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Finely-tuned gamma oscillations: Spectral characteristics and links to dyskinesia

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Abstract

Gamma oscillations comprise a loosely defined, heterogeneous group of functionally different activities between 30-100 Hz in the cortical and subcortical local field potential (LFP) of the motor network. Two distinct patterns seem to emerge which are easily conflated: Finely-tuned gamma (FTG) oscillations − a narrowband activity with peaks between 60-90 Hz − have been observed in multiple movement disorders and are induced by dopaminergic medication or deep brain stimulation (DBS). FTG has been linked with levodopa or DBS-induced dyskinesias, which makes it a putative biomarker for adaptive DBS. On the other hand, gamma activity can also present as a broad phenomenon (30-100 Hz) in the context of motor activation and dynamic processing. Here, we contrast FTG, either levodopa-induced or DBS-induced, from movement-related broadband gamma synchronisation and further elaborate on the functional role of FTG and its potential implications for adaptive DBS. Given the unclear distinction of FTG and broad gamma in literature, we appeal for more careful separation of the two. To better characterise cortical and subcortical FTG as biomarkers for dyskinesia, their sensitivity and specificity need to be investigated in a large clinical trial.

Keywords

Finely-tuned gamma; narrowband gamma; Parkinson's disease; adaptive deep brain stimulation; movement-related gamma synchronisation; dyskinesia; oscillations; local field potentials

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1 Introduction

Gamma rhythms generally refer to neural activities recorded within the 30-100 Hz frequency range (or higher) and are ubiquitous within the human motor system. The first link between voluntary movement and gamma rhythms was made by Hans Piper in the beginning of the 20th century, who demonstrated that EMGs recorded during strong voluntary contractions showed rhythmic activity at around 40 Hz (Piper rhythm) (Piper, 1907). Later, it was shown that this muscle rhythm was driven by comparable oscillatory activities in the contralateral motor cortex (Brown et al., 1998).Ever since, interest in the role of gamma oscillations in motor control soared leading to the observation that the gamma range comprises several heterogeneous activities, which are easily conflated in the scientific literature. Two main activities seem to crystallise.

First, finely-tuned gamma (FTG) oscillations comprise a narrowband activity with peak frequencies between 60-90 Hz and can be extracted from local field potentials (LFP) recorded from cortical and subcortical areas. FTG is primarily an induced activity in patients with Parkinson's disease (PD), either by dopaminergic medication or deep brain stimulation (DBS). Recently, FTG measured invasively over the motor cortex has been proposed as a promising biomarker for dyskinesia in adaptive stimulation algorithms (Swann et al., 2016).

Second, movement execution elicits a rapid increase of broad gamma activity that can be recorded from both cortical and subcortical motor regions contralateral to movement. This gamma event-related synchronisation (gamma ERS) is typically described as a prokinetic rhythm that promotes movement and encodes vigour of motor output (Androulidakis et al., 2007; Anzak et al., 2012). However, broad gamma ERS was also observed when movements were successfully stopped (Fischer et al., 2017; Ray et al., 2012) and it changes with different levels of alertness (Brücke et al., 2013), which suggests a more versatile role.

Adaptive deep brain stimulation (aDBS) aims to automatically adjust stimulation parameters in response to real-time detection of temporal changes in the patient's neurophysiological or clinical state. It has been suggested as an improvement to conventional continuous DBS of the subthalamic nucleus (STN) for PD given its potential to decrease side-effects while maintaining clinical efficacy (Arlotti et al., 2018; Little et al., 2013; Little and Brown, 2020; Swann et al., 2016; Velisar et al., 2019). In aDBS, the clinical state inferred from brain signals, peripheral biomarkers, or a combination of both determines when and how much to stimulate. Ideally, a prospective marker comprises as many of the following requirements as possible: signals need to be sensitive and specific to the pathological state, tightly time-locked to symptoms, reliable over time and localise to the respective target nucleus (Steiner et al., 2019); they must be calculable with low computational requirements, feasible for implantable devices and provide rapid feedback. Markers with a causal link to pathological symptoms allow DBS to be specifically patterned to maximally disrupt causal circuit dynamics (Little et al., 2016). However, secondary activities with good correlation to clinical state may still prove to be helpful as feedback.

In this review, we put emphasis on the FTG and discuss its functional role and potential use for aDBS in the future. At first, we describe spectral and temporal characteristics

of levodopa and DBS-induced FTG, and compare them with those of movement-related gamma synchronisation. We use our data to reproduce findings that support the narrative. Afterwards, we review literature on the potential functional role of FTG, such as its modulation with voluntary movement and changes in alertness and states of wakefulness. We conclude this section with the link between FTG and dyskinesias. The third part focuses on the potential use of the FTG in aDBS; either as a marker for stimulating the most effective circuit or as a biomarker to track dyskinesias.

2 Comparison of different gamma oscillations

FTG comprises oscillations in a narrow frequency band between 60-90 Hz. However, the scientific literature so far has not provided a clear distinction between FTG and movement-related gamma ERS with the two often considered equivalent and at times used interchangeably (Cheyne et al., 2008; Fischer, 2021; Jenkinson et al., 2013; Lofredi et al., 2018). Here, we first review the literature on these different gamma oscillations, compare their temporal and spectral characteristics and discuss how different analysis methods may lead to conflation.

2.1 Levodopa-induced finely-tuned gamma oscillations

FTG in motor cortex and basal ganglia can be induced by dopaminergic medication − primarily levodopa − in PD patients (Table 1) or hemiparkinsonian rats after 6-OHDA (6-Hydroxydopamine) lesion (Table 2). Levodopa-induced FTG occurs minutes to hours after levodopa intake in about 23% of PD patients (López-Azcárate et al., 2010) and comprises a narrowband activity with slightly varying peak frequencies across subjects between 60-90 Hz (Table 3). It is present at rest (Figure 1A) or during the execution of a motor task, where it appears either continuously (Figure 2) or sporadically (Jenkinson et al., 2013, see section 3.1). Levodopa-induced FTG has been recorded from a widely distributed network including STN (Cassidy et al., 2002), GPi (Brown et al., 2001; Williams et al., 2002), Zona incerta(Pogosyan et al., 2006; Trottenberg et al., 2006), thalamus (Kempf et al., 2009), striatum (Halje et al., 2012) and motor cortex (Swann et al., 2018, 2016; Williams et al., 2002). Significant coherence at FTG frequencies has been reported across the cortico-basal ganglia-thalamic loop (Brown et al., 2001; Cassidy et al., 2002; Lalo et al., 2008). Despite its ubiquity, within every nucleus it is highly focal (Pogosyan et al., 2006; Trottenberg et al., 2006). Apart from PD, thalamic FTG has been detected in a variety of neurological disorders including ET, dystonia and myoclonic epilepsy, where it was not related to dopaminergic medication(Kempf et al., 2009).

2.2 Stimulation-induced finely-tuned gamma oscillations

Recently, FTG activity was reported in patients with PD in the absence of dopaminergic medication; either during or after continuous high-frequency stimulation of the STN at 130Hz (Table 4 and Figure 1B). More specifically, we reported DBS-induced FTG in about a third of patients starting with a slight delay of a few seconds after stimulation was switched on and slightly decreasing in frequency over time (Wiest et al., 2021). In 4 out of 5 patients, FTG was observed for several seconds after stimulation was switched off; either outlasting continuous DBS or starting de-novo after stimulation offset. Similar to levodopa-

induced FTG, DBS-induced FTG is sharply tuned and occupies a narrow frequency band between 60-90 Hz (Figure 1B), with peak frequencies slightly varying across subjects (Table 3). The occurrence of such a finely-tuned oscillatory activity concomitantly with DBS raises the question of entrainment. In a previous study on levodopa-induced FTG, Swann and colleagues described that cortical FTG peak frequencies shifted from ~80 Hz to a subharmonic of stimulation when 130 Hz STN-DBS was switched on (Swann et al., 2016). This argues in favour of entrainment of cortical FTG to DBS. However, DBS-induced FTG off medication in STN and STN-cortical coherence were not locked at a subharmonic of the stimulation frequency (Muthuraman et al., 2020; Wiest et al., 2021) and the authors showed relatively sustained stimulation after-effects arguing against simple entrainment.

2.3 Movement-related broadband gamma synchronisation

Following the first observations of Hans Piper, numerous human studies confirmed movement-related changes in the gamma band (Table 5) and extended the frequency range from 30-100 Hz (Figure 1C) and sometimes even beyond up to 400 Hz (Anzak et al., 2012). Broadband gamma synchrony at movement onset has been recorded in the contralateral motor cortex (Cheyne and Ferrari, 2013), STN, GPi and thalamus (Brücke et al., 2012; Litvak et al., 2012; Lofredi et al., 2018; Tan et al., 2013a) and increases on levodopa (Androulidakis et al., 2007). Moreover, gamma ERS peaks at movement onset and declines throughout the duration of sustained movements (Anzak et al., 2012; Lofredi et al., 2018; Muthukumaraswamy, 2010). Although most studies on basal ganglia electrophysiology were performed in PD, movement-related gamma synchronisation has been evidenced in healthy humans in motor cortex (Cheyne et al., 2008; Muthukumaraswamy, 2010) and patients with dystonia in the GPi (Brücke et al., 2008; Tsang et al., 2012) or essential tremor (ET) in the thalamus (Brücke et al., 2013).

Broadband movement-related gamma synchronisation appeared to correlate with gripping force, size and velocity of voluntary movements and motor effort (Anzak et al., 2012; Brücke et al., 2012; Joundi et al., 2013; Lofredi et al., 2018; Tan et al., 2013a). Brücke and colleagues found that baseline broadband gamma power recorded from thalamus before a Go cue correlated with reaction times in a Go-noGo task (Brücke et al., 2013). Thus, broadband gamma ERS may promote movement and encode vigour of motor output. The prokinetic nature of broad gamma ERS is underlined by studies in which movement preparation and passive limb displacements without active movements are accompanied by firing rate changes but not gamma synchronisation (Cassidy et al., 2002; Liu et al., 2008; Muthukumaraswamy, 2010) suggesting their involvement in movement initiation. A recent review suggested that small temporal shifts of cortical activity may unleash broadband gamma synchronisation in the basal ganglia and trigger movement initiation (Fischer, 2021) and broadband corticospinal gamma coherence may aid to optimally couple remote regions (Schoffelen et al., 2005). Interestingly, gamma ERS also occurred in successfully inhibited stop-trials without any obvious movements arguing for a more versatile role and suggesting that broadband gamma may relate to facilitation of dynamic processing instead of solely being prokinetic (Fischer et al., 2017; Ray et al., 2012). In line with this, broad gamma ERS has also been linked to arousal during sleep and alertness during cognitive tasks in epileptic patients (Gross and Gotman, 1999).

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Given the relatively large frequency range of movement-related gamma synchronisation, it is also possible that it is divided into multiple subunits. Crone and colleagues report two different gamma bands during movements − low gamma ERS from 35-50 Hz and high gamma ERS from 75-100 Hz − with distinct temporal and spatial characteristics (Crone et al., 1998). Low gamma oscillations often began after movement onset and were sustained throughout while high gamma ERS started during, or slightly before, movements and was short-lived, ending before completion of the movement response. This hints at different neurophysiological mechanisms.

2.4 Differences in spectral and temporal characteristics between FTG and movement-related gammasynchronization

Conflation and confusion of FTG and movement-related gamma in the literature may be partly due to different methods and parameter settings used for time-frequency decomposition, in which there is always a trade-off between frequency precision and temporal precision. When studying movement-related changes, methods and parameter settings with higher temporal resolution tend to be used to capture fast changes over time, which may lead to extension of synchrony along the frequency axis. When movement-related broad gamma ERS was reported in previous literature, normalised power spectra relative to a pre-cue baseline were presented and results were averaged across subjects and trials. Thus, the broad frequency band with activity increase shown in the averaged power spectra may be due to cross-subject variance. Inversely, when studying activities at rest, methods and settings with higher frequency precision are often used, as in most cases for FTG analysis. In addition, when FTG was reported, data from individual subjects were presented partly due to the paucity of the data. To get an overview of the variance in methods used for spectral decomposition see Tables 1, 2, 4 and 5.

Here, we used the same method with the same parameters (see Methods) for time-frequency decomposition and re-analysed previously published data to compare spectral and temporal characteristics of FTG and movement-related gamma ERS. As shown in Figure 1, broadband gamma ERS spans an eponymous larger frequency range and on average has a lower peak frequency compared to both levodopa-induced and DBS-induced FTG. The peak frequency, frequency bandwidth, average duration and peak amplitude of movement-related gamma ERS, levodopa-induced FTG and DBS-induced FTG are presented in Table 3. Movement-related gamma ERS is transient and vanishes after milliseconds to a few seconds whereas DBS-induced FTG may outlast stimulation for several seconds to more than a minute and levodopa-induced FTG may be present over many minutes to hours. Also, the relative amplitude increase of broad gamma ERS is less pronounced than that of DBS-induced FTG (Table 3).

3 Functional role of FTG

Given the paucity of studies on DBS-induced FTG, this section mostly relates to levodopa-induced FTG.

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3.1 FTG is modulated by movement

Levodopa-induced FTG in STN of PD patients is observable at rest, and its amplitude and frequency slightly increase with voluntary movements when compared to baseline (Alegre et al., 2005). This modulation is transient and subsides within 1-2 s. Similarly, FTG modulation with voluntary movements was observed in thalamic LFPs in patients with PD on levodopa and other pathologies (Kempf et al., 2009), indicating that movement-related modulation of the FTG in the basal ganglia and thalamus may reflect healthy motor function. Movement-related synchronisation in these two studies is sharper than broadband gamma ERS (Table 5) and unlikely due to differences in time-frequency decomposition. We reproduced their findings in a PD patient that displayed levodopa-induced FTG in the STN at rest while performing a joystick task (Figure 2). This suggests that levodopa-induced FTG is directly modulated by movement and likely not overlaid by broadband gamma ERS. In support of this, Lofredi and colleagues suggest that FTG may scale with motor output and broadband gamma may reflect local spiking in STN (Lofredi et al., 2018). On the other hand, a single observation in one PD patient revealed that levodopa-induced FTG may sporadically appear and disappear over time without time-locking to movements (Jenkinson et al., 2013).

Note, however, that cortical FTG seems to be relatively unaffected by voluntary movement when described at the single trial level (de Hemptinne et al., 2019; Miocinovic et al., 2018; Swann et al., 2016). Of note, simultaneous recordings of cortical and subcortical FTG so far are sparse. Whether both are equally modulated by movement would be best addressed in a controlled within subject movement task, which may be complicated by concomitant dyskinesias.

3.2 FTG varies with wakefulness, sleep stages, arousal and startle reactions

The connection between levodopa-induced FTG and wakefulness was suggested following the observation that in one PD patient STN-FTG disappeared, as he became drowsy (Brown et al., 2001). The authors suggest this ~70 Hz signal to be a carrier rhythm for motor commands while the patient is awake. In another study, Kempf and colleagues showed modulation of thalamic FTG throughout the sleep-wake cycle (Kempf et al., 2009). While FTG was manifest during waking, it was suppressed during slow-wave sleep and re-emerged during REM phases. Of note, FTG was not exclusively linked to periods of rapid eye movement and hence underlying motor processing. It should, however, be acknowledged that arousal, drowsiness and sleep stages are linked with other spectral changes in addition to FTG (Cantero et al., 2002; Santamaria and Chiappa, 1987).

Kempf and colleagues also report an increase of FTG amplitude and/or frequency in response to unexpected acoustic stimuli. Of note, startle-related FTG changes outlasted associated motor activation.

3.3 FTG accompanies dyskinesias

Following treatment with levodopa, PD patients may develop abnormal involuntary movements, referred as levodopa-induced dyskinesias (LID). First, we will discuss human

studies in support of and against a link between FTG and dyskinesias before moving to animal studies that support and challenge this connection.

3.3.1 Human studies supporting the link between FTG and levodopa-induced dyskinesia— Table 1 shows studies in which LFP recordings in the STN or over the motor cortex of PD patients displayed levodopa-induced FTG during episodes of dyskinesia, suggesting that the two might be related (Alonso-Frech et al., 2006; Fogelson et al., 2005; Swann et al., 2018, 2016). Swann and colleagues recorded FTG over the primary motor cortex (M1) and in STN with coherence between these two sites during periods of dyskinesia in two patients using chronically implanted pulse generators (Swann et al., 2016). All four measures (M1-FTG power, STN-FTG power, phase coherence and magnitude-squared coherence) in this study distinguished the dyskinetic from the non-dyskinetic state.Furthermore, the authors reported frequency shifts of levodopa-induced FTG as DBS frequency changes, suggesting entrainment of FTG at half the stimulation frequency. Swann and colleagues also report constant phase coupling between cortical and STN-FTG during dyskinesia regardless of whether DBS was switched on or off, suggesting that this phase relationship is unlikely explained by a subharmonic of stimulation. However, other studies up to date could not replicate FTG entrainment at a subharmonic frequency when patients were off medication (Muthuraman et al., 2020; Wiest et al., 2021). It is possible that activities in subcortical areas are less susceptible to entrainment and frequency shifting especially in the dopamine-deficient state.Alternatively, entrainment may also be dependent on stimulation currents.

3.3.2 Human studies challenging the link between FTG and levodopa-induced dyskinesia—A clear link between the presence of STN-FTG and LID in humans may be difficult to prove. Stimulation-induced FTG was recorded in the STN-LFP of PD patients when they were off dopaminergic medication while no dyskinesias were present and the FTG was not locked at a subharmonic of stimulation as reported for cortical FTG (Wiest et al., 2021). Even if subtle dyskinesias may have not been detected in this study, in 2 out of 5 subjects FTG only started after DBS offset and was absent during DBS when dyskinesias are supposed to be strongest. This paradox argues against a fixed temporal relationship between dyskinesias and DBS-induced FTG recorded in STN. Furthermore, the authors observed a broader post-DBS gamma rebound that comes in about 15 seconds after DBS offset (Wiest et al., 2021 and Figure 1B). While its frequency and broad character are more similar to movement-related gamma ERS, this activity appears movement-independent. Given the gap of several seconds from stimulation, this activity is unlikely to reflect the weaning of DBS-induced dyskinesias; it may rather represent a rebound following low-gamma desynchronization during DBS (Wiest et al., 2021, 2020). A different study used indirect measures to estimate subcortical electrophysiology and reports cross-frequency-coupling between FTG power and power at stimulation frequency off dopaminergic medication, without dyskinesias and not locked at a subharmonic of stimulation (Muthuraman et al., 2020). In addition, an earlier study found a more prominent change of low frequency activity (4-10 Hz) mirroring LID (Alonso-Frech et al., 2006). Fogelson and colleagues reported that over 70% of patients with STN macroelectrodes showing a negative correlation between levodopa-induced FTG and low-frequency power

were dyskinetic in the contralateral limb during recording (Fogelson et al., 2005). However, this study hinted at insufficient specificity and sensitivity since some patients displayed negative correlations without dyskinesias and others had dyskinesias without negative correlations.

3.3.3 Evidence from animal studies supporting the link between cortical FTG and dyskinesia—Several rodent studies (summarised in Table 2) support the link between FTG and dyskinesias. Halje and colleagues recorded FTG over the primary motor cortex during LID in hemiparkinsonian rats (Halje et al., 2012). Both cortical FTG and dyskinesias were reversed with a dopamine antagonist. Interestingly, this study found more prominent FTG in motor cortex than in striatum suggesting that loss of cortical dopaminergic innervation may be a key predisposing factor for LID, which makes cortex prone to network resonance at FTG frequency. However, it is still unclear if there exists a causal relationship between LID and cortical FTG or if it is epiphenomenal. The same study found a sigmoidal relationship between FTG power and dyskinesia severity and suggested that FTG frequencies may depend on the time of recording relative to levodopa intake (Halje et al., 2012). Dupre and colleagues demonstrated similar reversibility of cortical FTG and dyskinesia. Dyskinesias along with an 80 Hz oscillatory signal in the motor cortex could be induced by levodopa, D_1 and D_2 receptor agonists, reversed by a serotonin agonist and brought back using a serotonin antagonist (Brys et al., 2018; Dupre et al., 2016). This study casts doubt on the prevailing view of striatal hypersensitivity to dopamine and D_1R-mediated signalling in the dopamine-denervated striatum as a source for LID (Cenci and Konradi, 2010; Espay et al., 2018). Delaville and colleagues confirmed the link between FTG and LID and report coherence between motor cortex and STN or mPFC at FTG frequencies (Delaville et al., 2015). More recently, Güttler and colleagues proposed cortical gamma burst duration and amplitude as a correlative marker for LID (Güttler et al., 2020). Interestingly, FTG detected in the motor cortex in all four animal studies showed an initial frequency drop; a dynamic which was also observed at a different time scale in DBS-induced FTG in PD patients in STN (Wiest et al., 2021) but not in cortical human recordings (Swann et al., 2018).

3.3.4 Animal studies challenging the link between cortical FTG and dyskinesia—Although Dupre and colleagues report a positive relationship between dyskinesia and cortical FTG occurrence, they also provide compelling arguments against a direct relationship between the two (Dupre et al., 2016). First, in this study only forelimb AIMs (abnormal involuntary movements) were positively and constantly correlated with FTG. Orolingual AIMs only on the first day and axial AIMs never showed a positive correlation between the two. Second, while a serotonin agonist similarly improved LID and dopamine-agonist-induced dyskinesia, the FTG in motor cortex was diminished by varying degrees in both cases. Third, muscimol injection to the ventromedial thalamus before or after levodopa injection eliminates cortical FTG without modifying dyskinesia scores (Dupre et al., 2016). This supports the subcortical genesis of FTG and dissociation between cortical FTG and dyskinesia. Fourth, a recent study in 6-OHDA lesioned rats linked high-dose levodopa priming with an FTG ~80 Hz and LID; however, low-dose priming resulted in LID without FTG, indicating ~80 Hz FTG is not an exclusive marker for LID (Ye

et al., 2021). Instead, the authors found striatal broadband gamma and corticostriatal theta to high-gamma cross-frequency coupling (CFC) were enhanced in LID and sub-anaesthetic ketamine effectively reduced LID and theta to high-gamma CFC.

3.4 Controversies emanating from cortical and subcortical FTG

The literature discussed above points towards different relationships of cortical and subcortical FTG with dyskinesia, with more evidence supporting a positive relationship between cortical FTG and dyskinesia. It is unclear, however, if FTG is of cortical or subcortical origin. While neuronal spiking tends to be phase-locked to exaggerated beta oscillations (Kühn et al., 2005; Levy et al., 2002; Weinberger et al., 2006), phase locking of cortical spikes is negatively correlated with high gamma LFP (Dupre et al., 2016). This argues against earlier views of cortical subcircuits generating recurrent rhythms via interactions of pyramidal neurons and interneurons (Börgers et al., 2005; Lee and Jones, 2013). It rather supports the hypothesis that cortical FTG is driven by subcortical input such as thalamus (Jenkinson et al., 2013). Moreover, gamma coupling between STN and cortex is driven by STN (Litvak et al., 2012; Sharott et al., 2018) which affords a more executive role to the basal ganglia. However, Halje and colleagues report stronger FTG in cortex than in striatum suggesting a cortical origin.

Despite the abundance of literature on STN-cortex coherence in the gamma range (Brown et al., 2001; Cassidy et al., 2002; Lalo et al., 2008; Wiest et al., 2021), cortical and subcortical FTG differ with respect to sensitivity and specificity to dyskinesias, entrainment at half stimulation frequency and modulation by voluntary movements. Given this functional disparity, it is possible that both activities are unrelated.

4 Implications for deep brain stimulation

4.1 A marker for stimulating the correct circuit

In previous studies, FTG was shown to be focal to the dorsolateral STN and adjacent caudal Zona incerta in intraoperative recordings (Pogosyan et al., 2006; Trottenberg et al., 2006). A recent study recorded levodopa-induced FTG along the trajectory during lead implantation and found that FTG power was stronger superior of the STN than within STN (Ozturk et al., 2020). FTG was detected up to 10 mm above the dorsal STN border, an area likely within thalamus. Of note, the patient presented generalised choreiform dyskinesias during the recording. This is interesting since a common approach to improve stimulation-induced dyskinesias is to switch to more dorsal contacts that are likely placed within Zona incerta(Picillo et al., 2016). The antidyskinetic effect of this is believed to be mediated through stimulation of pallidofugal fibres resembling combined stimulation of ventral GPi and STN (Herzog et al., 2007).

It has been shown that cortical FTG can be unleashed by pallidotomy and its emergence was suggested to be mechanistically related to improvement in bradykinesia (de Hemptinne et al., 2019). DBS-induced FTG in the STN that starts a couple of seconds after DBS onset and outlasts stimulation by several seconds, as we reported in a previous study, may similarly reflect clinical improvement (Wiest et al., 2021).Recently, Muthuraman and colleagues

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reported CFC between FTG and DBS frequency in cortical (motor cortex, supplementary motor area, premotor cortex) and subcortical areas (STN and cerebellum) (Muthuraman et al., 2020). CFC negatively correlated with clinical impairment, and was only present when DBS was delivered to STN at clinically effective stimulation frequencies. Therefore, FTG or coherence at this frequency may serve as an indicator for good clinical response and as a marker of interference with the right neural circuit. The fact that FTG can be recorded from multiple nuclei within the basal ganglia loop and cortex is in support of this. Critically, the link between FTG and dyskinesia points in the same direction. While DBS-induced dyskinesias represent a bothersome side effect, they are also an indicator of stimulating the sweet spot when stimulation currents are sufficiently increased and the contact eliciting dyskinesia is generally the most effective in relieving PD symptoms (Picillo et al., 2016).

4.2 A feedback signal for aDBS

Although there is good reason to believe in a link between cortical FTG and dyskinesias based on preclinical and clinical studies, several points are unclear. Next, we will discuss advantages and disadvantages of cortical FTG as a biomarker and finish with a few challenges to its use in aDBS.

4.2.1 Advantages and promises of cortical FTG as a biomarker for levodopa-induced dyskinesia—

The specificity and sensitivity of separating periods with and without dyskinesia by means of cortical FTG is promising (Swann et al., 2016) and a couple of practical considerations speak in favour of cortical FTG as a control signal. First, while stimulating, STN-LFP has to be recorded in bipolar mode from contacts either side of stimulation in order to reduce stimulation artefacts, which limits the flexibility in selecting recording and stimulation contacts. In contrast, cortical sensing is less limited by the choice of available contacts for stimulation in the target structure. Second, STN-LFP is a low amplitude signal − gamma oscillations even lower than beta, which is still affected by stimulation artefacts delivered to adjacent contacts. Nevertheless, several studies have managed to extract meaningful information using externalised electrodes (Deffains et al., 2018; Little et al., 2013; Tinkhauser et al., 2017; Wiest et al., 2020 and more). However, whether signals in the gamma frequency band in the STN can be reliably detected in real-time from an implantable device in the presence of stimulation artefacts is still unclear. Third, even though DBS-induced FTG was recorded from STN in some cases, this activity is coherent with cortical activities at FTG frequencies as we showed in a previous study (Wiest et al., 2021) and ECoG electrodes placed over the motor cortex may have picked this activity up as well. Fourth, a recent study used wireless, multichannel streaming of LFPs during normal daily activities and found better decoding with multisite sensing (Gilron et al., 2021). They used STN-M1 coherence in the beta and gamma range to distinguish mobile from immobile states and found that multisite sensing can be particularly useful for individuals with milder motor fluctuations. Another study in PD patients undergoing DBS implantation concluded that contralateral sensorimotor ECoG recordings outperformed contralateral STN-LFPs for grip force decoding when different machine learning methods are used, with gradient boosted trees (XGBOOST framework) showing the highest performance (Merk et al., 2021).

4.2.2 Practical concerns of cortical FTG as a biomarker for levodopa-induced dyskinesia—

Cortical FTG has been trialled in two patients as a feedback signal to track dyskinetic states in a proof of principle study, however, this short-term study of aDBS could not show therapeutic superiority over cDBS (Swann et al., 2018).

A couple of practical concerns need to be considered when using cortical FTG as feedback signals for aDBS in long-term studies. First, chronic ECoG recordings require the insertion of subdural leads. Although these have not been linked with increased risks of infection (Sisterson et al., 2021), their insertion in addition to DBS electrodes creates a small additional risk of haemorrhage and disability. Second, currently existing FTG-based DBS algorithms would not modulate stimulation outside of periods with dyskinesia. Coupling the algorithm with an additional feedback loop to index bradykinesia or tremor might further improve symptom control. Third, signal to noise ratio for gamma band activities may still be low even if ECoG recordings were less affected by stimulation artefacts. In an earlier study using cortical sensing, data recorded from 3 out of 5 patients had to be excluded in part because the FTG did not rise over the amplifier signal to noise ratio when using the Medtronic Activa PC+S device (Swann et al., 2016). Despite a relatively high sampling rate for chronically implanted pulse generators with sensing capability which would require manufacturer approval to unlock more technical features, stimulation can still sometimes produce narrowband artefacts, due to aliasing, which need to be distinguished from physiological signal. Last but not least, the dyskinesia-related FTG may need to be differentiated from voluntary movement-related gamma ERS, based on the spectral characteristics or temporal dynamics, as we discussed.

4.2.3 Subcortical FTG may lack the specificity and consistency required for a biomarker for levodopa-induced dyskinesia—

FTG in subcortical areas, no matter if levodopa or stimulation-induced, is not consistently observed in every tested patient. The sparseness of FTG in many recordings argues for selective utility. In addition, levodopa and DBS-induced FTG appear to be unstable over time which makes them less reliable biomarkers (Jenkinson et al., 2013; Wiest et al., 2021). Given its modulation with different functional states (e.g. alertness), across other neurological conditions (dystonia, ET, myoclonic epilepsy) and other therapeutic interventions (e.g. post pallidotomy where it was suggested to represent clinical improvement), FTG in the basal ganglia or thalamic LFP has low specificity to levodopa or DBS-induced dyskinesias. In addition, FTG activity (46-70 Hz) has also been recorded in the basal ganglia of healthy alert rats at rest and further emphasised by movement and dopaminergic stimulation (Brown et al., 2002), suggesting that FTG in the basal ganglia may represent the physiological nature of the recorded structure. If DBS-induced FTG in the STN turns out to be unspecific to dyskinesias, this activity may have to be separated from dyskinesia-related FTG to prevent DBS from being switched off. Nevertheless, it is possible that very mild dyskinesias were missed in the studies reporting DBS-induced FTG in STN or STN-motor cortex coherence at FTG frequency (Muthuraman et al., 2020; Wiest et al., 2021). In that case, the time between FTG and dyskinesia onset and the link of FTG with symptom severity are crucial. If DBS-induced FTG in the STN appears only a few seconds to minutes before severe dyskinetic symptoms, it may indicate DBS currents close to side effect threshold and may

be useful to adjust currents before dyskinesias become manifest. Alternatively, if the time between DBS-induced FTG in the STN and dyskinesia appearance is variable and in the range of minutes, decreasing stimulation currents based on this FTG activity may lead to suboptimal stimulation adjustment. Similarly, if DBS-induced FTG in the STN also reflects mild dyskinesias, this might strengthen their pathophysiological correlation but lessen their utility as a biomarker to modulate stimulation.

5 Conclusions

We contrasted levodopa and DBS-induced FTG from broad movement-related gamma changes and appeal for more careful separation of the two in the future. We further reviewed the functional role of FTG, its link to dyskinesias and eventually its role as a biomarker for aDBS: be it as a marker for stimulating the right circuit or as a marker to track dyskinesias. Although preclinical and early clinical studies are reason to be optimistic about cortical FTG as a potential biomarker for dyskinesia, the utility of subcortical FTG recorded from STN is more questionable since it is not consistently measured in all patients and evidence supporting its link to dyskinesias is scarce. A large clinical study will be needed to quantify the sensitivity and specificity of both cortical and subcortical FTG to track the dyskinetic state and their robustness across patients, which may be facilitated by the advent of implantable pulse generators that allow for chronic data streaming during daily activities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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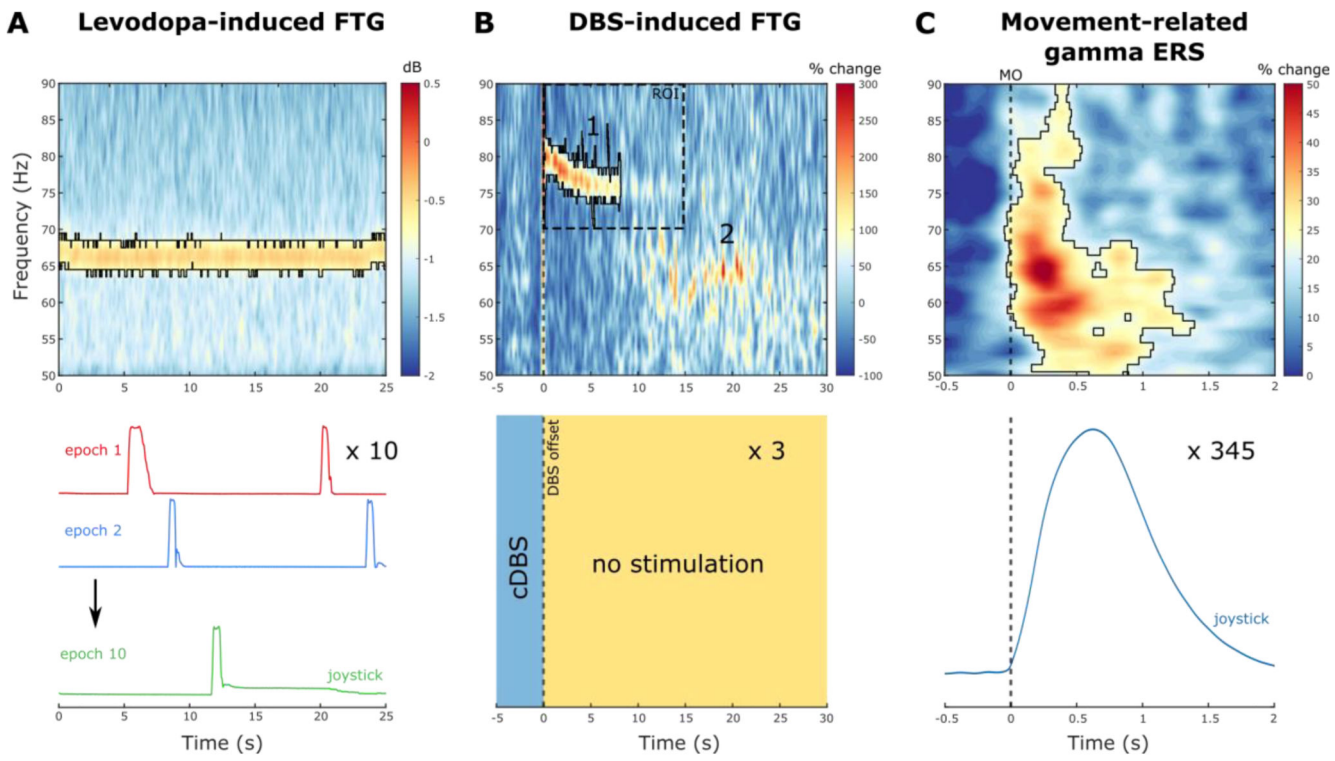

Figure 1. Comparison of different gamma rhythms.

A. Time-frequency spectrogram of levodopa-induced FTG at rest. The spectrogram of a 250 s recording during a joystick task on dopaminergic medication was divided into 10 segments of 25 s, which were averaged to cancel out movement effects. Bottom: Examples of the unaligned joystick movements of 3 epochs. **B**. Time-frequency spectrogram of activity changes in the gamma range after deep brain stimulation was switched off (at 0 s). Three consecutive blocks (3 minutes each) of continuous STN-stimulation were applied in this patient (with sufficient resting in between). Spectrograms were aligned to DBS offset, baseline normalised to a 60-second window before each stimulation block and averaged. A post-DBS induced FTG is observed (label 1) along with a broader post-DBS gamma rebound at a lower frequency band (label 2). Bottom: Schematic of when stimulation was switched off. C. Time-frequency spectrogram of broadband movement-related gamma activity off dopaminergic medication. 345 joystick movements from one patient were aligned to movement onset (at 0 s), baseline normalised using a 2-second windows (-2.5 to -0.5 s) and averaged. Bottom: Average of all 345 joystick movements aligned to movement onset (MO). Data in A-C was recorded from 3 different patients with Parkinson's disease with different bipolar configurations. The same time-frequency decomposition was performed using complex Morlet wavelet transform (50 cycles) for A-C (see Methods). The black contour contains all power estimates above the 70^{th}/90^{th} percentile (see Methods for details). The region of interest (ROI) to compute the contour is shown in B. In A and C the ROI corresponds to the shown axes. Note the different time axes and colour bars.

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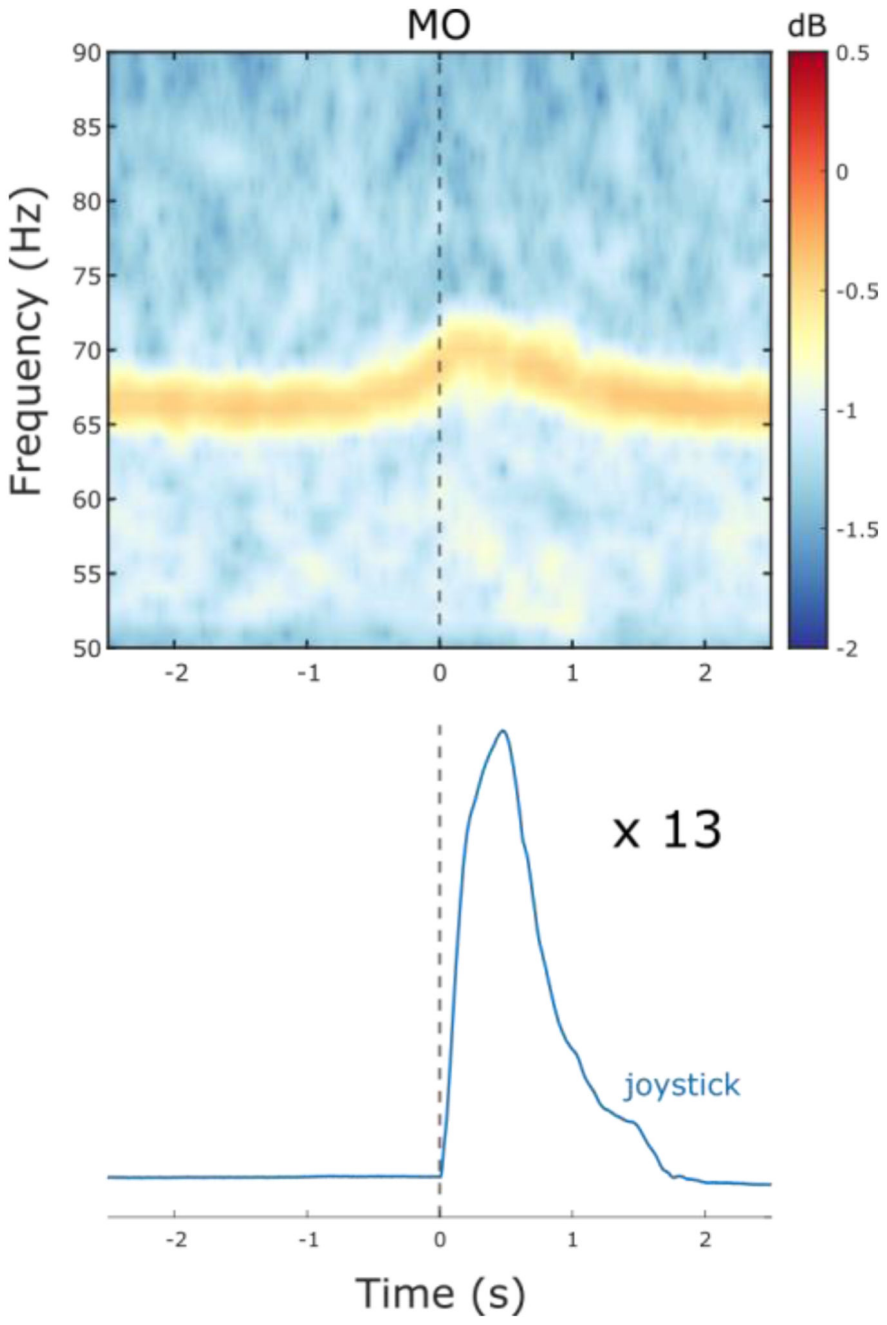

Figure 2. Levodopa-induced finely-tuned gamma (FTG) oscillations are modulated by movement.

A patient with Parkinson's disease performed a joystick task while contralateral local field potentials were recorded from an externalised electrode in the subthalamic nucleus. Time-frequency spectrogram on dopaminergic medication is shown. All 13 joystick movements were aligned to movement onset (MO) and averaged. Note the FTG frequency increase just before MO which lasts for about 1 s. Bottom: Average of all joystick movements aligned to MO.

Table 1

Levodopa-induced FTG in humans.

Studies presented in chronological order. M1: primary motor cortex; STN: subthalamic nucleus; GPi: internal segment of the globus pallidum; ET: essential tremor; PD: Parkinson's disease; ON: on dopaminergic medication; OFF: off dopaminergic medication; FFT: fast fourier transform.

Study	Location	Disorder	Medication	Dyskinesia	Methods	Main Findings
Gilron et al., 2021	M1, STN	PD	ON	yes	Welch's method (250 ms window, 50% overlap)	an implanted, bidirectional neural interface was used to stream data over long periods of daily living, STN-M1 coherence in beta and gamma bands distinguished mobile and immobile states, sleep suppresses subthalamic beta and cortical gamma as well as STN-M1 coherence in both bands
Ozturk et al., 2020	STN	PD	ON	yes	FFT (1 s Hamming window, 50% overlap)	FTG power is strongest superior of STN (>10 mm above, likely thalamus)
de Hemptinne et al., 2019	M1	PD	OFF	no	Welch's method (~0.5 s Hann window, 50% overlap, 0.95 Hz resolution) and short-time FFT (~0.5 s window, ~90% overlap)	FTG appeared with effective thermolesion of the pallidum in 3 patients
Swann et al., 2018	M1	PD	ON	yes	method unclear	proof of principle study leveraging cortical FTG as a biomarker for dyskinesias in 2 patients
Miocinovic et al., 2018	M1	dystonia	n.a.	no	method unclear	cortical FTG during dystonic postures in 2 patients
Swann et al., 2016	M1, STN	PD	ON	yes	Welch's method (512 ms window, FFT length: 1024 points)	dyskinesia is associated with FTG in M1 and STN and coherence between the two, dyskinesia-related oscillations are minimally affected by voluntary movements, FTG is entrained at half stimulation frequency
Cagnan et al., 2014	STN	PD	ON	no	short-time FFT (1 s Hann window, 75% overlap)	FTG oscillations in the STN of both hemispheres are co-modulated
López-Azcárate et al., 2010	STN	PD	ON	no	short-time FFT (~2 s Hann window, 75% overlap, ~0.5 Hz resolution)	levodopa induces STN-FTG in 3/13 patients
Kempf et al., 2009	ventral intermediate or centromedian nucleus of the thalamus	PD, ET, dystonia, myoclonic epilepsy	ON (if PD)	no	short-time FFT (0.5 s windows, 90% overlap 2 Hz resolution)	all patients presented an FTG peak which is modulated by movement and varied over the sleep-wake cycle, FTG is enhanced by statle-eliciting stimuli, sharply-tuned coherence at ~70 Hz between thalamus and GP
Alonso-Frech et al., 2006	STN	PD	ON	yes	short-time FFT (~1.28 s windows, 0% overlap)	low frequency power (4-10 Hz) may have a stronger link to levodopa-induced dyskinesias than FTG (60-80 Hz) power
Trottenberg et al., 2006	STN	PD	OFF	no	short-time FFT (~0.82 s windows)	gamma increase in 8/15 hemispheres 2 mm above the dorsal border of STN, gamma dropped 3 mm below the dorsal STN border, gamma LFP likely

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Study	Location	Disorder	Medication	Dyskinesia	Methods	Main Findings
						represents synchronous population activity in the upper STN/Zona incerta
Pogosyan et al., 2006	STN, Zona incerta	PD	OFF	no	short-time FFT	FTG activity has a major effect on neuron firing rate and information carrying capacity
Fogelson et al., 2005	STN	PD	ON	yes	short-time FFT (1 s Hann windows, 0% overlap, 1 Hz resolution)	negative correlation between low frequencies (5-32 Hz) and FTG (65-85 Hz) with contralateral levodopa-induced dyskinesias
Alegre et al., 2005	STN	PD	ON + OFF	no	Gabor transform	FTG power is modulated by movements, movement-related averages show an FTG amplitude and/or frequency increase at movement onset
Williams et al., 2002	STN, GPi, cortex	PD	ON	no	short-time FFT (1.28 s windows, 0.78 Hz resolution)	STN and GPi phase lead cortex in the 70-85 Hz band
Cassidy et al., 2002	STN, GPi	PD	ON	no	FFT	power within STN and STN-GPi coherence are dominated by FTG activity, coherence at FTG frequency increases with movement
Brown et al., 2001	STN, GPi	PD	ON	no	short-time FFT (1.024 s windows, 0% overlap 0.98 Hz resolution)	levodopa induces a fine gamma peak at ~70 Hz in STN, GPi and coherence between the two

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Table 2

Levodopa-induced FTG in animal studies.

Studies presented in chronological order. M1: primary motor cortex; GP: globus pallidum; STN: subthalamic nucleus; mPFC: medial prefrontal cortex; RFA: rostral forelimb area; DMS: dorsomedial striatum; DLS: dorsolateral striatum; thal: ventrolateral/ventroanterior nuclei of the thalamus; SNr: substantia nigra pars reticulate; FFT: fast fourier transform.

Study	Location	Disorder	Medication	Methods	Main Findings
Güttler et al., 2020	M1	6-OHDA lesioned rats	levodopa	complex Morlet wavelet convolution (6 cycles)	levodopa-induced dyskinesias (LID) appear with a concomitant increase in cortical FTG activity
Ye et al., 2021	M1, striatum	6-OHDA lesioned rats	levodopa	short-time FFT (10s Hann window, 0.5 Hz resolution)	80 Hz oscillations are not exclusive for LID, sub-anaesthetic ketamine has anti-dyskinetic effects
Brys et al., 2018	RFA, M1, DMS, DLS, GP, thal, STN, SNr	6-OHDA lesioned rats	levodopa	Method unclear (8 s windows, 50% overlap, 0.12 Hz resolution, frequency range: 0-250 Hz)	dyskinetic symptoms are associated with 80 Hz oscillations and are suppressed by serotonin agonists
Dupre et al., 2016	M1	6-OHDA lesioned rats	levodopa	FFT (no further details)	cortical high-gamma (70-110 Hz) LFP activity is associated with the development of LID
Belić et al., 2016	M1, striatum	6-OHDA lesioned rats	levodopa	short-time FFT (no further details)	the dyskinetic state is related to increased coherence between M1 and striatum at ~80 Hz
Salvadè et al., 2016	GP, frontal cortex	6-OHDA lesioned rats	levodopa	no details given	the development of LID was accompanied by a large gamma increase (60-80 Hz)
Delaville et al., 2015	STN, M1, mPFC	6-OHDA lesioned rats	levodopa, apomorphine	FFT (1 Hz resolution)	apomorphine and levodopa induce high-gamma activity in STN and cortex along with dyskinesias
Halje et al., 2012	M1, striatum	6-OHDA lesioned rats	levodopa	Welch's method (8 s Hann window, 50% overlap)	LID is strongly associated with 80 Hz LFP oscillations
Brown et al., 2002	STN	healthy rats	quinpirole	Method unclear (1 Hz resolution)	FTG is present in healthy rats at rest and increases with movement and dopaminergic medication

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Table 3

Comparison of different gamma activities.

Estimates for movement-related gamma ERS are based on the average of two PD patients performing a joystick task with 345 and 368 repetitions respectively. Estimates for DBS-induced FTG are based on 5 subjects with 3-6 stimulation blocks. If FTG was detected during and after stimulation (2 subjects), estimates of both instances were averaged. Estimates for levodopa-induced FTG are based on 6 PD patients performing a joystick task on dopaminergic medication. Different to movement-related gamma ERS, a narrowband FTG feature was present at rest. Spectrograms were divided into segments of 20-30 s and averaged to cancel out movement effects. Durations correspond to the extent of the contour in Figure 1. Amplitude, frequency and half-prominence width were computed based on the power spectrum of every time point using the *findpeaks* function and averaged for every subject (see details in Methods). All values are presented as mean [range]. MO: movement onset; ERS: event-related synchronisation.

	Movement-relatedgamma ERS	DBS-induced FTG	Levodopa-inducedFTG
duration (after MO or DBS stop in sec)	1.33 [1.27 - 1.39]	24.98 [7.67 - 53.96]	n.a.
amplitude (% change from baseline)	27.07 [25.51 - 28.64]	88.94 [44.78 - 198.41]	n.a.
frequency (Hz)	59.54 [58.67 - 60.42]	78.79 [74.90 - 82.71]	76.03 [68.15 - 84.55]
mean peak width (half-prominence in Hz)	7.89 [7.09 - 8.70]	4.09 [3.68 - 4.96]	5.41 [3.90 - 7.24]

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Table 4

DBS-induced FTG in humans.

Studies presented in chronological order. In both studies, DBS induces FTG off dopaminergic medication and without dyskinesias. M1: primary motor cortex; SMA: supplementary motor area; PMC: premotor cortex; STN: subthalamic nucleus; PD: Parkinson's disease, OFF: off dopaminergic medication; FFT: fast fourier spectrum

Study	Location	Disorder	Medication	Methods	Main Findings
Wiest et al., 2021	STN	PD	OFF	short-time FFT (1 s Hamming window,25% overlap, 1 Hz resolution)	DBS induces FTG during and/or after stimulation without detectable dyskinesias, FTG is not entrained at half stimulation frequency
Muthuraman et al.,2020	M1, SMA, PMC, STN, cerebellum	PD	OFF	multitaper method(seven orthogonal tapers were used)	cross-frequency coupling of FTG power to the power of clinically effective DBS frequency

Table 5

Broad movement-related gamma ERS.

These studies represent a non-systematic selection of relevant studies that are presented in chronological order. GPi: internal segment of the globus pallidum; STN: subthalamic nucleus; M1: primary motor cortex; SMA: supplementary motor area; ECoG:electrocorticography; EEG: electroencephalography; ET: essential tremor; PD: Parkinson's disease; OFF: off dopaminergic medication; ON: on dopaminergic medication; FFTL fast fourier transform; ERS: event-related synchronisation.

Study	Location	Disorder	Medication	Methods	Main Findings
Lofredi et al., 2018	STN	PD	ON + OFF	complex Morlet wavelet convolution (7 cycles, from 1-100 Hz, 1 Hz resolution)	broad STN gamma positively correlates with maximal velocity and negatively with symptom severity, gamma bursts correlate with average power and increase with larger movements,
Fischer et al., 2017	STN	PD	ON	Filter Hilbert method (from 50-120 Hz, bandpass filtering the data in 10 Hz wide bands shifted by 2 Hz)	broad STN gamma increases when finger taps are successfully stopped
Brücke et al., 2013	ventral intermediate nucleus (thalamus)	ET	OFF	short-time FFT (~0.41 s Hann windows, ~25% overlap, 2.4 Hz resolution)	movement-related gamnma activity is lateralised to the contralateral thalamus, baseline gamma activity correlates with reaction times suggesting pre-cue gamma may relate to arousal
Tan et al., 2013a	STN	PD	ON	complex Morlet wavelet convolution	broad power increase in the gamma band (55-90 Hz), gamma power was further enhanced during grips with greater effort
Tan et al., 2013b	STN	PD	ON + OFF	complex Morlet wavelet convolution	broad gamma (55-375 Hz) was reduced concomitant with decreasing grip force
Brücke et al., 2012	GPi	dystonia	OFF	short-time FFT(0.512 s Hann windows, ~80% overlap, ~1.95 Hz resolution)	pallidal LFPs were recorded during a choice-reaction-time task, broad contralateral gamma band (35-105 Hz) ERS occurred at movement onset, the larger and faster the movement, the stronger the gamma ERS
Anzak et al., 2012	STN	PD	ON + OFF	method unclear	broad gamma activity (55-375 Hz) and grip force are correlated, broad gamma increases with activities encoding maximal effort grips but gamma increases only have a trivial contribution to reaction time shortening
Litvak et al., 2012	STN, M1	PD	ON + OFF	multitaper method(0.4 s windows, ~87.5% overlap, 5 Hz resolution, 3 tapers used for gamma)	broad gamma peaks (60-90 Hz) in M1, STN and coherence between the two, gamma power increased with movement and levodopa, STN gamma drives cortical gamma
Ray et al., 2012	STN	PD	ON	Hermite functions analysis (3 s windows aligned to movement onset, time-frequency area A/2 = 5, from 6-100 Hz, resolution: 10 ms x 0.33 Hz)	gamma oscillations (60-100 Hz) respond robustly to stop-signals as well as go-signals
Joundi et al., 2012	STN	PD	ON	Hermite functions analysis (time-frequency area A/2 = 5, resolution: 167 ms x 2.7 Hz)	gamma ERS is more pronounced during fast arm reaching movements
Anzak et al., 2011	STN	PD	ON	short-time FFT (1 s windows,1 Hz resolution)	broad gamma increase (30-95 Hz) during verbal fluency tasks after controlling for motor output

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Study	Location	Disorder	Medication	Methods	Main Findings
Huo et al., 2011	M1	healthy children	OFF	complex Morlet wavelet convolution	broadband gamma increase (65-150 Hz) contralateral and ipsilateral to finger movements
Brücke et al., 2008	GPi	dystonia	OFF	short-time FFT (0.41 s Hann windows, ~25% overlap,2.4 Hz resolution)	prominent, perimovement increase in 60-80 Hz activity contralateral to movement
Cheyne et al., 2008	M1	healthy adults	OFF	complex Morlet wavelet transform (7 cycles, from 2-110 Hz, 21 Hz resolution)	broad gamma oscillations (65-80 Hz) were localised to the contralateral M1 during self-paced movements, high gamma activity increased only during movement, gamma activity is task-dependent
Ball et al., 2008	M1, SMA (ECoG, EEG)	epilepsy, healthy adults	OFF	multitaper method (0.32 s window, ~87.5% overlap, 2 tapers)	broad gamma increase (60-90 Hz) over the sensorimotor cortex contralateral to the side of arm movement, gamma activity started at movement onset and became more pronounced at movement end
Androulidakis et al., 2007	STN	PD, ET	ON + OFF	short-time FFT (~1 s Hann windows, ~99% overlap, ~1 Hz resolution)	bilateral, symmetrical broad gamma band increase occurred around movement onset and was more pronounced on levodopa