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Pathological basal ganglia activity in movement disorders

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Abstract

Our understanding of the pathophysiology of movement disorders, and associated changes in basal ganglia activities has significantly changed in the course of the last few decades. This process began with the development of detailed anatomical models of the basal ganglia, followed by studies of basal ganglia activity patterns in animal models of common movement disorders and electrophysiological recordings in movement disorder patients undergoing functional neurosurgical procedures. These investigations first resulted in an appreciation of global activity changes in the basal ganglia in parkinsonism and other disorders, and later in the detailed description of pathological basal ganglia activity patterns, specifically burst patterns and oscillatory synchronous discharge of basal ganglia neurons. In this review we critically summarize our current knowledge of the pathological discharge patterns of basal ganglia neurons in Parkinson's disease, dystonia and dyskinesias.

Keywords

Striatum; globus pallidus; subthalamic nucleus; Parkinson's disease; dystonia; dyskinesia

1. Introduction

The last decades have brought an enormous expansion of our knowledge of the pathophysiology of some of the most common movement disorders, specifically Parkinson's disease (PD), dystonia and dyskinesias. We use the term 'pathophysiology' here to refer to the changes in neuronal electrical activity that are associated with these diseases. In part, the progress in this field of research was driven by the development of suitable animal models of these conditions. For instance, the development of dopamine depletion models such as the 6-hydroxydopamine (6-OHDA) treated rat, or the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated monkey has been highly important for our current

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7. Conflicts of interests

The authors declare no actual or potential conflicts of interest.

understanding of the changes underlying the dopamine-sensitive symptoms of PD. Due to the fact that recordings can be made in animals before and after the induction of movement disorders, such studies have enabled us to rigorously test hypotheses regarding the consequences of biochemical or structural changes in the brain, and the relevance of such changes for the development of behavioral signs of these conditions.

Another highly valuable source of information has been electrophysiologic recordings in patients undergoing neurosurgical treatments for movement disorders. Treatments such as deep brain stimulation (DBS) or lesioning of the basal ganglia are often guided by microelectrode recordings which can then be used to study basal ganglia activity patterns. Furthermore, implanted DBS macroelectrodes can be used to record local field potentials (LFP) from the basal ganglia (or thalamus) for a few days postoperatively until the DBS electrode leads are internalized. Such signals have been correlated with treatment responses or motor behavior.

In the following, we will provide a brief overview of the systems anatomy of the basal ganglia and then describe the current knowledge of disease-related changes in firing patterns and LFPs in the basal ganglia and associated structures. These discussions will focus on studies in non-human primates and human patients because of the immediate relevance of this research for our understanding of the human diseases. While non-motor symptoms may also arise from basal ganglia dysfunction, we will not further comment on these, reflecting our very limited knowledge on the pathophysiologic abnormalities that are underlying these problems.

2. Basal ganglia systems anatomy

It has been known since the mid-1980s that the basal ganglia are arranged in topographically and functionally specific circuits that also involve discrete regions of the thalamus and cortex (the ‘segregated circuit hypothesis’, see Alexander et al., 1986, Alexander et al., 1990, Middleton and Strick, 2000). These circuits are named after the function of the cortical areas from which they originate as ‘motor’, ‘associative’, ‘limbic’, and ‘oculomotor’ circuits. With some exceptions, the different circuits are similar in their general anatomical arrangement. In terms of the basal ganglia involvement in the pathophysiology of movement disorders, the motor circuit is of particular relevance, and will be described in some detail here.

This circuit arises from precentral motor fields (Figure 1, left). Massive projections from these cortical areas terminate in the motor portion of the striatum (the putamen), with sparser connections in the lateral and dorsal motor portion of the subthalamic nucleus (STN) (Hartmann-von Monakow et al., 1978, Inase et al., 1999, Takada et al., 2001, Nambu et al., 2002). Anatomical studies in rats have shown that *corticostriatal* projections arise in part as collaterals from corticospinal fibers (Lei et al., 2004). Anatomical single-cell tracing studies in primates have also found examples of corticofugal neurons with collaterals to the striatum (Parent and Parent, 2006), although half of the sample of cortical neurons of the latter study provided unbranched input to the striatum (and were, thus, separate from the corticospinal tract). The conclusion that many corticostriatal neurons do not project to the spinal cord is also supported by electrophysiologic studies (Bauswein et al., 1989, Turner and DeLong, 2000).

The existing literature suggests that the *corticosubthalamic* pathway is separate from the corticostriatal pathway so that STN and striatum may receive different types of information (Parent and Parent, 2006) Data from experiments in cats and rats have suggested that the corticosubthalamic inputs may arise as axon collaterals of other corticofugal systems, such as the corticospinal tract (Iwahori, 1978, Kitai and Deniau, 1981, Giuffrida et al., 1985), but

this fact has not been sufficiently clarified in primates. In fact, the aforementioned single-cell tracing study of corticofugal fibers (Parent and Parent, 2006) included only two motor cortical neurons that provided terminals in the STN. One of these was found to subsequently invade the cerebral peduncle while the other eventually terminated in the red nucleus. The important question of the nature of cortical inputs to the basal ganglia is further complicated by the fact that the motor and non-motor corticosubthalamic pathways are likely to differ substantially in terms of their status as being collaterals of other projections.

Striatal projections to the basal ganglia output nuclei, the internal segment of the globus pallidus (GPi, termed the entopeduncular nucleus in rodents), and the substantia nigra pars reticulata (SNr) can be grouped into the monosynaptic 'direct' pathway and the polysynaptic 'indirect' pathway which involves neurons in the external pallidal segment (GPe) and the STN (Figure 1). The degree of separation of these circuits remains debated. Most recent studies suggest that the direct and indirect pathways arise from different sets of neurons in the striatum (reviewed in Gerfen and Surmeier, 2010), but single-cell tracing studies have shown that at least some of the striatal projections terminate in both segments of the pallidum (Levesque and Parent, 2005), suggesting that the separation may not be complete.

Basal ganglia output from GPi/SNr is mostly directed towards the ventrolateral and ventral anterior nuclei of the thalamus (VL and VA, respectively). VL and VA send relatively minor projections to the basal ganglia (McFarland and Haber, 2000, 2001, Smith et al., 2004), but project massively to the frontal cortical areas from which the motor circuit arises, thereby at least partially closing the cortico-subcortico-cortical motor loop. Collaterals of the GPi/SNr projection to VL/VA reach the intralaminar thalamic nuclei, i.e., the 'motor' centromedian nucleus and the 'non-motor' parafascicular nucleus. These nuclei project back to motor and non-motor regions of the striatum, and may function as a feedback system by which striatal processing is influenced by basal ganglia output (Smith et al., 2004). One of the important additional functions of the intralaminar thalamic nuclei is to provide saliency information to the striatum during procedural learning (Kimura et al., 2004, Minamimoto et al., 2009).

In addition to their role as components of the cortico-cortical circuits, the basal ganglia have descending connections to brain stem targets such as the pedunculopontine nucleus (Mena-Segovia et al., 2004, Aravamuthan et al., 2007, Hamani et al., 2007) or the superior colliculus (see reviews by Hikosaka, 2007, Kaneda et al., 2008, Liu and Basso, 2008).

Dopamine has been assigned a pivotal role in almost all of the normal functions of the basal ganglia. Under physiologic conditions, dopamine release in the striatum appears to be strongly involved in reward processing (Schultz and Dickinson, 2000, Cragg, 2006, Calabresi et al., 2007, Hikosaka, 2007, Wickens et al., 2007, Surmeier et al., 2009, Morris et al., 2010). In addition, the ambient level of dopamine in the striatum may regulate the general flow of cortical information through direct/indirect pathway systems in the striatum. Dysfunction of this system has traditionally been linked to the development of motor abnormalities in the absence of dopamine (parkinsonism), or with abnormalities in dopaminergic transmission (as may occur in levodopa-induced dyskinesias and in some forms of dystonia, see below). Interestingly, the dopaminergic projections may also have functions other than the modulation of synaptic transmission. Thus, there is a considerable body of evidence that the absence of dopaminergic transmission may trigger changes in the density and morphology of dendritic spines on striatal projection neurons (Ingham et al., 1998, Gerfen, 2006, Day et al., 2008, Smith et al., 2009, Villalba et al., 2009) which, in turn, may influence corticostriatal transmission. Pathology studies have not identified major changes in the number of cortical projection neurons (with the exception of cortico-cortical projection neurons in the pre-supplementary motor area (MacDonald and Halliday, 2002, Halliday et al., 2005)), so that it seems likely that the dendritic spine changes are a primary

striatal phenomenon, and not due to a reduction of the number of glutamatergic inputs to the striatum.

Recent research has shown that all of the other basal ganglia nuclei also receive dopaminergic inputs, although these projections and the dopamine concentrations in these nuclei are much smaller (Pifl et al., 1991, Rommelfanger and Wichmann, 2010). The importance of the dopaminergic input to the normal function of these extrastriatal areas (and to behavior) remains unclear, but it has been shown that dopamine receptor activation or blockade in these regions profoundly alters neuronal firing (reviewed in Rommelfanger and Wichmann, 2010). Furthermore, recent findings suggest that loss of dopamine can seriously interfere with the mechanisms underlying synaptic plasticity in the striatum and SNr (Picconi et al., 2003, Prescott et al., 2009), and it is possible that these changes contribute to the development of motor symptoms in PD or dyskinesias.

Other neuromodulators, such as serotonin, released in the striatum and other basal ganglia nuclei from projections of the brain stem raphe nuclei (Kalen et al., 1989, Di Matteo et al., 2008), or acetylcholine, released predominately in the striatum from terminals of interneurons, may also play a significant role in the regulation of basal ganglia activity and in the pathophysiology of movement disorders (Pisani et al., 2007, Di Matteo et al., 2008, Fox et al., 2009), but their function and the consequence of altered transmission at synapses involving these transmitters are less well characterized than those of dopamine.

The concept of the organization of the cortico-basal ganglia interactions into stable functionally segregated modules is gradually eroding, with increasing evidence that at least some information processing in the basal ganglia may undergo shifts between the different functional domains. This has been particularly shown for the involvement of the basal ganglia in procedural learning in which the striatal activation seems to gradually move from ‘non-motor’ to ‘motor’ areas (for instance, Miyachi et al., 2002). In reality, simultaneous involvement of motor and non-motor circuits in a given behavioral context is likely to be the norm rather than the exception, because few behaviors can be classified as being exclusively ‘motor’ or ‘non-motor’.

As a further qualifier of the segregated pathway hypothesis, there is increasing evidence for direct anatomical interactions between cerebellar and basal ganglia circuits (in addition to the known interaction between these circuits at the cortical level). Thus, virus tracing studies have suggested that the basal ganglia receive information from the deep cerebellar nuclei (Hoshi et al., 2005), and that they send projections to the cerebellar cortex (Bostan et al., 2010). Such interactions are not (yet) part of the pathophysiologic models mentioned below, but may become important in the future, particularly to explain aspects of tremor or dystonia.

3. Parkinson’s disease

PD is clinically defined by the presence of slowness of movement (bradykinesia), poverty of movement (akinesia), muscle stiffness (rigidity) and tremor at rest. This constellation of signs and symptoms is referred to as ‘parkinsonism’, is known to respond to dopamine replacement therapy, and is therefore considered to be a direct consequence of the pathological hallmark of the disease, the degeneration of dopaminergic neurons in the substantia nigra, pars compacta (SNc), and the loss of dopamine in the striatum. In order to develop a better understanding of the basal ganglia processes involved in the dopamine-responsive aspects of PD, a large number of studies have investigated the consequences of striatal dopamine loss on the electrical activities of basal ganglia neurons in animal models of the disease, or have characterized the electrical activities in the basal ganglia in patients.

Early studies of activity changes in the basal ganglia of MPTP-treated parkinsonian monkeys emphasized changes in the overall activity of basal ganglia nuclei (Miller and DeLong, 1987, Albin et al., 1989, DeLong, 1990). These studies were strongly influenced by previous 2-deoxyglucose imaging studies in the same animal model which had shown that the metabolic activity in GPe and VL/VA increases, while the activity in the STN and GPi was shown to be lower in MPTP-treated monkeys than in normal animals (Schwartzman et al., 1988, Mitchell et al., 1989). These metabolic changes were interpreted in terms of alterations in synaptic activity (Figure 1, right). Electrophysiological studies provided an explanation for these changes by demonstrating a reduction of activity in GPe, and increases in activity in the STN and GPi (Miller and DeLong, 1987, Albin et al., 1989, DeLong, 1990). Together with other studies, these findings resulted in the 'rate model' of movement disorders. Applied to PD, it explained the reduced firing rate in the GPe as a consequence of increased activity along the inhibitory indirect striato-pallidal pathway, which would then result in disinhibition of STN activities and facilitation of GPi firing. It was always understood that the increased activity in GPi could also be explained by reduced activity along the inhibitory direct pathway of the basal ganglia, but such changes have not been directly demonstrated. Downstream from GPi, increased basal ganglia output was thought to result in inhibition of thalamocortical projection neurons, reduced cortical activation, and slowing of movement.

Soon after its introduction, the rate model met with substantial criticism, because it did not explain some of the basic clinical findings in PD patients, including the fact that thalamotomy procedures did not result in worsening of parkinsonism (as one would expect based on the rate model), and that GPi lesions unexpectedly produced bradykinesia in normal monkeys while GPe lesions did not produce parkinsonism (Marsden and Obeso, 1994, Soares et al., 2004). Furthermore, although most studies to date have found that severe parkinsonism in MPTP-treated monkeys is indeed associated with reduced firing rates in GPe and increased firing rates in GPi (Miller and DeLong, 1987, Filion and Tremblay, 1991, Bergman et al., 1994, Boraud et al., 1996, Boraud et al., 1998, Heimer et al., 2002, Wichmann et al., 2002, Soares et al., 2004), other studies have reported unchanged GPe or GPi firing rates, or rate changes opposite to those predicted by the rate model (Wichmann et al., 1999, Raz et al., 2000, Wichmann and Soares, 2006, Leblois et al., 2007, Galvan et al., 2010). The reason for these differences is not clear, but may have to do with differences in the severity of parkinsonism induced by the dopaminergic lesion, the specific toxin treatment protocol, or the recording conditions used in these studies. Taken together, the available evidence suggests that changes in firing rates may play a role in the development of parkinsonism, but do not fully explain its appearance.

A significant factor interfering with the assessment of firing rate changes in parkinsonism is that firing rates throughout the basal ganglia are strongly dependent on the state of arousal of the subjects studied. Parkinsonism often results in profound state changes in patients (Menza et al., 2010) and monkeys (Daley et al., 2002, Fox and Brotchie, 2010), and such changes are often not well controlled in studies of firing rate changes in the basal ganglia in parkinsonism. Furthermore, many of the studies in rodents were done in anesthetized animals in which the depth of anesthesia was not (or could not be) adequately monitored. Thus, despite the fact that firing rates are technically easy to measure, the interpretation of firing rate changes in the parkinsonian state remains difficult.

Most authors have now turned away from exclusively firing rate-based models of the pathophysiology of parkinsonism, and towards models that take into account changes in basal ganglia firing patterns and synchrony. There are many different methods of characterizing firing patterns, but most involve some type of quantification of the degree of burstiness or regularity.

Increased burstiness (see example in Figure 2A) has emerged as one of the most reliable abnormalities of neuronal firing in the basal ganglia in parkinsonism, as shown in dopamine-depleted monkeys and in patients with Parkinson's disease (Filion, 1979, Bergman et al., 1994, Hutchison et al., 1994, Wichmann et al., 1999, Magnin et al., 2000, Soares et al., 2004, Wichmann and Soares, 2006). Specifically, bursting activity in the STN develops relatively early in the course of dopamine depletion, along with changes in discharge rates and metabolic markers (Vila et al., 2000, Ni et al., 2001, Breit et al., 2007). Mechanisms that would lead to bursting in the STN may include unopposed constitutive activity at post-synaptic dopamine D5 receptors (Baufreton et al., 2005, Rommelfanger and Wichmann, 2010), and rebound burst phenomena, caused by synchronous GABAergic inputs from GPe (Baufreton et al., 2003, Shen and Johnson, 2005, Bevan et al., 2007).

When fluctuations in firing patterns occur in a regular repeating fashion then the pattern can also be characterized as oscillatory in nature and the frequency and magnitude of the oscillations can be quantified by methods such as spectral analysis (Fourier transforms) or autocorrelograms. Such oscillatory activity is frequently also observed as oscillatory LFPs and can be detected using large-tipped (macro-) electrodes such as for example the contacts of deep brain stimulation electrodes in patients. Analysis of oscillatory activity in neuronal spike trains and LFPs in animal models of PD and in PD patients, has revealed the frequent occurrence of significant oscillatory activity in the beta frequency range (approximately 10 – 35Hz) throughout the extrastriatal basal ganglia (Figures 2–4). Neurons within the individual basal ganglia show an increased level of synchrony (e.g., Bergman et al., 1994, Heimer et al., 2002, Goldberg et al., 2004, Rivlin-Etzion et al., 2006, Hammond et al., 2007). Furthermore, the oscillatory activity is in synchrony between STN, GPi and cortex and is suppressed by the administration of levodopa (Figures 2 and 3, and reviews by Brown, 2003, Gatev et al., 2006, Hammond et al., 2007). Several studies have revealed that neurons in the STN tend to fire in synchrony at beta frequencies and that this oscillatory activity is coherent with the beta-band LFP oscillatory activity and maximal in the motor region of the STN (Kuhn et al., 2005, Weinberger et al., 2006). This indicates that there is synchronous activity at the oscillation frequency in a large population of neurons. This could lead to a breakdown in the ability of individual neurons to process and relay specific information and thus to effectively control complex movements.

The generation of the oscillatory activity is still not clearly understood. It is unlikely that the oscillations are produced by a single oscillatory 'driver' in the basal ganglia, and more probable that they arise from network oscillatory resonance, in particular between GPe and STN (Plenz and Kitai, 1999, Holgado et al., 2010), or are driven from cortex via the hyperdirect pathway. Loss of dopamine in the basal ganglia produces changes in neuronal and synaptic properties that would tend to promote this type of oscillatory activity (see, Bevan et al., 2002, Terman et al., 2002, Weinberger and Dostrovsky, 2011).

In addition to the beta oscillatory activity, abnormalities in oscillations in two other bands have frequently been reported, i.e., low-frequency activity (<10Hz) and high-frequency gamma band activity (>60 Hz). Gamma band activity has been shown to be decreased in the dopamine depleted state, and to respond to dopaminergic treatment, and thus, its occurrence is believed to be prokinetic, whereas the increased beta and alpha activity is thought to be antikinetic (Figure 4, see also Brown, 2003, Brown and Williams, 2005).

It is very likely that dopamine loss in the basal ganglia causes or contributes to many of the motor signs of PD, and that it results in profound changes in basal ganglia neuronal activity (rate, pattern, synchronized oscillatory activity, synaptic plasticity). However, the link between specific changes in basal ganglia discharge and the behavioral manifestations of PD remains tenuous. This question has been addressed with studies in which animals were

chronically (or multiple times) exposed to dopaminergic toxins (Bezard et al., 1999, Leblois et al., 2007). Early studies by Bezard et al. suggested that the neuronal activity in STN and GPi was increased prior to the onset of motor symptoms (Bezard et al., 1999). While these changes were interpreted as a potential sign for a compensatory role of the presymptomatic changes (Bezard et al., 2003), they could also be interpreted as evidence for a threshold of activity changes which has to be surpassed before parkinsonian signs can develop. More recent animal studies have found, however, that some of the neuronal activity changes (particularly oscillatory activities) appear only after the emergence of parkinsonism (Leblois et al., 2007), concluding that they cannot be interpreted as primary causes of the behavioral phenotype. Similar conclusions have also been drawn from studies in rodents in which nigrostriatal dopaminergic transmission was acutely disrupted by dopamine receptor blockade or by acute treatment with 6-hydroxydopamine. In distinction to chronically 6-OHDA-treated animals (e.g., Mallet et al., 2008a), these animals do not develop oscillatory activities (Mallet et al., 2008b). Likewise, despite the consistent finding of increased burst firing in the basal ganglia in parkinsonism, treatments with dopaminergic agents do not consistently reduce burst firing in the basal ganglia of parkinsonian animals or patients (compare Tseng et al., 2000, Lee et al., 2001, Levy et al., 2001). Local injections of dopamine D1-like receptor agonists into the primate GPi or SNr, or D5 receptor activation in the rodent STN were also found to increase rather than decrease burst firing in these nuclei (Baufreton et al., 2003, Kliem et al., 2007).

4. Dystonia

The pathophysiology of dystonia, a disorder in which normal movements are disrupted by co-contraction of agonist and antagonist muscles and by excessive activation of inappropriate muscle groups (overflow), is much less well understood than that of PD, primarily because the condition is caused by a large and heterogeneous group of diseases with presumably different pathophysiologic backgrounds, and because there are no phenomenologically reliable animal models for dystonia (Raike et al., 2005).

Despite a considerable amount of research, little is known about the brain abnormalities that underlie the dystonic phenotype. Most forms of dystonia are not caused by large-scale neurodegeneration and are therefore thought to be due to abnormal function of otherwise relatively intact brain circuits. Some forms of dystonia are probably caused by basal ganglia dysfunction, but others may result from disordered function at other brain locations, such as the cerebellum or cerebral cortex.

Early metabolic studies in primate models have suggested that dystonia may be associated with reduction of activity along the putamen-GPe connection, and increased inhibition of STN and GPi by GPe efferents (figure 1 and Hantraye et al., 1990, Mitchell et al., 1990). Pharmacologic studies of drug-induced dystonia suggested that the condition is associated with a shift of the balance towards the direct pathway (Casey, 1992, Gerlach and Hansen, 1997). Single-cell recording studies in patients undergoing functional neurosurgery have reported that discharge rates in GPe and GPi are low (Lenz et al., 1998, Vitek et al., 1999, Vitek, 2002, Zhuang et al., 2004, Starr et al., 2005, Tang et al., 2007), although in some patients firing rates have been found to be as high as in PD patients (Hutchison et al., 2003).

Dystonia can be associated with disturbances in dopaminergic transmission (Wichmann, 2008), and in these cases may arise from striatal pathology. For instance, dystonia may develop acutely or delayed in normal individuals treated with dopamine-receptor blocking agents. Dystonia also occurs in patients with PD, either as a manifestation of the disease, or as the result of exposure to dopaminergic drugs. Furthermore, in one form of hereditary dystonia (DYT-5), patients present with dystonia and parkinsonism which are eliminated by

treatment with levodopa (so-called DOPA-responsive dystonia). Altered dopamine metabolism may also occur in the most common genetic form of dystonia, primary generalized dystonia (DYT1, Augood et al., 2002, Balcioglu et al., 2007, Zhao et al., 2008).

In contrast to PD, there have been relatively few studies examining oscillatory neuronal firing and LFPs in dystonia patients. Thus, much less is known about the possible role of such activity changes in mediating the symptoms. Oscillatory activity in the GPi in dystonic patients is typically different from that observed in PD. The predominant beta oscillations that are characteristic for PD are absent and instead there appears to be increased spectral power in the 4 – 10 Hz band, especially in GPe (Silberstein et al., 2003). However, Starr et al. reported that oscillatory activity of GPi neurons is fairly similar to that in PD and suggested that an important difference between dystonia and parkinsonism may be the coupling of abnormal synchrony and oscillatory activity with specific mean firing rate changes (lower rates in dystonia and higher rates in PD, see figure 5 and Starr et al., 2005, Schrock et al., 2009). As noted before, this is not necessarily the case in all patients (Hutchison et al., 2003).

The final common pathway linking many of the different forms of dystonia may be abnormalities in cortical processing. Imaging studies in dystonic patients have demonstrated widespread changes in the activity of the primary motor cortex, SMA, anterior cingulate and dorsolateral prefrontal motor areas (for instance, Carbon et al., 2004, Asanuma et al., 2005). A large number of studies have demonstrated cortical sensory abnormalities (Berardelli et al., 1998, Hallett, 1998, Butefisch et al., 2005). Finally, intracortical excitability may also be increased (Deuschl et al., 1995, Kaji et al., 1995, Ikeda et al., 1996, Hamano et al., 1999, Sommer et al., 2002), and motor learning and plasticity may be disturbed (summarized in Breakefield et al., 2008). Given these extensive cortical activity changes, it is possible that the observed changes in the basal ganglia are in part not primary, but reflect some of the complex cortical alterations. For instance, altered sensorimotor maps similar to those in cortex, have been identified in the putamen (Delmaire et al., 2005) and thalamic levels (Lenz and Byl, 1999, Lenz et al., 1999). However, such changes were not seen in recent GPi recording studies (Chang et al., 2007, Tang et al., 2007).

5. Dyskinesias

Strictly speaking, the term ‘dyskinesia’ refers to an impairment in the ability of performing a voluntary movement. However, it is most commonly used to refer to involuntary spasmodic or repetitive movements such as those associated with chorea, i.e., irregular, brief and jerky involuntary movements. Unlike dystonia, there are no abnormal postures or sustained muscle contractions. Dyskinesias are heterogeneous in origin. They may arise without an identifiable cause, or secondary to other diseases. Examples for secondary types dyskinesia are ballismus, a characteristic form of large-amplitude proximal movements, which often occurs as a consequence of ischemic strokes in the STN (Ristic et al., 2002, Postuma and Lang, 2003, Lee et al., 2005), the involuntary movements associated with the use of dopaminergic drugs in PD (Fahn, 2000, Schrag and Quinn, 2000, Obeso et al., 2004), or movements seen with the long-term use of dopamine-receptor blocking drugs in patients with psychiatric or gastrointestinal diseases (tardive dyskinesias, see, e.g., review by Soares-Weiser and Fernandez, 2007). These varied conditions are grouped together here, because they share certain pathophysiologic features which will be described below.

Over the last decades, it has been shown that abnormalities in many of the basal ganglia nuclei can result in dyskinetic movements, including the striatum, GPe and STN. A potential causative role of striatal activity changes in some forms of dyskinesias or other hyperkinetic movement disorders (including myoclonus and tics) is supported by studies of the effects of

GABA receptor antagonists in the striatum (Yoshida, 1991, Yoshida et al., 1991, Darbin and Wichmann, 2008, McCairn et al., 2009, Worbe et al., 2009). Furthermore, levodopa-induced dyskinesias are thought to arise from activity changes in the striatum (e.g. see review by Calabresi et al., 2010), subsequently resulting in altered firing rates and patterns of neurons throughout the rest of the basal ganglia-thalamocortical circuitry.

In terms of an involvement of GPe activity, GABA receptor blockade in this nucleus has been linked to dyskinetic movements (Grabli et al., 2004, Bronfeld et al., 2010). Similarly, STN inactivation is associated with ballismus, as shown through studies using electrolytic STN lesioning or injections of fiber-sparing excitotoxins or GABA-receptor agonists into the STN (Whittier and Mettler, 1949, Carpenter et al., 1950, Bergman et al., 1990, Hamada and DeLong, 1992a, b, Wichmann et al., 1994).

In contrast to the use of the rate model to explain the hypokinetic features of parkinsonism as a consequence of increased basal ganglia output to the thalamus (see above), the development of involuntary movements can be understood as the result of reductions in basal ganglia output to the thalamus. This is supported by studies in animals and humans with drug-induced dyskinesias which have provided evidence that the neuronal activity in the basal ganglia output nuclei is strongly reduced in animals or in humans with parkinsonism, who display dyskinesias after being treated with dopamine receptor agonists (Filion et al., 1991, Papa et al., 1999, Levy et al., 2001). Likewise, studies in the late 1980s and early 1990s showed that the ballistic movements seen with STN inactivation are accompanied by substantial reductions of firing in GPe and GPi, in this case easily understood as a consequence of reduced or eliminated glutamatergic STN inputs to these nuclei (Hamada and DeLong, 1992a, b). It is also conceivable that GABA-receptor antagonist injections in GPe results directly or indirectly in enhanced inhibition of GPi which may then contribute to dyskinetic movements.

In terms of the rate model it is paradoxical that GPi inactivation rarely (if ever) leads to dyskinesias. In fact, GPi lesioning is clinically used to abolish dyskinesias in patients with treatment-resistant hyperkinetic movements. This observation argues strongly against the possibility that cessation of GPi activity alone results in dyskinesias (e.g., Obeso et al., 2000), and suggest that a certain level of GPi activity, as well as abnormalities of basal ganglia output other than rate changes play an important role in the development of involuntary movements (Picconi et al., 2003, Silberstein et al., 2005, Alonso-Frech et al., 2006). The role of oscillatory activity in mediating dyskinesias has not been extensively studied. There are, however, a few reports in PD patients reporting significant alterations in oscillatory power in STN and GPi during periods of dyskinesias (Silberstein et al., 2005, Alonso-Frech et al., 2006) and these point to the possible involvement of such abnormal activity in the pathogenesis of dyskinesias.

6. Conclusion

The identification of abnormalities in firing rates or patterns in the basal ganglia and related areas in movement disorders remains a highly important field of research, because such findings may eventually help us to a better understanding of the involvement of the basal ganglia in parkinsonism, and the development of new treatments to help patients with these devastating diseases more specifically and with fewer side effects than currently possible. The facts described in the preceding sections demonstrate how much has been learned about changes in the basal ganglia activity in movement disorders. Most of these disorders are associated with changes in firing rates and firing patterns. The behavioral phenotypes of the individual disorders may depend strongly on the specific combination of rate and pattern abnormalities.

Of course, much still needs to be learned. For instance, we still do not know which of the rate or pattern changes cause specific disease phenotypes. We also need to better understand the importance of finding overlapping firing abnormalities in different movement disorders (such as PD and dystonia), to appreciate the regional specificity of firing rate and pattern changes, and to gauge the importance of subtle abnormalities (such as the duration or structure of bursts), as well as the development of synchronous network activities and deficits in synaptic plasticity. Furthermore, comparatively little is known about the downstream consequences of the firing rate and pattern abnormalities in the basal ganglia on information processing in thalamic, cortical and brainstem activities, yet these downstream effects will eventually determine the behavioral consequences of abnormal basal ganglia discharge.

Finally, researchers begin to realize that the assumption that a given disease is a ‘basal ganglia disease’ may need revision. We are gaining a much better appreciation for the widespread structural or biochemical changes that accompany diseases such as PD or dystonia which involve many brain regions other than the basal ganglia. It is therefore possible that some of the motor abnormalities in diseases such as dystonia or forms of dyskinesias do not originate in the basal ganglia, but in other areas, such as the thalamus, cortex, brain stem, or the cerebellum.

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Abbreviations

6-OHDA	6-hydroxy dopamine
CM	centromedian nucleus of thalamus
CMA	cingulate motor area
DBS	deep brain stimulation
EMG	electromyogram
GPe	external pallidal segment
GPi	internal segment of the globus pallidus
LFP	local field potentials
M1	primary motor cortex
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
PD	Parkinson’s disease
Pf	parafascicular nucleus of the thalamus
PMC	premotor cortex
PPN	pedunculopontine nucleus
SMA	supplementary motor area
SNc	substantia nigra, pars compacta
SNr	substantia nigra pars reticulata

STN	subthalamic nucleus
VL	ventrolateral nucleus of the thalamus
VA	ventral anterior nuclei of the thalamus

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Highlights

- Movement disorders are associated with varying combinations of changes in discharge rate and oscillatory synchronized bursting activities
- The specific combination of these changes may determine the eventual behavioral disease manifestations
- The link(s) between basal ganglia firing abnormalities and movement disorder symptoms are not (yet) established

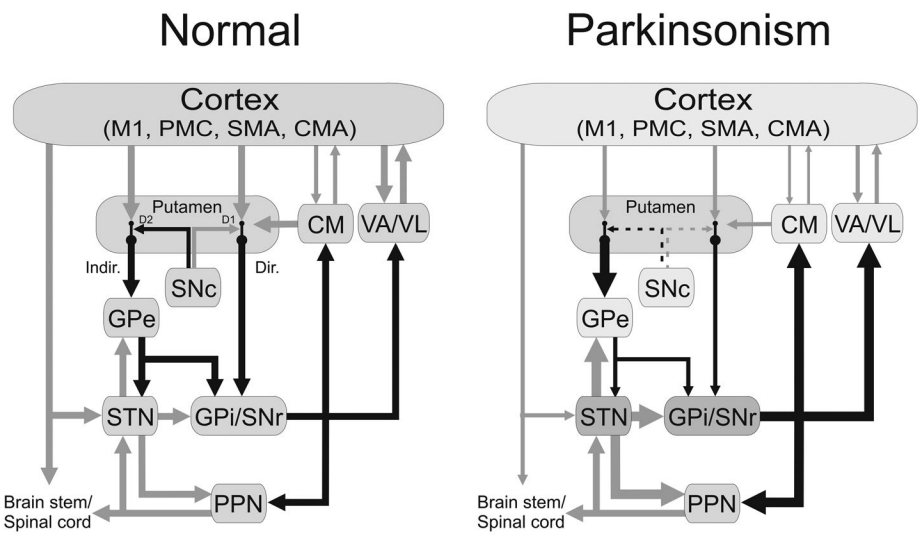

Figure 1.

Parkinsonism-related changes in overall activity (‘rate model’) in the basal ganglia-thalamocortical motor circuit. Black arrows indicate inhibitory connections; gray arrows indicate excitatory connections. The thickness of the arrows corresponds to their presumed activity. Abbreviations: CM, centromedian nucleus of thalamus; CMA, cingulate motor area; Dir., direct pathway; D1, D2, dopamine receptor subtypes; Indir., indirect pathway; M1, primary motor cortex; Pf, parafascicular nucleus of the thalamus; PMC, premotor cortex; PPN, pedunculopontine nucleus; SMA, supplementary motor area. See text for other abbreviations. Reprinted, with permission, from Galvan and Wichmann (2008).

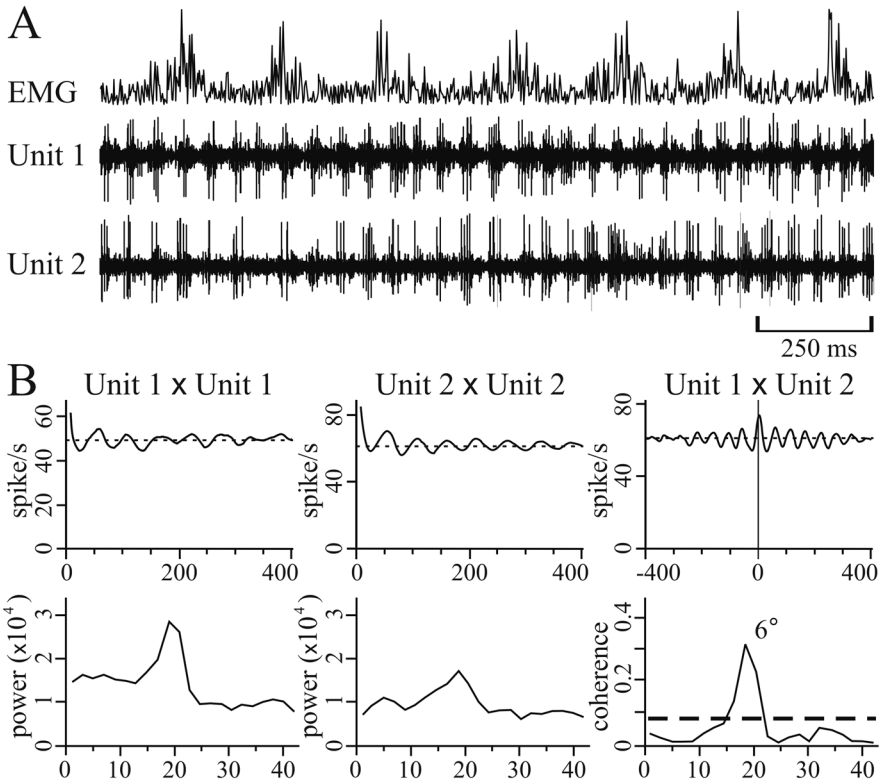

Figure 2.

Example of intraoperative microelectrode recordings in a patient with PD. A, The second and third trace (Unit 1 and Unit 2, respectively) show the discharge activity of two simultaneously recorded STN neurons during wrist tremor, as demonstrated with the recording of rectified wrist extensor electromyographic activity (EMG, top trace). The two neurons generated oscillatory bursts in synchrony with each other. B, Correlograms (top row) and spectra (bottom row) of the traces shown in A (the total sample time used to construct these plots was 29 sec). In all correlograms, the lines indicate mean firing rate. In the cross-correlogram (right panel of top row), Unit 1 is used as the trigger. The thick dashed line in the coherence function indicates the level of significant coherence, and the number by the peak is the phase difference. Reprinted, with permission, from Levy et al (2000).

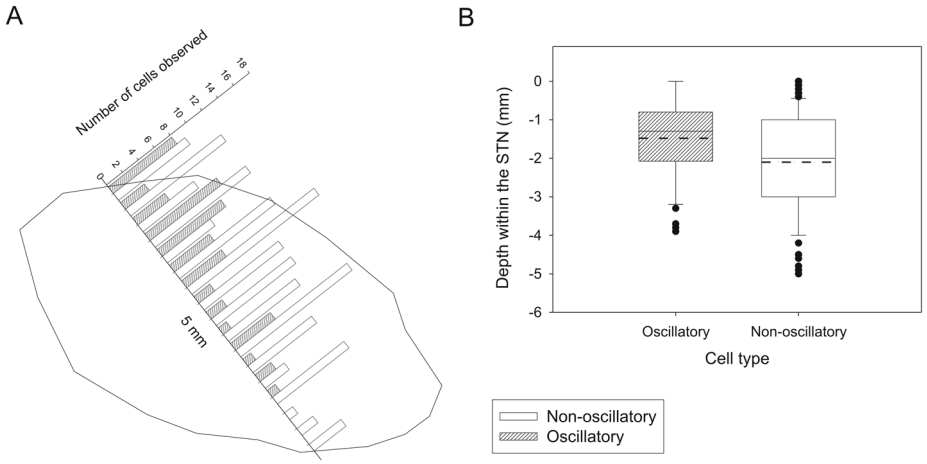

Figure 3.

Distribution of oscillatory and non-oscillatory cells located within the STN in a microelectrode recording study of 14 patients with PD. A. Histogram showing the distribution of oscillatory (n = 56) and nonoscillatory (n =144) cells located within the STN from top to bottom (0 to −5 mm, respectively), binned in 0.3-mm intervals. The x-axis also represents the typical trajectory of a microelectrode track through STN superimposed on the outline of the STN taken from the sagittal 12.0-mm lateral stereotactic STN map (Schaltenbrand and Wahren, 1977). Most of the oscillatory cells were found in the more dorsal portion of the STN, whereas the non-oscillatory cells were equally distributed along the nucleus. B: box plots of oscillatory and non-oscillatory cells' distribution within the STN. Solid and dashed lines indicate the median and the mean depths, respectively (means ± SE: −1.5 ± 0.1 and −2.1 ± 0.1 mm for oscillatory and nonoscillatory cells, respectively; $P < 0.001$, t-test). Note the smaller number of observations in the last millimeter of STN attributed to the fact that in many cases the extent of the STN is < 5 mm. Reprinted, with permission, from Weinberger et al. (2006).

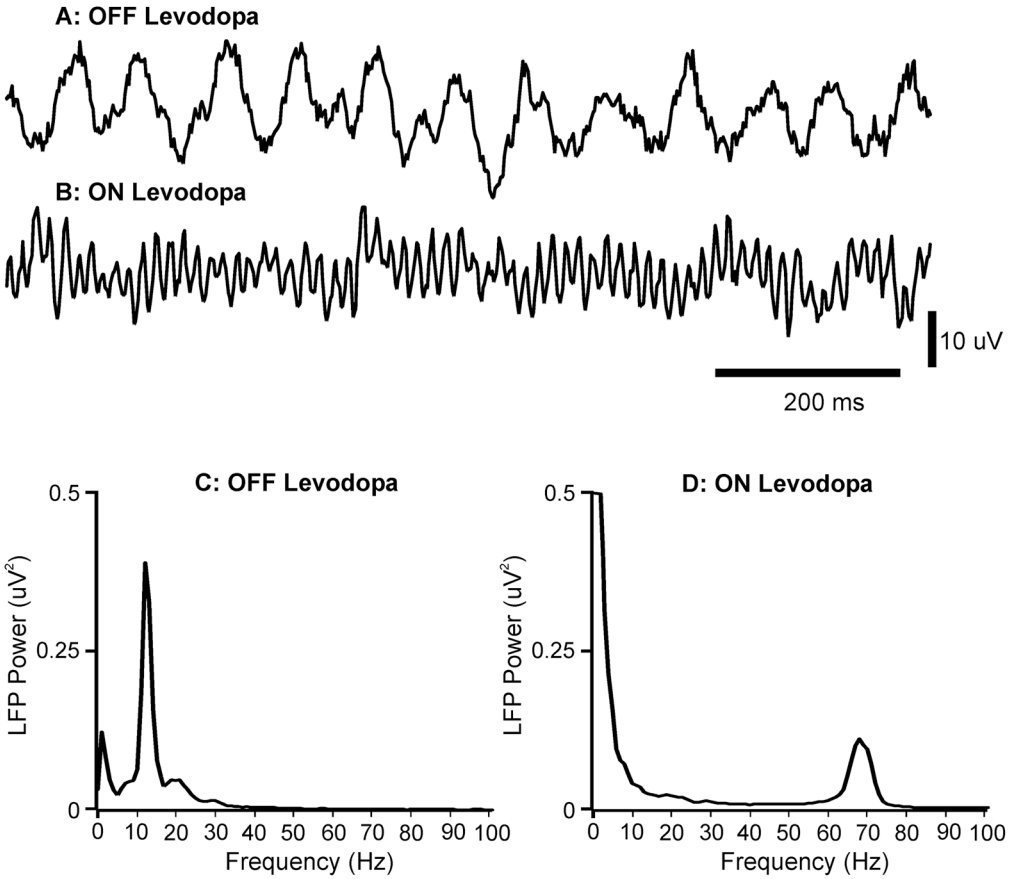

Figure 4.

Field potential signals recorded in a patient with PD with a macroelectrode positioned in the subthalamic area. A. Field potential signals recorded after overnight withdrawal of medication. B. Field potential signals recorded after subsequent levodopa challenge. C. Power spectrum of field potentials recorded after overnight withdrawal of medication (140 s record). D. Power spectrum of field potential signals recorded after subsequent levodopa challenge (140 s record). There was a spectral peak at around 13 Hz off medication, and at around 70 Hz after levodopa treatment. Reproduced, with permission from Brown and Williams (2005).

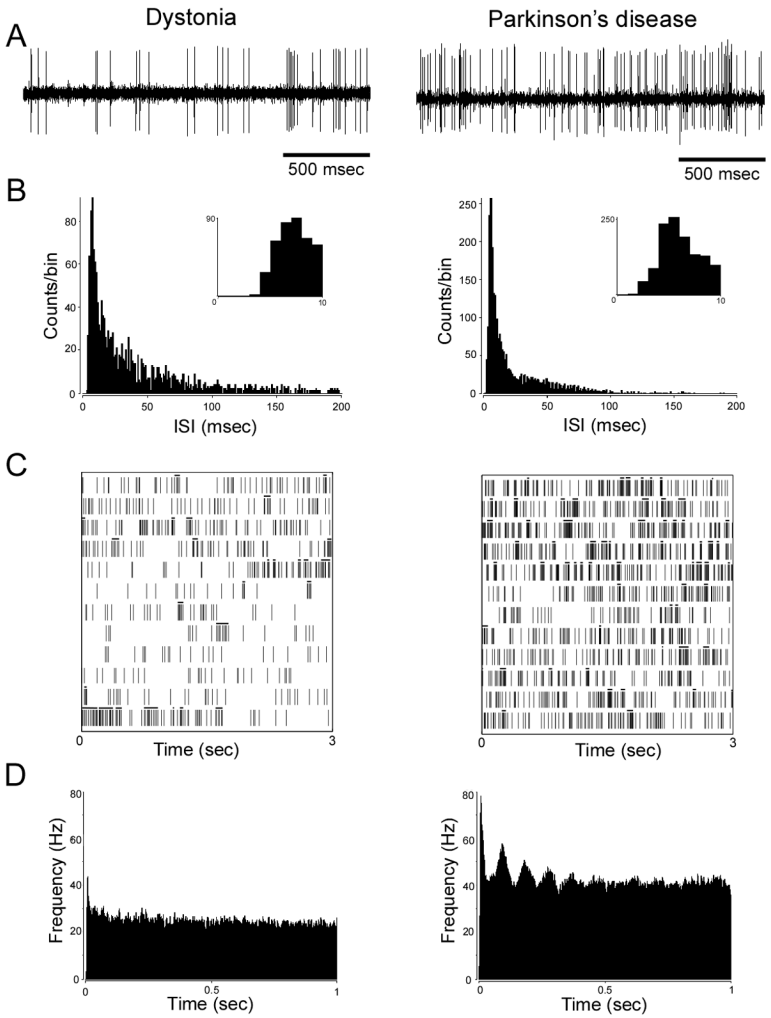

Figure 5.

Examples of electrophysiological recordings from STN cells in a patient with cranial-cervical dystonia (left column) and a patient with akinetic-rigid parkinsonism (PD, right column). A: A 2-s interval of neuronal recordings. B: interspike interval (ISI) histograms, bin size of 1 ms. Inset: expanded timescale demonstrating the absence of ISIs of <3-ms duration, consistent with the neuronal refractory period. C: raster diagrams showing bursting discharge. Bursts as defined by the Poisson "surprise" method (surprise value = 5) are labeled with a black bar above spikes that constitute a burst. Note the higher proportion of bursts per total number of spikes shown in the dystonia neuron (0.40 vs. 0.26 in the PD neuron). Consecutive rows (3 s of data per row) from bottom to top represent continuous 36-s recordings. D: autocorrelograms. The right autocorrelogram shows oscillatory activity of about 11 Hz. The unit on the left was not found to have significant oscillations. Reprinted, with permission, from Schrock et al. (2009).