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Abnormal Bursting as a Pathophysiological Mechanism in Parkinson's Disease

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Abstract

Despite remarkable advances in Parkinson's disease (PD) research, the pathophysiological mechanisms causing motor dysfunction remain unclear, possibly delaying the advent of new and improved therapies. Several such mechanisms have been proposed including changes in neuronal firing rates, the emergence of pathological oscillatory activity, increased neural synchronization, and abnormal bursting. This review focuses specifically on the role of abnormal bursting of basal ganglia neurons in PD, where a burst is a physiologically-relevant, transient increase in neuronal firing over some reference period or activity. After reviewing current methods for how bursts are detected and what the functional role of bursts may be under normal conditions, existing studies are reviewed that suggest that bursting is abnormally increased in PD and that this increases with worsening disease. Finally, the influence of therapeutic approaches for PD such as dopamine-replacement therapy with levodopa or dopamine agonists, lesions, or deep brain stimulation on bursting is discussed. Although there is insufficient evidence to conclude that increased bursting causes motor dysfunction in PD, current evidence suggests that targeted investigations into the role of bursting in PD may be warranted.

Keywords

burst; Parkinson's disease; basal ganglia

Introduction

Parkinson's disease (PD) is a debilitating, age-related neurological condition affecting nearly 1% of the population and growing with a projected annual cost of over \$50 billion in the United States alone by 2040 [1]. PD is a multi-system disease that affects wide areas of the brain, including substantial cell loss in dopaminergic, noradrenergic and serotonergic cell groups. While there are significant non-motor deficits in PD [2], PD is usually diagnosed and characterized in terms of dopamine-dependent motor dysfunction, including muscle rigidity, bradykinesia (slowness of movement), akinesia (poverty of movements), and resting tremor. The leading hypothesis on the origin of motor dysfunction in PD is that the loss of dopamine leads to abnormal neural activity in the basal ganglia, and that abnormal basal ganglia output influences thalamocortical interactions which, in turn, disrupts motor

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planning and execution (reviewed in [3]). Additionally, abnormal basal ganglia output may disrupt motor function through its outputs to the superior colliculus [4] and motor networks located in the brainstem [5] that control automatic processes such as muscle tone and locomotion. It was originally hypothesized that changes in neuronal firing rates within the basal ganglia were the primary pathophysiologically-relevant phenomenon (the ‘rate model’; [6, 7]); however, experimental findings testing this model have given inconsistent results and several predictions of the model have not been validated [8]. Other pathophysiological mechanisms have also been proposed including increased oscillatory activity particularly in the beta range of frequencies, increased synchronization of neuronal activity, and increased bursting. This review will focus specifically on the role of increased burst firing of basal ganglia neurons.

The outline of this review is as follows. The first section will attempt to define exactly what a burst is. The second section will describe several methods of detecting and analyzing bursts, particularly those used in PD research. Third, the functional significance of bursts is under normal conditions will be explored. Lastly, existing studies will be reviewed that investigate a pathophysiological role for abnormal bursting in PD, both in humans and in animal models. Specifically, studies investigating (1) if bursting is increase, decreased, or unchanged in PD, (2) if abnormalities in bursting progress with motor symptoms over time and (3) whether therapeutic approaches for PD (dopamine-replacement therapy, lesions, or deep brain stimulation) affect bursting will be examined.

What is a burst?

The term ‘burst’ is (vaguely) defined as a cluster of spikes from a single neuron that differs from other spikes in a particular way, usually being more closely spaced in time than neighboring spikes (Figure 1). As a consequence, investigators do not agree on what counts and does not count as a burst. This has resulted, in turn, in two main approaches to the problem of defining and detecting bursts: *template-based*, *system-specific* (and sometimes investigator-specific) approaches in which the start and termination of a burst is specially designed based on an investigator's knowledge and expectation of neural activity (referred to categorically as Template methods below) and *general statistical* approaches where a burst is a statistically significant spiking event. Rather than attempting to come up with a general definition for the promiscuous term ‘burst’, it may be more practical to distill out what the essential aspects of what a burst is:

1. *Transient*. One essential aspect of a burst is that it is a temporally short event, often consisting of just a handful of spikes. Two spikes (a doublet) are often not considered sufficient to count as a burst. A change in firing lasting for several seconds to minutes may not be considered a long burst but rather a change in background activity.
2. *Increase*. The second essential aspect of a burst is that spikes occur at a faster rate than at a previous time. It is often unclear just how large an increase in rate is required to constitute a burst.
3. *Reference Period or Activity*. The increase in spiking occurs with respect to some reference period of time or spiking activity. For system-specific template methods, this reference point is often *implicitly* defined based on an investigator's knowledge of spiking activity of neurons in their system. A general template defining the start and termination of a burst is defined as it detects most of the visually identifiable bursts. In statistical methods, a burst is considered to be an isolated event that is embedded on a backdrop of spiking activity. A neuron may fire with a particular pattern under some defined basal conditions prior to the burst event and returns to that pattern after burst cessation. In this case, the reference spiking must be defined

explicitly since a statistical model must be chosen. More complex background firing patterns operating over multiple time scales may require more complicated analyses [9].

A possible fourth element of a burst is that a burst is physiologically relevant, i.e. it is an information-carrying signal, not necessarily just a statistical anomaly. Let us consider a neuron that typically fires at 1 ± 1 Hz (mean $\pm$ SD) but sometimes fires in clusters of 3 spikes at 5 Hz (a statistically significant event by the investigator's method of choice). However, its post-synaptic neuron has a relatively low input resistance (and thus a fast membrane time constant) and demonstrates no reliable response in its spiking to this statistically significant 5 Hz "burst". Weak bursts such as these could be considered to be insignificantly (physiologically speaking) significant (statistically speaking). Although this may prove difficult to determine experimentally for any given neuron, it is important to note that the post-synaptic cell may determine the lower and upper bounds of what constitutes a physiologically-relevant burst signal in the presynaptic neuron.

An interesting special case prominent throughout the literature is with regard to neurons that have prominent oscillatory activity [10]. The neuron is said to fire bursts at the top of an oscillation. Using a template method, an investigator could choose to define a burst as a group of spikes where each ISI must be a less than a specific length and preceded by an ISI of several hundred milliseconds. In this case, each cluster of spikes is considered a burst. Thus the percentage of spikes in bursts is close to 100%. This definition is in stark contrast to a statistical approach in which the oscillatory firing pattern is the reference. In that case, a burst would be considered to be a group of spikes in which the neuron fires a greater number of spikes per cycle than expected. In Figure 1B, a neuron fires approximately 4 spikes on each cycle. On the fourth cycle, 8 spikes are generated. Thus according to this definition that is the only burst in that spike train. As this illustrates, the method by which a burst is defined may greatly affect our measurements of bursting and their subsequent interpretation.

In the same sense, one complication with any definition of a burst is in comparing two groups of spike trains in which the reference activity differs substantially. This is often done when comparing the activity of two different classes of neurons or before and after an experimental manipulation. To illustrate, consider a basal ganglia neuron that develops a strong oscillatory pattern after administration of a neurotoxin such as 6-OHDA or MPTP. To accurately measure changes in bursting, one would want to use the same burst detection method in both cases. This may become cumbersome in practice as several methods assume a particular distribution (e.g. Poisson Surprise). Thus, even though bursts and oscillations in PD are hypothesized to be independent [11, 12], a given method may not be able to be used for detecting bursts in the presence of significant oscillations. Careful consideration of such methodological details should be used in comparisons such as these, regardless of whether system-specific template or statistical methods are used.

A central assumption of this background firing activity aspect of bursting is stationarity, i.e. it does not change significantly over time [13, 14]. Non-stationarity may result from intrinsic factors within a neuron, extrinsic input to a neuron, changes in state of the animal or changes in the preparation (e.g., brain movements). Several useful statistical tests have been developed to detect non-stationarities [15]. Practically speaking, non-stationarities in spike trains are usually addressed with moving windows [16-18]. However, it can become particularly complex when long stable periods are not well defined (Figure 1C).

It is also imperative to recognize that a given neuron type may be capable of producing bursts by different mechanisms [19], possibly even at different locations along the somatodendritic tree. For example, a burst caused by a rapid series of excitatory post-synaptic potentials (EPSPs) may be fundamentally different from a low-threshold spike

(LTS) burst caused by activation of T-type calcium channels (Ca_v3). Differentiating burst mechanisms is important because they may implicate a particular input driving bursting as well as suggesting a drug target for therapeutic intervention. Analyzing the voltage of a neuron preceding and during bursting using intracellular recordings may also be useful in determining the electrophysiological signature of a particular type of burst.

Finally, it is important to recognize that the study and analysis of bursts of activity is not unique to neuroscience, as it appears to be a fairly ubiquitous natural phenomenon [20, 21]. Thus, burst methods developed in other fields may be useful to studies of bursting of neural activity.

Burst Detection and Analysis

Several methods have been devised to detect bursts in spike trains, typically from extracellular recordings in which the neuron's voltage is not accessible. The following list is not intended to be an exhaustive review of all methods available.

- The Quantity of 'Burstiness'. The simplest approach is to attempt to create a single value to represent the burstiness of a spike train or minimally categorize a spike train as 'bursty'. This is often done before and after an experimental manipulation to determine if some aspect of bursting has changed. This is sometimes as simple as a property of the distribution of interspike intervals (ISI) such as the mean, median, or coefficient of variation or may be much more complex [22, 23]. One common such metric is the burst index, which is the reciprocal of the mode divided by the firing rate [24]. Unfortunately as a global measure, methods such as these are unable to identify individual burst events and are strongly influenced by the background activity of the neuron. Furthermore, changes in pauses, significant transient periods of decreased neuronal activity, can have a large effect on global measures of burstiness.
- Template-based methods. The simplest method for detecting individual bursts is to detect when a particular ISI threshold is crossed. This 'threshold ISI' can be a fixed parameter [25-27] optionally requiring a preceding (or following) period of quiescence [28, 29] or can be determined from the ISI distribution [30-32]. The logarithm of the ISIs may also be used [33]. While intuitively simple and easy to implement, these methods do not allow for testing of the statistical significance for individual bursts. The histogram method [30] detects the presence of any bursts in a spike train using a chi-square test.
- Discharge Density Histogram (DDH) method [11]. This method utilizes the discharge density (the number of spikes within a small time window applied across the spike train) rather than ISIs. If a histogram of these discharge density values does not follow a Poisson distribution and has a positive skew then the spike train contains bursts. Some investigators choose to categorize a neuron as bursty at this point if this is the case. However, the histogram can then be used to determine the threshold ISI for the burst so that individual bursts can be identified.
- Poisson and Rank Surprise methods. The Poisson Surprise (PS) method [34] determines the probability that a sequence of spikes occurs in a small time interval in comparison to a Poisson (or random) spike train with the same average firing rate. The negative logarithm of this probability is termed its 'surprise' value [35, 36]. While popular, this method assumes that the underlying ISI distribution is Poisson (a parametric approach). The Rank Surprise (RS) method [37] removes this assumption by using ranks of ISIs instead of the actual ISIs (nonparametric).

- Robust Gaussian Surprise (RGS) method [18]. This method allows for the simultaneous detection of bursts and pauses in spike trains using the logarithm of ISIs rather than the raw ISIs. Bursts are detected as statistical outliers of a central distribution of all ISIs from all spike trains in an experimental group. Each burst is assigned a Bonferroni-corrected (to correct for multiple testing) surprise value as previously described for the PS and RS methods.

After burst detection, summary statistics of individually identified bursts are often calculated. This often includes the metric of interburst rate and various measures of burst intensity: mean intraburst frequency, maximal intraburst frequency, mean number of spikes per burst or mean burst duration. The percent of all spikes in bursts is also sometimes calculated; however, this metric is not indicative of changes to burst rate or burst intensity. Further analysis of the relationship between individual bursts and other physiological process (e.g. local field potentials or behavioral metrics) should always be performed whenever possible.

Bursting as a Physiological Mechanism

An important role for bursts has been suggested in a variety of physiological processes such as spatial localization [38], visual processing [39, 40], direction selectivity [41], feature extraction [42, 43], reward learning [44], and attention [45]. But what is so special about bursts? Several hypotheses have been put forth regarding the physiological role of bursts, particularly at the synapse. One hypothesis of pre-synaptic function [46] is that bursts are more reliable in releasing neurotransmitter than single spikes. A single spike invading the presynaptic terminal causes the release of a vesicle with some probability; hence multiple spikes are more likely to release vesicles than just a single spike [47]. This can be enhanced or diminished if short-term plasticity (facilitation or depression, respectively) occurs at that synapse. An interesting consequence of having a synapse that is both facilitating and depressing is that a synapse may show a particular frequency preference, or resonance, at which transmission is particularly effective [48]. Another hypothesis is that bursts may be more effective at the release of other neuroactive molecules such as neuropeptides [49].

Greater release of neurotransmitter may have significant effects on the post-synaptic cell. For example, bursts in the presynaptic neuron may evoke sufficient excitatory post-synaptic potentials to generate an action potential. On the other hand, if the pre-synaptic neuron releases GABA then sufficient inhibitory post-synaptic potentials may be evoked to prevent spiking. However, if that inhibitory input is sufficient to de-inactivate $\text{Ca}_v3.1$ (T-type) calcium channels, then a rebound low-threshold calcium spike (LTS) may result [50]. This may be particularly important in PD as changes in bursting have the potential to modify rebound LTS bursting in the motor thalamus, possibly resulting in motor dysfunction [51, 52].

Another post-synaptic effect of bursts is that bursts may activate different types of receptors. One example of this involves the “spill-over” of neurotransmitter to receptors in neighboring active zones or located extrasynaptically [53]. This may involve the activation of NMDA receptors whose magnesium block may be partially relieved by earlier spikes in the burst. This may activate metabotropic receptors, which may generate a long-lasting change in neuron's voltage.

A final possible effect of bursts is to induce LTP (long-term potentiation) or LTD (long-term depression) at the synapse [46]. This may result from increases in intracellular calcium in the presynaptic and/or postsynaptic neuron during the burst, the activation of metabotropic receptors, etc.

Bursting as a Pathophysiological Mechanism in PD

Is bursting in basal ganglia neurons increased, decreased, or unchanged in PD?—Many studies in dopamine-depleted animals, including MPTP-treated non-human primates (NHPs), and awake, 6-OHDA-treated rodents, as well as intraoperative recordings in PD patients undergoing neurosurgical procedures have investigated this question. Although this review focuses on data from awake subjects, it should be noted that it is often difficult, particularly in the operating room, to control the level of anesthesia or drowsiness at the time of the recording. Data from each species will be discussed in turn.

NHPs: Early studies in NHPs described a noticeable increase in burstiness of neurons in the globus pallidus internal segment (GPi), globus pallidus external segment (GPe) with lesion of the nigrostriatal pathway [54] or MPTP treatment [55-57]. These observations were analyzed in further detail in later studies using more quantitative techniques (described above). Using an autocorrelogram-based estimation method on non-oscillatory cells, Bergman and colleagues show an increase in the percentage of bursty neurons (STN: 69% control, 79% MPTP, 15% increase; GPi: 78% to 84%, 8% increase), a decrease in the average burst duration (STN: 121 to 81 ms, 33% decrease; GPi: 213 to 146 ms, 31% decrease), and no change in the number of spikes per burst in the subthalamic nucleus (STN) and GPi after MPTP treatment [58]. Thus, more STN and GPi neurons fired bursts with a faster intraburst frequency in the parkinsonian state. Using the DDH method, Boraud [59, 60] also found that the percentage of bursty neurons in the GPi increased dramatically from approximately 20% to 75% (275% increase); however, it is unclear why the percentage of bursty neurons in the normal GPi differs substantially from the aforementioned Bergman paper in which 78% of normal GPi neurons were considered bursty. These findings have also been confirmed using the PS method [61, 62]. Wichmann et al. [61] found a 257% and 67% increase in the proportion of spikes in bursts in the GPi and SNpr, respectively (two monkeys were lightly anesthetized in this study; GPi: 1.3% to 4.6%; SNpr: 0.8% to 1.3% after MPTP treatment). Soares et al. [62] also found an increase in the proportion of spikes in bursts in the GPi (0.3% to 0.9%, 200% increase) and STN (1.2% to 2.3%, 92% increase). Mixed results have been found for the GPe with one series of studies finding no effect of MPTP [59, 60, 63] and another finding an increase in bursting [62, 64]. A recent study [65] using a machine learning algorithm also found that increased bursting best discriminated normal from MPTP spike trains in the GPi and STN with the best overall feature discriminating the parkinsonian state being differences in STN intraburst frequency (74 Hz to 120 Hz; 62% increase). Together, these studies that bursting is increased in the STN, GPi, and SNpr in the Parkinsonian state with perhaps more moderate effects in the GPe.

Wichmann and Soares [64] conducted a detailed study noting significant differences in a variety of intraburst and interburst metrics from the GPe, STN, and GPi before and after MPTP treatment. A common finding between structures was that the average length of a burst increased after MPTP. A decrease in the ISIs leading up to the burst was found in both pallidal segments in both normal and MPTP conditions. Intriguingly, the ISI immediately preceding the onset of the burst was often positively correlated with burst length supporting the idea that some of these bursts may be generated by a rebound mechanism. This ISI was enhanced after MPTP in the GPe and STN but decreased in the GPi. Further study of these results is needed to determine how such complex changes in bursting could disrupt basal ganglia processing in the Parkinsonian state.

6-OHDA rodents: Numerous studies have investigated changes in the activity of basal ganglia neurons in unilaterally lesioned 6-OHDA rodents, particularly the anesthetized rat. Neurons in the striatum [66], globus pallidus (GP) [67-69], STN [70, 67, 71], and SNpr [72-75, 71] of 6-OHDA rats develop a strong preference to oscillate in-phase or out-of-

phase with the slow (< 1 Hz) oscillation in the cortex [76, 77]. However, only a few studies have recorded the activity of single neurons in the awake rodent where neural activity is not entrained by this oscillation. An initial study in locally anesthetized, immobilized 6-OHDA-treated rats noted that bursting increased in the GP as compared to controls [78]. Further studies in the SNpr and entopeduncular nucleus (EP; the rodent homolog of GPi) found that bursting was low in these structures with no significant increase in the proportion of bursting (DDH method) neurons in the lesioned group when compared to controls [79, 80]. On the other hand, a decrease in the proportion of bursty STN neurons (DDH method) was found after 6-OHDA injections [81]. However, there was no change in the intensity of bursting. An increase in interburst rate (PS method) was also found in the striatum in 6-OHDA treated rats [82].

PD patients: Recordings have been made from late stage, medically intractable PD patients undergoing ablative or deep brain stimulation procedures. Although it is difficult to determine whether bursting is increased in these patients due to lack of pre-disease control recordings in addition to the inability to control the level of arousal at the time of recording, a couple of studies have directly compared recordings from PD patients to recordings from normal NHPs. An increase in bursting in PD patients has been found in both the GPi [83] and STN [84], but not in the GPe [83]. However, it is important to note that the recordings in the GPe were not targeted at the motor territory of the GPe.

Changes in bursting have also been investigated in patients undergoing neurosurgery for other diseases (Huntington's disease, HD; dystonia; and essential tremor, ET). Starr et al. [83] found that the proportion of spikes in bursts in the GPi was increased in PD and dystonia in comparison to normal NHPs. One metric of bursting (burst index) was increased in dystonia as compared to PD (not confirmed using the PS method). An increase in bursting in dystonia over PD has been replicated in the GPi [85] and also found in the STN [86]. Starr et al. also found that there was no difference in bursting in the GPe between normal NHPs, dystonia, and PD. An increase in bursting in the GPi was also seen in PD patients when compared to HD patients [87], although recent studies suggest that bursting may be increased in HD [88]. However, it is hypothesized that the activity of basal ganglia neurons may be altered in dystonia and HD [7, 89]. A better control may be essential tremor, which is thought to be more cerebellar in origin [90]. A two-fold increase in the number of bursty STN neurons with no change in burst intensity was found in PD patients when compared to ET patients [91].

Together, these results in PD patients are in general agreement with the above studies in animal models of PD; namely, that increases in bursting are found in the STN and GPi.

The mechanisms responsible for this enhanced bursting of basal ganglia neurons are not known but may result from factors such as changes in the intrinsic properties of neurons, extrinsic synaptic input, synaptic plasticity, or gene expression. For example, STN and SNpr neurons recorded in isolated brain slices from dopamine-depleted rats or under acute dopaminergic blockade display increased bursting behavior [92-94], possibly due to upregulation of rebound HCN3-mediated currents [95]. Changes in synaptic plasticity may further enhance these neurons propensity to fire in bursts [96-98]. Further studies are needed to determine the causal role, if any, for such mechanisms in augmenting burst generation within the basal ganglia in PD.

Does bursting progress with symptoms?—If bursting plays a causal role in PD symptomatology then one might expect that one or more symptoms may get worse as abnormal bursting progressively increases in frequency or in intensity. In their original studies, Miller and DeLong describe that bursting in the GPi became more pronounced

during a series of five MPTP injections that were sufficient to induce parkinsonism [55]. With more severe parkinsonism, oscillatory bursting (12-15 Hz) was observed. Intriguingly, with recovery they note that bursting gradually diminished.

The time course of bursting after 6-OHDA injections has mostly been studied in the anesthetized rat. Dopaminergic terminals that are exposed to intrastriatal 6-OHDA injections begin to degenerate within a few hours after injection [99]. Cell bodies begin to degenerate over the next few days. 50% of dopaminergic neurons are lost within 2 weeks with continued degeneration occurring 8 to 16 weeks [100, 99]. Behavioral deficits may progressively worsen over this time period [101]. Recordings from anesthetized 6-OHDA treated rats show a progressive increase in the number of bursty STN neurons over this time period [102, 103]. Further studies are needed to determine whether the onset of abnormal bursting occurs immediately before or at the onset of motor dysfunction.

Together, these studies in animal models suggest that abnormal bursting may progressively worsen with disease progression. They suggest that changes in bursting may appear early in the course of the disease and may precede the emergence of beta oscillations [104-107]. This hypothesis has been difficult to test in humans because surgery is typically reserved for only advanced patients with medically intractable PD. Nevertheless, a recent study found no difference in the burst indices of STN neurons in two different stages of PD: an early-stage PD group (average UPDRS-III score of 27 off medication) and a late-stage PD group (average UPDRS-III score of 42, off medications) [108]. Further studies are needed to replicate those results and to show whether burst metrics correlate with motor deficits at the time of recording.

Do therapeutic approaches for PD affect bursting?—If abnormal bursting drives one or more symptoms in PD then one might expect that therapeutic approaches for that symptom may reduce bursting to normal levels. Before continuing on to review current evidence on this topic, three important considerations must be made. The first is that none of the aforementioned treatments for PD (i.e. dopamine-replacement therapy, brain lesions, and deep brain stimulation) specifically reduce or suppress bursting alone nor are they limited to one particular target (e.g., bursty cell bodies of SNpr or GPi/EP output neurons). This confound will need to be addressed with more specific experimental manipulations. Secondly, many of these therapeutic approaches have motor side effects, such as dyskinesias, indicating that “normal” levels of activity were not restored. Confounds such as these may introduce many false negatives (e.g., bursting was not changed because the recorded neuron was not part of the ensemble causing a motor symptom) and false positives (e.g., bursting was changed due to simultaneous activation/inhibition of the recorded neuron even though it was not part of the ensemble causing a motor symptom).

Dopamine-Replacement Therapy: Many symptoms of PD (e.g. bradykinesia, akinesia, rigidity, tremor) are responsive to treatment with the dopamine precursor levodopa and dopamine receptor agonists. Initial studies found that administration of levodopa had no significant effect on the proportion of bursty GPe neurons (DDH method) in MPTP-treated NHPs [59, 60]. However, there was a significant reduction in the proportion of bursty GPi neurons. Another study using chronic administration of levodopa found that the proportion of bursty neurons (DDH method) in the SNpr increased although several other metrics of bursting did not change [109]. There was no effect of levodopa administration on bursting in striatal neurons.

Several studies have investigated the effects of systemically administered dopamine agonists, particularly the non-selective D1/D2 receptor agonist apomorphine [110], on bursting in basal ganglia neurons. Particular attention was paid to studies in which

dyskinesias were not observed. Ruskin et al. [79, 80] noted that there were no bursty SNpr or EP neurons in locally anesthetized, 6-OHDA-treated rats before or during administration of apomorphine (DDH method); however, a large increase in the proportion of bursty EP neurons was found after co-administration of SKF-38393 (partial D1 agonist) and quinpirole (D2 agonist). It is unclear, however, whether such doses are dyskinetic since these rats were immobilized. There was no effect of apomorphine in the interburst rate (PS method) of striatal neurons; however, there was a large increase in the intraburst rate. Apomorphine caused an increase in the interburst rate of striatal neurons on the non-lesioned side.

The effect of systemic apomorphine on bursting has also been investigated in PD patients. In an early study, Hutchison et al. found that administration of a therapeutic dosage of apomorphine did not affect the overall burst index of GPe or GPi neurons [24]. However, a later study of the same authors found a 27% and 61% increase in the proportion of spikes occurring in bursts in the GPe and GPi, respectively [111]. A significant increase in the proportion of spikes in bursts has also been found in the STN [112].

Two recent studies investigated the effects of local application of SKF-82959 (a D1/D5 receptor agonist) and quinpirole (a D2 receptor agonist) in MPTP-treated NHPs. Application of SKF-82959 increased burst firing (PS method) in the GPi but had no effect in the SNpr [113]. Application of quinpirole reduced bursting (PS method) in the GPe, had no effect in the GPi, and increased bursting in the SNpr [114].

Although inconsistent, these results cast doubt on the hypothesis that there is a global, normalizing reduction in bursting that occurs throughout the basal ganglia with dopamine-replacement therapy.

Brain Lesions and Deep Brain Stimulation: Lesions of the basal ganglia have been used to treat the motor dysfunction in PD for nearly 75 years [115, 116]. Despite this long history, the author was unable to find any publications specifically investigating the effect of lesions (permanent or pharmacological) on bursting in efferent targets in awake, PD model animals or PD patients.

Another very effective approach for medically intractable PD is deep brain stimulation (DBS), often of the STN or GPi [117]. While the mechanisms of action of high frequency DBS are not known [118-121], several studies have investigated whether bursting is changed during or immediately following DBS (in humans) or HFS (high frequency stimulation in rodents or non-human primates) with the hypothesis that behaviorally effective stimulation would restore the abnormally increased bursting to normal, non-pathological levels.

STN-HFS/DBS: Initial studies in MPTP-treated NHPs suggested that STN-HFS regularized the firing pattern of GPe and GPi neurons [122]. When bursts (PS method) were analyzed specifically in another paper [123], it was discovered that in response to STN-HFS, the interburst rate increased in the GPe and decreased in GPi (this was significant in one animal but not in a second animal, possibly due to a small sample size). Furthermore, there was a significant increase in the intraburst firing rate in the GPe but no change in the GPi. A later modeling study of the aforementioned data reproduced the finding that bursting in the GPi is reduced (interburst rate, intraburst rate and burst duration) with STN-HFS, although their simulations did not capture increased bursting in the GPe [124].

The effect of STN-DBS on STN neurons has also been studied. An initial study in PD patients found that several STN neurons developed a greater tendency to burst with the

stimulation [125]. A later study found that bursting neurons (detected with the DDH method) changed their firing pattern to a random pattern [126].

One study has looked at the effect of STN-DBS on bursting in SNpr neurons [127]. The authors found a 51% decrease in the percentage of spikes occurring in bursts (DDH method), albeit none of the SNpr neurons were particularly bursty before DBS.

Another study has looked at the effect of therapeutic STN-HFS on simultaneously recorded neurons from the STR, GP, SNpr and STN in the awake, 6-OHDA-treated rat [128]. A decrease in burst rate and proportion of spikes in bursts (PS method) was found in GP and STN neurons while no effect was seen in STR or SNpr neurons.

GPe-HFS/DBS: A recent study investigated the effect of GPe-HFS on STN and GPi neurons in MPTP-treated NHPs [129]. They found that acute GPe-HFS reduced the proportion of bursty neurons (PS method) in the STN and GPi. There was no significant change in bursting in the thalamus (VA/VLo or VPLo) even though VA/VLo neurons developed an out-of-phase firing pattern with respect to GPi neurons.

GPe-HFS/DBS: GPi-HFS was previously shown to have no effect on bursting (PS method) in the GPe or GPi in MPTP-treated NHPs [130]. A similar study in humans found that during GPi-DBS most GPi neurons became loosely entrained to the stimulus, suggesting a more regular firing pattern, although some cells showed no change in firing pattern [131]. A reduction in the proportion of time spent bursting (PS method) was found in the period immediately following stimulation.

Conclusions

Overall, there is good evidence to suggest that there is an abnormal increase in bursting in many basal ganglia nuclei (particularly the STN and GPi), although the physiological mechanisms underlying bursting and its increase are largely unknown. Additionally, there is some evidence that suggests that bursting may correlate with increases in bursting. However, there is insufficient evidence at this time to conclude that increased bursting is a causal agent in the generation of motor dysfunction in PD.

If increased bursting caused one or more motor symptoms then one might expect that therapeutic manipulations may reduce bursting. However, the data is inconclusive as bursting was found to increase, decrease, and remain unchanged despite improved motor function. It is clear, however, that current therapies for PD (dopamine replacement therapy and HFS/DBS) do not appear to simply cause a global restoration of bursting to normal, non-pathological levels. Rather than simply a global loss of bursting in all basal ganglia structures, a more complex and mixed picture emerges [132]. Further experimental and computational studies, particularly at the network-level, are needed to determine how abnormally increased bursting actually disrupts normal motor function, how existing therapies are able to revitalize these dysfunctional neural networks, and suggest new targets by which therapy may be improved.

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Figure 1.

Illustrative examples of bursting. **A.** A typical example of a burst (arrow) occurring from a neuron that typically fires in single spikes. **B** illustrates the special case of bursts in an oscillatory spike train. Depending on the method used, either all spikes are considered bursts or only the middle cluster of spikes is considered a burst (see text). **C.** The process of defining bursts can be quite complex, especially when there are nonstationarities in the background firing activity of a given neuron. The arrow points to a particularly strong burst. The arrowheads point to two other putative bursts.