Neurobiology of Disease 41 (2011) 2–10

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Bursts and oscillations as independent properties of neural activity in the parkinsonian globus pallidus internus

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ARTICLE INFO

Article history:
Received 27 May 2010
Revised 10 August 2010
Accepted 12 August 2010
Available online 19 August 2010

Keywords:
Parkinson's disease
Microelectrode recording
Intra-operative
Electrophysiology
Basal ganglia
Spectral analysis

ABSTRACT

Bursts and oscillatory modulations in firing rate are hallmark features of abnormal neuronal activity in the parkinsonian Globus Pallidus internus (GPi). Although often implicated together in the pathophysiology of parkinsonian signs, little is known about how burst discharges and oscillatory firing (OF) relate to each other. To investigate this question, extracellular single-unit neuronal activity was recorded from 132 GPi cells in 14 Parkinson's disease patients. We found that burst firing was equally prevalent in OF and non-oscillatory firing (NOF) cells ($p>0.5$). More than half of the cells were characterized by either aperiodic bursty activity or OF, but not both. OF and NOF cells had statistically-indistinguishable levels of mean burstiness ($p=0.8$). Even when bursting and OF co-existed in individual cells, levels of burstiness and oscillatory power were seldom correlated across time. Interestingly, however, the few OF cells with spectral peaks between 8–13 Hz (α-range) were substantially burstier than other cells ($p<0.01$) and showed an unique burst morphology and stronger temporal correlations between oscillatory power and burstiness. We conclude that independent mechanisms may underlie the burst discharges and OF typical of most neurons in the parkinsonian GPi.

Introduction

Parkinson's disease (PD) is a chronic neurologic disorder with cardinal motor signs of muscle rigidity, tremor, slowness of movement (bradykinesia), and/or paucity of movement (akinesia). The fact that lesions placed in the globus pallidus internus (GPi) significantly ameliorate most of these signs indicates that the GPi plays an important role in the pathophysiology of parkinsonian motor signs (Coban et al., 2009; de Bie et al., 1999; Vitek et al., 2003). In animal models of parkinsonism (Filion and Tremblay, 1991; Miller and DeLong, 1987; Raz et al., 2000), and in idiopathic PD (Dogali et al., 1994; Hutchison et al., 1994; Lozano et al., 1996; Vitek et al., 1998), GPi neurons exhibit a constellation of abnormalities in spiking activity including elevated firing rates and altered firing patterns.

Although classical models of PD pathophysiology focus on altered GPi firing rates, growing evidence suggests that an increased prevalence of burst discharges (Kaneoke and Vitek, 1996) may be more important in the pathophysiology of PD (Bergman et al., 1994; Boraud et al., 1996, 1998, 2000; Filion and Tremblay, 1991; Hutchison et al., 1997; Starr et al., 2005; Wichmann and Soares, 2006). The mechanistic underpinnings of elevated bursting activity and its true clinical significance remain unclear, however. For example, medical and surgical therapies that reduce PD motor signs do not consistently reduce bursting activity in the BG (Chen et al., 2001; Hahn et al., 2008; Levy et al., 2001; McCairn and Turner, 2009).

In addition to increased burst discharges, oscillatory firing (OF; abnormal rhythmic modulations in firing rate) in the α- (8–13-Hz) and β- (13–30-Hz) frequency ranges is a common characteristic of BG activity in both PD patients and animal models of PD (Gatev et al., 2006; Levy et al., 2002b; Rivlin-Etzion et al., 2006a; Starr et al., 2005; Weinberger et al., 2006). Treatments that ameliorate PD signs [e.g., dopamine replacement therapy (DRT)] also reduce α- and β-frequency oscillations in spiking (Heimer et al., 2006; Levy et al., 2001) and local field potential (LFP) activity (Brown et al., 2001) in the GPi. Other anti-parkinsonian therapies, such as Deep Brain Stimulation (DBS) are also reported to decrease α- and β-frequency oscillations in the GPi (McCairn and Turner, 2009). However, not all studies support these findings (Foffani et al., 2006). Thus, the mechanisms and clinical significance of oscillatory firing also remain a topic of debate (Degos et al., 2009; Leblois et al., 2007; Mallet et al., 2008).

While oscillations and bursts are each consistent features of the parkinsonian BG, it remains unclear whether the two occur independently or are closely linked phenomena. The oscillations in neuronal firing rate associated with parkinsonism are often described

Abbreviations: OF, oscillatory firing; NOF, non-oscillatory firing.

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doi:10.1016/j.nbd.2010.08.012

as periodic bursts of neural activity, which has led to the frequent assumption that oscillations and bursts are closely linked, co-occurring phenomena (Rubin and Terman, 2004; Terman et al., 2002). For example, Galvan and Wichmann suggested that oscillations may be caused by rebound bursting within BG loops (Galvan and Wichmann, 2008). In contrast, based on theoretical considerations, Kaneoke and Vitek (1996) proposed that oscillations and bursts may represent two distinct processes. Existing evidence suggesting that they may be separate phenomena includes the observation that not all OF is bursty (Wichmann and Soares, 2006), and the fact that bursts and oscillations are not affected in a similar manner by pharmacologic and surgical therapies (see previous text). Here, we determined the degree to which OF and bursty activity in the GPi of PD patients are related to each other and to the severity of parkinsonian signs. An improved understanding of the relationship between bursts and oscillations will facilitate the analysis of pathophysiologic relationships between types of abnormal GPi activity patterns and specific parkinsonian signs.

Methods

Patient population

Single-unit recordings in the GPi were obtained from patients with PD undergoing microelectrode-guided stereotactic surgery for the placement of GPi DBS electrodes. All patients were responsive to levodopa (3,4-dihydroxy-L-phenylalanine) and had developed levodopa-induced dyskinesias or motor fluctuations. The severity of disease was assessed prior to surgery according to 27 sections of the Unified Parkinson's Disease Rating Scale (UPDRS). The UPDRS scores were assessed by different neurologists approximately one month prior to surgery, both off and on DRT. The responsiveness to DRT for each patient was quantified as the percentage improvement in his or her total UPDRS score following DRT. Scores were not available for 3 of the 14 patients. Anti-parkinsonian medications were withheld for at least 12 h before the surgery and all PD patients displayed overt parkinsonian symptoms without dyskinesias during the procedure. PD patients with severe off-period dystonia were excluded from the study. All subjects gave informed consent according to a protocol approved by the University of California San Francisco Institutional Review Board. All work was carried out in accordance with the Code of Ethics of the World Medical Association.

Surgical procedures and data collection

The methods used for microelectrode-guided stereotactic implantation of DBS electrodes in the GPi were similar to those described previously (Starr, 2002). Single-unit recordings were obtained using glass-coated platinum/iridium microelectrodes with 0.4–1.0-MΩ impedance (Microprobe, Gaithersburg, MD, or FHC, Inc., Bowdoin, ME). Signals were band-pass filtered (300–5000 Hz), amplified, played on an audio monitor, displayed on an oscilloscope, and digitized (20-kHz sampling rate) using the Guideline System 3000 or 4000 (FHC, Inc.). Microelectrodes were advanced into the brain using a motorized microdrive (FHC, Inc.). In a typical surgical case, one to two microelectrode penetrations separated by 2–3 mm were made serially through the GPi on each side. The GPe and GPi were distinguished by recording a 1–2-mm interval of electrical silence corresponding to the white matter laminae between the GPe and GPi. Cells were recorded at approximately every 300–800 μm along each trajectory through the GPi. Spontaneous neuronal activity of well-isolated cells was collected for 37.7 s on average (SD = 18 s).

All patients were sedated with propofol for the initial surgical incision and skull opening. Propofol was stopped at least 30 min prior to neuronal recording, which is sufficient time to wash out its known effect on single-unit discharge (Raz et al., 2008). All patients were awake and alert, and were asked to remain as still as possible with eyes open during periods of neuronal recording.

Data analysis

Digitized spike trains were imported into off-line spike sorting software (Plexon Inc., Dallas TX) for discrimination of single-unit action potentials by cluster-cutting in principal components space. This software generated a record of the time of occurrence (reduced to millisecond accuracy) for each action potential waveform detected. The spike times were used to calculate discharge rate, bursting, and oscillatory activity (see following text). Analyses were performed in the Matlab computing environment (The Mathworks, Natick, Massachusetts). Neuronal data were included in this study only if action potentials could be discriminated with a high degree of certainty as indicated by the presence of a clear refractory period in the inter-spike interval (ISI) histogram (>3 ms). Neurons were excluded if the size of their action potentials varied considerably in unison with the cardiac cycle. Fig. 1A illustrates the single-unit isolation that was typical for the recordings used in this study.

Burst firing

Bursts were detected using the Poisson Surprise Method (Legendy and Salcman, 1985; Wichmann et al., 1999). Each period of increased neuronal discharge was assigned a surprise value (S) that quantified the likelihood that this period of activity was a burst (i.e., a discrete period of elevated firing rate), rather than part of the neuron's ongoing stochastic firing pattern. The surprise value (S) can be represented as:

$$S = -\log(P)$$

where P is the probability that a Poisson spike train with the same mean firing rate would generate more spikes than emitted by the burst in the same time period. Bursts were identified as a sequence of at least three inter-spike intervals (ISIs) with a Poisson surprise value >5 ($P<0.00001$). For each such burst, immediately-adjacent preceding and trailing spikes were added incrementally to maximize the Poisson surprise value. The onset and offset of a burst were set as the times of the first and last spikes of the burst. Fig. 1B provides an example of this burst detection method in operation. The overall "burstiness" of a cell was quantified as the fraction of spikes that occurred during bursts relative to the total number of spikes in the cell's recorded spike train. The fraction of *time* each cell spent in bursts was also calculated. The two measures of burstiness (fraction of spikes and fraction of time in bursts) were found to correlate very closely with each other across cells (Spearman R = 0.99, $p<0.0001$, not shown), indicating that the two measures were redundant. All subsequent analyses used fraction of spikes in bursts as the single measure of the overall amount of burst discharges ("burstiness") in a cell's spike train.

We examined the magnitude and timing of changes in a neuron's mean firing rate around the time of burst onset (i.e., burst morphology) by generating burst-triggered averages of a neuron's instantaneous firing rate (i.e., ISI^{-1}) for each cell in which >5 bursts were detected. To aid comparisons between cells, a cell's mean firing rate during the 200 ms prior to burst onset was subtracted from its peri-burst average.

Oscillatory activity

Rhythmic modulations in neuronal firing rate (i.e., "oscillatory" firing) were quantified using a spike shuffling method (Rivlin-Etzion et al., 2006b) designed to control for artifactual autocorrelations that arise from the neuronal refractory period. Neuronal spike times were represented as a delta function with a temporal resolution of 1 ms.