Paradoxes of Functional Neurosurgery : Clues From Basal Ganglia Recordings

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ABSTRACT

Deep brain stimulation (DBS) can be remarkably effective in treating movement disorders such as Parkinson's disease, dystonia and essential tremor. Yet these effects remain essentially unexplained, -even paradoxical. Equally challenging is the fact that DBS of motor targets in the basal ganglia appears to reverse abnormalities of movement without any obvious deleterious effects on remaining aspects of movement. Here we explore the extent to which the noisy signal hypothesis might help solve some of these apparent paradoxes. Essentially the hypothesis, first tentatively advanced by Marsden and Obeso (1994), suggests that disease leads to a pattern of basal ganglia activity that disrupts local & distant function and that surgery acts to suppress or over-ride this noisy signal. Critical to the success of this theory is that differ1ent disease phenotypes are associated with different patterns of noisy signal and we survey the evidence to support this contention, with specific emphasis on different types of pathological synchronisation. However, just as DBS may suppress or over-ride noisy signals in the basal ganglia, it must equally antagonise any remaining physiological functioning in these key motor structures. We argue that the latter effect of DBS becomes manifest when baseline motor performance is relatively preserved, i.e. when pathological activity is limited. Under these circumstances, the deleterious effects of DBS are no longer obscured by its therapeutic actions in suppressing noisy signals. Whether true, over-simplified or simply incorrect, the noisy signal hypothesis has served to focus attention on the detailed character of basal ganglia discharge and its variation with disease and therapy.

Key Words: *Synchronisation, basal ganglia, Parkinson's disease, deep-brain stimulation*

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INTRODUCTION

Explanations of the pathophysiology of conditions like Parkinson's disease (PD) and dystonia have been dominated by the Albin and Delong model[1, 2] and its subsequent modifications.[3] Central to this model and its progeny has been the division of the basal ganglia into two distinct pathways, differentially affected by dopaminergic input, and with reciprocal actions on movement. In parkinsonism, the crux of the model is that there is unrestrained tonic inhibition of the thalamus by the globus pallidus interna (GPi), turning off the motor thalamus's facilitation of cortical motor areas and impeding voluntary movement. But why then does lesioning or deep brain stimulation (DBS) of the motor thalamus not cause prominent akinesia? In hyperkinesias, like dystonia and levodopa-induced dyskinesias, the essence of the model is that there is decreased tonic inhibition of the thalamus by GPi, leading to unrestrained facilitation of cortical motor areas and excessive movement. But why then do pallidotomy and pallidal DBS relieve dyskinesias and dystonia, when they should make it worse? Indeed, the same procedures in this area may relieve PD. And finally, why do lesions or DBS of the subthalamic nucleus (STN) or GPi not lead to new deficits, attributable to loss of the physiological function of these nuclei?

Some of these paradoxes were highlighted in Marsden and Obeso's classic Brain paper in 1994,[4] where they also considered among several possible solutions whether it is the pattern of basal ganglia activity in PD that may be disruptive, rather than the net level of inhibition of thalamic cortical facilitation. The same year saw Bergman and Delong's landmark paper in the Journal of Neurophysiology establishing the abnormal patterning of activity in STN and pallidum in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated primate model of parkinsonism.[5]

Here we would like to review the evidence supporting current explanations for these neurosurgical paradoxes. At the heart of these lies the noisy signal hypothesis, -that disease leads to a pattern of basal ganglia activity that disrupts local & distant function and that surgery acts to suppress this noisy signal.[4, 6] The fact that the same surgery may improve different phenotypes argues that there may be several phenotype specific noisy patterns. Thus pallidal DBS can ameliorate dystonia, levodopa-induced and tardive dyskinesias and parkinsonism.[7-9]

So how good is the evidence of a noisy signal in PD and is there any evidence of a different abnormal patterning in dystonia and dyskinesias? The obvious way to explore this hypothesis is to record directly from patients with motor disorders undergoing functional neurosurgery. We can do this in two ways; we can either record single or pairs of neurons, and with minimal extra effort, local field potentials (LFPs) with microelectrodes intra-operatively, or record LFPs from the DBS electrodes themselves post-operatively, prior to their connection to the subcutaneous stimulator. The significance of LFP oscillations is that they are the product of synchronised activity across large populations of local neuronal elements and hence provide a practical and sensitive index of pathological synchronisation.[10]

WHY DOES PARKINSONISM IMPROVE WITH DBS?

In parkinsonian patients withdrawn from their antiparkinsonian medication both neuronal and LFP recordings confirm an exaggerated synchronisation of neuronal activity in the STN and pallidum from about 10-30 Hz. The precise range of frequencies involved varies between studies but for convenience it is often termed the beta band, by analogy with the activity across similar, but not identical frequencies, noted in clinical studies of scalp electroencephalographic activity. There have been several recent reviews of the role that excessive synchrony may play in PD[10-13] and here we will concentrate on the evidence that treatments for parkinsonism, may entail suppression of this pathological activity.

Like pathological synchronisation in animal models of PD, the oscillatory LFP activity in the beta band in the basal ganglia-cortical loop of PD patients is suppressed by treatment with dopaminergic drugs, with those frequencies below 20 Hz being most exquisitely sensitive (Fig 1).[14] More importantly, the degree of drug-induced improvement in bradykinesia and rigidity correlates with the degree of suppression of synchronisation in the beta band in both the STN and cortex[15, 16] and with the incidence of neurons oscillating over this frequency range within the STN.[17] Likewise, the degree of STN DBS induced improvement in bradykinesia and rigidity (but not tremor) correlates with the degree of suppression of synchronisation in the beta band at the cortex[16] and STN DBS suppresses beta LFP activity in the pallidum in patients that have had both nuclei implanted.[18] However, in patients it has been more difficult to show whether STN DBS also suppresses beta activity in the region of the STN itself. This is because of stimulation-induced electrical artefacts. One way round this has been to record
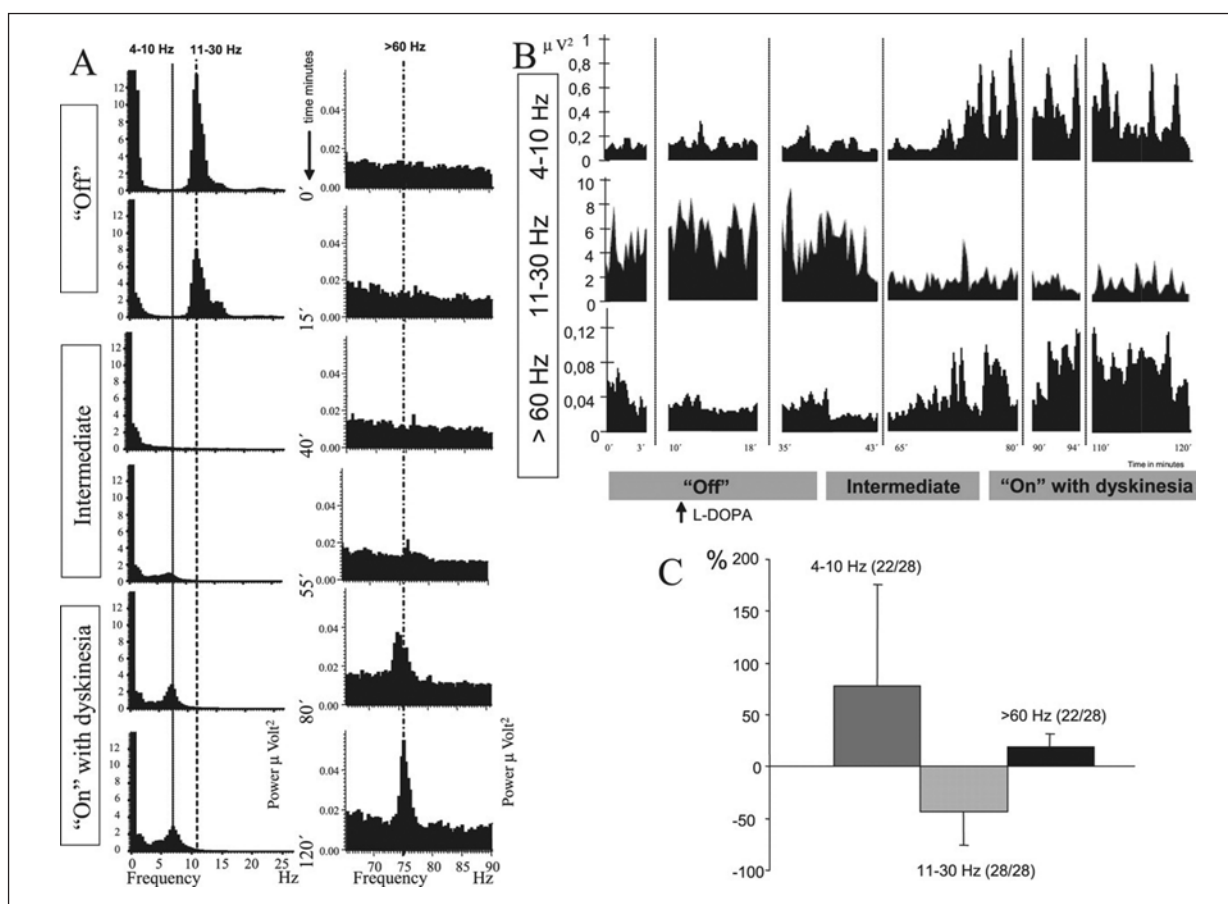
Fig.1. Evolution of the different patterns of synchronised activity evident in the LFP recorded from STN in one PD patient. Autospectra of LFP activity show a peak in the 10–30 Hz frequency band whilst the patient is 'Off'. This changes to peaks in the 4–10 Hz and 60–80 Hz frequency bands in the dyskinetic 'On' state following treatment with levodopa at 0 minutes (A, B). The relative magnitude of the change in logarithmic power in the three bands from the 'Off' to the 'On' motor states and the number of recorded subthalamic nuclei (in brackets) where this occurred is shown in C. Figure is taken from reference 36, with permission.

the immediate after effects of STN DBS in those patients with a delayed return of bradykinesia and parkinsonism upon cessation of DBS, but even here the results have been mixed. One study reports a suppression of beta activity while therapeutic effects last,[19] but another failed to replicate this finding.[20] On the other hand, recordings simultaneous with STN DBS in the MPTP treated parkinsonian monkey have shown that DBS suppresses local synchrony, albeit at lower frequencies than in the human.[21]

The likely suppression of synchrony by DBS does not, by itself, prove that synchronised activity is mechanistically important in driving parkinsonism. More persuasive evidence comes from experiments in which, rather than stimulate the STN in chronically implanted patients at therapeutic high frequency, patients are temporarily

stimulated at low frequency. This artificially induces synchronisation at the stimulation frequency in projection targets of the STN. Stimulation at frequencies of 5, 10 and 20 Hz does exacerbate bradykinesia, although the effects are relatively small, perhaps because imposed synchrony consists of single rather than bursts of events per cycle or because synchronous activity is already present near 'ceiling' levels.[22-25] Importantly, these deleterious effects are relatively frequency selective and are absent with stimulation at 50 Hz, which neither simulates pathological activity nor is an effective suppressant of ongoing activity (Fig 2).[22]

How might synchronisation in the beta band impair motor processing in basal ganglia-cortical loops, leading to bradykinesia? Here it is important to stress that it is not activity in this band *per se* that is deleterious, but
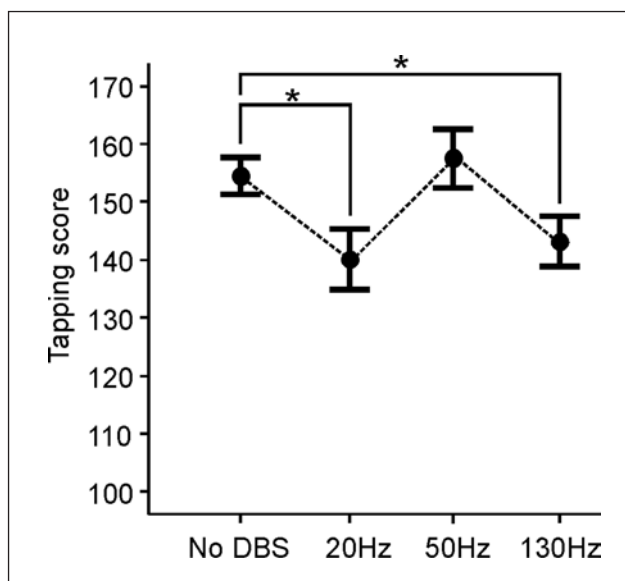
Fig. 2. Response to bilateral STN DBS at different frequencies in 27 sides from PD patients with finger tapping performance within normal range in absence of stimulation. The lower limit of normal range was 127 taps per 30 s in a control group of 10 healthy age matched subjects. Each patient was studied up to three times in the 'off' medication condition and data from the session with best performance without DBS taken for each hand. Note that tapping performance was significantly, albeit relatively modestly, impaired with stimulation at 20 Hz and 130 Hz, but not with stimulation at 50 Hz. Stimulation at 20 Hz likely impairs tapping by inducing synchronisation in the beta band, whereas stimulation at 130 Hz may have deleterious effects on sides with relatively preserved task performance by suppressing remaining physiological activity.[22] Stimulation at 50 Hz has neither of these effects. DBS at 130 Hz improved performance on those sides with baseline performance below normal range (data not shown). In this, the most common situation, high frequency DBS is acting to suppress prevalent pathological rather than physiological activity. Accordingly, the effects of stimulation depend on both frequency and baseline state. * = p <0.05, two-tailed unpaired t-test (unpaired used because of 15 out of 108 missing values).

rather the extent of synchronisation in this frequency band. Lower degrees of beta synchrony are seen in healthy humans, where they seem to favour processing related to postural or tonic modes of contraction,[26, 27] by in part upregulating the motor reinforcing effects of relevant sensory input.[28, 29] Additionally, in both physiological and parkinsonian states beta synchrony is suppressed prior to voluntary movement, although perhaps not so effectively in untreated PD.[30, 31] This raises the possibility that pervasive synchronisation in this frequency band constrains the ability of individual neurones to code in time and space, as adjacent and spatially distributed neurons preferentially fire locked to the beta rhythm.[10] Once released these neurones can more effectively engage in the dynamic assembly formation and rate coding necessary for the processing of movement.[32, 33] Here it is interesting to note the parallel with the center-surround model of basal ganglia function in so far as the exaggerated spatial extension of synchrony in the basal ganglia might contribute to loss of motor selectivity in Parkinson's disease.[34-37]

The exaggerated spatial extension of synchrony in the basal ganglia of patients with PD appears relatively frequency selective, occurring over 10-30 Hz in basal ganglia-cortical loops, and is effectively suppressed by dopamine, most likely, but not exclusively, at the level of the cortico-striatal inputs.[12] The beta synchrony recorded in STN and GP may be therefore largely propagated from the striatum, but whether the synchrony is already spatially extensive across cortical inputs to the striatum and is failed to be filtered in the striatum or the spatial extension of oscillatory activity occurs at the striatum in the absence of dopamine remains to be established. It is also unclear whether all activity between 10 and 30 Hz has similar pathophysiological significance, with growing evidence that it is those frequencies towards the bottom of this range that are particularly pathological.[14, 38, 39] Moreover, synchrony at different frequencies may have subtly different effects on motor control. For example, direct STN stimulation at 5 and 10 Hz, but not at 20 Hz, increases the variability of tapping, suggesting that basal ganglia circuits involved in temporal patterning and

regularity of movement may be disrupted by activities synchronised at frequencies different form those involved in movement speed.[23]

Treatment with levodopa not only suppresses beta activity, but also is associated with increases in gamma band activity in the STN LFP (Fig 1). This has been reported in two particular ranges, from 60-90 Hz[30, 40-47] and 230-350 Hz.[45, 48] As these activities are also increased during movement and, at least at 60-90 Hz, parallel physiological activity in cortical motor areas, they have been considered essentially prokinetic, favouring processing related to movement,[48, 49] in line with the general role of such frequencies in active processing.[50] This raises the interesting possibility that some of the therapeutic action of DBS might actually be due to driven activity that perhaps mimics the synchronisation in the gamma band.[42, 51] In this theory, the new output driven by the stimulation might be of positive advantage in basal-ganglia-cortical loops and their targets rather than simply neutralising the effects of pathological synchronisation at lower frequency. However, supportive experimental evidence is relatively lacking,[52] and it is difficult to see how the imposition of gamma synchrony would necessarily improve other conditions like dystonia and tremor, in which there is no evidence to suggest a lack of synchronisation at frequencies above 30 Hz.

DYSTONIA AND LEVODOPA-INDUCED DYSKINESIAS: WHY DO THESE IMPROVE WITH DBS?

Again, a reasonable starting point in identifying any noisy signal in dystonia and levodopa induced dyskinesias would be to record directly from the basal ganglia in patients with these conditions. Several studies have suggested that there is excessive oscillatory activity < 10 Hz in the LFP recorded in the pallidum in patients with primary dystonia,[53, 54] distinct from the LFP pattern recorded in untreated (non-dyskinetic) patients with PD. This pathological LFP activity reflects the synchronisation of local pallidal neurons in this frequency band and is, at least in part, oscillatory. Accordingly, some patients show discrete peaks in their LFP power over 3 Hz to 10 Hz and spike triggered averages of pallidal LFPs in patients with primary dystonia can be clearly oscillatory.[55] This oscillatory activity <10 Hz may be mechanistically important in dystonia, as there is evidence to implicate theta activity in the basal ganglia in sensorimotor integration and motor learning,[56-58] abnormalities in which are a longstanding and recurring theme in dystonia.[59]

Nevertheless, a plausible mechanism need not mean that exaggerated low frequency (<10 Hz) pallidal activity is actually relevant in dystonia. Here, there are several significant observations. First, this low frequency activity may be suppressed during effective sensory trick manoeuvres.[60] Second, dystonic muscle activity in primary dystonia also seems to involve an abnormal descending drive at frequencies under 10 Hz.[61, 62] Third, the low frequency activities at pallidal and muscle levels are coherent,[63] and, in line with a link between low frequency activity in the pallidum and that in dystonic muscle, the amplitude of pallidal LFP activity <10 Hz band correlates with the intensity of dystonic muscle contraction over time.[64] Furthermore, microelectrode studies suggest that power and oscillatory spike triggered averages of LFP activity in this frequency band are concentrated in the internal segment of the globus pallidus, the site where functional neurosurgery seems most effective.[55] In itself, though this coupling between muscle and pallidal activity could still be epiphenomenal if it represented simple afferent return to the pallidum. In this regard, it is noteworthy that pallidal neurons may respond to peripheral stimuli and this responsiveness is increased in dystonia.[65] Against this possibility, however, is the observation that pallidal LFP activity preceded phase locked activity in dystonic muscles in a patient with myoclonic dystonia.[66]

Not all patients with primary dystonia have clear 3-10 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 low frequency oscillations in the pallidal LFP only relate to the mobile elements of dystonia, and may not contribute to relatively tonic involuntary muscle activity.[63] By exclusion then, tonic involuntary activity may depend on very slow, arrhythmic but synchronised bursting in the pallidum or non-synchronised neuronal activity which is not represented in the LFP. Several studies of single neuron activity in the pallidum and thalamus suggest an excessive tendency to arrhythmic bursting at very low frequencies in dystonia, frequencies that may also be represented in dystonic muscle activity.[67-69] Whether or not such very low frequency bursts are synchronised between neurons remains unclear and the LFP studies summarized above largely ignored spectral components with frequencies under 3 Hz, as these may reflect movement artefact.

Most levodopa induced dyskinesias are at least phenomenologically similar to mobile dystonias, so is there any evidence for similar changes in pallidal

activity in dyskinetic PD patients? Silberstein et al.[54] were the first to draw attention to the predominance of pallidal LFP activity <10 Hz in patients with advanced PD during treatment with levodopa similar to that in primary dystonia. Many of these patients would have been dyskinetic at the time of recording, although unfortunately this was not explicitly documented in their study. More persuasive evidence that dyskinesias in PD patients may be related to an analogous 3-10 Hz activity to that in mobile dystonia was recently reported by Obeso and colleagues, who found a temporal concordance between elevated STN LFP activity in this band and dyskinesias (Fig 1).[41] These findings were paralleled by changes in LFP activity in the substantia nigra pars reticulata (easier to record than the rodent equivalent of GPi) in the 6-hydroxydopamine lesioned rodent model of parkinsomism, once dyskinesias had been induced by levodopa.[70]

In summary, the more mobile elements of dystonia and levodopa-induced dyskinesias appear closely associated with an excessive synchronisation of pallidal activity over the 3-10 Hz band, which may therefore represent our candidate hyperkinesia-specific noisy signal. However, activities at other frequencies are also implicated. For example, there is an inverse relationship between pallidal LFP activity in the beta band and dyskinetic EMG[71, 72] paralleling the association between low levels of pallidal beta LFP activity and dyskinesia in the dystonic dt^{sz} mutant hamster.[73] It may be that under some circumstances the disproportionate attenuation of synchronisation in the beta band might lead to the inadequate suppression of unwanted motor programs and thereby to hyperkinesias.

In reality, it may not be the level of synchrony in one particular band that uniquely dictates the presence of mobile dystonia and dyskinesias but the balance between various contrasting activities. Thus there is evidence of a reciprocal relationship between LFP activity over 8-30 Hz and prokinetic activity in the 60-90 Hz band in hyperkinetic rats[74] and in the subthalmic area of PD patients.[46] In the latter case, the reciprocal relationship is most prominent around 50 minutes after a levodopa challenge in tandem with dyskinesias. Importantly, this negative correlation arises through spontaneous changes in subjects asked to rest quietly, i.e. in the absence of voluntary movement, and negative covariations between signals are present over periods of tens of seconds. These negative covariations could arise from endogenous processes that result in fluctuations in basal ganglia state with multi-second periodicities and are increased by dopaminergic activity. It may therefore be relevant that similar fluctuations have been noted in neuronal discharge rate in many basal ganglia sites, including the STN, in the awake rodent, and that these are exacerbated by dopaminergic agonists, particularly in the setting of dopamine receptor supersensitivity.[75, 76] These slow fluctuations have been associated with the appearance of apomorphine induced stereotypies in rats,[75] and may, conceivably provide an explanation for the fluctuations in the balance between oscillatory processes in different bands over multisecond periods in the subthalamic area evident once plasma levodopa levels approach their peak.[46]

The evidence presented above suggests that changes in synchronisation patterns between neurons in the basal ganglia may provide the noisy signal in mobile dystonia and dyskinesia, yet, so far the suppression of these patterns of synchronised activity by BDS in dystonia and levodopa induced dyskinesias remains essentially presumptive, although there is one report of contralateral dyskinesias induced by stimulation of the STN at 5 Hz in patients with PD.[77]

WHY DOES DBS NOT LEAD TO MOTOR IMPAIRMENTS ATTRIBUTABLE TO LOSS OF PHYSIOLOGICAL FUNCTIONING IN THE TARGET NUCLEUS?

So there seems to be evidence in favour of the noisy signal hypothesis, whereby functional neurosurgery procedures can suppress different phenotype specific noisy signals. But this raises one further paradox, again highlighted in Marsden and Obeso's classic 1994 Brain paper: why does functional neurosurgery not also impair movement, for just as it may suppress pathological activity it should suppress physiological activity? Could it be that the loss of physiological function is compensated for elsewhere in the motor system or is it that the physiological role of the basal ganglia is too subtle and difficult to detect?[4] In fact, recent work suggests that there can be motor deficits following functional neurosurgery, with respect to both simple motor functions like finger tapping[78] and more complex visuomotor tasks.[79] This was shown by considering the effects of high frequency (~130 Hz) DBS of the STN in the context of baseline task performance. In patients with poor task performance without DBS on the day of study, there was the expected improvement upon stimulation. However, in patients that performed well on the day of study, high frequency DBS

(but not DBS at 50 Hz) actually compromised motor performance (Fig 2). Presumably in these subjects the deleterious effects of DBS were not overshadowed by the beneficial effects of suppressing noisy signals. It must be acknowledged, however, that the scale of these effects was not great: for example simple tapping was slowed in good performers by about 10 %, perhaps because some degree of compensation for loss of basal ganglia function does occur.[78]

The concept that STN DBS may actually impair certain functions in some patients is not just of theoretical interest. The speech,[7, 80] cognitive,[7, 81, 82] and postural impairments[7, 83, 84] that can sometimes follow STN DBS may fall into the category of disturbed physiological functioning, and, presumably, the rarity of these effects following GPi DBS[7] argues that the latter nucleus is less involved in these aspects of behaviour or that the bigger size of the GPi allows more selective targeting of motor areas related to the limbs. Further, there has been a general presumption in the literature that those functions that may deteriorate following DBS are those that are already compromised prior to surgery.[83-86] This may in part explain the discrepancies observed between prospective studies of selected patients and the occurrence of adverse events in larger populations.[7] The data reviewed above encourage, for example, prospective studies of speech before and after surgery that focus not just on those patients with pre-operative impairment in speech, but also those on those with relatively intact speech mechanisms.

SUMMARY AND CLINICAL IMPLICATIONS

There is increasing evidence to suggest that there are several relatively phenotype specific patterns of synchronised and disruptive activity in the basal ganglia that can be suppressed by lesioning or DBS, thereby possibly explaining some of the paradoxically beneficial effects of functional neurosurgery. Of course paradoxes do not just go away; they are replaced by others. For example, parkinsonian tremor seems closely related to the cerebellar system, as evidenced by the therapeutic effectiveness of surgical procedures targeting cerebellar input areas of the thalamus.[87] However, in this case just how does STN DBS suppress parkinsonian tremor? The question is made all the more pertinent by the observation that, although tremor related discharge may be encountered during intra-operative microelectrode recordings in STN, synchronisation of units must be relatively low or inconstant, as coupling between STN

LFPs and tremor is surprisingly weak. Indeed, the inconsistency of phase locking between tremor cells in the pallidum has been well documented[88] and the relevance of tremor frequency band oscillations in the basal ganglia to limb tremor in the MPTP treated primate model of PD has recently been questioned.[89] Another important paradox suggests that the noisy signal hypothesis may be more complex than hitherto espoused. If functional neurosurgery acts by suppressing phenotype-specific disruptive and noisy signals then these signals should be suppressed to equal effect at different sites along the basal ganglia-cortex circuit. But, although lesions or DBS in the GPi may relieve bradykinesia,[7, 90] albeit to a lesser extent and in a less stable manner over time than in the STN,[7, 91] similar procedures in the motor thalamus that can include pallidal projection zones are only effective treatments for tremor and rigidity.[4] The implication is that the processing disturbed by noisy signals to give bradykinesia has already occurred by the thalamus, -either in GPi or in its brainstem projections. This unexpected deduction requires further investigation and corroboration.

Few physicians or patients would dispute that currently available treatments, whether pharmacological or neurosurgical, are suboptimal. It is largely our incomplete understanding of the pathophysiology of conditions like parkinsonism and dystonia that impedes further development. For example, current evidence points to excessive low frequency synchronisation in basal ganglia-cortical circuits in Parkinson's disease,[13] yet we do not know the key neurotransmitter imbalances that initiate or sustain such synchronisation, limiting pharmacological target selection. Similarly, DBS is empirically delivered as regular electrical pulses at high frequency, but this may not be the most effective and energy conservative means of controlling pathological synchronisation in PD,[92] nor may it be optimal for manipulating plastic change in dystonia, where adoption of some of the novel theta burst stimulation modes employed to good effect in the cortex[93] might be a worthwhile approach. In addition, the identification of electrical biomarkers of disease activity at the site of stimulation may readily lead to more economical 'sense and stimulate,' demand led closed loop systems. Finally, recent behavioural studies during DBS suggest that we must be wary of the effects of this treatment on those functions of the basal ganglia, whether motor or cognitive, that might be relatively spared by disease: a consideration that may become more important as novel targets are considered for primarily psychiatric diseases and the fashion grows for operating on PD early rather than late.

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