Kv7 Channels Regulate Pairwise Spiking Covariability in Health and Disease

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Abstract

Low-threshold M-currents are mediated by the Kv7 family of potassium channels. Kv7 channels are important regulators of spiking activity, having a direct influence on the firing rate, spike time variability, and filter properties of neurons. How Kv7 channels affect the joint spiking activity of populations of neurons is an important and open area of study. Using a combination of computational simulations and analytic calculations, we show that the activation of Kv7 conductances reduces the co-variability between spike trains of pairs of neurons driven by common inputs. This reduction is beyond that explained by the lowering of firing rates and involves an active cancellation of common fluctuations in the membrane potentials of the cell pair. Our theory shows that the excess covariance reduction is due to a Kv7 induced shift from lowpass to bandpass filtering of the single neuron spike train response. Dysfunction of Kv7 conductances is related to a number of neurological diseases characterized by both elevated firing rates and increased network-wide correlations. We show how changes in the activation or strength of Kv7 conductances give rise to excess correlations which cannot be compensated for by synaptic scaling or homeostatic modulation of passive membrane properties. In contrast, modulation of Kv7 activation parameters consistent with pharmacological treatments for certain hyperactivity disorders can restore normal firing rates and spiking correlations. Our results provide key insights into how regulation of a ubiquitous potassium channel class can control the coordination of population spiking activity.
Introduction

Potassium-mediated M-currents are a common intrinsic property of neurons in cortical, subcortical, and hippocampal regions (Brown and Passmore, 2009, Delmas and Brown, 2005, Jentsch, 2000). M-currents have slow activation kinetics, lack inactivation dynamics, and decrease overall cellular excitability (Aiken et al., 1995, Gu et al., 2005, Higgs et al., 2007, Lawrence et al., 2006, Peters et al., 2005). M-currents are due to heteromeric channels composed of Kv7.2/3 and Kv7.3/5 subunits that are encoded by the KCNQ gene family (Wang et al., 1998, Selyanko et al., 2001, Peters et al., 2005). Dysfunction of Kv7 channels is related to a number of disease: shifts in Kv7 activation have been related to tinnitus (Li et al., 2013), mutations involved in peripheral nerve hyper-excitability decrease Kv7 surface expression (Wuttke et al., 2007), and changes in both voltage-sensing and surface expression have been related to neonatal epilepsy (Soldovieri et al., 2006). Kv7 mutations are also associated with the most common childhood epilepsy condition, rolandic epilepsy (Coppola et al., 2003, Neubauer et al., 2008). Despite the evidence of reduced Kv7 activation in tinnitus, chronic pain, and epilepsy, there lacks a coherent mechanistic theory for how Kv7 channels contribute to physiological signatures of such disease states.

Two common neural correlates of tinnitus and epilepsy are elevated firing rates and excess spike train synchronization (Norea and Eggermont, 2003, McCormick and Contreras, 2001). While a decrease in Kv7 activation is expected to increase firing rates, it remains unclear how Kv7 channels shape the coordinated activity of populations of neurons. The temporal correlation between the spike trains of pairs of neurons is an important signature of network function. Spiking correlations are modulated by attention, stimulus tuning and presentation, learning, behavioral context, and sensory adaptation (Adibi et al., 2013, Gutnisky and Dragoi, 2008, Wang et al., 2011, Cohen and Kohn, 2011). While specific arrangements of correlated activity across a population of neurons can benefit cortical representation (Abbott and Dayan, 1999,
Averbeck et al., 2006), in many cases widespread and unstructured correlations are deleterious to coding (Josi et al., 2009, Sompolinsky et al., 2001). Previous studies of slow voltage-activated conductances like Kv7 have focused on single neuron statistics (Benda et al., 2010, Muller et al., 2007, Naud and Gerstner, 2012, Schwalger et al., 2010, Fisch et al., 2012), and little is known about their impact on the correlation of spiking activity between neurons. The dysfunction of Kv7 conductances in diseases characterized by increased correlations makes this a critical subject to study.

We consider a pair of model spiking neurons with voltage-gated Kv7 conductances that receive fluctuating, partially correlated synaptic inputs. We show that Kv7 conductances reduce firing rates and spike train correlations. Using a perturbative theoretical framework (de la Rocha et al., 2007, Shea-Brown et al., 2008), we relate the reduction in pairwise correlation to how Kv7 conductances shape single-neuron filter properties. The theory shows that the reduction in correlations is beyond that expected from the reduction in firing rates (de la Rocha et al., 2007) and involves an active cancellation of correlated inputs. This decoupling of firing rates and correlations by Kv7 conductances prevents homeostatic plasticity from simultaneously correcting for Kv7 pathology-induced increases in firing rates and correlations. However, we show that treatments that directly affect the Kv7 conductances can restore normal spiking activity. Our work provides important predictions about how regulation of a common membrane potassium channel controls the temporally coordinated activity across populations of neurons in both health and disease states.
Methods

Modeling

We describe pyramidal neurons with an exponential integrate-and-fire (EIF) model (Fourcaud-Trocmé et al., 2003) including a voltage-activated potassium (Kv7) conductance. The membrane potential \( V \) obeys:

\[
C \frac{dV}{dt} = g_L(V_L - V) + g_x x (V_x - V) + g_L \Delta \exp \frac{V - V_T}{\Delta} + I(t),
\]

(1)

\[
\tau_x \frac{dx}{dt} = x_\infty(V) - x,
\]

(2)

\[
x_\infty(V) = \left(1 + e^{-\frac{V-V_xh}{D_x}}\right)^{-1}.
\]

(3)

The first three terms on the right-hand side of Eq. (1) describe the leak, Kv7, and spiking currents respectively. The passive membrane properties are determined by the leak conductance \( g_L \) and reversal potential \( V_L \). The Kv7-mediated M-current has a gating variable \( x \), with equilibrium \( x_\infty(V) \). The voltage-dependence of \( x_\infty \) is given by its half-activation voltage \( V_xh \) and activation slope \( D_x \). As the voltage changes, \( x \) relaxes to \( x_\infty \) with time constant \( \tau_x \). Finally, the Kv7 current is determined by the maximum conductance \( g_x \) and \( K^+ \) reversal potential \( V_x \). The exponential term describes a phenomenological action potential with an initiation threshold \( V_T \) and steepness \( \Delta \). When the voltage reaches \( V_T \) it depolarizes exponentially until it hits a threshold \( V_{th} \) at time \( t_j \), then decays linearly to the reset potential \( V_{re} \): \( V(t) = V_{th} - \frac{t-t_j}{\tau_{ref}} (V_{th} - V_{re}) \).

When the voltage reaches \( V_{re} \), its dynamics again become governed by Eqs. (1)-(3). This explicit spike shape, in contrast to the usual reset rule for integrate-and-fire models, allows action potentials to directly activate the Kv7 conductance. Parameter values are given in Table 1.

We model the total synaptic input to a pair of pyramidal neurons as partially correlated Gaussian white noise: \( I_i(t) = \mu + g_L \sigma D \left( \sqrt{\xi_c(t)} + \sqrt{1 - \xi_c(t)} \right) \). Here, \( I_i \) denotes the input to
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C$</td>
<td>Membrane capacitance</td>
<td>1 $\mu$F/cm$^2$</td>
</tr>
<tr>
<td>$g_L$</td>
<td>Leak conductance</td>
<td>0.1 mS/cm$^2$</td>
</tr>
<tr>
<td>$V_L$</td>
<td>Leak reversal potential</td>
<td>-55 mV</td>
</tr>
<tr>
<td>$g_x$</td>
<td>Peak Kv7 conductance</td>
<td>0.3 mS/cm$^2$</td>
</tr>
<tr>
<td>$\tau_x$</td>
<td>Kv7 activation time constant</td>
<td>200 ms</td>
</tr>
<tr>
<td>$V_{zh}$</td>
<td>Kv7 half-activation voltage</td>
<td>-40 mV</td>
</tr>
<tr>
<td>$D_x$</td>
<td>Slope of Kv7 activation</td>
<td>8 mV</td>
</tr>
<tr>
<td>$V_x$</td>
<td>Kv7 reversal potential</td>
<td>-85 mV</td>
</tr>
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<td>$\Delta$</td>
<td>Action potential steepness</td>
<td>1.4 mV</td>
</tr>
<tr>
<td>$V_T$</td>
<td>Action potential initiation threshold</td>
<td>-50 mV</td>
</tr>
<tr>
<td>$V_{th}$</td>
<td>Action potential threshold</td>
<td>30 mV</td>
</tr>
<tr>
<td>$V_{re}$</td>
<td>Action potential reset</td>
<td>-72 mV</td>
</tr>
<tr>
<td>$\tau_{ref}$</td>
<td>Action potential width</td>
<td>2 ms</td>
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<tr>
<td>$\mu$</td>
<td>Input mean</td>
<td>0 $\mu$A/cm$^2$</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Input standard deviation</td>
<td>8 mV</td>
</tr>
<tr>
<td>$c$</td>
<td>Fraction of common input</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table 1: Model parameters.

neuron $i$ of the pair, with $i = 1, 2$. The input is composed of a baseline $\mu$ and fluctuations, which are broken up into two parts. One part, $\xi_c(t)$, is common to both neurons while the other part, $\xi_i(t)$ is specific to neuron $i$. Both $\xi_c(t)$ and $\xi_i(t)$ are Gaussian white noise processes with 0 mean and unit amplitude. The parameter $\sigma$ denotes the strength of the noise and $D = \sqrt{\frac{2\sigma}{g_L}}$ scales the noise amplitude to be independent of the membrane timescale. With this noise scaling, the infinitesimal variance of diffusion of the passive membrane voltage is $(g_L\sigma D)^2$. The parameter $c$ defines the fraction of shared input to the two neurons so that the infinitesimal covariance of the passive membrane voltage diffusion is $c(g_L\sigma D)^2$. Simulations were performed using an Euler-Maryama method with a timestep of 0.1 ms and a 1 s initial transient period excluded to ensure that the system had reached statistical equilibrium.
Statistics

Spike Count Statistics

A spike count from neuron $i$, $n_i^T(t)$, is the number of spikes occurring within the window $(t, t + T)$. For a given window length $T$ and trial length $L$, we compute a sequence of spike counts from neuron $i$ on each trial using windows that overlap by $T/2$: $\{n_i^T(0), n_i^T(T/2), ..., n_i^T(L - T)\}$. We use angular brackets, $\langle \cdot \rangle$, to denote averaging over trials. The firing rate of neuron $i$ is simply:

$$r_i = \langle n_i^L \rangle / L.$$

The spike count variance of neuron $i$ and covariance between the spike counts of neurons 1 and 2 are respectively:

$$\text{Var} \left( n_i^T \right) = \left( \langle n_i^T \rangle^2 \right) - \langle n_i^T \rangle^2,$$

$$\text{Cov} \left( n_1^T, n_2^T \right) = \langle n_1^T n_2^T \rangle - \langle n_1^T \rangle \langle n_2^T \rangle.$$  \hspace{1cm} (4)

Finally, the correlation coefficient of the spike counts 1 and 2 is:

$$\text{Corr} \left( n_1^T, n_2^T \right) = \frac{\text{Cov} \left( n_1^T, n_2^T \right)}{\sqrt{\text{Var} \left( n_1^T \right) \text{Var} \left( n_2^T \right)}}.$$  \hspace{1cm} (5)

Spike Train Covariance

The spike train from neuron $i$ is the point process $y_i = \sum_{j=1}^{n_i^L} \delta(t - t_j)$, where $t_j$ is the time of the $j$th spike, $\delta(t)$ the Dirac delta function and $n_i^L$ the number of spikes emitted by neuron $i$ during the trial of length $L$. The spike train cross-covariance between neurons 1 and 2 describes the probability that an action potential will occur in each spike train, separated by a time lag $s$:

$$q_{12}(s) = \frac{1}{L} \int_0^L \langle y_1(t) y_2(t - s) \rangle dt - r_1 r_2$$

By subtracting the product of the firing rates $r_1 r_2$, we correct for the chance coincidence of
action potentials. The spike count covariance is related to the integral of the cross-covariance function (Cox and Isham, 1980):

$$\text{Cov}(n^T_1, n^T_2) = \int_{-T}^{T} q_{12}(s)(T - |s|) ds,$$

(6)

where the term $(T - |s|)$ arises from the spike counting window.

**Linear Response Theory**

As in past studies (de la Rocha et al., 2007, Shea-Brown et al., 2008, Vilela and Lindner, 2009, Litwin-Kumar et al., 2011), we use a well-established linear approximation to relate $y(t)$ to an input stimulus $s(t)$. To transition from the temporal to frequency domain we define the Fourier transform of the time series $x(t)$ as $\hat{X}(f) = \mathcal{F}(x(t)) = \int_{-\infty}^{\infty} e^{-2\pi i ft} x(t) dt$. We consider the rate-corrected spike train $\hat{Y}(f) = \mathcal{F}(y(t) - r)$. Our linear theory is based on the following ansatz:

$$\langle \hat{Y}_{i|s}(f) \rangle \approx \hat{S}(f) \hat{A}_i(f),$$

(7)

where $\hat{S}(f)$ is the Fourier transform of $s(t)$ and $\hat{A}_i(f)$ is the neuron’s linear response function (or transfer function). In brief, $\langle \hat{Y}_{i|s}(f) \rangle$ is then the trial-averaged fluctuation of spike train $i$ about the time-averaged firing rate conditioned on the realization of the stimulus $s(t)$.

For numerical simulations, we compute the transfer function $\hat{A}_i(f)$ as

$$\hat{A}_i(f) = \frac{\hat{Q}_{is}(f)}{\hat{Q}_{ss}(f)},$$

(8)

where $\hat{Q}_{is}(f)$ is the cross-spectrum between the stimulus and spiking response and $\hat{Q}_{ss}(f)$ is the stimulus power spectrum. We computed these in MATLAB using the pwelch function with a Bartlett window. We approximate the cross-spectrum of two neurons’ activity, assuming that
their spike trains are conditionally independent given the stimulus, as:

$$\hat{Q}_{ij}(f) \approx \hat{A}_{i}(f)\hat{A}_{j}^{\ast}(f)\hat{Q}_{ss}(f),$$ (9)

where $$\hat{A}^{\ast}$$ denotes the complex conjugate of $$\hat{A}$$. To relate spike count statistics to spike train statistics, we use the Wiener-Khinchin theorem (Risken, 1996) to relate the cross-covariance function to the cross-spectrum of the two neurons’ activity and rewrite Eq. (6):

$$\text{Cov}(n_{1}^{T}, n_{2}^{T}) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} \hat{Q}_{ij}(f)e^{\pi i j f T} (T - |s|)dfds$$ (10)

$$= \int_{-\infty}^{\infty} \hat{Q}_{ij}(f)k_{T}(f)df$$ (11)

Here $$k_{T}(f) = \frac{1}{\pi f^{2}}\sin^{2}(\pi f T)$$ is the Fourier transform of the window function $$(T - |s|)$$.

Inserting Eq. (9) into Eq. (11) and using the fact that the stimulus has a white power spectrum $$\hat{Q}_{ss}(f) = \sigma^{2}$$, we then estimate the spike count covariance as:

$$\text{Cov}(n_{1}^{T}, n_{2}^{T}) = c\sigma^{2} \int_{-\infty}^{\infty} \hat{A}_{1}(f)\hat{A}_{2}^{\ast}(f)k_{T}(f)df$$ (12)

For a general exposition of linear response for covariance transfer in networks of spiking neurons see Trousdale et al. (2012). The theory states that the way a pair of neurons transfer correlated inputs to covariable spiking outputs is determined by how each neuron transfers the correlated portion of its input to modulations of its spiking output.

Solving for the Firing Rates and Response Functions with Fokker-Planck Theory

In this section we review the calculation for the transfer function first developed in Richardson (2007) and extended to models with voltage-activated conductances in Richardson (2009). We
refer the reader to these past studies for a full derivation of these techniques. For earlier treatments of spiking responses in stochastic neural network activity, see Abbott and van Vreeswijk (1993), Ginzburg and Sompolinsky (1994), and for a useful exposition of Fokker-Planck techniques in neural networks, see Fourcaud and Brunel (2002).

In the equilibrium state, the voltage distribution associated with Eqs. (1)-(2), \( P_0(V, x) \), obeys the continuity and flux equations (Risken, 1996)

\[
\begin{align*}
- \frac{\partial J_0}{\partial V} &= \frac{\partial P_0}{\partial t} = r_0 \left( \delta(V - V_{th}) - \delta(V - V_{re}) \right) \quad (13) \\
- \frac{1}{g_L \sigma^2} \frac{\partial P_0}{\partial V} &= CJ_0 + I_0 P_0 \quad (14)
\end{align*}
\]

where \( I_0 = g_L(V - V_L) + g_L \Delta e^{(V - V_T)/\Delta} + g_x x_0(V - V_x) - \mu_0 \), with \( \mu_0 \) being the mean of the input current. We use a separation of timescales to self-consistently solve for the steady-state Kv7 activation \( x_0 \) and density of non-refractory neurons, \( P_0 \). We then recover the firing rate from the normalization condition \( \int_{-\infty}^{\infty} P_0 dV + r_0 \tau_{ref} = 1 \). The density \( P_0 \) does not describe the neuron during an action potential. In order to take into account the membrane voltage during action potentials, we add the distribution of the membrane voltage during spikes. For the linear spike shape described above, the full equilibrium density is \( P_0(V) + r_0 \tau_{ref} \Theta(V - V_{re}) \), where \( \Theta(V) \) is the Heaviside function.

We investigate the response of the system to inputs that fluctuate in time by considering the time-varying responses to a periodic input as a perturbation from the equilibrium state: \( I_i(t) = \mu_0 + \hat{\mu}_1 e^{2\pi i ft} + g_L \sigma D \xi_i(t) \). Here \( \hat{\mu}_1 \) is the amplitude of the input modulation and is taken to be small. To first order in \( \hat{\mu}_1 \), the periodic input induces periodic modulations in the system at the same frequency \( f \). We decompose the probability density, probability flux, firing rate,
and Kv7 activation into steady-state and modulated components:

\[ P = P_0 + \hat{P}_1 e^{2\pi if t}, \quad J = J_0 + \hat{J}_1 e^{2\pi if t}, \quad r = r_0 + \hat{A} e^{2\pi if t}, \quad x = x_0 + x_1 e^{2\pi if t}. \]

We solve for the modulated components in the Fourier domain after obtaining the equilibrium solution to Eqs. (13)-(14). They obey the first order continuity and flux equations:

\[ -\frac{\partial \hat{J}_1}{\partial V} = 2\pi f \hat{P}_1 + \hat{A} \left( \delta (V - V_{th}) - e^{-2\pi f \tau_{ref}} \delta (V - V_{re}) \right) \]

\[ -\frac{\partial \hat{P}_1}{\partial V} = \frac{1}{g_L \sigma^2} \left( \mu_0 \hat{P}_1 + C \hat{J}_1 + g_x \hat{x}_1 (V - V_x) P_0 - \hat{\mu}_1 P_0 \right) \]

We also take into account the distribution of voltage during action potentials so that:

\[ \hat{P}_1 = \hat{P}_\mu + \gamma_x \hat{x}_1 \hat{P}_x + \hat{A}_{\tau_{ref}} \hat{P}_{sp}, \quad \hat{J}_1 = \hat{A}_\mu + \gamma_x \hat{x}_1 \hat{A}_x. \]

\( \gamma_x = g_x / g_L \) is the non-dimensionalized peak Kv7 conductance. For the linear spike shape we have, the voltage density occupied by action potentials is

\[ \hat{P}_{sp} = \frac{e^{-2\pi f \tau_{ref}(V_{th} - V)} \Theta(V_{th} - V_{re})}{V_{th} - V_{re}}. \]

Since the first order flux equation Eq. (16) is linear in \( \hat{x}_1 \) and \( \hat{\mu}_1 \), we can separate Eqs. (15),(16) into two systems: one set of equations for the modulations related to \( \hat{x}_1 \), and one set of equations for the modulations related to \( \hat{\mu}_1 \). The modulations due to \( \hat{\mu}_1 \) obey:

\[ -\frac{\partial J_\mu}{\partial V} = 2\pi f \hat{P}_\mu + \hat{A}_\mu \left( \delta (V - V_{th}) - e^{-2\pi f \tau_{ref}} \delta (V - V_{re}) \right) \]

\[ -\frac{\partial P_\mu}{\partial V} = \frac{1}{g_L \sigma^2} \left( I_0 \hat{P}_\mu + C \hat{J}_\mu - \mu_0 P_0 \right) \]
and those due to $\hat{x}_1$ obey:

$$
- \frac{\partial J_x}{\partial V} = 2\pi i f \hat{P}_x + \hat{A}_x \left( \delta (V - V_{th}) - e^{-2\pi f \tau_{ref}} \delta (V - V_{ref}) \right)
$$

(20)

$$
- \frac{\partial P_x}{\partial V} = \frac{1}{g_L \sigma^2} \left( I_0 \hat{P}_x + C \hat{J}_x \right) + \frac{V - V_x}{\sigma^2} P_0.
$$

(21)

We solve Eqs. (18)-(19) and (20)-(21) numerically for $\hat{P}_\mu, \hat{P}_x, \hat{A}_\mu, \text{ and } \hat{A}_x$. Again taking advantage of the slow kinetics of Kv7 activation, we then self-consistently calculate $\hat{P}_1$ and $\hat{x}_1$, which we use in Eq. (17) to calculate the transfer function $\hat{A}$. See (Richardson, 2009), where this method was developed, for a full exposition of the self-consistent solution of Fokker-Planck equations for neurons with slow voltage-activated conductances. This method can easily be adapted to the case of spike-activated conductances or currents.

## Results

### Effect of Kv7 Conductances on Single-Neuron Activity

Kv7 channels are ubiquitous in the nervous system, and their modulation is a cellular correlate of many neurological disorders. The influence of these channels on the transfer of common input fluctuations to correlated variability in output spike trains is unknown. We used an exponential integrate-and-fire (EIF) model to examine how Kv7 conductances affect the statistics of pairwise spiking activity (see Methods). We modeled Kv7 as a dynamic, voltage-gated conductance with slow activation $x(t)$ and no inactivation kinetics. The model neuron received input from a large pool of presynaptic neurons, which we approximated as Gaussian white noise with mean $\mu$ and variance $\sigma^2$ (Fig. 1A). The stochastic input induced variability in the neuron model membrane potential and spike train outputs. We considered how the presence of Kv7 conductances in the model neuron (+Kv7) affects its input-output transfer when compared to a neuron that lacked Kv7 conductances (-Kv7). We first describe how Kv7 conductances impact the statistics of a
single neuron, before presenting our main results for correlation transfer by pairs of neurons.

When the input mean $\mu$ is constant in time, the output statistics are also time-invariant. In this equilibrium state, the membrane potential spent the majority of its time in the subthreshold voltage range. Even though the Kv7 activation $x_\infty(V)$ was small for subthreshold $V$, the slow Kv7 activation caused it to interact strongly with the equilibrium membrane potential distribution (Fig 1B). The Kv7 activation $x(t)$ fluctuated around a steady-state value, reducing the neuron’s firing rate from 22 sp/s (-Kv7) to 8 sp/s (+Kv7) through a hyperpolarizing shift of the steady-state membrane potential distribution (Fig. 1B). In response to a step increase of the stimulus mean $\mu$, the neuron’s firing rate transiently increased, then decreased to a new steady-state level as the Kv7 conductance accumulated (Fig. 1C). The neuron’s steady state firing rate increased with $\mu$, but to a lesser degree for the +Kv7 neuron than the -Kv7 neuron (Fig. 1D). This shows that Kv7 activation divisively scales firing rates, a well known consequence of outward currents that provide spike-driven negative feedback (Ermentrout, 1998, Benda and Herz, 2003).

We next asked how the Kv7 conductance affects the single-neuron responses to time-varying inputs (Kndgen et al., 2008). To study the dynamic response we let $I(t) = \mu_0 + \hat{\mu}_1 \sin(2\pi ft)$ with $f$ being low frequency ($f = 1$ Hz) and $\hat{\mu}_1$ being small relative to the background fluctuations $\sigma^2$. The Kv7 current tracked the sinusoidal input and provided negative feedback (Fig. 2B, orange curve) that cancelled off both the static ($\mu_0$) and fluctuating ($\hat{\mu}_1 \sin(2\pi ft)$) components of the input current (Fig 2B, compare green and blue curves). The membrane voltage was noisy and varied over repeated presentations (cycles) of the stimulus (Fig 2A, B bottom). Performing sufficient cycle averaging allowed for an estimate of the effect of Kv7 conductance on the instantaneous firing rate of the neuron over the cycle. The stimulus induced a sinusoidal modulation of the instantaneous firing rate, $r(t) = r_0 + |A| \sin(2\pi ft - \phi)$, where $r_0$ is the firing rate without the dynamic stimulus, and $|A|$ and $\phi$ are the amplitude and phase shift of the
response respectively (Fig. 2C). Importantly, the +Kv7 neuron reduced the response amplitude $|A|$ compared to the -Kv7 neuron (Fig. 2C, compare blue and black curves), reflecting the Kv7 induced cancellation of the dynamic input current (Fig. 2B).

In order to examine whether the Kv7-mediated reduction in response gain was frequency-specific, we carried out a similar analysis for inputs across frequency $f$ and calculated the transfer function $|A(f)|$ of the +Kv7 and -Kv7 model neurons. The transfer function measures how strongly a neuron modulates its instantaneous firing rate in response to an input of a given frequency. We saw that the +Kv7 model had a reduced $|A(f)|$ at all frequencies compared to the -Kv7 neuron. This was especially true at low $f$, imparting a band-pass shape to the +Kv7 transfer function (Fig. 2D). For a mathematical exposition of how adapting currents give rise to band-pass transfer functions, see (Benda and Herz, 2003).

Throughout our study we made use of a theoretical framework to predict the transfer functions of the +Kv7 and -Kv7 neuron models. The theory requires that $\mu_1$ is sufficiently small to ensure a linear input-output relationship ($r(t)$ inherits the sinusoidal time dependence of $I(t)$) and that the activation dynamics of the Kv7 conductance are much slower than the passive membrane time constant. These assumptions allowed us to calculate the transfer function $A(f)$ and the time-averaged firing rate $r_0$ using a well-documented perturbation technique (Richardson 2007, 2009; see Methods). The theory gave excellent estimates of both the steady-state and instantaneous firing rates (Figs. 1B, 2C and D; compare theory to simulations curves).

**Effect of Kv7 Conductances on Covariability of Pairwise Activity**

The central aim of our study was to explore how Kv7 conductances affect the covariability of the spike train outputs from pairs of neurons. We modeled two pairs of neurons: a pair with Kv7 conductances (+Kv7 pair) and a pair without (-Kv7 pair). As before, each neuron received a fluctuating input with mean $\mu$ and variance $\sigma^2$. The neurons were not synaptically coupled, but
they shared a fraction of their input $c > 0$ (Fig. 3A). This shared input drove coherent membrane potential fluctuations and sometimes caused the neurons to spike synchronously (Fig. 3A, top, arrows). In order to isolate the effect of the Kv7 conductance on how the neuron pair transferred input correlations to their outputs, we kept the statistics of the input ($\mu$, $\sigma^2$, and $c$) and all other model parameters identical between the neuron pairs. The magnitude of the peak of the spike train cross-covariance function $q_{12}(s)$ (see Methods) of the $+\text{Kv7}$ pair was 34% that of the $-\text{Kv7}$ pair, and the $+\text{Kv7}$ covariance function was lower for all time lags (Fig. 3B). Thus, activation of Kv7 conductances decorrelated the spike train responses of neuron pairs receiving common inputs.

To quantify this reduction of output covariation across different time scales, we counted the number of spikes that each neuron of a pair emitted in windows of $T$ milliseconds, $n_1^T$ and $n_2^T$, and computed the covariance of $n_1^T$ and $n_2^T$, $\text{Cov}(n_1^T, n_2^T)_{\pm \text{Kv7}}$, as a function of window size (see Methods). For short $T$, $\text{Cov}(n_1^T, n_2^T)$ corresponds to synchrony of individual action potentials. For long $T$, it corresponds to covariation of the firing rates. The $+\text{Kv7}$ neuron pair had a much lower spike count covariance than the $-\text{Kv7}$ pair across all window sizes (Fig. 3C, top). To correct for the trend that $\text{Cov}(n_1^T, n_2^T)$ increases with $T$, we considered the ratio of the $+\text{Kv7}$ and $-\text{Kv7}$ pairs’ spike count covariances. This showed that the $+\text{Kv7}$ pair had, depending on window size, 20-30% as much spiking covariability as the $-\text{Kv7}$ pair (Fig. 3C, bottom).

To relate pairwise covariance to single neuron filter properties, we used a perturbation theory that has been previously used for $-\text{Kv7}$ integrate-and-fire models (de la Rocha et al. (2007); see Methods). For weak input correlations ($|c| << 1$), our theory relates the output spike count covariance $\text{Cov}(n_1^T, n_2^T)$ to the input covariability, $c\sigma^2$, and the single-neuron transfer function, $A(f)$, via:

$$\text{Cov}(n_1^T, n_2^T) = c\sigma^2 \int_{-\infty}^{\infty} |\hat{A}(f)|^2 k_T(f) \, df.$$  \hspace{1cm} (22)
Here the kernel $k_T(f)$ relates spike count statistics over a window of length $T$ to the spike train statistics. It is useful to consider this theory in two regimes, the long time window regime $T \to \infty$ and the short time window regime $T \to 0$. In these opposing cases Eq. (22) reduces to:

\[
\text{Cov} \left( n_{T \to \infty}^1, n_{T \to \infty}^2 \right) \propto |\hat{A}(0)|^2, \tag{23}
\]

\[
\text{Cov} \left( n_{T \to 0}^1, n_{T \to 0}^2 \right) \propto \int_{-\infty}^{\infty} |\hat{A}(f)|^2 df. \tag{24}
\]

Thus for long $T$ only the low frequency transfer $A(0)$ is important, while for short $T$ the entire frequency transfer $A(f)$ impacts $\text{Cov} \left( n_T^1, n_T^2 \right)$.

The spike count covariance predicted with linear response theory in Eq. (22) was in excellent agreement with spike count covariance computed from simulations for both the -Kv7 and +Kv7 neuron pairs (Fig. 3B, C, solid lines). Further, the relative reduction in covariance was larger for long $T$ than for short $T$ (Fig. 3C, bottom). This is expected from Eqs. (23)-(24) and the fact that the slow negative feedback Kv7 conductance shaped $A(f)$ more prominently at low $f$ (Fig. 2D). In total, our theory shows that the shaping of single-neuron filtering by Kv7 conductances (Fig. 2) can account for the large decrease in the covariability of pairwise activity (Fig. 3).

A widely used, normalized measure of the similarity between two spike trains is the spike count correlation coefficient, \( \text{Cov}(n_T^1, n_T^2)/\sqrt{\text{Var}(n_T^1)\text{Var}(n_T^2)} \) (Averbeck et al., 2006, Cohen and Kohn, 2011). The weak input correlation $c$ provided a theoretical estimate for \( \text{Cov}(n_T^1, n_T^2) \) in Eq. (22), however a similar theory for \( \text{Var}(n_T^1) \) remains elusive (Farkhooi et al., 2011, Muller et al., 2007, Naud and Gerstner, 2012, Toyoizumi et al., 2008). The difficulty stems from the history dependence of the slow adaptation current that makes the spike trains into non-renewal processes, precluding a simple relationship between spike train and spike count variance (Cox and Isham, 1980).
A number of studies have investigated the role of M-currents and similar mechanisms in reducing the variability of single-neuron spike trains (Benda et al., 2010, Muller et al., 2007, Schwalger et al., 2010, Fisch et al., 2012). This raised the question of how the effect of Kv7 conductances on pairwise covariability related to their effect on single-neuron variability. The reduction in $\text{Cov}(n_1^T, n_2^T)$ due to Kv7 conductances could be accompanied by an equivalent reduction in $\text{Var}(n^T)$, so that the spike count correlation would remain unaffected. Analysis of the spiking simulations showed that this was not the case (Fig. 3D), and rather the reduction in the covariance was the dominant effect over changes in single-neuron variability. Thus, while our remaining analysis will be restricted to $\text{Cov}(n_1^T, n_2^T)$, allowing the use of the linear response theory, the influence of Kv7 on spike count correlation is expected to be qualitatively similar.

We next used our theory to build a mechanistic understanding of how Kv7 conductances control the transfer of covariability.

**Kv7 Conductance Decouples Firing Rates and Pairwise Spiking Covariability**

Including Kv7 conductances in the model dynamics drastically reduced both firing rates and pairwise spiking correlations. Previous work has linked changes in firing rates to changes in spike count correlations at long time intervals $T$ (de la Rocha et al., 2007). Thus, it is important to determine if the reduction of covariance with Kv7 (Fig. 3) can be explained solely by a reduction in firing rate (Fig. 1D).

To this end, we ranged over the input mean ($\mu$) and variance ($\sigma^2$) to effectively explore a range of firing rates and covariance values accessed by +Kv7 and -Kv7 pairs. For higher firing rates, there was a broad range of ($\mu, \sigma^2$) pairs that produced the same output firing rate but a distribution of output covariance values (Fig. 4A, shaded regions). Nevertheless, for any fixed firing rate the presence of Kv7 conductances shifted the region of spike count covariance...
to lower values. This was especially true for the low firing rates that characterize spontaneous activity in many cortical areas (Hromadka et al., 2008), where there was little overlap between the rate-covariance spaces of pairs with Kv7 conductance and pairs without (Fig. 4A). Thus, the reduction of spiking covariability by Kv7 conductances cannot be explained by a simple lowering of firing rate.

To gain intuition into the mechanisms behind the reduction in spike train covariability with Kv7, we focused on a specific example within the \((\mu, \sigma^2)\) plane. Specifically, we considered the \((\mu, \sigma^2)\) studied earlier (Figs. 1-3; indicated with black and blue markers in Fig. 4A, B). To correct for firing rates we studied a second +Kv7 neuron pair with a higher input mean \(\mu\) so that they matched the firing rate (22 spk/s) of the -Kv7 pair (indicated with orange markers in Fig. 4A, B). This rate correction produced an approximate multiplicative scaling of the transfer function \(A(f)\), so that the rate-corrected +Kv7 pair responded to high-frequency inputs with the same response gain as the -Kv7 pair (Fig. 4C, black and orange curves for \(f > 10\text{Hz}\)). However, the Kv7 conductance still produced an overall band-pass \(A(f)\) so that the low-frequency transfer \(A(f)\) was below that of the -Kv7 transfer for low frequencies (Fig 4C, black and orange curves for \(f < 10 \text{ Hz}\)). Thus, while the Kv7-induced change in single-neuron filtering of high-frequency inputs \(A(f)\) could be accounted for by the change in firing rates, the change in low-frequency filtering could not.

Our theory shows that the low-frequency transfer \(A(f)\) affects spiking covariability at both short and long windows \(T\) (Eqs. (23)-(24)). Thus, the shift from low-pass to band-pass transfer with Kv7 conductances accounted for much of the reduction in spiking covariability, especially at long timescales (Fig. 4D). Since matching firing rates between the +Kv7 and -Kv7 neuron pairs did not correct for the low frequency attenuation of the transfer function by Kv7 conductances, the Kv7-induced reduction in spiking covariability was not solely due to a lowering of firing rates.
Sub- and Suprathreshold Kv7 Activation can Contribute to Covariance Cancellation

Kv7 conductances impact both single neuron (Figs. 1, 2) and pairwise spiking statistics (Fig. 3) through attenuation of the transfer of low frequency inputs to spike train outputs. This was because Kv7 currents actively cancelled input fluctuations (Fig. 5A, compare black and blue curves), even when we compensated for the mean Kv7 current (Fig. 5A, compare black and orange curves). To understand how this input cancellation shaped $A(f)$ we next investigated the impact of Kv7 conductances on the membrane potential response to fluctuating inputs.

We considered the linear approximation $V(t) \approx \langle V \rangle + \hat{\mu}_1 V_1(f) \sin(2\pi ft - \phi)$, where $\hat{\mu}_1$ again defines the amplitude of the input modulation. $V_1(f)$ is the transfer function for the membrane potential response, defined as $V_1(f) = \int_{-\infty}^{\infty} V P_1(V,f) dV$, with $P_1(V,f)$ being the first order perturbation of the density $P(V,f)$ induced by $I(t)$ (see Methods). In contrast to the effect of Kv7 conductance on firing rate responses, Kv7 conductances increased the amplitude of membrane potential responses to intermediate frequency inputs (Fig. 5B, blue vs. black curves). In the case of high firing rates (-Kv7) the membrane potential did not respond strongly to inputs because it was comparatively dominated by spiking and repolarization. In the +Kv7 case, the membrane potential was better able to respond to inputs without being influenced by spiking dynamics because of the lower firing rate (Rosenbaum and Josi, 2011). This effect disappeared at low frequencies, however, as the Kv7-mediated current canceled off the input-driven membrane potential fluctuations (Fig 5B, black vs orange curves). When the mean effective input was the same (in the rate-corrected model of Fig 4B-D), the Kv7 conductance clearly reduced the membrane potential response to slow inputs, preventing them from driving spiking activity (Fig. 5A, B).

Previous theoretical investigations of spike-frequency adaptation have often focused on spike-driven recruitment of negative feedback (Ermentrout, 1998, Benda and Herz, 2003, Farkhooi et
al., 2011, Schwalger et al., 2010, Naud and Gerstner, 2012). To isolate the relative contributions of spike-driven and subthreshold activation of Kv7 conductances to stimulus transfer, we defined an activation threshold of -47 mV for the Kv7 conductance. We chose it 3 mV above the initiation threshold $V_T = -50$ mV in order to ensure that only successfully generated spikes would contribute to spike-driven activation. We then examined two models of Kv7: one with only the portion of the Kv7 activation curve $x_\infty(V)$ below -47 mV contributing to $x(t)$ dynamics (subthreshold activation, Fig. 5C) and one with only the portion of the activation curve above -47 mV contributing to $x(t)$ (suprathreshold activation, Fig. 5D).

Kv7 conductances are strongly activated by depolarized membrane potentials. However, in our model the subthreshold activation accounted for most of the effect of Kv7 on canceling the input mean $\mu$, as reflected by the firing rates and membrane potential transfer functions (Fig. 5E, G). This was due to the fact that the timescale of Kv7 activation was long, so that it interacted strongly with the equilibrium distribution of the membrane potential—which was mainly subthreshold (Fig. 1B). Subthreshold activation of Kv7 conductance accounted for most of its reduction of spiking covariability on both short and long timescales (Fig. 5H, black vs. solid green vs. blue curves). Here, subthreshold activation of $x(t)$ led to a cancelation of input fluctuations on long timescales (Figs. 2B and 5A), which necessarily reduced the transfer of fluctuations to spiking responses. In contrast, suprathreshold Kv7 activation had a smaller impact on correlation transfer (Fig. 5H, black vs. dashed green vs. blue curves). We remark that while the sub- and supra-threshold activation curves sum to the total $x_\infty$, the effects of sub- and supra-threshold activation on the membrane voltage and spiking responses do not sum to give the response with the full Kv7 activation, since the voltage and Kv7 activation interact nonlinearly (Eqs. (1)-(3)). In total, the subthreshold activation of Kv7 cancelled slow input fluctuations and reduced pairwise spike train covariance beyond what was expected by a simple lowering of firing rates (de la Rocha et al., 2007).
Kv7 Conductances, Homeostatic Plasticity and Pathological Activity

A number of neurological diseases characterized by hyperactivity and hypersynchrony have been related to Kv7 channel dysfunction (Jentsch, 2000, Cooper and Jan, 2003). We modeled Kv7-related hyperactivity disorders with a reduced Kv7 conductance strength, where we decreased the mean Kv7 conductance $g_x$ from 0.025 mS/cm$^2$ to 0.01 mS/cm$^2$. A decrease in $g_x$ is consistent with a decrease in Kv7 surface expression, as seen in neonatal and rolandic epilepsies (Coppola et al., 2003, Neubauer et al., 2008, Soldovieri et al., 2006). This modulation increased the spontaneous firing rate from 8.1 to 15.7 sp/s, and also led to a 2.3-3.2x increase in the covariance of spike counts (depending on the window size). Modeling Kv7-related hyperactivity instead with a shift in the $V_{1/2}$ had a similar effect on rates and spike count covariances (Fig. 7).

We modeled a homeostatic modulation in response to the reduced Kv7 conductance with a shift of model parameters. The parameters $V_L$ and $g_L$ control the passive membrane properties, and their modulation can mimic homeostatic changes in slow currents (Brickley et al., 2001, Hong and Lnenicka, 1995, Desai et al., 1999, van Welie et al., 2004, Fan et al., 2005) and single-neuron integration (Litwin-Kumar et al., 2011, Burkitt et al., 2003). The scaling of synaptic strength is also a common target for homeostatic regulation (Turrigiano et al., 1998). We modeled a change in synaptic strength as a global scaling of all inputs to the neuron. This corresponded to multiplying the input by a factor $\alpha$: $\mu \rightarrow \alpha \mu$ and $\sigma \rightarrow \alpha \sigma$. We required that the homeostatic regulation of each model parameter ($g_L$, $V_L$, and $\alpha$) restore the firing rates from the pathologic models to that of the control model (Fig. 6A-C).

Despite firing rate matching, all three homeostatic regulations failed to restore the low-frequency transfer function $A(f)$ (Fig. 6D). Since the low-frequency response affects spike count covariances at both short and long timescales, none of the three homeostatic corrections restored $\text{Cov} \left( n_1^T, n_2^T \right)$ to control levels (Fig. 6E). This failure was robust over a wide range of homeo-
static modulation. For instance, if the modulation was defined so that $\text{Cov}(n^T_1, n^T_2)$ for large $T$ matched control values, then firing rates for the pathologic model would be much lower than those in the control model (Fig. 6F). In sum, homeostatic modulation of passive membrane properties or synaptic scaling could not correct for pathological activity due to changes in the Kv7 conductance.

Neurological disorders related to Kv7 pathology are often treated pharmacologically. The antiepileptic and analgesic drugs flupirtine and retigabine, for instance, act by hyperpolarizing the voltage-activation curves of Kv7.2 and Kv7.3 channels (Main et al., 2000, Tatulian et al., 2001). We next investigated whether homeostatic or exogenous modulation of the Kv7 half-activation voltage $V_{1/2}$ could correct for hyperactivity and hypersynchrony induced by pathological changes in the maximum Kv7 conductance $g_x$, and vice versa. We started with the same reduction in $g_x$ as explored above. Decreasing $V_{1/2}$ by 12 mV restored the mean Kv7 conductance to the control value 0.025 mS/cm$^2$ and restored the control firing rate (Fig. 7A). Furthermore, shifting Kv7 activation allowed the treated Kv7 conductance to cancel slow inputs in the same way as in the control case, restoring the single-neuron response function and pairwise covariance to control levels (Fig. 7B, C). We also examined a disease model characterized by a 10 mV increase of $V_{1/2}$ (Fig. 7D), which decreased the mean Kv7 conductance $g_x x_0$ to 0.013 mS/cm$^2$. This shift of $V_{12}$ of Kv7 channels is associated with hyperexcitability in a mouse model of tinnitus (Li et al., 2013). An increase in the maximal Kv7 conductance $g_x$ restored the mean activation as well as the control levels of activity and spiking covariability (Fig. 7E, F). Both parameters of the Kv7 activation modulated rate and covariance similarly, allowing modulations of each parameter to compensate for pathological changes in the other (Fig. 7G). These results suggest that, while intrinsic homeostatic processes triggered by changes in firing rate may not be able to correct for pathological changes in Kv7 conductances, drugs directly targeting any parameter of the Kv7 activation can restore spiking activity to normal levels.
Discussion

Kv7 channels mediate voltage-activated K\(^+\) conductances that control overall cellular excitability (Aiken et al., 1995, Gu et al., 2005, Higgs et al., 2007, Lawrence et al., 2006, Peters et al., 2005). These channels are present throughout the nervous system (Brown and Passmore, 2009, Delmas and Brown, 2005, Jentsch, 2000), and their dysfunction is involved in several disease states (Cooper and Jan, 2003, Li et al., 2013, Passmore et al., 2003, Shah and Aizenman, 2014, Zheng et al., 2012). Using a well-established theoretical framework to study correlation transfer in spiking neurons (de la Rocha et al., 2007), we showed that the recruitment of Kv7 conductances provides an input-driven negative feedback that cancels correlating inputs and reduces the covariability of pairwise spiking activity in model neurons. Pathological loss of Kv7 conductance due to changes either in its strength or activation leads to both increased firing rates and synchrony. Using our theory we showed that homeostatic regulation of passive membrane properties or input strength, triggered by changes in firing rates, did not maintain normal pairwise spiking activity. However, modulation of the activation of the Kv7 conductance could correct for both hyperactivity and hypersynchrony induced by pathological reduction of Kv7 conductances.

Adaptation and Population Coding

Correlations in trial-variable neural activity (“noise correlations”) play a large role in shaping population-wide activity (Averbeck et al., 2006). In particular, they can facilitate or impair population coding, depending on the spatial structure of the noise correlations and the relationship between them and the encoded signal (Abbott and Dayan, 1999, Josi et al., 2009, Sompolinsky et al., 2001). Adaptation to repeated stimulation reduces both single-neuron variability and pairwise noise correlations in sensory cortex (Adibi et al., 2013, Gutnisky and Dragoi, 2008). In specific cases this has promoted improved population-based stimulus estimation (Gutnisky and Dragoi, 2008) and discrimination (Wang et al., 2011). However, the specific biophysical mecha-
nisms by which adaptation protocols affect population responses are, in general, unknown.

The main two mechanisms of sensory adaptation, as understood from single-unit activity, are thought to be synaptic depression and the recruitment of intrinsic slow outward currents (Kohn, 2007). The reduction of firing rates by both of these mechanisms is well-understood. More recently, synaptic depression has been predicted to reduce pairwise correlations by causing failures in shared, correlating inputs (Rosenbaum et al., 2012). Previous theoretical investigations of the intrinsic mechanisms of adaptation and population coding have focussed on how spike-driven processes shape the variability of uncorrelated neurons (Naud and Gerstner, 2012, Farkhooi et al., 2011). We have now shown that activity-dependent outward currents often associated with adaptation can also reduce noise correlations by canceling correlating inputs at the membrane potential. The combination of these results suggests that Kv7 channels improve population coding. This prediction is consistent with recent studies that document, after cochlear damage, an overall reduction of Kv7 conductance in auditory pathways and associated behavioral deficits in acoustic detection tasks (Li et al., 2013).

Intrinsic Membrane Properties and Pairwise Activity

There have been a recent suite of studies investigating the mechanics of correlation transfer by spiking neurons. Many of these studies have focused on the role of spike initiation dynamics in shaping the timescale over which correlations are transferred (Galan et al., 2006, de la Rocha et al., 2007, Shea-Brown et al., 2008, Tchumatchenko et al., 2010, Abouzeid and Ermentrout, 2011, Barreiro et al., 2012, Hong et al., 2012, Ratte et al., 2013). In contrast, we have shown how slow intrinsic currents that are not involved in spike initiation can also determine the transfer of correlation by neuron pairs.

Our linear response theory explicitly linked Kv7-induced modulations of correlation transfer to modulations of single-neuron transfer functions, particularly at low frequencies. For very
low frequency inputs this corresponds to a divisive modulation of the firing rate–current curve (Fig. 1D). Previous in vitro experimental work in somatosensory and motor cortex using the drug XE991, a Kv7 antagonist, has shown a subtractive, rather than divisive, effect of Kv7 conductances on the firing rate curves in low-noise conditions (Guan et al., 2011). In low-noise conditions ($\sigma = 0$), we also saw that Kv7 conductance induced a subtractive shift in the firing rate curves (data not shown). It is known that strong fluctuations can “linearize” firing rate curves so that subthreshold static inputs can elicit responses (Burkitt et al., 2003). Subtractive modulations of firing rate-current curves in low noise conditions can become divisive modulations with higher noise (Doiron et al., 2001). In fact, when Guan et al. (2011) drove their neurons with large fluctuations to measure $A(f)$ they saw that XE991 caused an overall increase in $A(f)$, even when firing rates were matched (compare their Fig. 7C to our Fig. 4C). Thus, there is strong experimental evidence that Kv7 conductances shape single-neuron transfer functions, and given our theory we expect that Kv7 conductances also determine the correlation transfer by pairs of neurons. This prediction can be verified using well-established experimental protocols (de la Rocha et al., 2007, Litwin-Kumar et al., 2011).

We modeled the Kv7 conductance as a deterministic conductance, separate from the membrane noise. This corresponds to the limit of an infinite population of Kv7 channels. The stochastic opening of a finite population of M-channels gives rise to distinct effects on single neuron spiking statistics (Schwalger et al., 2010, Fisch et al., 2012). The effect of stochastic M-channel dynamics on pairwise activity remains an open question. We expect, however, that it could limit the ability of M-channels to cancel input correlations by introducing noise into the relationship between the input and Kv7 current.

Diseases and Homeostatic Plasticity

Homeostatic processes regulate the strength of both intrinsic and synaptic currents in neocortical neurons (Desai et al., 1999, Turrigiano et al., 1998). They are mediated by calcium sensors
and other signaling pathways, and maintain stable firing rates (Ibata et al., 2008, MacLean et al., 2003, Brickley et al., 2001). Failures of homeostatic mechanisms lead to pathological activity. In models of Kv7 dysfunction, we showed that changes in passive membrane properties or synaptic scaling that correct for an increase in firing rates could not correct for hypersynchrony (Fig. 6F). We did not investigate homeostatic plasticity of the spike initiation threshold or the action potential slope, both of which would be controlled by fast sodium channels. A previous study of homeostatic plasticity of neurons’ intrinsic properties has shown that the amplitude of fast sodium currents increases in response to activity deprivation, increasing their excitability (Desai et al., 1999). In our model, this would have a similar effect to changing the leak reversal potential: bringing the resting potential and spike threshold closer. It would be a less effective modulation with respect to Kv7 activation since decreasing spike threshold would decrease the subthreshold activation of the Kv7 conductance, which plays a strong role in covariance cancellation (Fig. 5H). Changes in the conductance density of fast sodium channels could also change the steepness of action potential initiation (the parameter Δ), but since the effects of this are limited to the high-frequency region of the response function $A(f)$ (Fourcaud-Trocme et al., 2003), it would not have a large effect on spiking covariability (Eq. 22). So, changes in the strength of fast sodium conductances would be unlikely to correct for hypersynchrony induced by Kv7 dysfunction.

The interaction between different mechanisms of correlation generation and cancellation remains an open area of research. Homeostatic or pharmacological down-regulation of inward currents with similar kinetics to Kv7, such as persistent sodium current, could perhaps compensate for pathological loss of Kv7 conductance. Indeed, persistent sodium current is implicated in some forms of epilepsy and is a target of some anti-epileptic drugs (Stafstrom, 2007). Likewise, homeostatic up-regulation of other subthreshold-activated potassium conductances (Ping and Tsunoda, 2012, Ransdell et al., 2012) could perhaps partially compensate for loss of Kv7 conductance. Changes in the covariation of two neurons’ activity could also affect synaptic currents
through spike timing–dependent plasticity, or could trigger changes in intrinsic excitability (Cudmore et al., 2010). We have shown how one intrinsic property, Kv7 conductance, can contribute to decorrelating neural activity. Furthermore, dysfunction of Kv7 conductance gives rise to hypersynchronous, high-firing rate activity which cannot be corrected for by simple homeostatic mechanisms. How dysfunction of Kv7 currents interacts with other activity-dependent processes remains an open question with important implications for the understanding of healthy neural activity and the correction of pathological hyperactivity.
References


Figure Captions

Figure 1: Kv7 conductances control a neuron’s equilibrium state and overall firing rate. A, Schematic of our model. A large pool of presynaptic neurons projects to the model neuron. We approximate the total synaptic input as Gaussian white noise with mean $\mu$ and variance $\sigma^2$. B, Top: the membrane potential of the model neuron without (black) and with (blue) a Kv7 conductance, both with the same realization of input noise. Bottom: the Kv7 activation fluctuates over time around a steady-state mean value. Dashed line: mean Kv7 activation $x_0$, computed from a Fokker-Planck theory of the model neuron with a Kv7 conductance (Methods). The neuron’s dynamics are governed by Eqs. (1)-(3), and the parameters of the neuron and the noisy input are given in Table 1. Right: activation of Kv7 conductances decreases the neuron’s firing rate by a slight hyperpolarization and tightening of the equilibrium membrane potential distribution. Solid lines: membrane potential distributions computed from the Fokker-Planck theory. Shaded lines: simulations. C, In response to a step input (top) the Kv7 conductance accumulates until it reaches a new steady state (bottom). This implements spike-frequency adaptation, as reflected by the instantaneous firing rate computed by averaging the spike trains from 20000 realizations (middle). D, Kv7 conductances reduce the gain of the firing rate curve. Circles mark the firing rates at $\mu = 0$, used in panel B. Steady-state firing rates computed using the Fokker-Planck theory ($r_0$ of Eq. (13)).

Figure 2: Kv7 conductances shape responses to dynamic inputs. A, Top: the membrane currents of a -Kv7 model in response to a sinusoidal current injection. We added a static bias of $g_L\sigma D\sqrt{c}$ so that the minimum of the sine wave was at 0 for visualization purposes in A and B. Bottom: the membrane potential responses to the sine input on two different trials. B, Kv7 current provides negative feedback of the input, canceling its mean and reducing its amplitude. $I_{Kv7}$ and $Input + I_{Kv7}$ currents are from a single trial, and low-pass filtered for ease of visualization. C, The firing rate response to the sine input is obtained by averaging the spike train responses across trials. The sine input induces a sinusoidal modulation of the firing rate in response. Kv7 conductances reduce the equilibrium firing rate (dashed line) and the amplitude of the response modulation. The peak-to-trough response modulation is given by twice the transfer function $A(f)$. Solid lines: theory. Shaded lines: simulations. D, Response functions showing the amplitude of the modulation induced in the firing rate by a sine input of fixed strength. Kv7 conductances reduce the response amplitude for all input frequencies, and shape the response function to be band-pass rather than low-pass. Solid lines: theory. Shaded lines: simulations.
Figure 3: Kv7 conductances reduce pairwise covariability. 

A, Pairs of neurons (shaded and solid) with (blue) and without (black) Kv7 conductances were stimulated by partially correlated Gaussian white noise. Fluctuations of the common input give rise to synchronous spikes (top, arrows) and to covariable modulations of the two neurons’ spike counts (bottom). 

B, Cross-covariance functions of pairs with (blue) and without (black) Kv7 conductances. 

C, Top: covariance of spike counts as a function of the counting window length $T$. Bottom: ratio of the spike count covariances, with Kv7 / no Kv7. The Kv7 conductance reduces spike count covariances by 70-80%. 

D, Top: spike count correlation for pairs with and without Kv7 conductances. Bottom: the ratio of the correlations. Kv7 conductance reduces the correlation by 40-50%.

Figure 4: Kv7 conductance shapes the relationship between firing rate and covariance. 

A, The range of firing rates and covariances obtained by sweeping over the input mean $\mu$ and variance $\sigma^2$ for pairs with Kv7 (blue shaded region) and without (grey shaded region). Inset: range of $\mu$ and $\sigma$. 

B, Increasing the input mean can correct for the difference in firing rates between pairs with and without Kv7. 

C, Firing rate linear response functions for the -Kv7 (black), +Kv7 (blue), and +Kv7 with high $\mu$ (orange) models. 

D, Spike count covariance as a function of window size. The Kv7 conductances reduce spiking covariability even when firing rates are corrected.

Figure 5: Sub- and suprathreshold activation of Kv7 contributes to covariance reduction. 

A, $I(t) + I_{Kv7}$ for the three cases of Fig. 4B-D. Currents were low-pass filtered for visualization. 

B, The filter response of the membrane potential as a function of input frequency $f$. Kv7 conductance lowers the firing rate, allowing the membrane to better track inputs without being interrupted by spiking (black vs. blue). K v7 also cancels low-frequency membrane potential responses (blue and compare black vs. orange). Solid lines: theory. Shaded lines: simulation. 

C,D, The separate sub- and suprathreshold activation functions of the Kv7 conductance. Most of the activation curve lies in the suprathreshold regime. 

E, The subthreshold activation accounts for most of the steady-state Kv7 activation, since the membrane potential spends the most time in the subthreshold regime. 

F, The suprathreshold activation accounts for the spike-activated portion of the Kv7 conductance. 

G, Membrane potential response functions. The subthreshold activation of Kv7 cancels off the input mean and slow inputs, and the suprathreshold activation shapes the membrane potential responses to slow and intermediate inputs. 

H, Top: spike count covariance as a function of window size $T$ for the models with only sub- or suprathreshold Kv7 activation and the +Kv7 and -Kv7 models. Bottom: ratio of spike count covariance in the various conditions compared to the control case.

Figure 6: Homeostatic compensation for Kv7 dysfunction corrects for pathological firing rates but not covariances. 

A, Correction for firing rates through the leak reversal potential. 

B, Correction for firing rates through the leak conductance. 

C, Correction for firing rates through synaptic scaling of the input mean and variance. We set $V_L = V_r$ and $\mu = 1.7 \ \mu A/cm^2$ to give the same firing rates, response functions, and covariances as $V_L = -55 \ mV$ and $\mu = 0 \ \mu A/cm^2$. 

D,E, Firing rate response functions and spike count covariances for all three homeostatic mechanisms. 

F, The paths through rate-covariance space obtained by varying $g_x$ (black), $V_L$ (magenta), $g_L$ (orange), and $\alpha$ (green), starting from the disease state (intersection at black square). The points corresponding to the cases of A-E are marked by color-matched squares.
Figure 7: Treatments targeting Kv7 channels can correct for pathological firing rates and covariances.  
B,C, Compensating for the weakened conductance with a hyperpolarization of the activation curve can restore the responses and spiking covariability to control levels.  
D, Top: model of a pathological shift in the activation of Kv7 conductance. Bottom: treatment that increases the strength of the conductance (orange) can restore the firing rate.  
E,F, Compensating for a pathological depolarization of the activation curve by strengthening the conductance can restore the responses and spiking covariability to control levels.  
G, The paths through rate-covariance space obtained by varying $g_x$ and $V_{1/2}$ from the control state (black) and from the disease states (green and orange curves). All paths lie in a tight region of rate-covariance space.
A

B

C

D

Rate (sp/s)

Input Freq. (Hz)

Sp. Count

Cov. (sp²)