis, indicate that beta oscillations are increased in the GPi of PD patients when compared to dystonia patients. On the other hand, articles showed a high degree of heterogeneity among them, when reporting results in the STN and M1. From the two included articles reporting STN-LFPs, a maximum degree of homogeneity in their results regarding LF power was observed; however, they showed contrasting results in the beta range. One article showed increased beta power in PD (Geng et al., 2017), whereas the other showed no differences in the beta range between diseases (Wang et al., 2016). However, while the presence of exaggerated beta oscillations in the dystonic STN is in theory physically possible, the role of other potential confounding factors might have contributed to discrepancy of results across studies. In the study of Geng et al., only one of the eight dystonia patients included received aripiprazole/clonazepam during the recordings. This patient showed an increment on beta oscillations, compared with the OFF-medication dystonia patients. In contrast, 11 of the 12 patients included in the Wang et al. study were regularly treated with either anticholinergics or benzodiazepines. Although medication was stopped at least 12 h prior to the measurements in this study, it is well known that many benzodiazepines possess a long half-life (being ~15 h for alprazolam, 10–20 h for Lorazepam, and 30–40 h for clonazepam (Mihic et al., 2017)). This is relevant, as it has been observed that benzodiazepines produce an increment in beta activity, and a reduction of theta activity in the human motor system (Jensen et al., 2005). Therefore, it is possible that the increment in beta activity observed in those dystonia patients could be due to a potential incomplete washout. A third article (Neumann et al., 2012, excluded from the analysis) also showed increased beta power in STN recordings of PD patients when compared to dystonia. Furthermore, a recent study found that beta oscillations were significantly increased in the ventro-medial STN of PD patients, when compared to OCD patients (Rappel et al., 2018). In the aforementioned study, beta oscillations also seemed to be increased in the dorso-lateral STN of PD patients in comparison to OCD patients. However, this difference was not significant, probably due to the use of Bonferroni correction in the PSD estimates, as it tends to be hyper-conservative when tests are correlated (consecutive frequency bins) (Conneely and Boehnke 2007). Therefore, an overall increased beta power in the parkinsonian STN cannot be confirmed or excluded with the data available. Regarding the pooled ratios of beta power in the resting-state M1, they showed no significant differences between diseases. Nevertheless, slight, but significantly increased beta power in the parkinsonian M1 could be appreciated in two of the three articles included. It could be possible that beta oscillations in cortical PD motor structures slowly become increased as the progression of the disease gradually affects cortical structures (Braak et al., 1996). Another option is that, similarly to LF oscillations in the M1, the interaction of beta oscillations with either other frequency bands, or in the information flow to subcortical structures in terms of coherence, could play a bigger role in the pathophysiology of the disease on the M1, rather than the increase of beta power itself. The clinical significance of beta oscillations has been more widely described than that of LF oscillations. The physiological role of beta oscillations in the suppression of voluntary movements has been broadly described on EEG studies with healthy subjects (Heinrichs-Graham et al., 2017). Exaggerated beta oscillations are a well-known phenomenon in the PD motor system (Brown and Marsden 1999). Nevertheless, there is an ongoing debate whether these are causative or an epiphénomén of pathological features. Evidence of their causative role comes from studies indicating that bradykinesia is exaggerated if DBS is applied with stimulation frequencies in the beta range (Eusebio et al., 2008). The same holds when the motor cortex is stimulated with stimulation frequencies in the beta range using transient alternating current stimulation (Joundi et al., 2012). Recently, it has been shown that beta oscillations present a bursting behavior (Tinkhauser et al., 2017), and the amplitude of such bursts is higher in PD when compared to dystonia (Wang et al., 2018; Pina-Fuentes et al., 2019). Given that higher beta power was found in the PSD estimates of PD, in comparison with those of dystonia, higher burst amplitudes are expected in PD, as amplitude and power are representations of the same phenomenon, in either the time or the frequency domain (i.e. a high beta peak in the PSD estimates of a signal is expected to translate into high amplitudes of such signal filtered around the frequency of the peak). However, the fact that burst amplitudes are consistently increased in PD, indicates that the power difference found between PD and dystonia is evenly distributed over time, which support the role of increased beta oscillations in the maintenance of a continuous hypokinetic state.

4.3. Symptom-related oscillatory profile

While particular oscillatory patterns for dystonia and PD have been shown in this meta-analysis, certain studies have suggested that abnormal oscillations could be primarily linked to certain features of each disease, rather than the whole pathology. Increased LF oscillations in the GPi and LF coherence with other CBGTC structures have been associated with phasic components of dystonia (Liu et al., 2006; Barow et al., 2014), whereas tonic components have been associated with coherence in the delta (0–4 Hz) range (Chung and Huh 2016). Similarly, beta oscillations in the parkinsonian STN have been correlated with motor symptoms (Neumann et al., 2016), especially bradykinesia and rigidity, but not tremor (Beudel et al., 2017). However, the presence of increased beta oscillations in bradykinetic-rigid syndromes other than PD is yet to be explored.

4.4. Implications for adaptive DBS systems

Currently, adaptive DBS systems are being explored, which could employ either beta amplitude in PD (Little et al., 2016; Piña-Fuentes et al., 2017; Arlotti et al., 2018) or LF amplitude in dystonia (Neumann et al., 2017; Pina-Fuentes et al., 2018, 2019) as physiomarkers in closed-loop algorithms. However, as shown in the articles included in this meta-analysis, LF and beta oscillations are present, to a greater or lesser extent, in both PD and dystonia networks, which is probably due to the physiological role that both oscillations have in the regulation of movement. Therefore, it is up to now not yet established in which degree LF and beta activity are considered to be pathologically increased, and to which extent stimulation should be aimed to suppress them. This is relevant for aDBS systems, as currently an arbitrary threshold has been used to determine the moments in which oscillations are considered to be increased, and subsequently triggering stimulation (Little et al., 2013; Arlotti et al., 2016). In this meta-analysis, LF power in PD was consistently found to be roughly two thirds the amount found in dystonia, in both the GPi and the STN. Similarly, beta power in dystonia was found to be roughly two thirds the amount found in PD in the GPi. These findings could provide a rationale to explore stimulation paradigms in which a threshold for stimulation could be set at two thirds of the maximum LF or beta activity, in dystonia and PD, respectively.
4.5. Limitations

Although we strived to homogenize the data included on the meta-analysis, potential sources of bias have to be pointed out. First, data had to be extrapolated from PSD estimates or plots, since direct descriptions of means ± SDs of LF or beta power were not reported in the articles. Second, some articles use measures of central tendency/dispersion other than mean ± SD to report differences in local oscillatory activity between PD and dystonia, and outcomes were presented on different power units. For this reason, means and/or SDs had to be often estimated from other measures of central tendency/dispersion. This may have led to both over- and underestimations of the differences between PD and dystonia. Nevertheless, as information had to be extrapolated for all articles, individual data was exposed homogeneously to this bias. Next to this, ratios are robust parameters, which allow to maintain the power relation between conditions relatively constant, and the use of random-effects on the analysis took into account aleatory variations on the data. Furthermore, although a publication bias towards positive results could be present in the literature, articles with negative findings were also included. Moreover, recordings were different among studies. However, each structure belonged to the core motor network of the CBGTC loop (motor cortex, STN or GPi), and the statistical analysis was divided into subgroups according to the anatomical structure recorded. Given the heterogeneity of the experimental paradigms, only rest recordings could be included. The use of different tasks or comparison methods, such as coherence, could possibly lead to more insight. Finally, the pathological role of prominent oscillations can only be inferred, since we only described studies directly comparing PD and dystonia, in the absence of controls.

4.6. Future perspectives

Since currently data comparison of PD and dystonia patients from similar subcortical structures faces many difficulties, several approaches can be explored to study the disease-related neurophysiological characteristics beyond PSD estimates. One exiting possibility is the use of modelling basal ganglia modulation and the effects of DBS (Guo et al., 2013). Also, following other fields within neurosciences (e.g. fMRI), anonymous data sharing in uniform reporting styles might be useful (Poldrack and Gorgolewski 2017). Furthermore, the development of implantable DBS systems that are able to provide chronic recordings will counteract some of the physical limitations that intraoperative recordings currently face (Swann et al., 2018), such as the limited time available for recording, or the necessity of having the electrodes externalized in order to record.

5. Conclusion

The current meta-analysis provides quantitative high-level evidence which confirms that LF are increased in the GPi and STN of dystonia patients, while beta oscillations are increased in the GPi of PD patients. More studies are required to provide a more definite answer regarding increased beta oscillations in the parkinsonian STN.

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Author contributions

1) Research project: A. Conception, B. Organization, C. Execution;
3) Manuscript: A. Writing of the first draft, B. Review and Critique, C. Modification of subsequent versions.

DPF 1BC 2ABC 3BC, JMvD 2C 3B, GD 2C 3B, JvZ 2C 3B, TVl 2C 3B, MT 2C 3B, MB 1ABC, 2AB, 3AC.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.02.015.

References


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