Research Article

Neuron-Type-Specific Utility in a Brain-Machine Interface: a Pilot Study

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Context: Firing rates of single cortical neurons can be volitionally modulated through biofeedback (i.e. operant conditioning), and this information can be transformed to control external devices (i.e. brain-machine interfaces; BMIs). However, not all neurons respond to operant conditioning in BMI implementation. Establishing criteria that predict neuron utility will assist translation of BMI research to clinical applications.

Findings: Single cortical neurons (n = 7) were recorded extracellularly from primary motor cortex of a Long-Evans rat. Recordings were incorporated into a BMI involving up-regulation of firing rate to control the brightness of a light-emitting-diode and subsequent reward. Neurons were classified as 'fast-spiking', 'bursting' or 'regular-spiking' according to waveform-width and intrinsic firing patterns. Fast-spiking and bursting neurons were found to up-regulate firing rate by a factor of 2.43 ± 1.16, demonstrating high utility, while regular-spiking neurons decreased firing rates on average by a factor of 0.73 ± 0.23, demonstrating low utility.

Conclusion/Clinical Relevance: The ability to select neurons with high utility will be important to minimize training times and maximize information yield in future clinical BMI applications. The highly contrasting utility observed between fast-spiking and bursting neurons versus regular-spiking neurons allows for the hypothesis to be advanced that intrinsic electrophysiological properties may be useful criteria that predict neuron utility in BMI implementation.

Keywords: Brain-computer interface, Brain-machine interface, Firing rate, Modulation, Motor cortex, Neuron, Operant conditioning, Spike width, Upregulation, Waveform width

Introduction

One of the main goals of brain-machine interfaces (BMI) is to improve quality of life by facilitating activities of daily living for people who experience motor impairment. BMIs record cortical activity, and transform this information into control signals for external devices.[1–7] For example, there have been impressive demonstrations of BMI-controlled computer cursors and robotic arms in people with tetraplegia.[2,3]

BMIs are often implemented through operant conditioning, whereby firing rates of single cortical neurons can be volitionally modulated through biofeedback.[8,9] This paradigm involves the setting of a task rule that determines when the BMI is triggered. During training, an association is created when the task rule is met and rewarded in a timely manner. Learning is evident when the time required to complete the task is reduced over repeated presentations. Naturally, the utility of a neuron in a BMI is predicted by its adaptability to meet the BMI task rule. However, not all neurons in a BMI contribute to improving control, while the inclusion of certain neurons can even cause clear decrements in control.[10] Thus, the ability to differentiate between neurons with high and low utility, prior to their inclusion in a BMI, would be valuable for optimizing the effectiveness/accuracy of BMI control.[10,11]

Cortical neurons can be classified electrophysiologically by waveform-width. A bimodal distribution of neuronal populations, into narrow- and wide-waveforms has been reported in motor cortex of rats.[12,13] Preliminary evidence indicates that classifying neurons based on waveform-width alone may predict the utility of a neuron in BMI implementation, in that narrow-waveform neurons outperform wide-waveform neurons.[11] However, wide-waveform neurons make up the majority (~60–70%) of extracellular

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recordings in the neocortex,[14,15] so exclusion of neurons based on waveform-width alone may be too restrictive. Interestingly, the firing patterns of these two populations differ considerably, as narrow-waveform (i.e. fast-spiking) neurons fire at short repetitive intervals[12,14] while wide-waveform neurons fire either in a clustered pattern (i.e. bursting) or at long repetitive intervals (i.e. regular-spiking).[14,16] It remains unknown if classifying neurons based on intrinsic firing patterns, in addition to waveform-width, can improve the predictive power of the neuron selection process prior to BMI implementation. The objective of this pilot study was to describe the utility (i.e. ability to meet a task rule) of three types of cortical neurons (i.e. fast-spiking, bursting, regular-spiking), differentiated based on waveform-width and intrinsic firing patterns, during an operant conditioning BMI protocol involving up-regulation of neuronal firing rate.

Materials and Methods

Animal Model and Microelectrode Array

An adult Long-Evans rat underwent electrode implantation in the forepaw representation of the motor cortex (M1). The University of Toronto Animal Care Committee approved the animal use protocols described below. The electrode consisted of an array of eight Parylene-C-insulated tungsten electrodes (2×4 configuration; 500 μm inter-row distance; 250 μm inter-electrode distance). Each probe had a shaft diameter of 75 μm with the tips sharpened to 2 μm, resulting in an impedance of ~0.5 MΩ at 1 kHz (Microprobes for Life Sciences, Gaithersburg, MD, USA).

Experimental Setup

To perform the operant conditioning experiments, the rat was placed in a chamber (Med-Associates Inc™, St. Albans, VT, USA) with food and liquid dispensers providing chocolate-flavored pellets (Bio-Serv, Flemington, NJ, USA) and 10% sucrose solution, respectively. A light-emitting-diode (LED) provided visual feedback. The chamber components (i.e. dispensers and LED) were controlled in real-time with custom-made programs using CBMEX, a MATLAB™ (Mathworks, Natick, MA, USA) software development kit to read the time-stamps from the a data acquisition system (Cerebus®, Blackrock Microsystems, Salt Lake City, UT, USA), and an Arduino UNO board (Ivrea, Italy).

Spike Sorting, Baseline Recordings and Neuron Selection

Single neuron activity was recorded and processed with the data acquisition system. When a single probe of the electrode array was recording multiple distinct waveforms, the spikes were sorted and assigned as separate neurons in real-time. The spike-sorting method was implemented based on time-amplitude windows, which were placed manually on the spike waveform trough and peak.[17] Once a neuron was isolated, its firing rate and interspike interval (ISI) histogram, which describe neuron firing patterns, were computed from a 5 min recording (i.e. baseline; Fig. 1a). During this baseline recording the rat received no feedback (i.e. no auditory cues or visual feedback), but did receive rewards at random times to engage the animal. The criteria used to select a neuron for subsequent experimentation (i.e. association and up-regulation protocols; see below) included: 1) a minimum refractory period of 1 ms,[18] and 2) a signal-to-noise ratio (SNR) of two or greater.[19]

BMI Protocols: Association and Up-Regulation

The BMI consisted of separate association and up-regulation protocols (Fig. 1a) to train the brain to control the brightness of an LED by increasing the firing rate of single neuron activity. The association protocol involved a threshold (i.e. 0.5 to 1.5 standard deviations [SD] above average baseline firing rate), where rewards were obtained frequently over a 5-min period. The purpose of the association protocol was to create an association in the brain between a bright LED (i.e. high firing rate) and the acquisition of a reward. The association protocol was followed by an up-regulation protocol involving a higher threshold (i.e. 1.5 to 5 SD above average baseline firing rate), where rewards were obtained infrequently to encourage increases in neuron firing rate. The up-regulation protocol was a maximum of 20 mins in duration or up to 20 rewards, whichever was reached first.

Each protocol consisted of a sequence of trials, each involving the same closed-loop paradigm (Fig. 1b). A trial started with an auditory cue (i.e. 750 ms 'beep') and the activation (i.e. turning ON) of visual feedback (i.e. LED). M1 neural activity was recorded, sorted and entered into an algorithm that transformed single neuron firing rate to the brightness of the LED. Power input to the LED was regulated to adjust brightness using pulse-width modulation, reflecting the firing rate of the neuron. The LED displayed maximum brightness when the firing rate reached the threshold-crossing value, and the minimum brightness corresponded to no neural activity. A reward was provided when firing rate was maintained above the threshold-crossing value for at least 1 s. The trial finished when a reward was dispensed, followed by a 10 s pause for the rat to retrieve the reward before a new trial started. There was no time limit to complete a given trial.

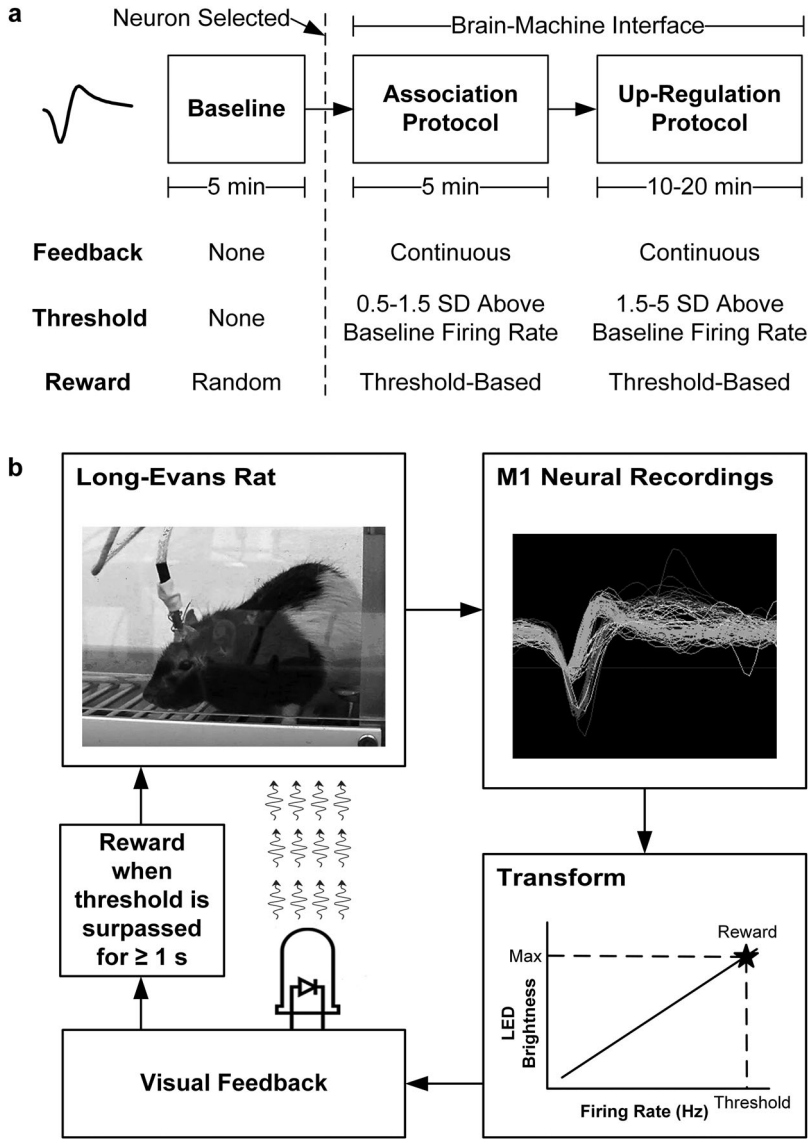

Figure 1 a) Experimental timeline. b) Paradigm of the BMI protocols. A rat was placed in an operant conditioning chamber. M1 neural activity was recorded, sorted and entered into an algorithm that transformed single neuron activity to the brightness of a LED (i.e. visual feedback). Constant visual feedback was provided to the rat, and a reward was delivered when the firing rate was maintained above the threshold-crossing value for ≥ 1 s.

Data Analysis

Neurons were classified post-hoc in two steps. First, neurons were classified based on waveform-width as either narrow (290±90 μs) or wide (570±140 μs).[15] However, waveform-width classification alone is unable to differentiate between bursting and regular-spiking neurons. Hence, a second classification system was employed. ISI histograms were used to differentiate bursting and non-bursting neurons. The percentage of ISIs < 5 ms is greater than 5% for bursting neurons, producing a 'sharp' peak in the ISI histogram. Conversely, the percentage of ISIs < 5 ms is less than 5% for non-bursting (i.e. fast-spiking and regular-spiking) neurons, producing a 'broader' peak in the ISI histogram.[15] However, tonic firing rates of up to 800 Hz have been reported in fast-spiking neurons.[14] Thus, ISI histogram classification alone may not clearly differentiate between bursting and fast-spiking neurons. To differentiate between all three types of neurons encountered in the present experiments, both classification systems were required.

SNR was calculated as: $A/(2*SD_{noise})$, where A is the trough-to-peak voltage (μV) of the waveform averaged across baseline, and SD_{noise} is the SD of the residuals from each waveform after the average has been subtracted.[19] Waveform-width was calculated as the

trough-to-peak duration (μs) of the waveform averaged across baseline. Firing rates (Hz) were calculated over 500 ms bins. Baseline firing rate was calculated as the average spike count per bin of each neuron divided by the duration of baseline. ISI histograms were computed in 1 ms increments, from 0 to 1000 ms. Percentage of ISI < 5 ms was calculated as the percentage of counts per interval < 5 ms, from the total number of counts across 1000 intervals.

To quantify changes in firing rate during the BMI protocols, a Firing Rate Index (FRI) was calculated as the average firing rate during the second half of a given protocol, normalized to the average firing rate of the first half. In this way, FRI values > 1 indicate increases in firing rate from the first to the second half of a protocol, while FRI values ≤ 1 indicate either no change or decreases in firing rate from the first to the second half of a protocol.

To quantify changes in the time required to obtain a reward during the BMI protocols, a Learning Index (LI) was calculated as the inverse of the average trial duration during the second half of each protocol normalized to the average trial duration of the first half. Trials spanning the halfway-crossing point of each protocol were included in the half for which the majority of the trial duration took place. In this way, LI values > 1 indicate positive learning (i.e. decreases in trial duration), with higher values representing greater learning, while LI values ≤ 1 indicate no positive learning. To visualize changes in the time required to obtain a reward during the up-regulation protocol, learning curves showing the moving average[20] across three trials with 66% overlap were plotted for each neuron.

Data are reported as mean ± SD where applicable.

Results

Neuron-Type Classification

Seven neurons were conditioned in the present BMI protocols (average SNR = 2.99 ± 0.81). Three neurons were classified as narrow-waveform (Fig. 2a-c, left column; average waveform-width = 233 ± 33 μs) and four were classified as wide-waveform (Fig. 2d-g, left column; average waveform-width = 508 ± 32 μs). Based on the ISI histogram (Fig. 2, middle column), narrow-waveform (i.e. fast-spiking; Fig. 2a-c) neurons had an average percentage of ISI < 5 ms = 1.67 ± 2.20% (average baseline firing rate = 4.50 ± 3.31 Hz). Wide-waveform neurons were further sub-classified into bursting (Fig. 2d-e; average percentage of ISI < 5 ms = 12.45 ± 9.40%; average baseline firing rate = 3.02 ± 1.58 Hz) and regular-spiking (Fig. 2f-g; average percentage of ISI < 5 ms = 0.05 ± 0.07%; average baseline firing rate = 0.66 ± 0.23 Hz) neurons.

BMI: Firing Rate Index

During the association protocol (data not shown), when the threshold was set at a relatively low level, the rat obtained 17.0 ± 3.6 rewards with fast-spiking neurons, 17.5 ± 9.2 rewards with bursting neurons and 16.0 ± 2.8 rewards with regular-spiking neurons. During this protocol, FRI values were 1.12 ± 0.07 for fast-spiking neurons, 0.96 ± 0.22 for bursting neurons and 1.06 ± 0.09 for regular-spiking neurons. During the up-regulation protocol (Fig. 2, right column), when the threshold was set at a higher level, 20 rewards were obtained with all neurons (see tick marks in the upper portion of each panel in the right column), except for one regular-spiking neuron which received only 5 rewards within the 20 min time limit (Fig. 2g). During this protocol, FRI values were 2.72 ± 1.44 for fast-spiking neurons, 1.77 ± 0.36 for bursting neurons and 0.73 ± 0.23 for regular-spiking neurons.

BMI: Learning Index

During the association protocol (data not shown), LI values were 1.71 ± 0.73 for fast-spiking neurons, 1.67 ± 0.86 for bursting neurons and 1.32 ± 0.25 for regular-spiking neurons. Figure 3 shows learning curves for fast-spiking (left; LI = 13.16 ± 6.91), bursting (middle; LI = 4.95 ± 2.32) and regular-spiking (right; LI = 0.66 ± 0.67) neurons during the up-regulation protocol.

Discussion

Herein we describe the utility of three types of cortical neurons (i.e. fast-spiking, bursting and regular-spiking), differentiated based on waveform-width and intrinsic firing patterns, during an operant conditioning BMI protocol involving up-regulation of neuronal firing rate. During the up-regulation protocol, the firing rate of fast-spiking and bursting neurons increased by a factor of 2.43 ± 1.16 (all neurons produced FRI values $>$ 1.49), demonstrating high adaptability to meet the task rule (i.e. high levels of learning; LI = 9.88 ± 6.74). In contrast, the firing rate of regular-spiking neurons decreased on average by a factor of 0.73 ± 0.23 (both neurons produced FRI values < 0.89), demonstrating low adaptability to meet the task rule (LI = 0.66 ± 0.67). Such contrasting utility is clearly displayed in the learning curves (Fig. 3), where all fast-spiking and bursting neurons showed a progressive reduction in the time required to earn a reward, resembling an inverse exponential curve, which is absent for regular-spiking neurons. These results indicate that, compared

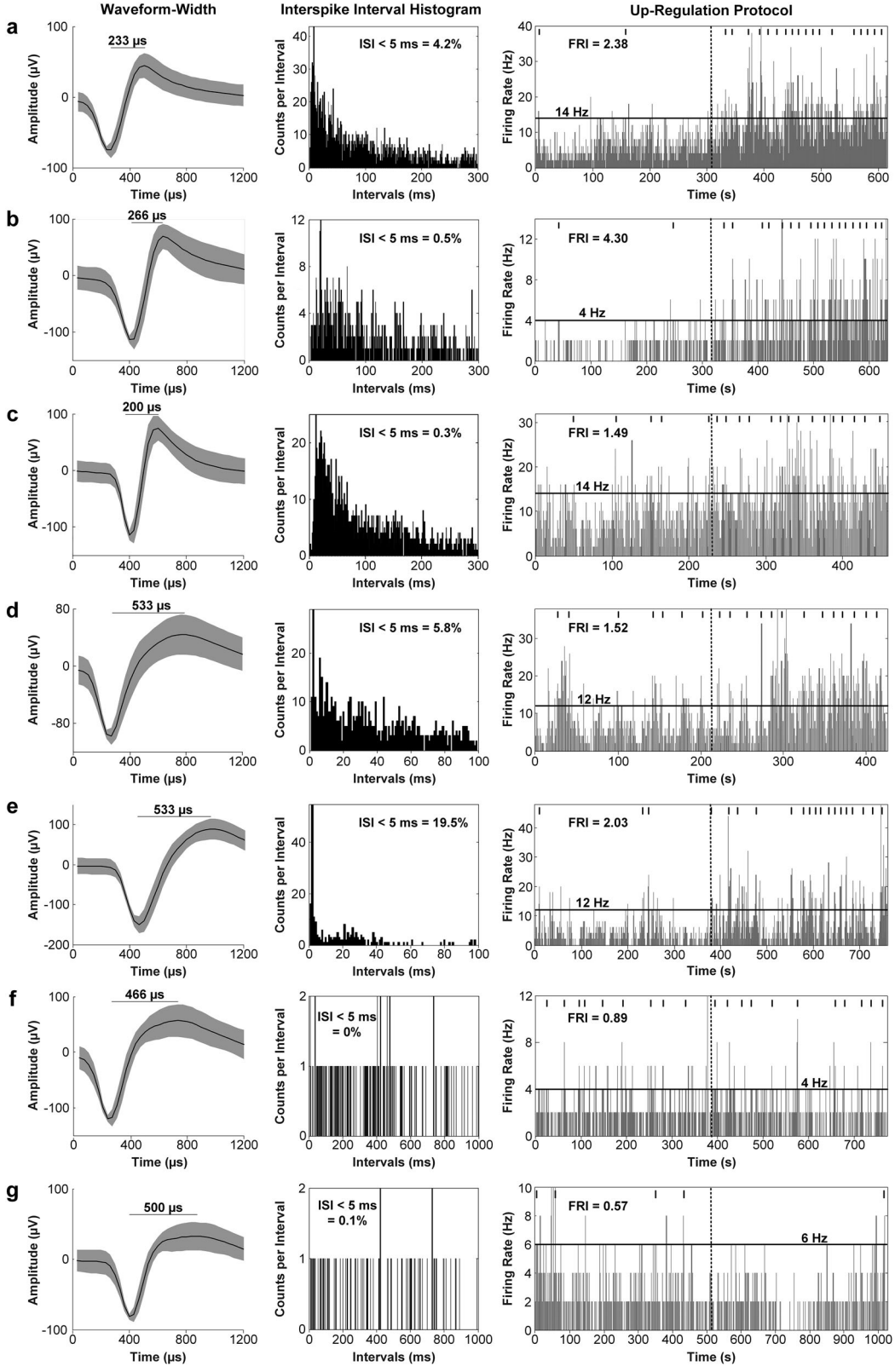

Figure 2 Waveform-width (left column), interspike interval (ISI) histogram (middle column) and up-regulation protocols (right column) for each neuron (a-g). The left column of each panel shows the waveform for each neuron, averaged across all neuron firings during baseline recordings (solid black line; shaded region represents ± SD), and the corresponding waveform-width. The middle column of each panel shows the ISI histogram for each neuron, and the corresponding percentage of ISI < 5 ms. The right column of each panel shows firing rate (grey vertical bars; 500 ms increments), threshold (horizontal black line), reward acquisitions (upper tick marks) and the corresponding firing rate index (FRI) for each neuron during the up-regulation protocol. Vertically dashed lines represent the division for FRI calculations (see text for details).

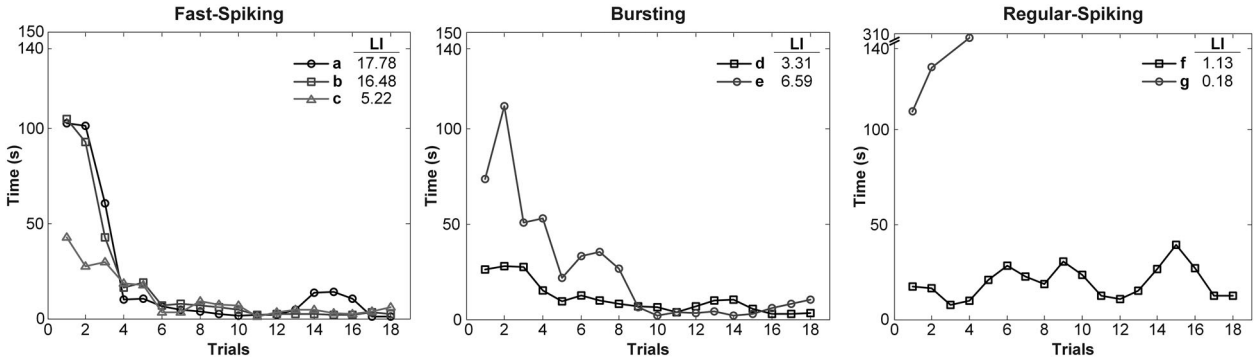

Figure 3 Learning curves and learning indices (LI) for fast-spiking (left), bursting (middle) and regular-spiking (right) neurons during the up-regulation protocol, corresponding to data from Fig. 2a-g. Each data point represents the moving average across 3 trials, with 66% overlap.

to fast-spiking and bursting neurons, regular-spiking neurons lack utility in BMI implementation involving up-regulation of neuronal activity. However, it would be premature to draw definitive conclusions from these few observations, suggestive as they are.

A recent paper by Best *et al.*[11] concluded that the utility of neural ensembles in BMIs may be predicted by spike waveform-widths alone, in that narrow spiking (i.e. narrow-waveform) neurons outperform wide spiking (i.e. wide-waveform) neurons. Our findings are consistent with this conclusion, in that we found a clear distinction in utility between fast-spiking and regular-spiking neurons (i.e. narrow- and wide-waveform, respectively). However, Best *et al*. classified waveform-widths after excluding neurons with baseline firing rates < 1 Hz. Based on our data, Best *et al.* were comparing fast-spiking (i.e. narrow-spiking) and bursting (i.e. wide-spiking) neurons, since our regular-spiking neurons had baseline firing rates < 1 Hz. Indeed, our data also indicate that there may be a division in utility between fast-spiking ($LI = 13.16 \pm 6.91$) and bursting ($LI = 4.95 \pm 2.32$) neurons. However, the 1 Hz cut-off alone may be too restrictive for predicting utility in BMI implementation since presently, this criteria would have excluded a fast-spiking neuron with high utility (Fig 2b; baseline firing rate $= 0.69 \pm 0.96$). The present data demonstrate that a two-step process involving first differentiation between narrow- and wide-waveform neurons, whereby narrow-waveform neurons are always included, followed by further differentiation of wide-waveform neurons based on intrinsic firing patterns (e.g. ISI or baseline firing rates) may predict utility more reliably than waveform-width classification alone.

Limitations

The possibility that the observed firing rate modulation with fast-spiking and bursting neurons during the up-regulation protocol was the result of general excitation due to auditory cues (e.g. 'beep'), visual feedback (e.g. bright LED) or the simple prospect of a reward cannot be excluded. However, it is likely that the observed firing rate modulation was instead due to volitional control of the BMI. During the association protocol, the rat received roughly the same number of rewards (i.e. auditory cues and maximum LED brightness; 16.86 ± 4.49 rewards) as during the up-regulation protocol (17.86 ± 5.67 rewards), but at a relatively greater rate (3.25 ± 0.83 rewards/min during association versus 1.67 ± 0.73 rewards/min during up-regulation) due to the lower more readily achievable threshold of the association protocol. If modulation of firing rate was the result of the rat having been exposed to auditory cues, visual feedback or due to the simple prospect of a reward, firing rates would be expected to increase similarly or possibly to a greater extent during the association protocol compared to the up-regulation protocol; however, this was not observed. Firing rates during the association protocol demonstrated little to no modulation (i.e. FRI values close to 1), regardless of neuron-type ($FRI = 1.06 \pm 0.13$). The inclusion of control trials involving only auditory cues, or only visual feedback, or only rewards in future studies will help to strengthen our assertion that the BMI was indeed under volitional control.

Conclusion/Clinical Relevance

Fast-spiking and bursting neurons showed high utility, while regular-spiking neurons showed low utility, during an operant conditioning BMI protocol involving up-regulation of neuronal firing rate in a rat model. The ability to select neurons with high utility in BMI implementation will be important to potentially minimize training times and maximize information yield in future clinical applications, such as BMI-controlled

functional electrical stimulation-based restoration of grasping function,[21] considering that human neuron types, or their correlates, respond similarly to BMI training as neuron types found in rats. Albeit preliminary data, the highly contrasting utility observed presently between fast-spiking and bursting neurons versus regular-spiking neurons allows for the hypothesis to be advanced that intrinsic electrophysiological properties (i.e. waveform-width and firing patterns) may be useful criteria that predict neuron utility in BMI implementation.

Abbreviations

BMI	Brain-Machine Interface
FRI	Firing Rate Index
ISI	Interspike Interval
LED	Light-Emitting Diode
LI	Learning Index
M1	Primary Motor Cortex
SD	Standard Deviation
SD_{noise}	SD of the residuals from each waveform after the average has been subtracted
SNR	Signal-to-Noise Ratio

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Disclaimer statements

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Conflicts of interest None.

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References

1 Carmena JM, Lebedev MA, Crist RE, O'Doherty JE, Santucci DM, Dimitrov D, *et al.* Learning to control a brain–machine interface for reaching and grasping by primates. PLoS Biol 2003;1(2):193–208.
2 Collinger JL, Wodlinger B, Downey JE, Wang W, Tyler-Kabara EC, Weber DJ, *et al.* High-performance neuroprosthetic control by an individual with tetraplegia. Lancet 2013;381(9866):557–64.
3 Hochberg LR, Bacher D, Jarosiewicz B, Masse NY, Simeral JD, Vogel J, *et al.* Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature 2012;485(7398):372–5.
4 Musallam S, Corneil BD, Greger B, Scherberger H, Andersen RA. Cognitive control signals for neural prosthetics. Science 2004;305(5681):258–62.
5 Santhanam G, Ryu SI, Yu BM, Afshar A, Shenoy KV. A high performance brain–computer interface. Nature 2006;442(7099):195–8.
6 Velliste M, Perel S, Spalding MC, Whitford AS, Schwartz AB. Cortical control of a prosthetic arm for self-feeding. Nature 2008;453(7198):1098–101.
7 Wessberg J, Stambaugh CR, Kralik JD, Beck PD, Laubach M, Chapin JK, *et al.* Real-time prediction of hand trajectory by ensembles of cortical neurons in primates. Nature 2000;408(6810):361–5.
8 Fetz EE. Operant conditioning of cortical unit activity. Science 1969;163(3870):955–8.
9 Fetz EE, Baker MA. Operantly conditioned patterns of precentral unit activity and correlated responses in adjacent cells and contralateral muscles. J Neurophysiol 1973;36(2):79–104.
10 Wahnoun R, He J, Helms Tillery SI. Selection and parameterization of cortical neurons for neuroprosthetic control. J Neural Eng 2006;3(2):162–71.
11 Best MD, Takahashi K, Suminski AJ, Ethier C, Miller LE, Hatsopoulos NG. Comparing offline decoding performance in physiologically defined neuronal classes. J Neural Eng 2016;13(2):026004.
12 Baeg EH, Kim YB, Jang J, Kim HT, Mook-Jung I, Jung MW. Fast spiking and regular spiking neural correlates of fear conditioning in the medial prefrontal cortex of the rat. Cereb Cortex 2001;11(5):441–51.
13 Bartho P, Hirase H, Monconduit L, Zugaro M, Harris KD, Buzsaki G. Characterization of neocortical principal cells and interneurons by network interactions and extracellular features. J Neurophysiol 2004;92(1):600–8.
14 Connors BW, Gutnick MJ. Intrinsic firing patterns of diverse neocortical neurons. Trends Neurosci 1990;13(3):99–104.
15 Katai S, Kato K, Unno S, Kang Y, Saruwatari M, Ishikawa N, Inoue M, Mikami A. Classification of extracellularly recorded neurons by their discharge patterns and their correlates with intracellularly identified neuronal types in the frontal cortex of behaving monkeys. Eur J Neurosci 2010;31(7):1322–38.
16 Degenetais E, Thierry AN, Glowinski J, Gioanni Y. Electrophysiological properties of pyramidal neurons in the rat prefrontal cortex: an in-vivo intracellular recording study. Cereb Cortex 2002;12(1):1–16.
17 Santhanam G, Sahani M, Ryu S, Shenoy K. An extensible infrastructure for fully automated spike sorting during online experiments. Conf Proc IEEE Eng Med Biol Soc 2004;6:4380–4.
18 Jackson A, Fetz EE. Compact movable microwire array for long-term chronic unit recording in cerebral cortex of primates. J Neurophysiol 2007;98(5):3109–18.

19 Suner S, Fellows MR, Vargas-Irwin C, Kenji Nakata G, Donoghue JP. Reliability of signals from a chronically implanted, silicon-based electrode array in non-human primate primary motor cortex. IEEE Trans Neural Syst Rehabil Eng 2005;13(4): 524–41.

20 Gulati T, Ramanathan DS, Wong CC, Ganguly K. Reactivation of emergent task-related ensembles during slow-wave sleep after neuroprosthetic learning. Nat Neurosci 2014;17(8):1107–13.

21 Moritz CT, Perlmutter SI, Fetz EE. Direct control of paralysed muscles by cortical neurons. Nature 2008;456(7222):640–3.