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Journal of Neuroscience Methods 147 (2005) 99–113

JOURNAL OF NEUROSCIENCE METHODS

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Decomposing rhythmic hippocampal data to obtain neuronal correlates

J.A. Gillis [a,b,*], W.P. Luk [a,d,1], L. Zhang [a,c,d,1], F.K. Skinner [a,b,c,e,2]

[a] *The Toronto Western Research Institute, UHN, Toronto, Ont., Canada M5T 2S8*
[b] *Department of Physiology, University of Toronto, Toronto, Ont., Canada M5S 1A8*
[c] *Faculty of Medicine (Neurology), University of Toronto, Toronto, Ont., Canada M5B 1W8*
[d] *Institute of Medical Science, University of Toronto, Toronto, Ont., Canada M5S 1A8*
[e] *IBBME, University of Toronto, Toronto, Ont., Canada M5S 3G9*

Received 28 May 2004; received in revised form 3 February 2005; accepted 25 March 2005

Abstract

Characterizing hippocampal electrical rhythmic activities requires a broadly applicable methodology that lends itself to physiological interpretation. In the intact hippocampal preparation, spontaneous rhythmic field potentials are exhibited in the 3–4 Hz range which evidence suggests is due to discharges in the inhibitory interneuron population. Because field rhythms arise as a network effect and models must be built from the neuron up, we focus on developing a methodology to deconstruct the non-stationary rhythms into its important constituents. This study uses 50 CA1/CA3 local field potentials to determine the important constituents, and an additional field recording and two intracellular recordings are examined subsequently. We determine the suitability of several time–frequency techniques. Distinct regions in the time–frequency domain which account for the signal behaviour are then characterized in terms of duration and frequency. These characteristics are interpreted as arising from a statistical mixture distribution. The decomposition of the 50 recordings yields three components whose patterns of activity match those of the intracellular recordings. We suggest that the statistical variability of the local field data can be linked to the variability of neuronal activities seen in intracellular data.

Keywords: Time–frequency; EEG; Cluster; Intracellular; Deconstruction; Mixture distributions; Oscillations

1. Introduction

Several brain structures including the hippocampus exhibit a diversity of rhythmic oscillations, often considered primarily in terms of frequency. The role of rhythms is frequently elucidated through correlative means (e.g., Sirota et al., 2003) with a focus on specific characteristics, and particularly frequencies. Extracellular and electroencephalogram (EEG) recordings of the hippocampus reveal the presence of rhythmic activities associated with distinct behavioural states. Coherent network rhythmic activity occurs in three main clusters in freely moving rodents: large amplitude irregular activity (LIA, 0.5–20 Hz), rhythmic slow activity (RSA, 4–10 Hz), and fast oscillatory activity (30–100 Hz) (Csicsvari et al., 2000; Vanderwolf, 1969). Although the role of these rhythms is not yet perspicuous, they have been functionally implicated in synaptic plasticity (Huerta and Lisman, 1993), sensory-motor behaviour (Oddie and Bland, 1998), and learning and memory processing (Kudrimoti et al., 1999).

These rhythms arise from networks of interconnected cells. Electrophysiological features of the specific cells are important and will depend on the particular brain structure involved. The general problem of completely characterizing hippocampal rhythms can be subdivided into spatial and temporal avenues of research, and their combination. On the spa-

* Corresponding author at: Division of Cellular and Molecular Biology, The Toronto Western Research Institute, Main Pavilion, Room MP13-308, 399 Bathurst Street, Toronto, Ont., Canada M5T 2S8.
Tel.: +1 416 603 5800x5066; fax: +1 416 603 5745.
E-mail address: jesse.gillis@utoronto.ca (J.A. Gillis).
[1] Division of Cellular and Molecular Biology, The Toronto Western Research Institute, Main Pavilion, Room MP13-411, 399 Bathurst Street, Toronto, Ont., Canada M5T 2S8.
[2] Division of Cellular and Molecular Biology, The Toronto Western Research Institute, Main Pavilion, Room MP13-317, 399 Bathurst Street, Toronto, Ont., Canada M5T 2S8.

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doi:10.1016/j.jneumeth.2005.03.006

tial side, recordings from multiple cells simultaneously offer an avenue to examine the variability in the cell and network rhythm within the hippocampus. In particular, multielectrode recordings allow an examination of the cellular variability that gives rise to network behaviour by recording from the individual cells in a rhythmic network (Nicolelis and Ribeiro, 2002). On the frequency side, at present, filtering and spectral analyses are used to characterize rhythmic data. The suitability of such techniques are data dependent, and particularly upon the degree to which the signal changes in time; that is, its non-stationarity. This is a well-known problem and specialized techniques have been developed for particular data sets (e.g., Achermann and Borbély, 1998). Developing data specific methodologies presents its own difficulties in terms of hypothesis and verifiability. A methodology developed specifically to suit the data may be unfalsifiable (e.g. overfitting), while a methodology not specifically developed to be suitable to the data can be biasing if, for example, a chosen filter is inappropriate. Ideally, a methodology is both testable and unbiased, or, at least, testable in its biases. We attempt to satisfy this balance by taking a very broad look at neuronal population rhythms, developing an interpretation testable against physiology, and then comparing with intracellular data. Recently, the investigation of the frequency of neuronal firing has been expanded and broadened to include spike correlations and more complex elements of the pattern in time and frequency (e.g., Gray et al., 1989; Nicolelis et al., 1995; Rieke et al., 1997). Specifically, using time–frequency techniques allows the examination of the variability of rhythm in the temporal domain—signals with changing frequency distributions are known as non-stationary in this context. Further, because hippocampal rhythms are often examined in a correlative way, it is useful to obtain a characterization that is not dependent on external factors—finding a natural, a priori, characterization which can later be examined for independent patterns.

In this paper, we focus on the variation of the population rhythms seen in extracellular recordings in the time–frequency domain. We develop a method which allows us to reduce a population rhythm to basic characteristics and we apply the methodology to the experimental data of Wu et al. (2002). The aim of this paper is to use accepted techniques in a novel combination and thereby present a method which may be used to characterize hippocampal rhythms in a way that can be physiologically interpreted. More specifically, we hope to leave the methodology general enough to provide for broad applicability in deconstructing field potential rhythms and relating them to the activity of components, down to the level of neurons.

The method uses standard techniques of time–frequency (*T–F*) analyses, object identification and mixture distributions. *T–F* analysis is a technique for determining the frequency behaviour of a signal over time (e.g., Adeli et al., 2003); object identification uses the characteristics of a surface, often gradient or amplitude, to determine boundaries for regions in the surface (e.g., Ponomarev and Davis, 2003), typically on a surface; mixture distributions can be regarded as close to a form of cluster analysis and allows the probabilistic separation of data that arises from overlapping statistical distributions (e.g., Everitt and Bullmore, 1999). While these individual techniques have been used in neuroscience and biology previously, they have not been used together in this fashion before and constitute a novel methodology applied to rhythmic experimental data. We use *T–F* analysis as a natural framework to analyze a varying rhythm and then determine strongly contributory regions of the signal (in the *T–F* domain) using object identification, and analyze the properties of these signal characteristics using mixture distributions.

2. Methods

2.1. Data collection and processing

Structurally, the hippocampus is organized in layers so that connectivity occurs within a plane defined by the cell bodies (Johnston and Amaral, 1998), making it particularly well suited to analysis in slice. Hippocampal slice preparations have been a useful in vitro model system for the purpose of determining the cellular genesis of these rhythms. The slice preparation offers the convenience of single cell recordings and pharmacological manipulations but it contains only limited network connectivity. Functionally significant long-range neuronal hippocampal connections (Andersen et al., 2000; Li et al., 1994) and function (Hampson et al., 1999; Moser and Moser, 1998) are disrupted during the slicing procedure.

The disruption imposed by the slice model has recently been addressed by Wu et al. (2002) in their development of a novel in vitro mouse hippocampal preparation. Their approach is to isolate the whole hippocampus from 21- to 28-day-old mice and remove the dentate gyrus while maintaining CA3–CA1 connectivities. While perfusing the hippocampal isolate in vitro at 32 °C, Wu et al. observed 0.5–4.0 Hz spontaneous rhythmic field potentials (SRFPs) in their extracellular recordings. Their data suggest that the SRFPs represent the summation of inhibitory post-synaptic potentials arising from the pyramidal neuron population as the result of synchronous discharges of inhibitory interneurons. Because intracellular stimulation of individual interneurons did not alter local SRFPs, Wu et al. suggested an important role for the networking of interneurons in providing a basis for the rhythm observed. However, such interpretations are limited to the degree of precision to which the signal itself is characterized.

In this paper, we examined the SRFPs and associated rhythmic activities recorded from the mouse hippocampal isolate. The experimental methods have been described previously (Wu et al., 2002). Briefly, C57bl mice of 21–28 days old (Charles River, Que., Canada) were decapitated under halothane anaesthesia. The brain was dissected out, hemisectioned and placed in an ice-cold artificial cerebrospinal fluid (ACSFs) for several minutes before further dissection.