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Psychophysical inference of frequency-following fidelity in the neural substrate for brain stimulation reward

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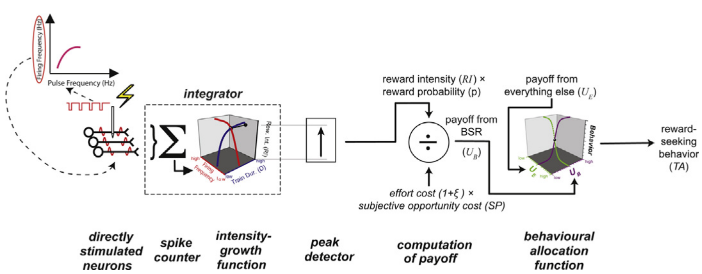
HIGHLIGHTS

- We test a model of frequency following in the substrate for brain stimulation reward.
- The measurement strategy is based on the counter model of reward integration.
- We measure current- vs. pulse-frequency trade-off functions in self-stimulating rats.
- The psychophysical data are well described by the model.
- The asymptotic value was high, implicating fast-firing, non-dopaminergic neurons.
- The function has important implications for Shizgal's 3D reward-mountain model.

GRAPHICAL ABSTRACT



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ABSTRACT

The rewarding effect of electrical brain stimulation has been studied extensively for 60 years, yet the identity of the underlying neural circuitry remains unknown. Previous experiments have characterized the directly stimulated ("first-stage") neurons implicated in self-stimulation of the medial forebrain bundle. Their properties are consistent with those of fine, myelinated axons, at least some of which project rostro-caudally. These properties do not match those of dopaminergic neurons. The present psychophysical experiment estimates an additional first-stage characteristic: maximum firing frequency. We test a frequency-following model that maps the experimenter-set pulse frequency into the frequency of firing induced in the directly stimulated neurons. As pulse frequency is increased, firing frequency initially increases at the same rate, then becomes probabilistic, and finally levels off. The frequency-following function is based on the counter model which holds that the rewarding effect of a pulse train is determined by the aggregate spike rate triggered in first-stage neurons during a given interval. In 7 self-stimulating rats, we measured current- vs. pulse-frequency trade-off functions. The trade-off data were well described by the frequency-following model, and its upper asymptote was approached at a median value of 360 Hz (IQR = 46 Hz). This value implies a highly excitable, non-dopaminergic population of first-stage neurons. Incorporating the frequency-following function and parameters in Shizgal's 3-dimensional reward-mountain model improves its accuracy and predictive power.

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1. Introduction

1.1. Inferring the physiological properties of the substrate underlying BSR using psychophysical inference

Electrical brain stimulation reward (BSR) has been studied for 60 years, yet the identity of the directly stimulated “first-stage” neurons is still unknown. The challenge of discerning the type(s) and origin(s) of the reward-relevant neurons of the medial forebrain bundle (MFB), the most extensively investigated locus of self-stimulation sites, reflects the considerable anatomical heterogeneity and complexity of this pathway [1–4]. Nonetheless, experiments employing pharmacological, psychophysical, neurochemical, electrophysiological, and optogenetic techniques have succeeded in narrowing down the set of candidate neural populations. In particular, psychophysical inference via behavioral trade-off methodology has been used to profile the physiological characteristics of the first-stage neurons. This method entails changing the value of a stimulation variable that affects reward pursuit and then determining the required compensatory change in another stimulation variable; the two changes trade off so as to hold behavior constant. The monotonicity of the function that maps the parameters of the electrical stimulation into the behavioral output makes it possible to infer properties of the first-stage neurons from behaviorally derived trade-off functions [5]. This method has been used to infer multiple properties, including recovery from refractoriness [6–9], conduction velocity [9–11], anatomical continuity [9,11,12] and the behaviorally relevant direction of conduction [11] in the fibers underlying the rewarding effect.

Neurons with properties that do not match those inferred from psychophysical studies can be ruled out as candidates for the directly stimulated stage of the circuitry underlying the rewarding effect. Dopamine (DA) neurons, which have figured prominently in the BSR and reward-circuitry literature [13], have fine, unmyelinated fibers [14]. These properties make them difficult to stimulate using the short pulse durations and relatively low currents employed in typical BSR studies. The conduction velocities of these fibers are too slow [9–11] and the refractory periods too long [6,7] to provide a good match to the inferred properties of the directly stimulated substrate for self-stimulation of the MFB. Moreover, the direction of the DA projections along the MFB is caudal–rostral [15], whereas the behaviorally relevant direction of conduction in at least some of the reward-relevant neural projections is rostral–caudal [11]. The importance of descending diencephalic projections in BSR had been proposed earlier by Huston et al. [16,17]. They demonstrated that self-stimulation of MFB sites could be acquired and maintained following destruction [16,18] or disconnection [19] of telencephalic structures, including the forebrain targets of the midbrain DA neurons.

The goal of the present experiment is to add to the existing portrait of the first-stage neurons a further physiological characteristic: their maximum firing rate. Implicit in prior models of BSR is perfect frequency following (green curve in Fig. 1): each directly stimulated neuron is assumed to fire once per pulse, regardless of the experimenter-set pulse frequency. However, it is more realistic to propose that frequency following breaks down as the pulse frequency becomes sufficiently high: there is a physiological limit to the firing rate of any axon.

At the core of the present experiment is a model of the frequency-following function that maps the pulse frequency set by the experimenter into the frequency of firing induced in the stimulated neurons. The form of the frequency-following function proposed by Forgie and Shizgal [20], is illustrated by the red curve in Fig. 1. Over an initial range, frequency following is perfect, and the function rises in scalar fashion. Just beyond this range is the roll-off region: the stimulated neurons begin to respond

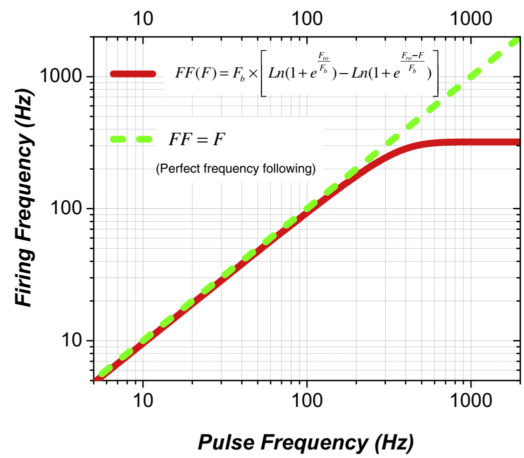

Fig. 1. The induced firing frequency as a function of the experimenter-set pulse frequency, shown on double logarithmic coordinates. Implicit in prior models of BSR is perfect frequency following, denoted by the green line: each directly stimulated neuron is assumed to fire once per pulse, regardless of the experimenter-set pulse frequency. The form of the frequency-following function proposed by Forgie and Shizgal [20] is denoted by the red curve. The firing frequency follows the experimenter-induced pulse frequency at low to moderate pulse frequencies but declines smoothly at high pulse frequencies until a maximum firing frequency is reached and maintained. Whether the electrically stimulated MFB fibers subserving intracranial self-stimulation respond in this manner is tested in the present experiment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

probabilistically to increases in pulse frequency, and the rate of increase in the induced firing frequency decreases, bending the simulated curve. Eventually, increases in pulse frequency fail to trigger additional action potentials and the frequency-following function levels off. The functional form is expressed below (Eq. (1)). (The frequency-following function and its derivation are described in more detail in Supplemental material 1, section S1.1)

$$FF(F) = F_b \times [Ln(1 + e^{\frac{F_{ro}}{F_b}}) - Ln(1 + e^{\frac{F_{ro}-F}{F_b}})] \quad (1)$$

where

F = the pulse frequency (Hz) set by the experimenter.

FF = the average firing frequency (Hz) induced in the directly stimulated neurons.

F_b = the parameter that describes the abruptness of the transition between the range of perfect frequency following and the point at which the frequency-following function levels off. This parameter sets the slope of the declining portion of the sigmoid-shaped first derivative of the frequency-following function (described in more detail in Supplemental material 1, Section S1.1).

F_{ro} = the pulse frequency at which the slope of the roll-off region is half-maximal in linear coordinates. This parameter defines the position of the frequency-following function along the abscissa. The first derivative of the frequency-following function is sigmoidal in shape (Figs. S1.1 and S1.2 in Supplemental material 1). The F_{ro} parameter is the pulse frequency corresponding to the mid-point of the declining portion of the sigmoid.

In addition to providing a further criterion for the identification of the first-stage substrate, the frequency-following capabilities of these neurons have important implications for Shizgal’s reward-mountain model. The model and associated three-dimensional (3D) measurement strategy have been used in previous studies to differentiate between actions of experimental manipulations on early and late stages of reward processing [21–27]. In the early versions of the model, perfect frequency following was assumed. This assumption is problematic because exceeding the frequency-following limit renders the effects measured by means of the 3D methodology ambiguous and easily misinterpreted. The maximum reward