Review

Gamma oscillations in the human basal ganglia

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ABSTRACT

Interest in beta activity in the basal ganglia has mushroomed since it was first identified in the subthalamic nucleus of patients with Parkinson’s disease in Jonathan Dostrovsky’s landmark paper (Levy et al., 2000). Here we consider a less explored phenomenon; namely gamma frequency synchronisation of neurons in the basal ganglia. Gamma oscillations have been reported in a distributed network involving the basal ganglia, thalamus and motor cortex, and have been described in a wide range of diseases as well as during increased arousal and voluntary movement. In Parkinson’s disease, gamma activity is promoted by dopaminergic therapy. These features suggest that its elevation may be involved in the production of movement and this hypothesis is supported by the correlation between the amplitude of gamma activity and limb kinematics. Here we review these data, discuss the functional anatomy of gamma activity in basal ganglia and question how closely it relates to the coding of movement parameters.

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Introduction

Functional neurosurgery affords the opportunity to record neuronal activity within the basal ganglia and thalamus of patients. Such data allow for the activity of single neurons to be directly determined, or inferences can be derived about how populations of neurons synchronise their activity either through the simultaneous recordings of multiple neurons or through assessment of the subcortical local field potential activity (LFP). The latter is thought to index common modulation of slow sub-threshold currents, primarily post-synaptic potentials, in a large local neuronal population and is considered to reflect mainly the ‘input’ to the local network (Logothetis, 2002; Mitzdorf, 1987). Although the precise processes summing to give the subcortical LFP remain unclear, the locking of single neurons to this activity over a wide range of frequencies provides strong support for its use as a surrogate measure of the pattern of underlying neuronal synchronisation in the basal ganglia (Kühn et al., 2005; Levy et al., 2002; Murthy and Fetz, 1996; Trottenberg et al., 2006; Weinberger et al., 2006).

Hitherto, the majority of interest in oscillatory activity in the basal ganglia has been focussed toward the beta (13–35 Hz) band, because activity in this range is exaggerated in untreated patients with Parkinson’s disease (PD). It is thought that this excessive synchronisation is pathological and may mediate some of the symptoms of the condition (Jenkinson and Brown, 2011). Here we will shift attention toward gamma activity in the BG and thalamus, which is a much less explored phenomenon. We define the gamma band as between...
35 and 100 Hz. Within this band, several independent processes may well exist, so we will focus on the finely-tuned gamma (FTG) between 60 and 90 Hz seen in basal ganglia and thalamic recordings. Such activity can be observed as an inconsistent feature in spectra of LFP activity at rest (Brown et al., 2001), or as a more consistent event related synchronisation (ERS) over the same frequencies, usually related to voluntary movement. However, when considering the FTG ERS we have to be careful not to conflate FTG reactivity with ERS in the broader gamma band, as, at least in the rodent, activities centred at around 50 and 80 Hz have different function (Berke, 2009; Nicolás et al., 2011; van der Meer et al., 2010).

FTG peaks and FTG reactivity

FTG has been found in recordings from the human thalamus, the internal segment of the globus pallidus (GPI) and subthalamic nucleus (STN) (Alegre et al., 2005; Alonso-Frech et al., 2006; Androulidakis et al., 2007a; Brown et al., 2001; Cassidy et al., 2002; Devos et al., 2006; Fogelson et al., 2006; Kempf et al., 2009; López-Azcárate et al., 2010; Pogosyan et al., 2006; Trottéron et al., 2006; Williams et al., 2002). FTG is sharply tuned to a narrow frequency range, and though it can range from 60 to 90 Hz across individuals, it is commonly centred around ~70 Hz (for examples see Kempf et al., 2009). The phenomenon is not related to any specific disease having been reported in patients with PD, essential tremor, dystonia and myoclonic epilepsy (Kempf et al., 2009). In patients with PD, FTG is increased following treatment with the dopamine prodrug levodopa, which also helps to restore motor function (Alegre et al., 2005; Alonso-Frech et al., 2006; Androulidakis et al., 2007b; Brown et al., 2001; Cassidy et al., 2002; Devos et al., 2006; Fogelson et al., 2005). FTG at the level of the basal ganglia and the motor cortex is observed to reactively increase in power during voluntary movement, although such evoked synchronisation may involve a wider range of gamma frequencies than the FTG itself (Androulidakis et al., 2007b). Modulation of FTG is also associated with the sleep/wake cycle, being suppressed during drowsiness and slow-wave sleep, but re-emerging during rapid-eye-movement (REM) sleep (Kempf et al., 2009). Taken together these observations suggest a circuit activity in the gamma range that is not pathological but primarily physiological in nature, an idea which is further supported by its presence in the basal ganglia of healthy rodents (Berke, 2009; Masimore et al., 2005; van der Meer et al., 2010). However, the most persuasive evidence that FTG may be a physiological phenomenon is the recording of reactivity with similar frequency in the motor cortices of healthy subjects (Ball et al., 2008; Cheyne et al., 2008; Huo et al., 2011; Muthukumaraswamy, 2010), and intracranial electrocorticography recordings in epilepsy patients (Crone et al., 1998; Flurtsheller et al., 2003). This observation is especially pertinent given that, at least in patients with PD, subcortical FTG is coherent with cortical activity, emphasising the close relationship between the activities at the two levels (Brown et al., 2001; Cassidy et al., 2002; Lalo et al., 2008; Litvak et al., in press; Williams et al., 2002). But if FTG is primarily physiological, then why are peaks in LFP spectra an inconsistent finding across recordings from patients at rest? One explanation may lie in the focality of the FTG. In an intra-operative microelectrode study, peaks in the gamma band in LFP spectra were identified in just over half the STN explored with patients at rest and off antiparkinsonian medication (Trottenberg et al., 2006). Where a peak was identified, it was limited to the dorsal STN and adjacent zona incerta. Even within this narrow region the peak could, in some patients, vary in frequency between microelectrode recording depths, further biasing against spatial summation. In contrast, a recent post-operative study reported that only 23% of PD patients showed FTG peaks within the STN when these were recorded from the contacts of DBS electrodes in patients on medication (López-Azcárate et al., 2010). Thus, it could be that the spatial focality of gamma synchronisation is so limited that it is often too small to be picked up using DBS macroelectrodes. Alternatively, the processes supporting gamma synchrony may be particularly susceptible to the temporary microlesional effects often seen in the immediate post-operative period (Chen et al., 2006b). It remains to be established whether the incidence of FTG increases in chronic LFP recordings.

The role of FTG in health

The expression of FTG requires a critical level of arousal. Hence, discrete peaks in FTG disappear when patients become drowsy and are absent in non-REM sleep stages I–IV (Brown et al., 2001; Kempf et al., 2009). Conversely, FTG peaks increase in amplitude following startling stimuli and FTG also emerges during REM sleep, which is itself associated with increased cortical arousal (Kempf et al., 2009). Interestingly, cells in the pedunculopontine nucleus (PPN) fire rapidly during wakefulness and REM sleep but not during non-REM sleep (Saper et al., 2001). Activity in the PPN, as part of the ascending reticular activating system (ARAS) produces cortical arousal, and is closely associated with the basal ganglia (Mena-Segovia et al., 2004). Sometimes, in the awake state, FTG comes in and out over time (Fig. 1) illustrates this phenomenon and demonstrates that although FTG always appears before self-paced voluntary movements, the interval between its appearance and movement can be very variable. It is as if FTG under these circumstances relates to minor changes in arousal as the subject passes in to (and out of) a state in which self-paced voluntary movements can be made.

However, this need not necessarily mean that FTG is a simple indicator of the global state of arousal. Indeed, the observation that FTG reactivity is often lateralised suggests that this may not be the case (Androulidakis et al., 2007b; Brücke et al., 2008). Lateralised, phasic increases in FTG just prior to and during movement would seem to imply a more motoric function. Consistent with this, studies of the ERS around movement show that gamma amplitude correlates with the speed and scale of voluntary movement in the contralateral limbs (Fig. 2; Brücke et al., 2012; Joubi et al., 2012a). Also, transcortical alternating current stimulation in the gamma range (70 Hz) has been shown to increase grip-force rate during a go/no-go task (Joubi et al., 2012b). Again, this needn’t necessarily mean that FTG codes for some specific kinetic parameter such as limb velocity. Instead, we suggest that FTG levels at any given instant might determine the vigour or effort applied in a response made at that time. As arousal is a necessary pre-requisite of response vigour, this may explain the importance of the former in the expression of FTG. Moreover, this speculative formulation has the advantage that it is compatible with recent demonstrations that FTG can be elicited in tasks in a way that cannot be simply explained within the framework of FTG coding for specific kinematic parameters. These are that increases in FTG are seen in response to the imperative stop-signals in a stop-signal reaction time task (Ray et al., 2012) and during switching in verbal fluency tasks (Anzak et al., 2011); neither can be correlated to motor parameters, but the execution of both is dependent on the effort applied.

Our notion is not entirely incompatible with existing theories of the function of gamma oscillations, such as those that have posited a role in selective attention in the visual and somatosensory systems (Bauer et al., 2006; Fries et al., 2001; for review see Womelsdorf and Fries, 2007). More generally, gamma oscillations have been suggested to be involved in “binding by synchronisation”; by which communication between spatially distinct by functionally associated areas are bound together by synchronisation of their action potentials (Fries, 2009; Singer, 1999).

The role of FTG in disease

The putative association of FTG with response vigour or effort is particularly interesting given the reduction in FTG seen when patients with PD are withdrawn from their dopaminergic therapy. Mazzoni et al.
(2007) have already proposed that the hypo-dopaminergic state attenuates motor vigour in PD, and here we suggest that the lack of FTG might help mediate this relationship. Accordingly there is a correlation between increases in gamma activity and improvements in motor impairment upon treatment with levodopa (Kühn et al., 2006; Litvak et al., in press).

Conversely, a phenomenon that may contribute to the vigour of actions might be expected to lead to hyperkinesia when exaggerated, and there is also circumstantial evidence linking FTG to dyskinesias and dystonia. A negative correlation between FTG and beta activity tends to be exaggerated when dyskinesias become manifest in patients with PD (Alonso-Frech et al., 2006; Fogelson et al., 2005; Silberstein et al., 2005). Similarly, the level of FTG correlates with the severity of involuntary EMG activity in cranial dystonia (Chen et al., 2006a). This association with hyperkinesias should be distinguished from the increased oscillatory activity in the low gamma frequency range (35–55 Hz) reported during periods of increased Parkinsonian tremor (Weinberger et al., 2009). However, whether FTG has a definite pathological role in disease remains unclear.

**Functional anatomy of FTG**

Simultaneous recordings of FTG from dual sites within the basal ganglia-thalamo-cortical circuit (be they STN and GPi, GPi and thalamus, or any of these subcortical sites and EEG or MEG) reveal that FTG is coherent between these sites (Brown et al., 2001; Cassidy et al., 2002; Kempf et al., 2009; Lalo et al., 2008; Williams et al., 2002). Elevated FTG in the STN is associated with an overall increase in the firing rates of neurons in this nucleus (Pogosyan et al., 2006). Assuming, therefore that gamma activity in the LFP is due to synchronised excitatory inputs, there are three likely possible sources. The first is the cerebral cortex, but the cortex is an unlikely source as FTG in the STN and GPi seems to drive (phase-lead) rather than be driven (phase-lag) by cortical activity (Lalo et al., 2008; Williams et al., 2002). A second possibility is that gamma is driven in the STN and GPi via input from the non-specific nuclei of the thalamus. It is known that stimulation of the centromedian and parafascicular nuclei (CM/PF) nuclei of the thalamus produces arousal (Steriade and Demetrescu, 1960) and these nuclei project directly to both the STN and the GPi (Sadikot et al., 1992). The CM/PF in turn receives innervation from the ARAS (see above), including the PPN (Jenkinson et al., 2009; Pahapill and Lozano, 2000). The final possibility is that gamma in the STN and GPi is driven directly by input from the ARAS, as the STN, and to a lesser extent the GPi, is innervated monosynaptically by the PPN (Jenkinson et al., 2009; Pahapill and Lozano, 2000). The larger input of the ARAS to the STN may be a reason why coherent FTG activity between STN and GPi tends to be led by STN (Brown et al., 2001). Given that FTG within the STN and GPi phase leads FTG in the cortex (Lalo et al., 2008; Litvak et al., in press; Williams et al., 2002), it seems reasonable to posit that the FTG is propagated via the ventrolateral thalamus to

Fig. 1. FTG in an awake patient with Parkinson’s disease. The subject is making self-paced voluntary movements of a manual joystick contralateral to the recorded subthalamic nucleus. The lower trace is the time-frequency plot of LFP spectral power. FTG has been arrowed in red. Note the 50 Hz line noise. FTG comes in and out over time, but always appears before self-paced voluntary movements. Nevertheless, the interval between FTG appearance and movement is very variable, as if FTG relates to minor changes in arousal as the subject passes in to (and out of) a state in which self-paced voluntary movements can be made.

Fig. 2. Gamma reactivity is related to scale of movement. LFP recordings from contralateral GPi of dystonic patients during small, medium and large forearm movements. Note that changes in amplitude were also associated with corresponding changes in the velocity of movement in this paradigm. Power in the Gamma band increases with increased movement amplitude (and velocity). Adapted, with permission, from Brücke et al. (2012).
cortex. The net result is a circuit connecting brainstem arousal centres to the cortex via the basal ganglia, either by direct input to the basal ganglia itself or via the CM/PF. However, as argued above, the function of these circuits may not be to subserve arousal per se, but to determine the level of response vigour.

What are the priorities in understanding FTG?

As is obvious, relatively little is known about FTG and here we have taken the opportunity to speculate about its neural underpinnings and possible function. We have made several core predictions. First, it is that FTG depends on arousal. Although this has been shown at a gross level, experimental evidence that can demonstrate a relationship between levels of FTG and more graded spontaneous fluctuations in arousal in awake subjects would be invaluable. Second, we have suggested that the function of FTG lies in the determination of response vigour, rather than arousal or the precise specification of kinematic parameters. Thus experiments are desirable in which FTG is recorded while the effort expended in a task is modulated, and kinematic parameters like force, are disengaged. Third, we have proposed a scheme for the functional connectivity underpinning FTG which could be tested through further intra- and post-operative recordings from multiple sites in the network from patients undergoing neurosurgery. Finally, more research is necessary to confirm or refute a role for FTG in the aetiology of movement disorders.

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