Loss or Gain of Function? Ion Channel Mutation Effects on Neuronal Firing Depend on Cell Type

Abstract (250 Words Maximum - Currently 231)

Ion channels determine neuronal excitability and disruption in ion channel properties in mutations can result in neurological disorders called channelopathies. Often many mutations are associated with a channelopathy, and determination of the effects of these mutations are generally done at the level of currents. The impact of such mutations on neuronal firing is vital for selecting personalized treatment plans for patients, however whether the effect of a given mutation on firing can simply be inferred from current level effects is unclear. The general impact of the ionic current environment in different neuronal types on the outcome of ion channel mutations is vital to understanding of the impacts of ion channel mutations and effective selection of personalized treatments. Using a diverse collection of neuronal models, the effects of changes in ion current properties on firing is assessed systematically and for episodic ataxia type 1 associated $K_V1.1$ mutations. The effects of ion current property changes or mutations on firing is dependent on the current environment, or cell type, in which such a change occurs in. Characterization of ion channel mutations as loss or gain of function is useful at the level of the ionic current, however the effects of channelopathies on firing is dependent on cell type. To further the efficacy of personalized medicine in channelopathies, the effects of ion channel mutations must be examined in the context of the appropriate cell types.

Significant Statement (120 Words Maximum - Currently 112)

Ion channels determine neuronal excitability and mutations that alter ion channel properties result in neurological disorders called channelopathies. Although the genetic nature of such mutations as well as their effects on the ion channel's biophysical properties are routinely assessed experimentally, determination of the role in altering neuronal firing is more difficult. Computational modelling bridges this gap and demonstrates that the cell type in which a mutation occurs is an important determinant in the effects of firing. As a result, classification of ion channel mutations as loss or gain of function is useful to describe the ionic current but care should be taken when applying this classification on the level of neuronal firing.

Introduction (750 Words Maximum - Currently 673)

Neuronal ion channels are vital in determining neuronal excitability, action potential generation and firing patterns (Bernard and Shevell, 2008; Carbone and Mori, 2020). In particular, the properties and combinations of ion channels and their resulting currents determine the firing properties of the neuron (Pospischil et al., 2008; Rutecki, 1992). However, ion channel function can be disturbed, resulting in altered ionic current properties and altered neuronal firing behaviour (Carbone and Mori, 2020). Ion channel mutations are a common cause of such channelopathies and are often associated with hereditary clinical disorders (Bernard and Shevell, 2008; Carbone and Mori, 2020).

The effects of these mutations are frequently determined at a biophysical level in heterologous expression systems that contain no endogenous ionic currents. why? These experiments can determine how the voltage dependent kinetics have changed, but only allow for rough predictions about how the firing rate of a neuron is affected.

Transfection of primary neuron cultures can overcome some of these limitations and changes in firing behaviour can more readily be assessed (Liu et al., 2019; Scalmani et al., 2006). However, the relative expression and conductance of the transfected ion channel in relation to endogenous currents can be variable. As the firing behaviour and dynamics of neuronal models can be dramatically altered by altering relative current amplitudes (Barreiro et al., 2012; Golowasch et al., 2002; Kispersky et al., 2012; Pospischil et al., 2008; Rutecki, 1992), primary neuronal do probably not provide definitive insight into the effects of a channelopathy on *in vivo* firing.

Ion channel transfection of primary neuronal cultures can overcome some of the limitations of cell culture expression. In transfected neuronal cell cultures firing can more readily be assessed as endogenous currents are present, however the expressed and endogenous versions of the same ion channel are present in the cell (Scalmani et al., 2006; Smith et al., 2018). To avoid the confound of both expressed and endogenous current contributing to firing, a drug resistance can be introduced into the ion channel that is transfected and the drug is used to silence the endogenous version of this current (Liu et al., 2019). Although addition of TTX-resistance to Na_V does not alter the gating properties of these channels (Leffler et al., 2005), the relative expression and conductance of the transfected ion channel in relation to endogenous currents can be variable and non-specific blocking of ion channels not affected by the channelopathy may occur. As the firing behaviour and dynamics of neuronal models can be dramatically altered by altering relative current amplitudes (Barreiro et al., 2012; Golowasch et al., 2002; Kispersky et al., 2012; Pospischil et al., 2008; Rutecki, 1992), primary neuronal cultures provide a useful general indication as to the effects of ion channel mutations but do not provide definitive insight into the effects of a channelopathy on *in vivo* firing.

The generation of mice lines is costly and behavioural characterization of new mice lines is required to assess similarities to patient symptoms. Although the generation of mouse lines is desirable for a clinical disorder characterized by a specific ion channel mutation, this approach becomes impractical for disorders associated with a collection of distinct mutations in a single ion channel. Because of the lack of adequate experimental approaches, a great need is present for the ability to assess the impacts of ion channel mutations on neuronal firing. A more general understanding of the effects of changes in current properties on neuronal firing may help to understand the impacts of ion channel mutations. Specifically, modelling approaches can be used to assess the impacts of current property changes on firing behaviour, bridging the gap between changes in the biophysical properties induced by mutations and clinical symptoms. Conductance-based neuronal models enable insight into the effects of ion channel mutations with specific effects of the resulting ionic current as well as enabling *in silico* assessment of the relative effects of changes in biophysical properties of ionic currents on neuronal firing . The effects of altered voltage-gated potassium channel $K_V1.1$ function is of particular interest in this study as it gives rise to the $I_{K_V1.1}$ current and is associated with episodic ataxia type 1. Furthermore, modelling approaches enable predictions of the effects of specific mutation and drug induced biophysical property changes.

$K_V1.1$ channels, encoded by the KCNA1 gene, play a role in repolarizing the action potential, neuronal firing patterns, neurotransmitter release, and saltatory conduction (D'Adamo et al., 1998) and are expressed throughout the CNS (Tsaur et al., 1992; Veh et al., 1995; Wang et al., 1994). Altered $K_V1.1$ channel function as a result of KCNA1 mutations in humans is associated with episodic ataxia type 1 (EA1) which is characterized by period attacks of ataxia and persistent myokymia (Parker, 1946; Van Dyke et al., 1975). Onset of EA1 is before 20 years of age (Brunt and van Weerden, 1990; Jen et al., 2007; Rajakulendran et al., 2007; Van Dyke et al., 1975) and is associated with a 10 times higher prevalence of epileptic seizures(Zuberi et al., 1999). EA1 significantly impacts patient quality of life (Graves et al., 2014). $K_V1.1$ null mice have spontaneous seizures without ataxia starting in the third postnatal week although impaired balance has been reported (Smart et al., 1998; Zhang et al., 1999) and neuronal hyperexcitability has been demonstrated in these mice (Brew et al., 2003; Smart et al., 1998). However, the lack of ataxia in $K_V1.1$ null mice raises the question if the hyperexcitability seen is representative of the effects of EA1 associated $K_V1.1$ mutations.

Using a diverse set of conductance-based neuronal models we examine the role of current environment on the impact of alterations in channels properties on firing behavior generally and for EA1 associated $K_V1.1$ mutations.

Materials and Methods

All modelling and simulation was done in parallel with custom written Python 3.8 software, run on a Cent-OS 7 server with an Intel(R) Xeon (R) E5-2630 v2 CPU.

Different Cell Models

A group of neuronal models representing the major classes of cortical and thalamic neurons including regular spiking pyramidal (RS pyramidal), regular spiking inhibitory (RS inhibitory), and fast spiking (FS) cells were used (Pospischil et al., 2008). To each of these models, a $K_V1.1$ current ($I_{K_V1.1}$); (Ranjan et al., 2019)) was added. A cerebellar stellate cell model from (Alexander et al., 2019) is used (Cb stellate). This model was also used with a $K_V1.1$ current ($I_{K_V1.1}$; (Ranjan et al., 2019)) in addition to the A-type potassium current (Cb stellate +$K_V1.1$) or replacing the A-type potassium current (Cb stellate $\Delta K_V1.1$). A subthalamic nucleus neuron model as described by (Otsuka et al., 2004) are used (STN) and with a $K_V1.1$ current ($I_{K_V1.1}$; (Ranjan et al., 2019)) in addition to the A-type potassium current (STN +$K_V1.1$) or replacing the A-type potassium current (STN $\Delta K_V1.1$). The properties and conductances of each model are detailed in Table 1 and the gating properties are unaltered from the original Cb stellate and STN models. For comparability to typical electrophysiological data fitting reported and for ease of further gating curve manipulations, a Boltzmann function

$$x_\infty = \left(\frac{1-a}{1+exp[\frac{V-V_{1/2}}{k}]} + a \right)^j \tag{1}$$

with slope k, voltage for half-maximal activation or inactivation ($V_{1/2}$), exponent j, and persistent current $0 \leq a \leq 1$ were fitted for the RS pyramidal, RS inhibitory and FS models (Pospischil et al., 2008). The properties of $I_{K_V1.1}$ were fitted to the mean wild type biophysical parameters of $K_V1.1$ (Lauxmann et al., 2021).

	RS Pyramidal	RS Inhibitory	FS	Cb Stellate	Cb Stellate $+K_V1.1$	Cb Stellate $\Delta K_V1.1$	STN	STN $+K_V1.1$	STN $\Delta K_V1.1$
g_{Na}	56	10	58	3.4	3.4	3.4	49	49	49
g_K	5.4	1.89	3.51	9.0556	8.15	9.0556	57	56.43	57
$g_{K_V1.1}$	0.6	0.21	0.39	—	0.90556	1.50159	—	0.57	0.5
g_A	—	—	—	15.0159	15.0159	—	5	5	—
g_M	0.075	0.0098	0.075	—	—	—	—	—	—
g_L	—	—	—	—	—	—	5	5	5
g_T	—	—	—	0.45045	0.45045	0.45045	5	5	5
$g_{Ca,K}$	—	—	—	—	—	—	1	1	1
g_{Leak}	0.0205	0.0205	0.038	0.07407	0.07407	0.07407	0.035	0.035	0.035
$\tau_{max,M}$	608	934	502	—	—	—	—	—	—
C_m	118.44	119.99	101.71	177.83	177.83	177.83	118.44	118.44	118.44

Table 1: Cell properties and conductances of regular spiking pyramidal neuron (RS Pyramidal), regular spiking inhibitory neuron (RS Inhibitory), fast spiking neuron (FS), cerebellar stellate cell (Cb Stellate), with additional $I_{K_V1.1}$ (Cb Stellate $\Delta K_V1.1$) and with $I_{K_V1.1}$ replacement of I_A (Cb Stellate $\Delta K_V1.1$), and subthalamic nucleus neuron (STN), with additional $I_{K_V1.1}$ (STN $\Delta K_V1.1$) and with $I_{K_V1.1}$ replacement of I_A (STN $K_V1.1$) models. All conductances are given in mS/cm^2. Capacitances (C_m) and $\tau_{max,M}$ are given in pF and ms respectively.

	Gating	$V_{1/2}$ [mV]	k	j	a
	I_{Na} activation	-34.33054521	-8.21450277	1.42295686	—
RS pyramidal,	I_{Na} inactivation	-34.51951036	4.04059373	1	0.05
RS inhibitory,	I_{Kd} activation	-63.76096946	-13.83488194	7.35347425	—
FS	I_{L} activation	-39.03684525	-5.57756176	2.25190197	—
	I_{L} inactivation	-57.37	20.98	1	—
	I_{M} activation	-45	-9.9998807337	1	—
$I_{Kv1.1}$	$I_{Kv1.1}$ activation	-30.01851852	-7.73333333	1	—
	$I_{Kv1.1}$ Inactivation	-46.85851852	7.67266667	1	0.245

Table 2: For comparability to typical electrophysiological data fitting reported and for ease of further gating curve manipulations, a Boltzmann $x_\infty = \left(\frac{1-a}{1+exp[\frac{V-V_{1/2}}{k}]} + a\right)^j$ with slope k, voltage for half-maximal activation or inactivation ($V_{1/2}$), exponent j, and persistent current $0 \leq a \leq 1$ were fitted for the (Pospischil et al., 2008) models where α_x and β_x are used. Gating parameters for $I_{Kv1.1}$ are taken from (Ranjan et al., 2019) and fit to mean wild type parameters in (Lauxmann et al., 2021). Model gating not listed are taken directly from source publication.

Firing Frequency Analysis

The membrane responses to 200 equidistant two second long current steps were simulated using the forward-Euler method with a $\Delta t = 0.01$ ms from steady state. Current steps ranged from 0 to 1 nA for all models except for the RS inhibitory neuron models where a range of 0 to 0.35 nA was used to ensure repetitive firing across the range of input currents. For each current step, action potentials were detected as peaks with at least 50 mV prominence and a minimum interspike interval of 1 ms. The interspike interval was computed and used to determine the instantaneous firing frequencies elicited by the current step. The steady-state firing frequency were defined as the mean firing frequency in 0.5 seconds after the first action potential in the last second of the current step respectively and was used to construct frequency-current (fI) curves.

The smallest current at which steady state firing occurs was identified and the current step interval preceding the occurrence of steady state firing was simulated at higher resolution (100 current steps) to determine the current at which steady state firing began. Firing was simulated with 100 current steps from this current upwards for 1/5 of the overall current range. Over this range a fI curve was constructed and the integral, or area under the curve (AUC), of the fI curve over this interval was computed with the composite trapezoidal rule and used as a measure of firing rate independent from rheobase.

To obtain the rheobase, the current step interval preceding the occurrence of action potentials was explored at higher resolution with 100 current steps spanning the interval. Membrane responses to these current steps were then analyzed for action potentials and the rheobase was considered the lowest current step for which an action potential was elicited.

All models exhibit tonic firing and any instances of bursting were excluded to simplify the characterization of firing.

Sensitivity Analysis and Comparison of Models

Current properties of currents common to all models (I_{Na}, I_K, I_A/$I_{K_V1.1}$, and I_{Leak}) were systematically altered in a one-factor-at-a-time sensitivity analysis for all models. The gating curves for each current were shifted ($\Delta V_{1/2}$) from -10 to 10 mV in increments of 1 mV. The slope (k) of the gating curves were altered from half to twice the initial slope. Similarly, the maximal current conductance (g) was also scaled from half to twice the initial value. For both slope and conductance alterations, alterations consisted of 21 steps spaced equally on a $\log_2$ scale.

Model Comparison

Changes in rheobase ($\Delta rheobase$) are calculated in relation to the original model rheobase. The contrast of each AUC value (AUC_i) was computed in comparison to the AUC of the unaltered wild type model (AUC_{wt})

$$AUC_{contrast} = \frac{AUC_i - AUC_{wt}}{AUC_{wt}} \tag{2}$$

To assess whether the effects of a given alteration on $AUC_{contrast}$ or $\Delta rheobase$ are robust across models, the correlation between $AUC_{contrast}$ or $\Delta rheobase$ and the magnitude of current property alteration was computed for each alteration in each model and compared across alteration types.

The Kendall's τ coefficient, a non-parametric rank correlation, is used to describe the relationship between the magnitude of the alteration and AUC or rheobase values. A Kendall τ value of -1 or 1 is indicative of monotonically decreasing and increasing relationships respectively.

KCNA1/K_V1.1 Mutations

Known episodic ataxia type 1 associated KCNA1 mutations and their electrophysiological characterization reviewed in (Lauxmann et al., 2021). The mutation-induced changes in $I_{K_V1.1}$ amplitude and activation slope (k) were normalized to wild type measurements and changes in activation $V_{1/2}$ were used relative to wild type measurements. The effects of a mutation were also applied to I_A when present as both potassium currents display prominent inactivation. In all cases, the mutation effects were applied to half of the K_V1.1 or I_A under the assumption that the heterozygous mutation results in 50% of channels carrying the mutation. Frequency-current curves for each mutation in each model were obtained through simulation and used to characterize firing behaviour as described above. For each model the differences in mutation AUC to wild type AUC were normalized by wild type AUC ($AUC_{contrast}$) and mutation rheobases are compared to wild type rheobase values ($\Delta rheobase$). Pairwise Kendall rank correlations (Kendall τ) are used to compare the the correlation in the effects of $K_V1.1$ mutations on AUC and rheobase between models.

Code Accessibility

The code/software described in the paper is freely available online at [URL redacted for double-blind review]. The code is available as Extended Data.

Results

To examine the role of cell specific current environments on the impact of altered ion channel properties on firing behaviour a set of neuronal models is used and properties of channels common across models are altered systematically one at a time. The effects of a set of episodic ataxia type 1 associated $K_V1.1$ mutations on firing was then examined across different neuronal models with different current environments.

Firing Characterization

Neuronal firing is a complex phenomenon and classification of firing is needed for comparability across cell types. Here we focus on the classification of two aspects of firing: rheobase (smallest injected current at which the cell fires an action potential) and the initial shape of the frequency-current (fI) curve. The quantification of the inital shape of the fI curve using by computing the area under the curve (AUC) is a measure of the initial firing at currents above rheobase (Figure 1A). The characterization of firing with AUC and rheobase enables determination of general increases or decreases in firing based on current-firing relationships, with the upper left quadrant (+ΔAUC and -Δrheobase) indicate an increase in firing, whereas the bottom right quadrant (-ΔAUC and +Δrheobase) is indicative of decreased firing (Figure 1B). In the lower left and upper right quad-

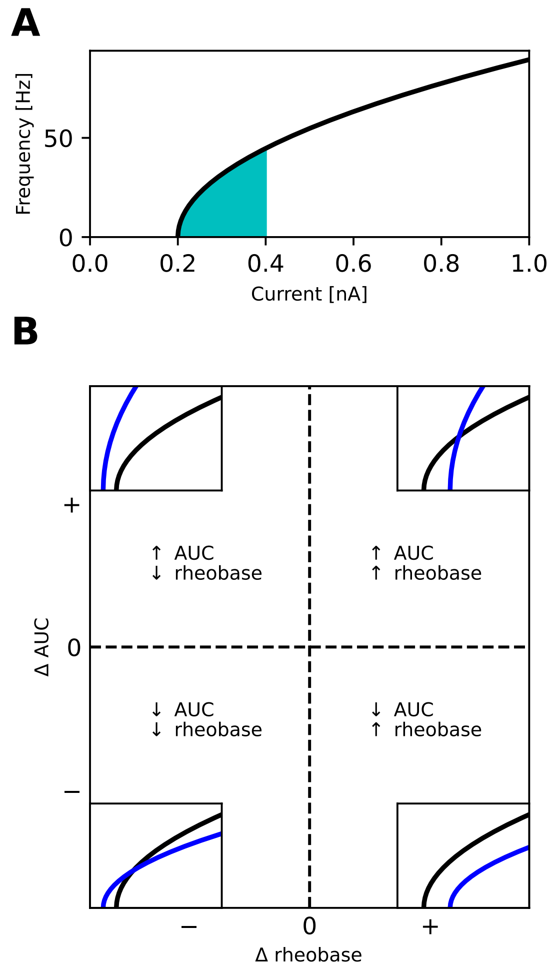

Figure 1: Characterization of firing with AUC and rheobase. (A) The area under the curve (AUC) of the repetitive firing frequency-current (fI) curve. (B) Changes in firing as characterized by ΔAUC and Δrheobase occupy 4 quadrants separated by no changes in AUC and rheobase. Representative schematic fI curves in blue with respect to a reference fI curve (black) depict the general changes associated with each quadrant.

rants, the effects on firing are more nuance and cannot easily be described as a gain or loss of excitability.

Considerable diversity is present in the set of neuronal models used as evident in the variability seen across neuronal models both in representative spike trains and their fI curves (Figure 2). The models chosen all fire repetitively and do not exhibit bursting. Some models, such as Cb stellate and RS inhibitory models, display type I firing whereas others such as Cb stellate $\Delta K_V1.1$and STN models have type II firing. Type I firing is characterized by continuous fI curve (i.e. firing rate is continuous) generated through a saddle-node on invariant cycle bifurcation and type II firing is characterized by a discontinuity in the fI curve (i.e. a jump occurs from no firing to firing at a certain frequency) due to a Hopf bifurcation (Ermentrout, 1996; Ermentrout and Chow, 2002). Other models lie on a continuum between these prototypical firing classifications. Most neuronal models exhibit hysteresis with ascending and descending ramps eliciting spikes with different thresholds, however STN $+K_V1.1$, STN $\Delta K_V1.1$, Cb stellate $\Delta K_V1.1$ have large hysteresis (Figure 2).

Sensitivity analysis

A one-factor-a-time sensitivity analysis enables the comparison of a given alteration in current parameters across models. Changes in gating $V_{1/2}$ and slope factor k as well as the current conductance affect AUC (Figure 3 A, B and C). Heterogeneity in the correlation between gating and conductance changes and AUC occurs across models for most currents. In these cases some of the models display non-monotonic relationships

(i.e. $|\text{Kendall } \tau| \neq 1$). However, shifts in A current activation $V_{1/2}$, changes in $K_V1.1$ activation $V_{1/2}$ and slope, and changes in A current conductance display consistent monotonic relationships across models.

Alterations in gating $V_{1/2}$ and slope factor k as well as the current conductance also play a role in determining rheobase (Figure 4 A, B and C). Shifts in half activation of gating properties are similarly correlated with rheobase across models, however Kendall τ values departing from -1 indicate non-monotonic relationships between K current $V_{1/2}$ and rheobase in some models (Figure 4A). Changes in Na current inactivation, $K_V1.1$ current inactivation and A current activation have affect rheobase with positive and negative correlations in different models (Figure 4B). Departures from monotonic relationships occur in some models as a result of K current activation, $K_V1.1$ current inactivation and A current activation in some models. Current conductance magnitude alterations affect rheobase similarly across models (Figure 4C).

$K_V1.1$

The changes in AUC and rheobase from wild-type values for reported episodic ataxia type 1 (EA1) associated $K_V1.1$ mutations are heterogenous across models containing $K_V1.1$, but generally show decreases in rheobase (Figure 5A-I). Pairwise non-parametric Kendall τ rank correlations between the simulated effects of these $K_V1.1$ mutations on rheobase are highly correlated across models (Figure 5J). However, the effects of the $K_V1.1$ mutations on AUC are more heterogenous as reflected by both weak and strong positive and negative pairwise correlations between models (Figure 5K).

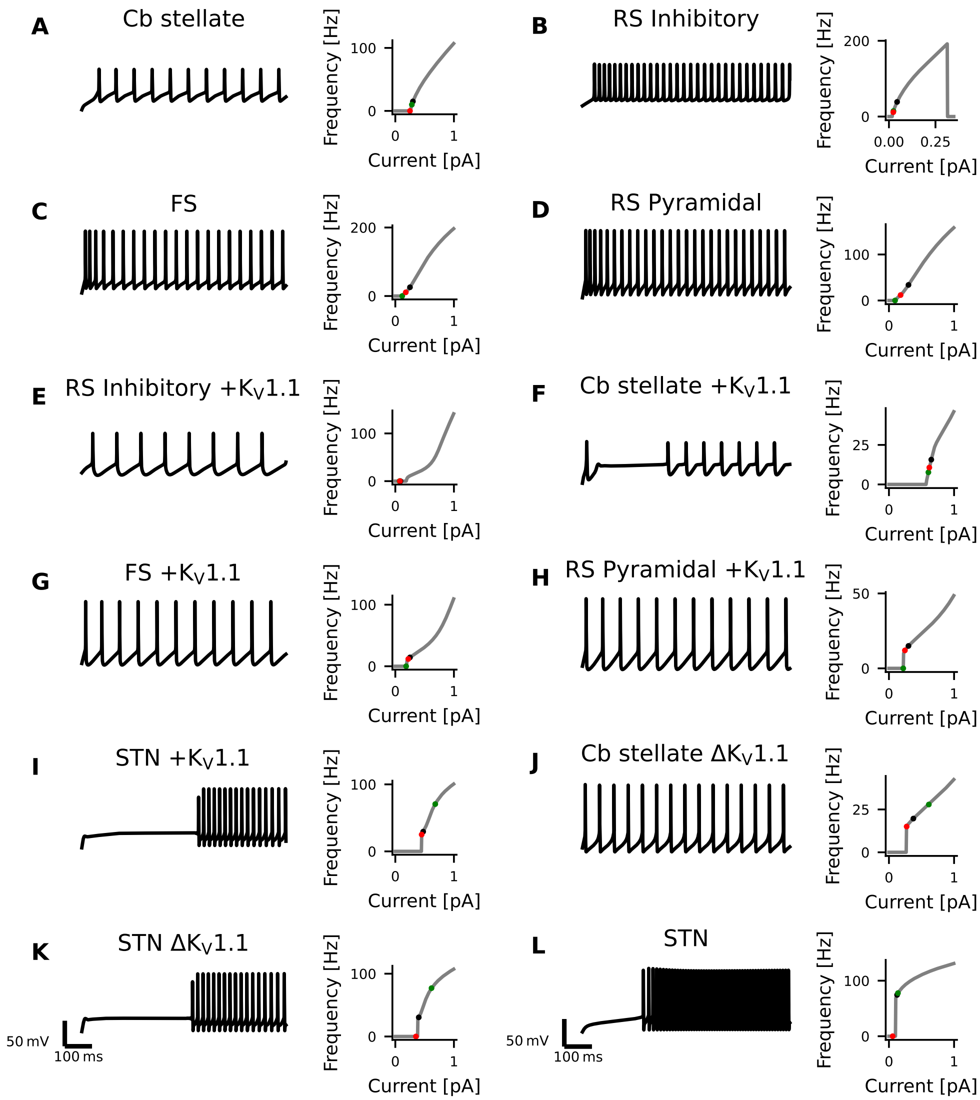

Figure 2: Diversity in Neuronal Model Firing. Spike trains (left), frequency-current (fI) curves (right) for Cb stellate (A), RS inhibitory (B), FS (C), RS pyramidal (D), RS inhibitory +K_V1.1 (E), Cb stellate +K_V1.1 (F), FS +K_V1.1 (G), RS pyramidal +K_V1.1 (H), STN +K_V1.1 (I), Cb stellate ΔK_V1.1(J), STN ΔK_V1.1(K), and STN (L) neuron models. Black marker on the fI curves indicate the current step at which the spike train occurs. The green marker indicates the current at which firing begins in response to an ascending current ramp, whereas the red marker indicates the current at which firing ceases in response to a descending current ramp (see Figure 2-1).

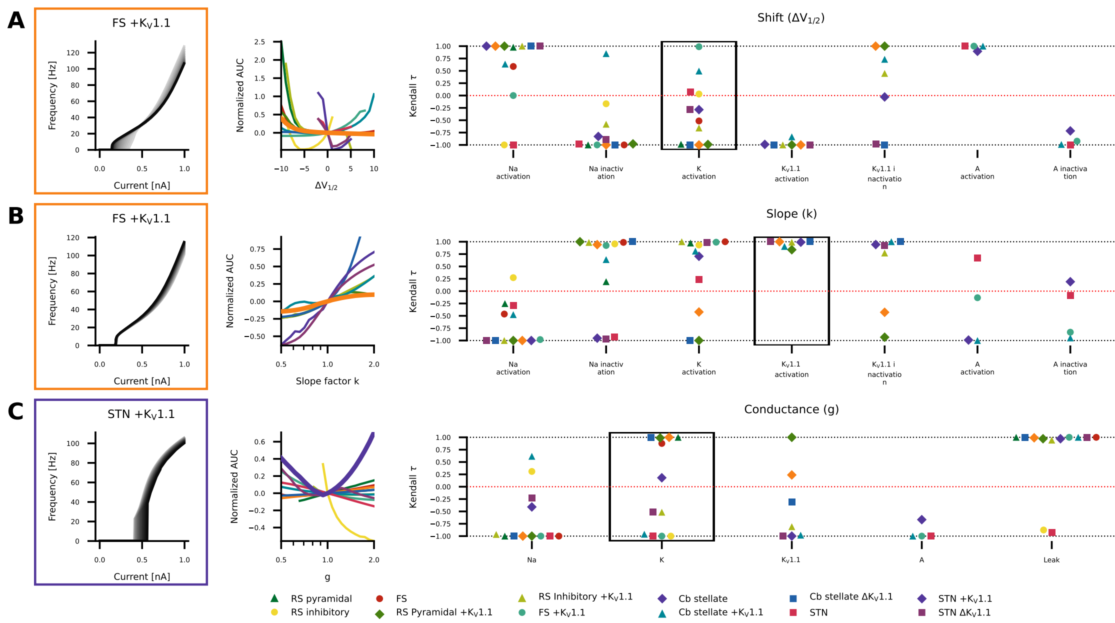

Figure 3: The Kendall rank correlation (Kendall τ) coefficients between shifts in $V_{1/2}$ and AUC, slope factor k and AUC as well as current conductances and AUC for each model are shown on the right in (A), (B) and (C) respectively. The relationships between AUC and $\Delta V_{1/2}$, slope (k) and conductance (g) for the Kendall τ coefficients highlights by the black box are depicted in the middle panel. The fI curves corresponding to one of the models are shown in the left panels.

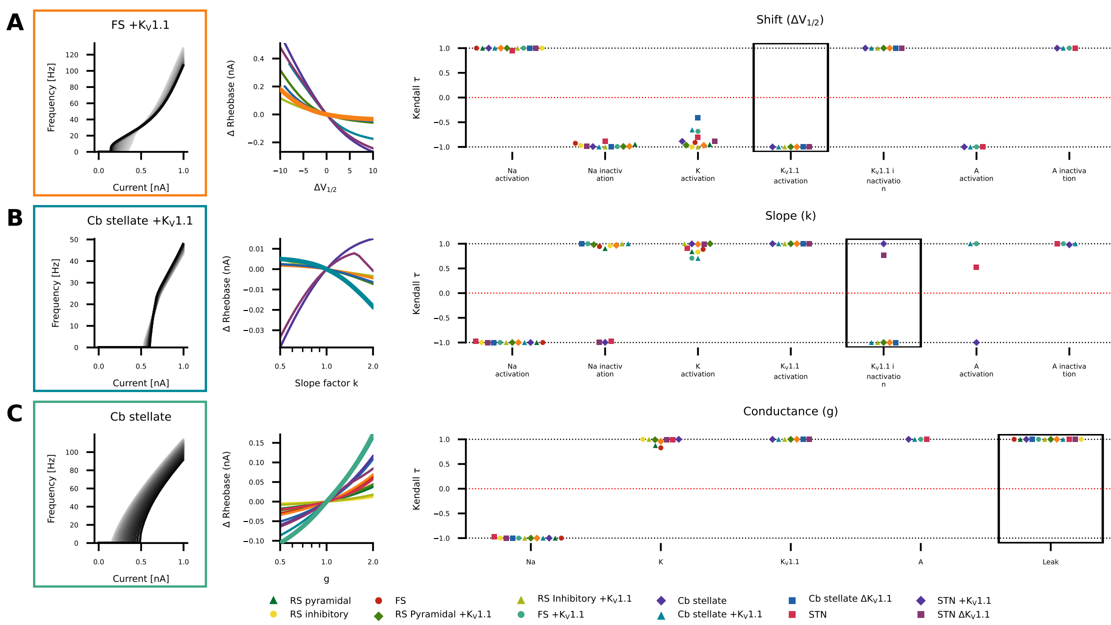

Figure 4: The Kendall rank correlation (Kendall τ) coefficients between shifts in $V_{1/2}$ and rheobase, slope factor k and AUC as well as current conductances and rheobase for each model are shown on the right in (A), (B) and (C) respectively. The relationships between rheobase and $\Delta V_{1/2}$, slope (k) and conductance (g) for the Kendall τ coefficients highlights by the black box are depicted in the middle panel. The fI curves corresponding to one of the models are shown in the left panels.

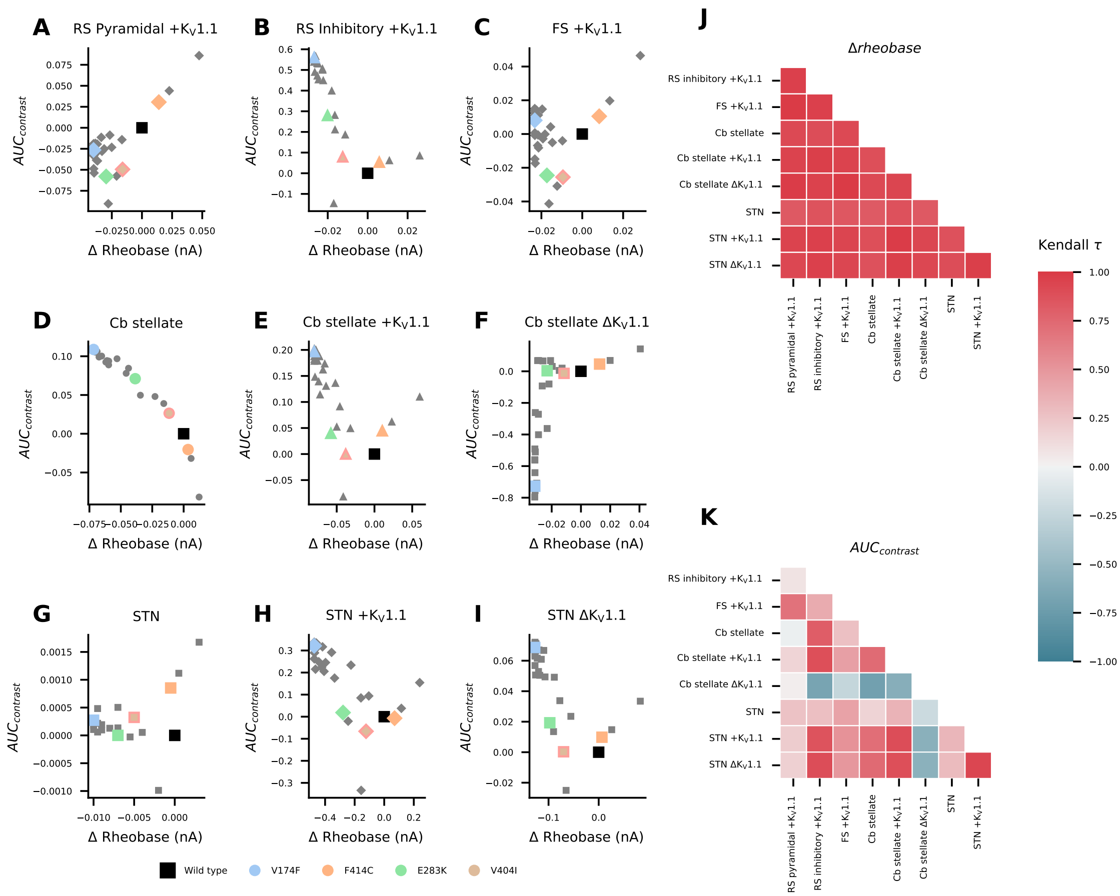

Figure 5: Effects of episodic ataxia type 1 associated $K_V1.1$ mutations on firing. Effects of $K_V1.1$ mutations on AUC ($AUC_{contrast}$) and rheobase (Δrheobase) compared to wild type for RS pyramidal +$K_V1.1$ (A), RS inhibitory +$K_V1.1$ (B), FS +$K_V1.1$ (C), Cb stellate (D), Cb stellate +$K_V1.1$ (E), Cb stellate $\Delta K_V1.1$(F), STN (G), STN +$K_V1.1$ (H) and STN $\Delta K_V1.1$(I) models V174F, F414C, E283K, and V404I mutations are highlighted in color for each model. Pairwise Kendall rank correlation coefficients (Kendall τ) between the effects of $K_V1.1$ mutations on rheobase and on AUC are shown in J and K respectively.

Discussion (3000 Words Maximum - Currently 1780)

Using a set of diverse conductance-based neuronal models, the effects of changes to current properties and conductances on firing were determined to be heterogenous for the AUC of the steady state fI curve but more homogenous for rheobase. For a known channelopathy, episodic ataxia type 1 associated $K_V1.1$ mutations, the effects on rheobase is consistent across cell types, whereas the effect on AUC is cell type dependent.

Validity of Neuronal Models

The $K_V1.1$ model from (Ranjan et al., 2019) is based on expression of only $K_V1.1$ in CHO cells and represents the biophysical properties of $K_V1.1$ homotetramers and not heteromers. Thus the $K_V1.1$ model used here neglects the complex reality of these channels *in vivo* including their expression as heteromers and the altered biophyiscal properties of these heteromers (Coleman et al., 1999; Isacoff et al., 1990; Rettig et al., 1994; Roeper et al., 1998; Ruppersberg et al., 1990; Wang et al., 1999). Furthermore, dynamic modulation of $K_V1.1$ channels, although physiologically relevant, is neglected here. For example, $K_V\beta2$ plays a role in K_V1 channel trafficking and cell membrane expression (Campomanes et al., 2002; Manganas et al., 2001; Shi et al., 2016) and $K_V1.1$ phosphorylation increases cell membrane $K_V1.1$ (Jonas and Kaczmarek, 1996). It should be noted that the discrete classification of potassium currents into delayed rectifier and A-type is likely not biological, but rather highlights the characteristics of a spectrum of potassium channel inactivation that arises in part due to additional factors such as heteromer composition (Glasscock, 2019; Stühmer et al., 1989), non-pore forming subunits (e.g. $K_V\beta$ subunits) (Rettig et al., 1994; Xu and Li, 1997), and temperature (Ranjan et al., 2019) modulating channel properties.

Additionally, the single-compartment model does not take into consideration differential effects on neuronal compartments (i.e. axon, soma, dendrites), possible different spatial cellular distribution of channel expression across and within these neuronal compartments or across CNS regions nor does it consider different channel types (e.g $Na_V1.1$ vs $Na_V1.8$). More realistic models would consist of multiple compartments, take more currents into account and take the spatial distribution of channels into account, however these models are more computationally expensive, require current specific models and knowledge of the distribution of conductances across the cell. Despite these limitations, each of the models can reproduce physiological firing behaviour of the neurons they represent (Alexander et al., 2019; Otsuka et al., 2004; Pospischil et al., 2008) and capture key aspects of the dynamics of these cell types. The firing characterization was performed on adapted firing and as such currents that cause adaptation are neglected in our analysis.

Current Environments Determine the Effect of Ion Channel Mutations

One-factor-at-a-time (OFAT) sensitivity analyses such as the one performed here are predicated on assumptions of model linearity, and cannot account for interactions between factors (Czitrom, 1999; Saltelli and Annoni, 2010). OFAT approaches are local and not global (i.e. always in reference to a baseline point in the parameter space) and therefore cannot be generalized to the global parameter space unless linearity is met (Saltelli and Annoni, 2010). The local space around the wild type neuron is explored with an OFAT sensitivity analysis without taking interactions between parameters into account. Comparisons between the effects of changes in similar parameters across different models can be made at the wild type locale indicative of experimentally observed neuronal behaviour. In this case, the role of deviations in the ionic current properties from their wild type in multiple neuronal models presented here provides a starting point for understanding the general role of these current properties in neurons. However, a more global approach would provide a more holistic understanding of the parameter space and provide insight into interactions between properties.

Characterization of the effects of a parameter on firing with non-parametric Kendall τ correlations takes into account the sign and monotonicity of the correlation. In other words Kendall τ coefficients provide information as to whether changing a parameter is positively or negatively correlated with AUC or rheobase as well as the extent to which this correlation is positive or negative across the parameter range examined. Therefore, Kendall τ coefficients provide general information as to the sensitivity of different models to a change in a given current property, however more nuanced difference between the sensitivities of models to current property changes, such as the slope of the relationship between parameter change and firing are not included in our analysis.

Although, to our knowledge, no comprehensive evaluation of how current environment and cell type affect the outcome of ion channel mutations, comparisons between the effects of such mutations in certain cells have been reported. For instance, mutations in the SCN1A gene encoding $Na_V1.1$ result in epileptic phenotypes by selective hypoexcitability of inhibitory but not excitatory neurons in the cortex resulting in circuit hyperexcitability (Hedrich et al., 2014). In CA3 of the hippocampus, mutation of $Na_V1.6$ similarly results in increased excitability of pyramidal neurons and decreased excitability of parvalbumin positive interneurons (Makinson et al., 2016). Additionally, the L858H mutation in $Na_V1.7$, associated with erythermyalgia, has been shown to cause hypoexcitability in sympathetic ganglion neurons and hyperexcitability in dorsal root ganglion neurons (Rush et al., 2006; Waxman, 2007). The differential effects of L858H $Na_V1.7$ on firing is dependent on the presence or absence of another sodium channel $Na_V1.8$ (Rush et al., 2006; Waxman, 2007). In a modelling study, it was found that altering the sodium conductance in 2 stomatogastric ganglion neuron models from a population models decreases rheobase in both models, however the initial slope of the fI curves (proportional to AUC) is increased in one model and decreased in the other suggesting that the magnitude of other currents in these models (such as K_d) determines the effect of a change in sodium current (Kispersky et al., 2012). These findings, in concert with our findings suggest that the current environment in which a channelopathy occurs is vital in determining the outcomes of the channelopathy on firing.

Cell type specific differences in current properties are important in the effects of ion channel mutations, however within a cell type heterogeneity in channel expression levels exists and it is often desirable to generate a population of neuronal models and to screen them for plausibility to biological data in order to capture neuronal population diversity (Marder and Taylor, 2011). The models we used here are originally generated by characterization of current gating properties and by fitting of maximal conductances to experimental data (Alexander et al., 2019; Otsuka et al., 2004; Pospischil et al., 2008; Ranjan et al., 2019). This practice of fixing maximal conductances based on experimental data is limiting as it does not reproduce the variability in channel expression and neuronal firing behaviour of a heterogeneous neuron population (Verma et al., 2020). For example, a model derived from the mean conductances in a sub-population of stomatogastric ganglion ”one-spike bursting” neurons fires 3 spikes instead of 1 per burst due to an L shaped distribution of sodium and potassium conductances (Golowasch et al., 2002). Multiple sets of current conductances can give rise to the same patterns of activity also termed degeneracy and differences in neuronal dynamics may only be evident with perturbations (Goaillard and Marder, 2021; Marder and Taylor, 2011). Variability in ion channel expression often correlates with the expression of other ion channels (Goaillard and Marder, 2021) and neurons whose behaviour is similar may possess correlated variability across different ion channels resulting in stability in neuronal phenotype (Lamb and Calabrese, 2013; Soofi et al., 2012; Taylor et al., 2009). The variability of ion currents and degeneracy of neurons may account, at least in part, for the observation that the effect of toxins within a neuronal type is frequently not constant (Khaliq and Raman, 2006; Puopolo et al., 2007; Ransdell et al., 2013).

Effects of KCNA1 Mutations

Moderate changes in delayed rectifier potassium currents change the bifurcation structure of Hodgkin Huxley model, with changes analogous to those seen with $K_V1.1$ mutations resulting in increased excitability due to reduced thresholds for repetitive firing (Hafez and Gottschalk, 2020). Although the Hodgkin Huxley delayed rectifier lacks inactivation, the increases in excitability seen are in line with both score-based and simulation-based predictions of the outcomes of *KCNA1* mutations. LOF KCNA1 mutations generally increase neuronal excitability, however the different effects of KCNA1 mutations across models on AUC are indicative that a certain cell type specific complexity exists. Increased excitability seen experimentally with $K_V1.1$ null mice (Smart et al., 1998; Zhou et al., 1998), with pharmacological $K_V1.1$ block (Chi and Nicol, 2007; Morales-Villagrán et al., 1996), by (Hafez and Gottschalk, 2020) and with simulation-based predictions of KCNA1 mutations. Contrary to these results, (Zhao et al., 2020) predicted *in silico* that the depolarizing shifts seen as a result of KCNA1 mutations broaden action potentials and interfere negatively with high frequency action potential firing, however comparability of firing rates is lacking in this study. Different current properties, such as the difference in I_A and $I_{K_V1.1}$ in the Cb stellate and STN model families alter the impact of KCNA1 mutations on firing highlighting that knowledge of the biophysical properties of a current and its neuronal expression is vital for holistic understanding of the effects of a given ion channel mutation both at a single cell and network level.

Loss or Gain of Function Characterizations Do Not Fully Capture Ion Channel Mutation Effects on Firing

The effects of changes in current properties depend in part on the neuronal model in which they occur and can be seen in the variance of correlations (especially in AUC) across models for a given current property change. Therefore, relative conductances and gating properties of currents in the current environment in which an alteration in current properties occurs plays an important role in determining the outcome on firing. The use of loss of function (LOF) and gain of function (GOF) is useful at the level of ion channels and whether a mutation results in more or less ionic current, however the extension of this thinking onto whether mutations induce LOF or GOF at the level of neuronal firing based on the ionic current LOF/GOF is problematic due to the dependency of neuronal firing changes on the current environment. Thus the direct leap from current level LOF/GOF characterizations to effects on firing without experimental or modelling-based evidence, although tempting, should be refrained from and viewed with caution when reported. This is especially relevant in the recent development of personalized medicine for channelopathies, where a patients specific channelopathy is identified and used to tailor treatments (Ackerman et al., 2013; Gnecchi et al., 2021; Helbig and Ellis, 2020; Weber et al., 2017). However, the effects of specific ion channel mutations are often characterized in expression systems and classified as LOF or GOF to aid in treatment decisions (Brunklaus et al., 2022; Johannesen et al., 2021; Musto et al., 2020). Interestingly, both LOF and GOF $Na_V1.1$ mutations can benefit from treatment with sodium channel blockers (Johannesen et al., 2021), suggesting that the relationship between effects at the level of ion channels and effects at the level of firing and therapeutics is not linear or evident without further contextual information. Therefore, this approach must be used with caution and the cell type which expressed the mutant ion channel must be taken into account. Experimental assessment of the effects of a patients specific ion channel mutation *in vivo* is not feasible at a large scale due to time and cost constraints, modelling of the effects of patient specific channelopathies is a desirable approach. Accordingly, for accurate modelling and predictions of the effects of mutations on neuronal firing, information as to the type of neurons containing the affected channel, and the properties of the affected and all currents in the affected neuronal type is needed. When modelling approaches are sought out to overcome the limitations of experimental approaches, care must be taken to account for model dependency and the generation of relevant cell-type or cell specific populations of models should be standard in assessing the effects of mutations in specific neurons.

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Figure/Table/Extended Data Legends

Figure 1: Characterization of firing with AUC and rheobase. (A) The area under the curve (AUC) of the repetitive firing frequency-current (fI) curve. (B) Changes in firing as characterized by ΔAUC and Δrheobase occupy 4 quadrants separated by no changes in AUC and rheobase. Representative schematic fI curves in blue with respect to a reference fI curve (black) depict the general changes associated with each quadrant.

Figure 2: Diversity in Neuronal Model Firing. Spike trains (left), frequency-current (fI) curves (right) for Cb stellate (A), RS inhibitory (B), FS (C), RS pyramidal (D), RS inhibitory +K_V1.1 (E), Cb stellate +K_V1.1 (F), FS +K_V1.1 (G), RS pyramidal +K_V1.1 (H), STN +K_V1.1 (I), Cb stellate ΔK_V1.1(J), STN ΔK_V1.1(K), and STN (L) neuron models. Black marker on the fI curves indicate the current step at which the spike train occurs. The green marker indicates the current at which firing begins in response to an ascending current ramp, whereas the red marker indicates the current at which firing ceases in response to a descending current ramp.

Figure 3: The Kendall rank correlation (Kendall τ) coefficients between shifts in $V_{1/2}$ and AUC, slope factor k and AUC as well as current conductances and AUC for each model are shown on the right in (A), (B) and (C) respectively. The relationships between AUC and $\Delta V_{1/2}$, slope (k) and conductance (g) for the Kendall τ coefficients highlights by the black box are depicted in the middle panel. The fI curves corresponding to one of the models are shown in the left panels.

Figure 4: The Kendall rank correlation (Kendall τ) coefficients between shifts in $V_{1/2}$ and rheobase, slope factor k and AUC as well as current conductances and rheobase for each model are shown on the right in (A), (B) and (C) respectively. The relationships between rheobase and $\Delta V_{1/2}$, slope (k) and conductance (g) for the Kendall τ coefficients highlights by the black box are depicted in the middle panel. The fI curves corresponding to one of the models are shown in the left panels.

Figure 5: Effects of episodic ataxia type 1 associated K_V1.1 mutations on firing. Effects of K_V1.1 mutations on AUC ($AUC_{contrast}$) and rheobase (Δrheobase) compared to wild type for RS pyramidal +K_V1.1 (A), RS inhibitory +K_V1.1 (B), FS +K_V1.1 (C), Cb stellate (D), Cb stellate +K_V1.1 (E), Cb stellate ΔK_V1.1(F), STN (G), STN +K_V1.1 (H) and STN ΔK_V1.1(I) models V174F, F414C, E283K, and V404I mutations are highlighted in color for each model. Pairwise Kendall rank correlation coefficients (Kendall τ) between the effects of K_V1.1 mutations on rheobase and on AUC are shown in J and K respectively.

Tables

	RS Pyramidal	RS Inhibitory	FS	Cb Stellate	Cb Stellate $+K_V1.1$	Cb Stellate $\Delta K_V1.1$	STN	STN $+K_V1.1$	STN $\Delta K_V1.1$
g_{Na}	56	10	58	3.4	3.4	3.4	49	49	49
g_K	5.4	1.89	3.51	9.0556	8.15	9.0556	57	56.43	57
$g_{K_V1.1}$	0.6	0.21	0.39	—	0.90556	1.50159	—	0.57	0.5
g_A	—	—	—	15.0159	15.0159	—	5	5	—
g_M	0.075	0.0098	0.075	—	—	—	—	—	—
g_L	—	—	—	—	—	—	5	5	5
g_T	—	—	—	0.45045	0.45045	0.45045	5	5	5
$g_{Ca,K}$	—	—	—	—	—	—	1	1	1
g_{Leak}	0.0205	0.0205	0.038	0.07407	0.07407	0.07407	0.035	0.035	0.035
$\tau_{max,M}$	608	934	502	—	—	—	—	—	—
C_m	118.44	119.99	101.71	177.83	177.83	177.83	118.44	118.44	118.44

Table 1: Cell properties and conductances of regular spiking pyramidal neuron (RS Pyramidal), regular spiking inhibitory neuron (RS Inhibitory), fast spiking neuron (FS), cerebellar stellate cell (Cb Stellate), with additional $I_{K_V1.1}$ (Cb Stellate $\Delta K_V1.1$) and with $I_{K_V1.1}$ replacement of I_A (Cb Stellate $\Delta K_V1.1$), and subthalamic nucleus neuron (STN), with additional $I_{K_V1.1}$ (STN $\Delta K_V1.1$) and with $I_{K_V1.1}$ replacement of I_A (STN $K_V1.1$) models. All conductances are given in mS/cm^2. Capacitances (C_m) and $\tau_{max,M}$ are given in pF and ms respectively.

Extended Data

Extended Data 1: TODO: Caption for code in zip file.

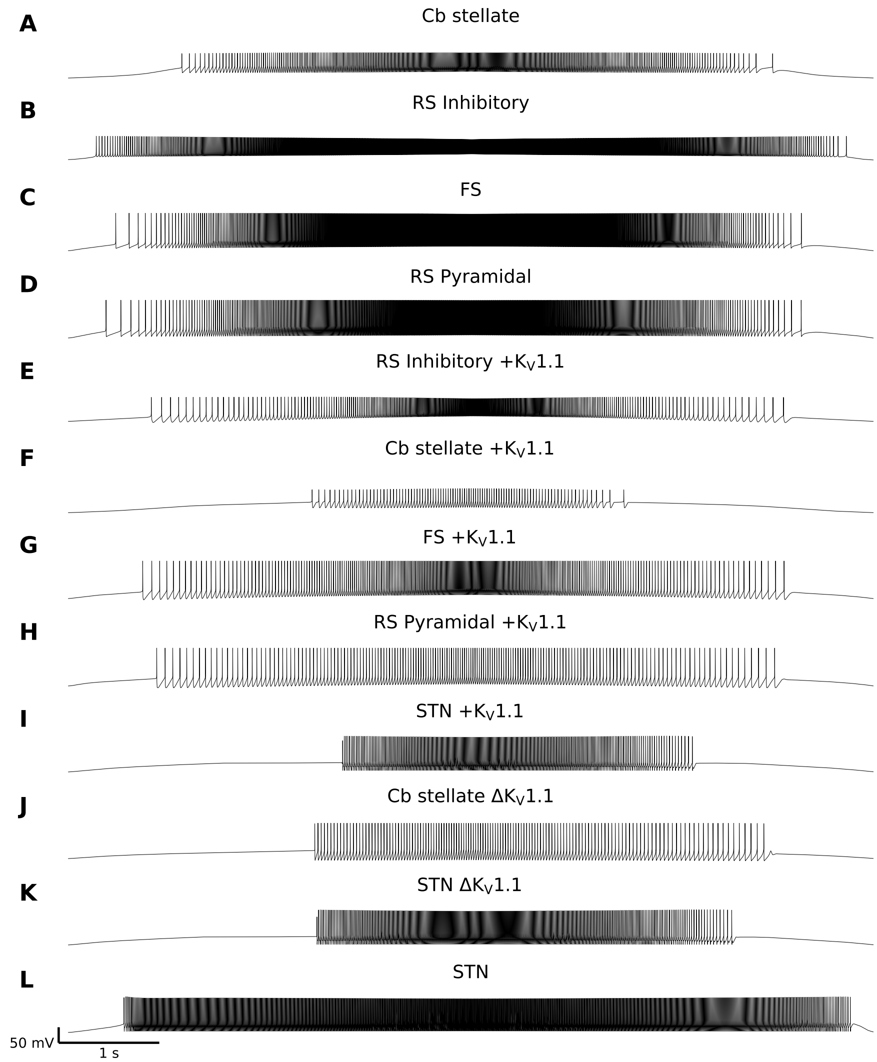

Figure 2-1: Diversity in Neuronal Model Firing Responses to a Current Ramp. Spike trains for Cb stellate (A), RS inhibitory (B), FS (C), RS pyramidal (D), RS inhibitory $+K_V1.1$ (E), Cb stellate $+K_V1.1$ (F), FS $+K_V1.1$ (G), RS pyramidal $+K_V1.1$ (H), STN $+K_V1.1$ (I), Cb stellate $\Delta K_V1.1$(J), STN $\Delta K_V1.1$(K), and STN (L) neuron models in response to a slow ascending current ramp followed by the descending version of the current ramp. The current at which firing begins in response to an ascending current ramp and the current at which firing ceases in response to a descending current ramp are depicted on the frequency current (fI) curves in Figure 2 for each model.