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Cortical Neurons Adjust the Action Potential Onset Features as a Function of Stimulus Type

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Abstract: Pyramidal neurons and interneurons play critical roles in regulating the neuronal activities in the mammalian cortex, where they exhibit different firing patterns. Pyramidal neurons mainly exhibit regular-spiking firing patterns, while interneurons have fast-spiking firing patterns. Cortical neurons have distinct action potential onset dynamics, in which the evoked action potential is rapid and highly variable. However, it is still unclear how cortical regular-spiking and fast-spiking neurons discriminate between different types of stimuli by changing their action potential onset parameters. Thus, we used intracellular recordings of regular-spiking and fast-spiking neurons, taken from layer 2/3 in the somatosensory cortex of adult mice, to investigate changes in the action potential waveform in response to two distinct stimulation protocols: the conventional step-and-hold and frozen noise. The results show that the frozen noise stimulation paradigm evoked more rapid action potential with lower threshold potential in both neuron types. Nevertheless, the difference in the action potential rapidity in response to different stimuli was significant in regular-spiking pyramidal neurons while insignificant in fast-spiking interneurons. Furthermore, the threshold variation was significantly higher for regular-spiking neurons than for fast-spiking neurons. Our findings demonstrate that different types of cortical neurons exhibit various onset dynamics of the action potentials, implying that different mechanisms govern the initiation of action potentials across cortical neuron subtypes.

Keywords: action potential; regular-spiking neurons; fast-spiking neurons; pyramidal neurons; rapidity; threshold; AP parameters; electrophysiology; rapidness; voltage-gated sodium channels

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1. Introduction

The interaction between pyramidal neurons and interneurons regulates neuronal activity in the cortex. Pyramidal neurons are the most abundant cells, accounting for approximately 80% of cortical neurons and acting as the cortex's primary output [1]. In contrast, interneurons account for approximately 15–20% of cortical neurons and help shape network activity patterns [1,2]. Because of their dissimilar functionality, the two neuron types exhibit different firing patterns. Pyramidal neurons exhibit a regular-spiking (RS) firing pattern, while most interneurons exhibit a fast-spiking (FS) firing pattern [3,4]. The difference in firing patterns between the principal cells and their counterparts can be attributed to several factors, such as the type and densities of voltage-gated ion channels, passive membrane properties, and neuron geometry. Although a specific cell type can produce a similar firing pattern, there is high variability in neuronal response between single cells and from one trial to another [5,6].

The variability in neuronal response refers to the inconsistent, seemingly random changes in the firing rate of an individual neuron or a population of neurons, even when presented with the same stimulus multiple times [5,7,8]. Neuronal information processing and its variable nature are usually studied considering firing rate and spike timing. The speed at which neuronal spikes are traveling is variable and affected by the history of the spike train [8,9]. Moreover, according to mathematical modellings of the neuro-spike

communication channel between two neurons, temporal coding is more effective than spike coding regarding the data rate that can be achieved at a specific frequency [9,10]. Previous studies have shown that different neuron types can detect subtle stimulus changes by adjusting their firing timing. For instance, neuronal oscillations improve the action potential (AP) precision in mammalian neurons, regardless of neuron type [11], while background noise improves tone discrimination in Parvalbumin-positive neurons in the primary auditory cortex [12]. Conversely, blocking inhibition in a random cortical network reduces the variability evoked by repeated stimulus [13]. Alternatively, several studies have shown that altering the AP shape can manifest neuronal encoding. For instance, stimulus history was shown as more reliably encoded in the AP shape rather than the neuron firing rate [13], and input synchrony was facilitated by changes in the axonal AP amplitude [13]. Regardless of whether variability is observed in the AP shape or firing rate, neuronal response variability can benefit information processing and indicate neurological and psychiatric disorders such as autism [8,14].

Mammalian neurons, particularly in the cortex, have distinct AP onset characteristics: rapid AP onset and threshold variability. Several mechanisms have been suggested to account for the two unique features, such as AP backpropagation [15], voltage-gated sodium channels (Nav) cooperative gating [16], and neuron geometry [17]. AP backpropagation, from the AP initiation site at the axon initial segment (AIS) to the soma, increases threshold variability, possibly indicating the distance difference between the initiation site and the soma [15,18]. Other studies have linked threshold variability to the inactivation of Nav due to prior spikes [19]. However, the precise mechanisms underlying the threshold variability and rapid AP onset, and their implications for the overall network function, remain actively investigated.

This study investigates how different stimulus types affect the AP shape, particularly AP onset parameters, in two types of cortical neurons. Here, we attempt to answer two questions: (1) do neurons change their AP shape in response to different stimuli (step-and-hold current vs. frozen noise current), and (2) do both neuron types (RS and FS) display similar AP shape changes due to different stimuli? Our results show that AP properties change significantly with each stimulus type. However, some changes are only observed in RS pyramidal neurons, not FS neurons. AP rapidity and threshold variability, in particular, are significantly higher when pyramidal neurons are evoked by noisy input compared to the constant step current, while FS neurons elicit similar AP rapidity regardless of the stimulus type. These differences in AP initiation parameters in response to different stimuli may indicate that different mechanisms govern how cortical neurons encode different stimuli.

2. Materials and Methods

2.1. The Neural Recordings and Selection Criteria

The intracellular recordings in this study were obtained from the GigaScience database, acquired from layer 2/3 of the somatosensory cortex in adult mice of both sexes. The detailed experimental procedures can be found in da Silva Lantyer et al. [20] and the data in reference [21].

The selected intracellular recording datasets were obtained from 20 RS and 20 FS neurons, repeatedly stimulated with conventional step-and-hold and frozen noise stimulation protocols. The included APs were at least 10 ms apart. The interspike interval was set to ensure it was short enough to include most spikes in the analysis since it was lower than the average RS and FS neuron firing rates (32 ± 7 Hz and 61 ± 9 Hz, respectively, see reference [22]), long enough to calculate the parameters for each AP without interfering with each other.

The experimental design involved the application of two distinct stimulation protocols: step-and-hold and frozen noise. The step-and-hold protocol included ten consecutive depolarization pulses of 500 ms, each with a step size of 40 pA and an inter-sweep interval of 6.5 s. The stimulus train was repeated 1–3 times, with a 20 s interval between repetitions.

Moreover, the frozen noise protocol entailed the injection of a somatic current obtained from an artificial neural network of 1000 neurons firing Poisson spike trains in response to a "hidden state" used to generate the current. The frozen noise stimulus contains a binary hidden state that represents the presence or absence of external stimulus immersed in noise, which mimic post-synaptic currents [23]. The neural responses to both protocols were recorded in RS pyramidal and FS neurons, and the first 50 spikes elicited by each stimulus from each neuron were used to calculate the AP parameters. The voltage was interpolated to a resolution of $\Delta t = 1$ µs using MATLAB's (R2022b) spline function, filtered with MATLAB's smoothdata function (Savitzky-Golay filter, w = 200) to reduce noise. The membrane potential's first- and second-time derivatives were computed using MATLAB's diff function. For more information on the protocols, see reference [20], and for more details about the frozen noise stimulation, see reference [23]. An example of the response to the two stimulation protocols in cortical RS pyramidal and FS neurons is shown in Figure 1.

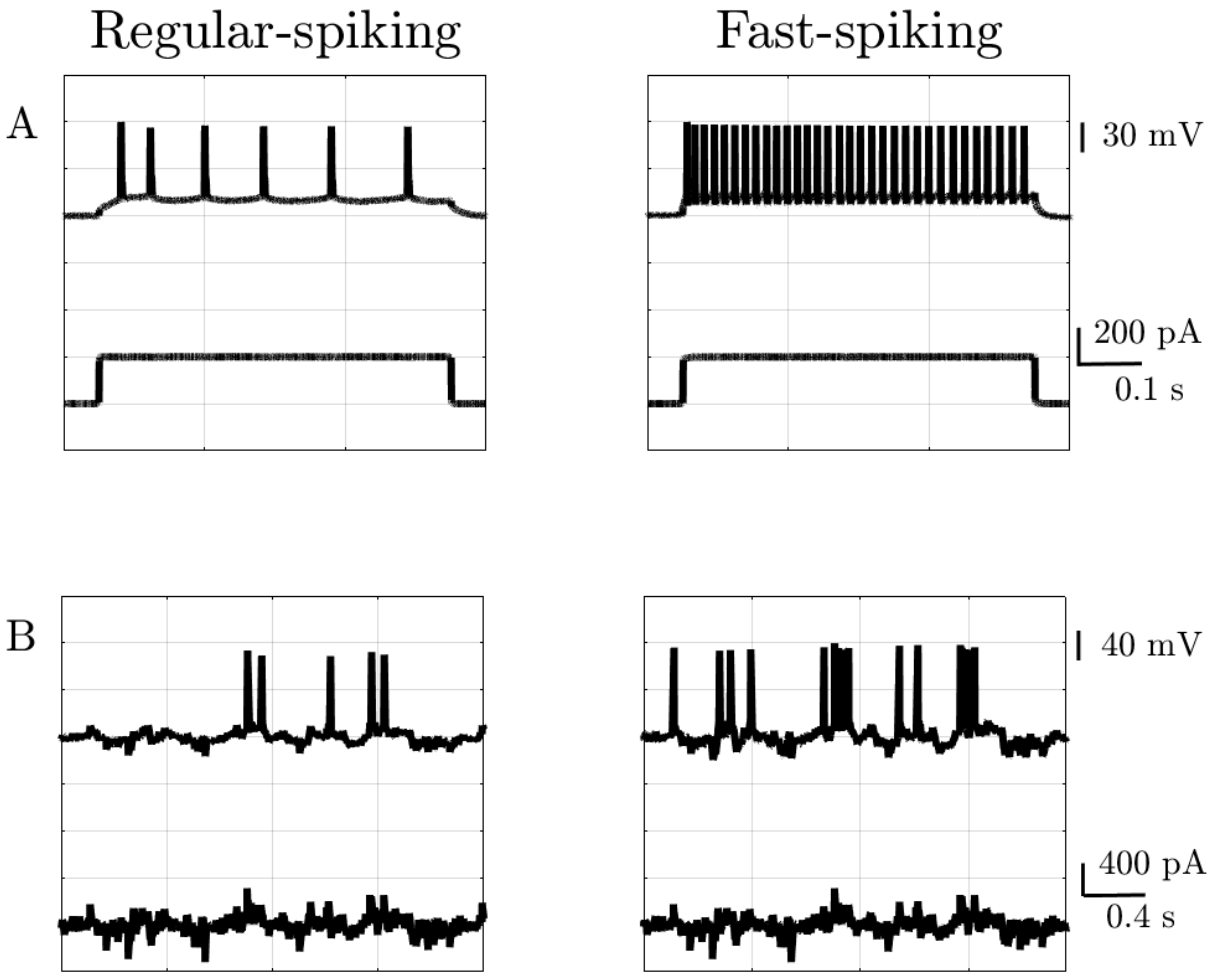


Figure 1. Neuronal response by different stimulus protocol in RS and FS cortical neurons. (**A**) Spike train (**top**) evoked in cortical RS pyramidal and FS neurons by a 0.5 s current pulse (**bottom**) with an amplitude of 200 pA (for this example); (**B**) Spike train (**top**) evoked in cortical RS pyramidal and FS neurons by a frozen noise stimulus (**bottom**). The frozen noise stimulus is the product of an artificial neural network that mimics post-synaptic current (for more details on frozen noise stimulus see reference [23]).

2.2. AP Parameters Quantification

Five parameters were calculated for each spike. AP rapidity was calculated using two methods: the inverse full width at half maximum of the $\ddot{V}_m$ peak (IFWd^2; [24,25]), and the phase slope method [16]. Notably, a recent previous study conducted by our team showed

that the IFWd^2 is a more consistent and reliable method for quantifying AP rapidity than the phase slope method [24]. Thus, AP rapidity refers to the rapidity calculated using the IFWd^2 method throughout this paper. The phase slope rapidity is reported here only as a reference for readers interested in comparing the reported values to other studies since it is the most common method for AP rapidity quantification. The AP threshold was chosen to be the potential at which $\dot{V}_m$ exceeds 25 mV/ms [15,16]. The AP amplitude was calculated as the difference between the AP peak and threshold potential, and the AP width was measured as the full width at half the AP amplitude.

2.3. Statistical Analyses

Statistical analyses were performed using IBM's SPSS Software Version 29. The analyzed AP parameters were evaluated using the Shapiro–Wilk normality test. Nonparametric tests were chosen due to the skewed distributions of the AP parameters. The Wilcoxon signed-rank test was used to separately compare the AP parameters induced by the two current clamp approaches (i.e., step-and-hold and frozen noise) for RS and FS neurons. Furthermore, univariate analyses were conducted using Mann–Whitney U tests for independence to investigate the effect of the stimulus type on the AP rapidity of different neuron types. All data are presented as the mean ± *SD*. The study results were considered significant at $p < 0.05$.

3. Results

The AP parameters were extracted and evaluated from 20 RS and FS somatosensory cortical neurons stimulated via the current clamp, step-and-hold, and frozen noise stimulation paradigms (Figure 2). The rapidity, threshold, amplitude, and width of each neuron type's APs of the first 50 neuronal responses were averaged and contrasted across neuron types and stimulation methods (see Table 1).

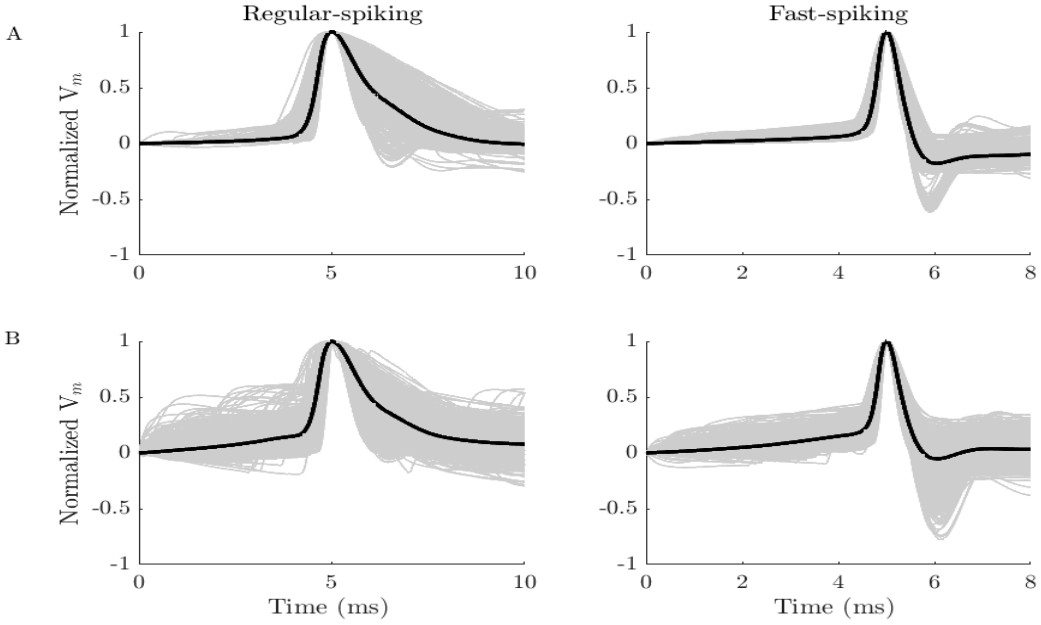


Figure 2. Comparison between normalized spike train evoked by (**A**) current step stimulus and (**B**) frozen noise stimulus; Gray traces: 1000 spikes from 20 neurons; Black trace: the mean of means of the AP evoked from the 20 neurons from each type.

Table 1. AP parameters (Mean ± *SD*) of RS and FS neurons in response to the conventional step-and-hold current and synaptic-like current (frozen noise current).

Parameters	Regular-Spiking Neurons		Fast-Spiking Neurons	
	Step-and-Hold	Frozen Noise	Step-and-Hold	Frozen Noise
Rapidity ($IFWd^2$)	3.97 ± 0.62	5.41 ± 0.19	6.40 ± 2.03	6.33 ± 1.76
Rapidity (Phase slope)	13.48 ± 3.89	24.24 ± 7.10	18.67 ± 4.81	25.54 ± 5.89
Threshold	−26.60 ± 4.30	−32.15 ± 8.05	−35.34 ± 4.29	−39.74 ± 4.78
Amplitude	81.12 ± 21.43	94.69 ± 18.16	74.88 ± 10.91	83.55 ± 10.88
Width	1.51 ± 0.36	1.35 ± 0.26	0.51 ± 0.09	0.49 ± 0.10

3.1. AP Waveform Parameter Differences Due to Stimulus Type

The calculated AP parameters (i.e., rapidity, threshold, amplitude, and width) for the somatosensory cortex RS and FS neurons were separately compared across the stimulation types (i.e., step-and-hold vs. frozen noise) to examine the effect of the stimulus type on the AP shape. The AP onset parameters were significantly different between the two stimulation types in RS pyramidal neurons. The Wilcoxon signed-rank test on the grand average of the rapidity of the AP revealed a significant increase in the rapidity of the AP for the RS neurons when the frozen noise was used as a stimulus compared to the conventional step-and-hold stimulation paradigm for both the $IFWd^2$ ($Z = -3.92$, $p < 0.001$, with an effect size of $r^2 = 0.38$; see Figure 3) and the phase slope method ($Z = -3.92$, $p < 0.001$, with an effect size of $r^2 = 0.38$; see Table 1).

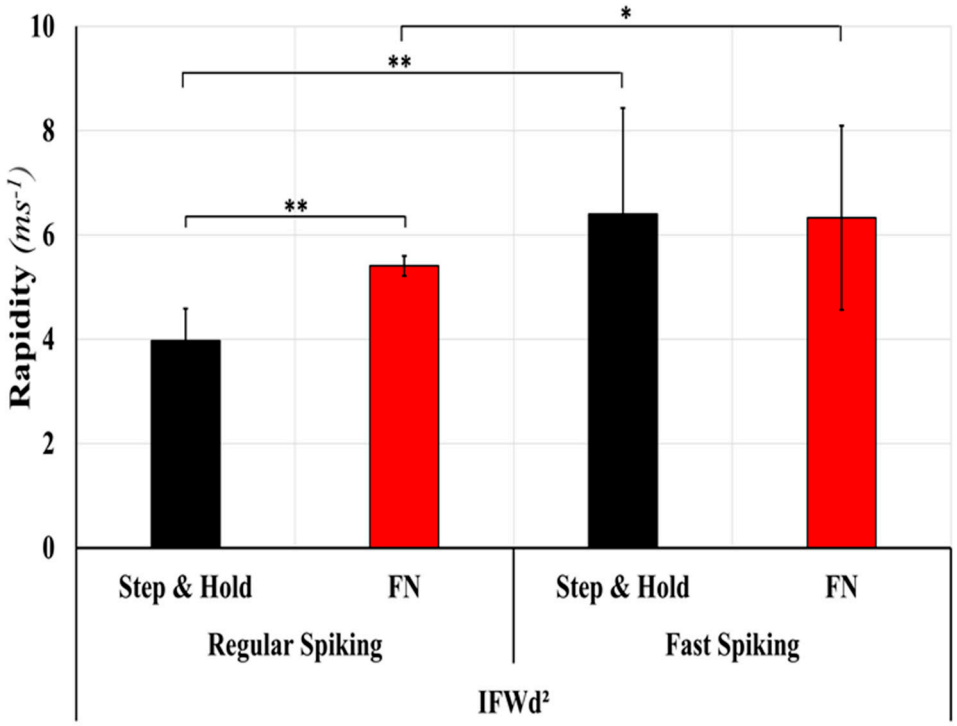


Figure 3. The effect of stimulation methods on the rapidity of action potential (mean ± *SD*) for two types of somatosensory cortical neurons: RS and FS. An increase in AP rapidity was observed when frozen noise (FN) stimulation was used compared to the conventional step-and-hold current clamp stimulation method. No significant difference in the rapidity was observed for the FS neurons (Wilcoxon signed-rank test). Additionally, there was a significant increase in AP rapidity of FS neurons compared to RS neurons, regardless of the stimulation configuration (Mann–Whitney U test; * denotes $p < 0.05$ and ** denotes $p < 0.01$).

Conversely, FS neurons showed no significant differences in the resulting average rapidity of the elicited APs compared across stimulus types (frozen noise vs. step-and-hold; IFWd^2: Z = −0.34, p = 0.97; see Figure 3). However, a significant increase in the AP phase slope-based rapidity for the frozen noise elicited responses compared to the step-and-hold current stimulation (Z = −3.92, $p < 0.001$, with an effect size of $r^2 = 0.38$; see Table 1).

Furthermore, RS and FS neurons both fired at different thresholds in response to the two stimulation protocols. A significant decrease in the average threshold potential was found when the frozen noise stimulation was used compared to the current step-and-hold stimulation for both RS (Wilcoxon signed-rank test: Z = −3.17, p = 0.002, with an effect size of $r^2 = 0.25$) and FS neurons (Wilcoxon signed-rank test: Z = −3.58, $p < 0.001$, with an effect size of $r^2 = 0.32$). Nevertheless, the threshold variation, a characteristic of somatic recording in central mammalian neurons, increased significantly for RS neurons but only slightly for FS neurons. The threshold variation, indicated by the threshold *SD*, almost doubled when RS neurons were stimulated by synaptic-like current (4.3 mV variation with step-and-hold current and 8.05 mV variation with frozen noise current), while the threshold variation only increased by 11.4% in FS neurons (Table 1). This outcome indicated that the AP onset parameters increased significantly in response to synaptic-like current compared to step-and-hold current, and the difference was significantly higher in RS pyramidal neurons while trivial in FS neurons.

The other AP parameters showed a similar pattern. The frozen noise stimulation elicited significantly larger APs determined by the averaged amplitude than the APs initiated with the current step-and-hold stimuli for RS neurons (Wilcoxon signed-rank test: Z = −3.88, $p < 0.001$, with an effect size of $r^2 = 0.38$) and FS neurons (Wilcoxon signed-rank test: Z = −3.47, $p < 0.001$ with an effect size of $r^2 = 0.30$). Lastly, in comparison with the current step-and-hold stimulation, the use of the frozen noise stimulation led to a significant decrease in the AP width for both RS neurons (Wilcoxon signed-rank test: Z = −2.88, p = 0.004, with an effect size of $r^2 = 0.21$) and FS neurons (Wilcoxon signed-rank test: Z = −2.50, p = 0.012, with an effect size of $r^2 = 0.16$; see Figure 4). Nonetheless, the difference in AP waveform in response to current step-and-hold and frozen noise stimulations was larger in RS cortical neurons than in FS neurons.

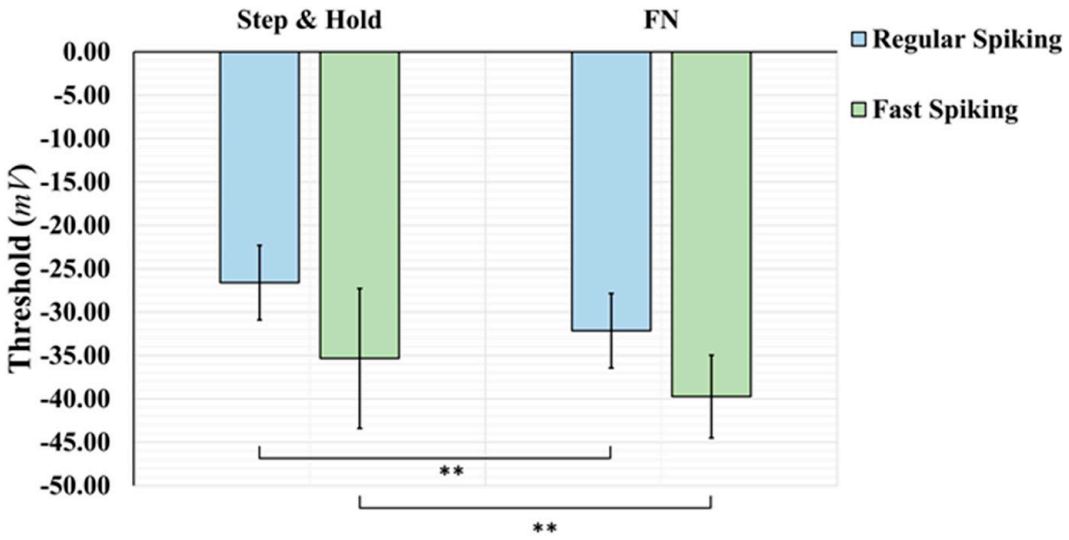


Figure 4. *Cont.*

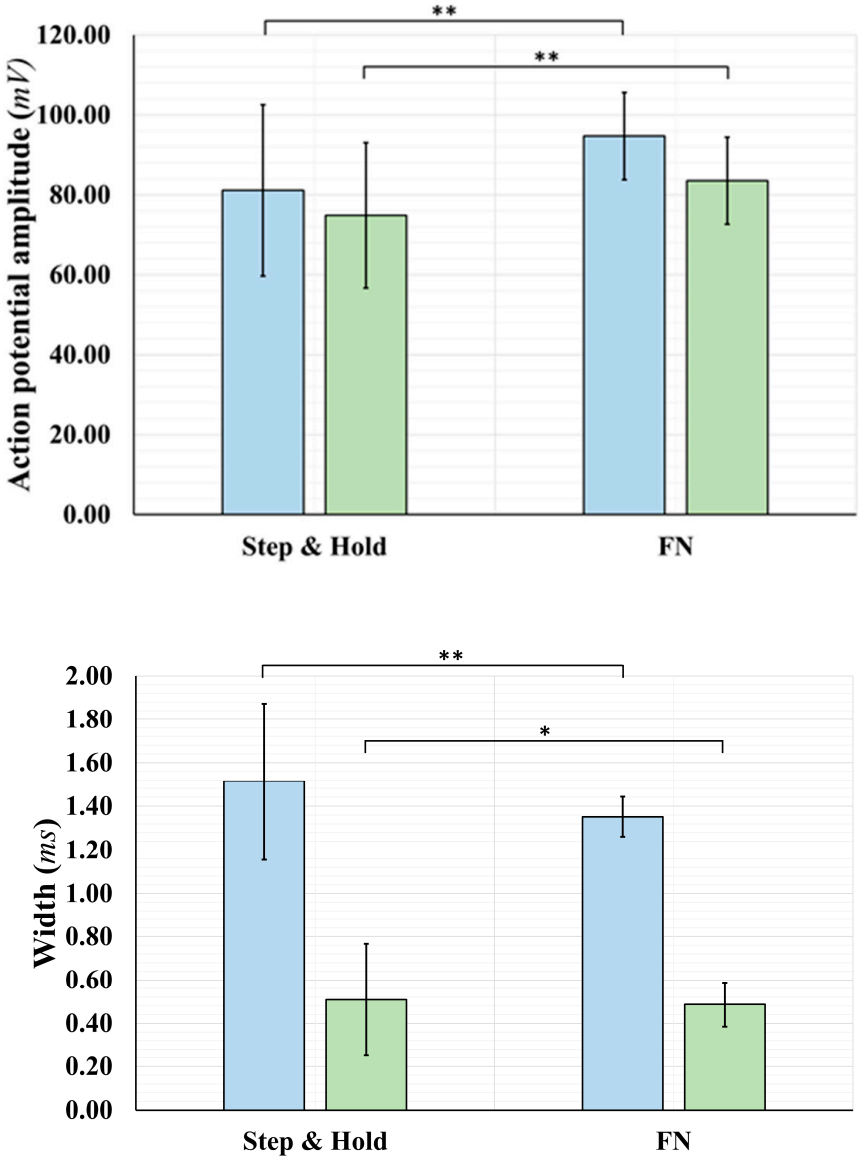


Figure 4. Differences in neural responses elicited via step-and-hold and frozen noise (FN) stimulation approaches for RS and FS neutrons. (**Top**): Significant decrease in the AP threshold when FN was used compared to conventional step-and-hold stimuli. (**Middle**): FN stimulation protocol led to a significant increase in the AP amplitude in both neuron types. (**Bottom**): The average AP's width was significantly narrower in FN than step-and-hold current-clamp stimulation (Wilcoxon signed ranks test; * denotes $p < 0.05$ and ** denotes $p < 0.01$).

3.2. Stimulation Method Effect on the AP Rapidity of Different Neuron Types

Further statistical analyses investigated the effects of the current step-and-hold and frozen noise stimulation techniques on the AP rapidity of the RS and FS neurons, quantified using the IFWd^2 and phase slope methods. For the IFWd^2 quantification method, the results indicated a significant increase in the AP rapidity for the FS neurons compared with the rapidity of the RS neurons for both the current step-and-hold (Mann–Whitney U test: $Z = -4.41$, $p < 0.001$, with an effect size of $r^2 = 0.46$) and frozen noise (Mann–Whitney U test: $Z = -2.11$, $p = 0.035$, with an effect size of $r^2 = 0.11$) stimulation protocols. Similarly, the use of the phase slope analysis method revealed a significant increase in the AP rapidity for the FS neurons compared with the RS neurons when the current step-and-hold stimulation was used (Mann–Whitney U test: $Z = -3.08$, $p = 0.002$, with an effect size of $r^2 = 0.24$). However, although an increasing trend in AP rapidity was observed for the FS neurons compared to

the RS neurons when frozen noise was used, there was no significant difference between the rapidity of the FS neurons and the RS neurons (Mann–Whitney U test: $Z = -0.81$, $p = 0.42$).

4. Discussion

We examined whether RS and FS somatosensory cortical neurons adjusted their AP shape in response to different stimulus types. We demonstrated that cortical neurons differentiate between stimulus types through their evoked AP shape. However, the difference in AP shape was more apparent in pyramidal RS neurons than in FS neurons. Interestingly, the resulting AP onset parameters from the two stimulation types were significantly different only in RS neurons. The average rapidity increased from 3.97 ms^{-1} for step-and-hold stimulation to 5.41 ms^{-1} for frozen noise stimulation. However, FS cortical neurons responded stereotypically regardless of the input stimulus (6.40 ms^{-1} for step-and-hold current and 6.33 ms^{-1} for frozen noise current). Furthermore, we found that AP onset dynamics were more variable in RS than in FS neurons. Synaptic-like stimulus (frozen noise) increased threshold variability in RS neurons by approximately 87%, while threshold variability was minimal for FS neurons regardless of the stimulus type (11% difference). These results suggest that the interplay of Na_v 1.2 and Na_v 1.6, among other factors, may encode the difference in stimulus by adjusting their activation mechanism.

Threshold variability and rapid AP onset are characteristics of cortical neurons. These two unique features can be attributed to several mechanisms. AP backpropagation from the spike initiation site at the AIS to the soma can distort the somatic AP, causing the onset dynamic to become highly variable and rapid compared to AIS AP [15]. Hence, a shift in the AP initiation site can influence AP onset parameters. Several studies have shown that the AIS adapts its length or shifts the AP initiation site after repetitive firing [26–28]. Thus, a shift in the AP initiation site may affect AP onset parameters in somatic recordings. However, while this shift can influence the somatic AP onset dynamics, AP backpropagation cannot adequately reproduce the observed AP onset dynamics [17,29].

An alternative explanation for the rapid and variable AP onset in mammalian neurons is due to neuron geometry: more precisely, the resistive coupling theory [17,30,31]. The differences in size and the small distance between the soma and AIS cause the sharp somatic AP onset and threshold variations observed in the soma of mammalian neurons [17,32]. Thus, the resistive coupling theory may explain the significant difference in AP rapidity between RS and FS cortical neurons, since the two neuron types have different geometry. If the AP initiation site shifts due to repetitive firing, the coupling resistivity between the soma and AIS may explain the increase in AP rapidity in the same RS neurons due to repetitive stimulation. The shift in the AP initiation site may be attributed to the inactivation of axonal sodium channels due to somatic depolarization spreading into the axon, occurring on a tenth-of-a-millisecond time scale [28]. Another explanation for the observed AP initiation properties was associated with the expression of multiple voltage-gated channels or their gating mechanism. Cooperative gating between sodium channels was suggested to reproduce the sharp AP onset and variability in modeling studies [16,33], which was supported by recent evidence in cardiac Na_v1.5 [34–37]. On the other hand, changes in resting potential could influence neuronal excitability and hence the AP shape. For instance, difference in resting potential between the soma and axon was observed in the cortical layer 5 pyramidal neuron, due to the differences in voltage-gated channels (such as Na_v, K_v, Ca_v, and HCN) between the two neuronal compartments [38], and the interaction among the different channels can influence the AP shape [39]. However, further investigation is needed to show whether the AP initiation site shifts between the two stimuli, a difference in voltage-gated channels expression, or cooperative gating could explain the observed results. Nonetheless, the comparison between RS and FS neurons in response to different stimuli, and possibly a hybrid of the two stimuli, can provide an interesting methodology to better understand the main mechanism underlying cortical neuron rapid and highly variable AP onset.

AP parameters can differentiate between neuron types [3,4]. Similar to our previous observations, $IFWd^2$ rapidity can significantly differentiate RS and FS neurons in response to step-and-hold current stimulation. Nevertheless, the average rapidity was higher for both neuron types than our previous observation (see reference [22] for further details). Although the recordings in this study and our previous one were obtained from the same database, the data were collected by different experimenters, possibly explaining the difference. Nonetheless, the same argument is still valid: $IFWd^2$ rapidity can differentiate neuron types even though the value reported here is higher. Furthermore, the difference in AP parameters between RS and FS neurons aligns with previous studies comparing neuron types in response to current pulses [3,4], while the difference diminishes between the two neuron types in response to synaptic-like current. Neuron-type classification is usually studied in response to current pulses [3,4], which can provide a straightforward and simpler paradigm to differentiate neuronal firing patterns. Alternatively, synaptic-like stimulation is more complex and usually used to study neuron behavior under more realistic conditions. However, it would be interesting to investigate how the AP waveform changes with the selective blockage of certain ion channels in different neuron types. In conclusion, the findings emphasize the role of the complex interaction between different ion channels shaping the AP, while highlighting the need for further investigation to understand the mechanisms of AP waveform generation and their effect on neuronal information processing.

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