Basal Ganglia 3 (2014) 187–195

Contents lists available at ScienceDirect

Basal Ganglia

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

Review

Abnormal bursting as a pathophysiological mechanism in Parkinson's disease

C.J. Lobb *

Department of Biology, Emory University, Atlanta, GA 30322, United States

ARTICLE INFO

Article history:
Available online 13 November 2013

Keywords:
Burst
Parkinson's disease
Basal ganglia

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.

© 2013 Elsevier GmbH. All rights reserved.

Contents

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

* Correspondence to: 1510 Clifton Road NE, Department of Biology, Emory University, Atlanta, GA 30322, United States. Tel.: +1 0114047271320.
E-mail address: clobb@emory.edu

2210-5336/$ – see front matter © 2013 Elsevier GmbH. All rights reserved.
http://dx.doi.org/10.1016/j.baga.2013.11.002

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 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 (Fig. 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 distil 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].

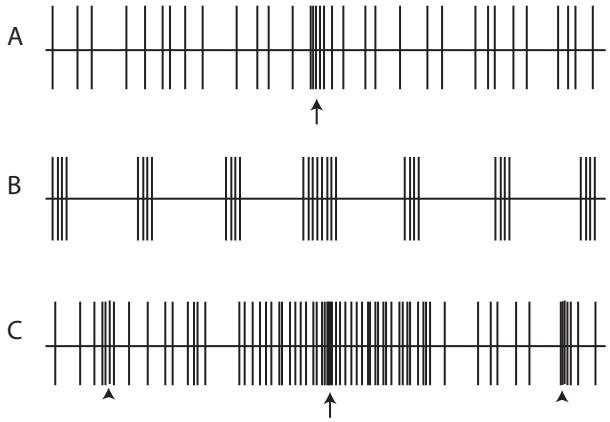

Fig. 1. Illustrative examples of bursting: (A) a typical example of a burst (arrow) occurring from a neuron that typically fires in single spikes, (B) illustrates the special case of bursts in an oscillatory spike train. Depending on the method used, either all spikes are considered bursts or only the middle cluster of spikes is considered a burst (see text). (C) The process of defining bursts can be quite complex, especially when there are non-stationarities 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.

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 pre-synaptic 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

Download English Version:

https://daneshyari.com/en/article/3036128

Download Persian Version:

https://daneshyari.com/article/3036128

Daneshyari.com