The Role of Synchronised Low Frequency Activity in Globus Pallidus Interna in Dystonia

Chiung-Chu Chen[1,2] and Peter Brown[1]

Abstract- Here we explore how abnormal spatio-temporal patterning of neuronal activity in the pallidum may contribute to dystonia. A critical feature of this abnormal patterning seems to be excessive synchronisation of neuronal activity over a 4-10 Hz frequency band. This is most readily apparent as fluctuation in the local field potential in this frequency band. Such activity correlates with the level of dystonic muscle activity and is concentrated in the internal segment of the globus pallidus, which is also the optimum surgical target in dystonia. It remains to be seen whether the abnormal low frequency activity is associated with dystonia through an abnormal processing of afferent information in the pallidum or to a more direct influence on the motor drive to dystonic muscles, which involves, at least in part, similar frequencies.

Key Words: Dystonia, Pallidum, Synchronisation, Local field potential, Deep brain stimulation

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INTRODUCTION

Dystonia is characterised by sustained or intermittent involuntary muscle contractions causing twisting or repetitive movements or abnormal postures. It is generally classified as a hyperkinesia and has been attributed to reduced pallidal inhibition of a tonic thalamocortical excitatory input in the classical model of basal ganglia function[(1)]. However, this explanation has been challenged by the observation that pallidotomy, and perhaps even high frequency pallidal stimulation, reduce dystonia while abolishing pallidal outflow[(2)]. Accordingly, recent attention has focussed on whether it could be the patterning of pallidal activity, rather than the mean level of tonic activity, that underlies dystonia. Abnormal patterning could involve disturbed somatosensory relationships within the pallidum, altered patterning of pallidal activity over time, or a combination of the two.

DISORGANISATION OF SENSORY REPRESENTATION IN PALLIDUM

The pallidum is partly somatotopically organised so that abnormal spatial patterning may lead to abnormal representation of the body. Several observations suggest sensory inputs play an important role in dystonia[(3-6)].

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Enlargement of the receptive fields of neurons in the basal ganglia-cortical loop may be a key pathophysiological feature in this disorder. For example, reorganisation occurs in the somatic sensory thalamus, a pallidal-received structure, in patients with dystonia[7,8]. Consistent with this finding, the receptive field properties of neurons in both the thalamus and pallidum are altered in patients with dystonia[9]. In particular, the number of cells with receptive fields in the pallidum is significantly higher in dystonia than in other movement disorders[9]. Furthermore, cells with sensory inputs in patients with dystonia have receptive fields that include the dystonic limb, in line with an enlarged sensory representation of the affected limb.

However, the exact relationship between changes in receptive fields and neuronal activity in the pallidum and the development of dystonia remains unclear. Vitek has proposed that focal changes in the receptive region of one pallidum representing the arm or hand would lead to focal dystonia involving the arm or hand, and changes throughout the pallidum bilaterally may be expected to result in general dystonia[1].

DISORGANISATION OF TEMPORAL PATTERNING OF PALLIDAL ACTIVITY

Microelectrode recordings from the globus pallidus in dystonic patients reveal marked abnormalities in the temporal patterning of neuronal discharge; neurons firing in irregularly grouped discharges with intermittent pauses[1,10,11]. Likewise, analysis of interspike intervals in the endopeduncular nucleus (homologue of globus pallidus interna) of dystonic dt^{sz} (mutant dystonic hamsters) hamsters shows an increased proportion of neurons with a burst-like firing pattern compared to normal animals[12]. Evidence also exists from animal models of dystonia of burst discharge in other nodes of the cortico-basal ganglionic loop involved in motor control. Increased bursting has been noted in the monkey motor thalamus after induction of dystonia by intrathalamic injection of the GABA antagonist bicuculline[13] and dystonic movements corresponding to putaminal burst discharge have been seen after intraputaminal injection of bicuculline in the cat[14].

SPATIO-TEMPORAL DISORGANISATION OF PALLIDAL ACTIVITY

Of course spatial and temporal disorganization of pallidal activity may not be mutually exclusive aspects of dystonia. One way that the two may be combined that has received considerable interest in Parkinson's disease[15] is through abnormal synchronisation across neurons displaying burst-like firing patterns. Neurons might then lose some of their spatial and temporal independence in information coding, and, in so far as the pallidum is topographically organized, this would lead to loss of the type of specificity stressed by Lenz[9]. No microelectrode study has so far attempted to explore the degree of synchronization between pairs of neurons in dystonia. However, an alternative means of studying changes in the pattern of local neuronal synchrony is through a frequency based analysis of local field potentials (LFPs). Like the scalp EEG, the recording of activity in the LFP relies on the fact that unsynchronized neuronal depolarization and hyperpolarisation is cancelled out and lost. Action potentials themselves are unlikely to contribute much to the LFP as they are very brief, and synchronisation is rarely so precise that such short-lived events might summate. However, as the timing of neuronal discharge is dictated by membrane state, fluctuations in the LFP should also be locked to the timing of discharges. Thus fluctuations in LFPs have been shown to bear close relationship to both the timing of membrane depolarisation and neuronal discharge in the basal ganglia[16-18]. Accordingly, changes in LFP activity can be considered as a surrogate marker of alterations in the degree and nature of synchronisation between local neurons[19], and this was recently confirmed with respect to the predominant LFP activity recorded in dystonia[20]. Thus simultaneously recorded LFPs and neuronal activity from microelectrodes inserted into the pallidum in awake patients with primary dystonia have demonstrated oscillatory and semi-oscillatory spike-triggered averages, confirming that low frequency fluctuations in the LFP are synchronous with local neuronal discharge (Fig. 1). The recording of LFPs has several advantages. First, LFPs can be recorded both intra-operatively from microelectrodes, but also post-operatively, directly from the

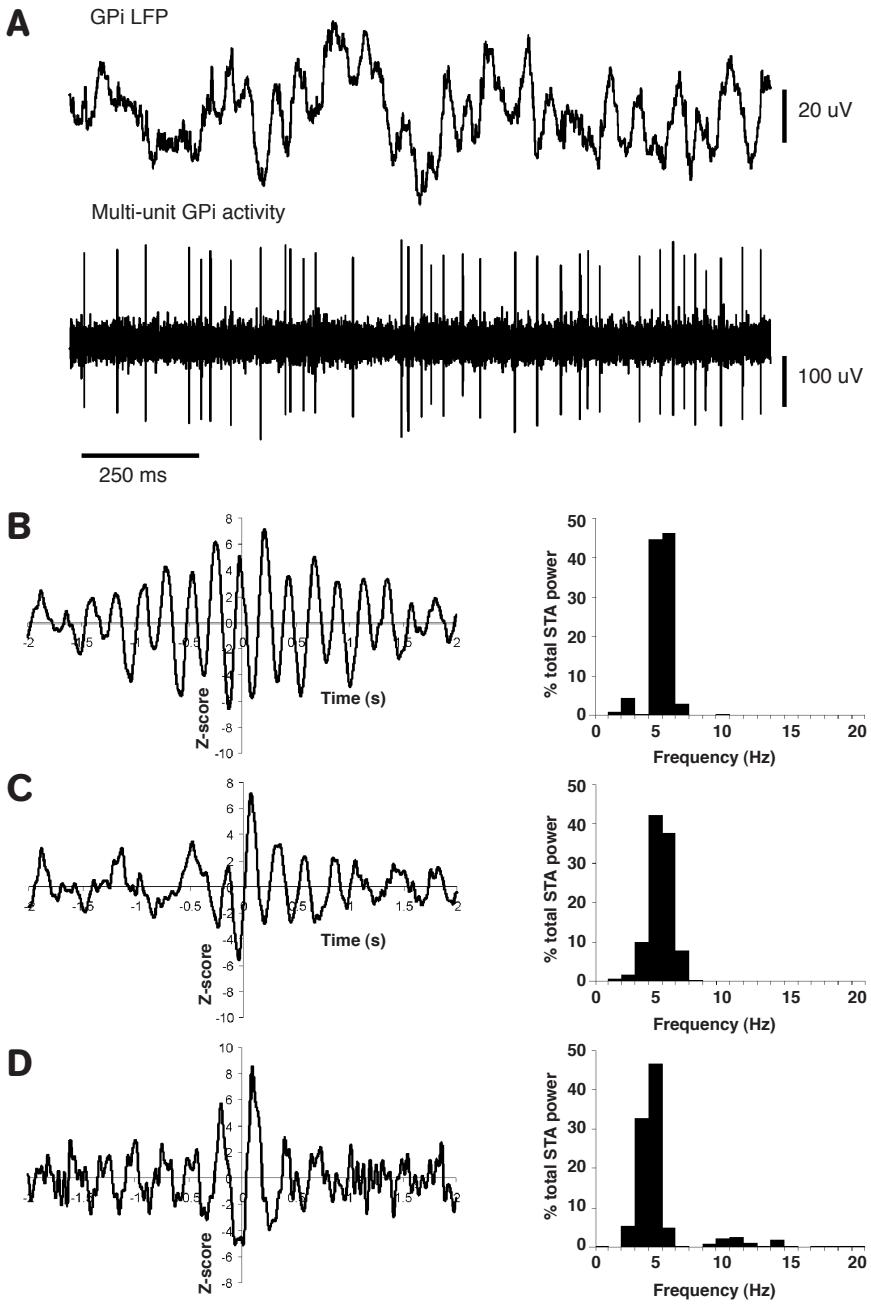

Figure 1. Pallidal LFP oscillations are locked to unit activity. (A) Example of raw LFP and multiunit activity. (B-D) STAs and corresponding STA (Spike Triggered Average) spectra from three patients with primary dystonia. STAs were derived from multiunit data and were normalized by the standard deviation of the STA of the same LFP but after time-shifting the latter, so that y-axes are plotted as z scores. Spectra are plotted as % of the total power in the 2-20 Hz band. STAs have more than one significant peak centered around time zero, indicating that LFP activity and neuronal discharge were locked. Spectra confirm that this locking occurred over a band including 4-10 Hz.

deep brain stimualtion (DBS) electrode, during the interval between implantation and subsequent connection of the DBS electrode to an implantable pulse generator stimulating device. Post-operative recordings are less affected by time constraints and avoid the confounding effects of ongoing or recent anaesthesia. Second, as the LFP samples from a large population of neurons it is a more sensitive index of synchronisation than the analysis of correlated firing in pairs of neurons.

The first report of activity in the pallidal LFP was in a patient with myoclonic dystonia, and involved the 4-8 Hz frequency band[21]. Soon after this, prominent activity was reported over an overlapping frequency band of 4-10 Hz in a large series of patients with primary dysto-

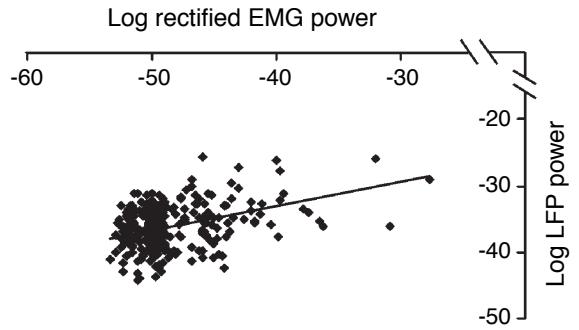

Figure 2. Relationship between log pallidal LFP activity over 4-10 Hz and log rectified sEMG activity. p<0.0001 and r=0.383. (Adapted, with permission[25]).

nia[22]. The level of this activity was shown to exceed that in patients with Parkinson's disease. Silberstein and colleagues proposed that pallidal LFP activity in the 4-10 Hz band might relate to synchronised, relatively non-oscillatory bursting across neurons. Such bursting may be particularly prominent during dyskinesias in primates and PD patients[23,24] and during hemiballismus[11], which bear some phenomenological resemblance to dystonia. The potential relevance of pallidal LFP activity in this frequency band was increased by subsequent studies indicating that it correlates[25] and is coherent[26] with levels of dystonic EMG. Fig. 2 illustrates the correlation between pallidal LFP activity over 4-10 Hz and dystonic EMG.

IS LOW FREQUENCY ACTIVITY IN THE PALLIDAL LFP REALLY IMPORTANT IN DYSTONIA?

However, not all patients with primary dystonia have prominent LFP power in the 4-10 Hz band[20,25]. One important consideration when dealing with LFP oscillations is can they be epiphenomenal and directly (through movement related artefact) or indirectly (through movement related re-afferance) linked to involuntary movements. The most important evidence against this possibility to date is the selective spatial distribution of the LFP oscillations. Positive correlations between LFP activity over the 4-10 Hz range and dystonic EMG are strongest at the pair of contacts of deep brain stimulating electrodes sited in the target globus pallidus interna (GPi)[25]. Similar LFP activity recorded with microelectrodes is concentrated in GPi and spike triggered averages with components in this band are almost exclusively limited to GPi[20]. As this is the site where lesioning or high-frequency stimulation is most effective[27-31], these topographical findings support a functional link between population synchrony in this band and dystonia.

Whether this functional link relates to an abnormal processing of afferent information at the pallidal level or to a more direct influence on the motor drive to dystonic muscles, is unclear. Note that increases in LFP activity at similar frequencies occur during and, importantly, between paroxysms of dystonia in the dystonic *dt^{sz}* mutant hamster, suggesting that the spectral changes at low frequency are not merely a consequence of the attacks of dystonia and do not simply accompany afferent activity[12]. It may be relevant, therefore, that patients with primary dystonia have evidence of an abnormal descending drive to muscles at similar frequencies[32-34].

CAN ONE ABNORMALITY ACCOUNT FOR ALL DYSTONIA?

The studies quoted above all relate to primary dystonia, and even within this group there are patients who do not have clear 4-10 Hz activity in their pallidal LFP. This may reflect sampling error or peri-operative oedema and microlesional effects. However, Aziz and colleagues have raised another interesting possibility and this is that fluctuations in the the pallidal LFP at low frequency only relate to the mobile elements of dystonia, and may not contribute to tonic involuntary muscle activity[26]. In addition, oscillatory synchronisation at higher frequency may also be a factor in dystonia[25].

CONCLUSION

Although correlations between pallidal low frequency activity and dystonic EMG supports the notion that pallidal dysfunction is central to the pathogenesis of dystonia, correlation cannot prove causality, so more studies are necessary in this field, particularly to investigate the temporal relationship between dystonic EMG and LFP

fluctuations. Nevertheless, the fact that low frequency LFP activity is maximal in the GPi, where lesioning or high frequency stimulation is most effective, would support a mechanistic link between synchronized activity at low frequency and dystonic EMG activity.

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