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The Ascent of Channels with Memory

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One of the great mysteries of neuroscience is why neurons express so many different types of ion channels with such wide-ranging expression heterogeneity. In this issue of *Neuron*, Garden and colleagues add a new piece to this puzzle by demonstrating that the "memory" of various functional maps in regions of the medial entorhinal cortex resides in conductance gradients of two types of ion channels expressed in layer II stellate neurons.

The importance of voltage-gated ion channels in mediating and sculpting electrical signals in the brain is well established. The choice of the squid axon by Hodgkin and Huxley (Hodgkin and Huxley, 1952) for their pioneering studies was somewhat fortuitous in the sense that there are only two main types of ion channels responsible for the action potential in squid: sodium and potassium. If the techniques had been available in the late 1940s and Hodgkin and Huxley had chosen to explore the ionic basis of electrical signals in a mammalian cortical neuron, their task would have been much more difficult. For example, we now know that there are over 52 genes encoding the pore-forming subunits of the "classical" voltage-gated ion channels in mammalian neurons: 4 Na_v, 36 K_v, 8 Ca_v, and 4 HCN (Vacher et al., 2008). These classical channels, and many other voltage-sensitive channels, encompass numerous auxiliary subunits, and many can be assembled with heteromers of multiple subunits and splice variants, rendering the combinatorial diversity of voltage-gated ion channels truly staggering. One of the great mysteries of neuroscience is why neurons express so many different types of channels and why there is such heterogeneity in expression patterns both within a given neuron as well as across different brain regions.

From the standpoint of information processing, a single neuron can be broadly divided into three interrelated modules: *input*, *integration*, and *output*. Historically, voltage-gated ion channels were postulated to play a crucial role at the *output* end of a neuron. A passive integrator feeds an algebraic sum of its inputs to a nonlinear device (the cell body), which fires action potentials depending on the inputs they receive (Bullock, 1959). The role of various voltage-gated ion channels in modulating the microanatomy of single action potentials and their bursts have been teased apart, and significant information is available about the activation, deactivation, and inactivation dynamics of various ion channels within those millisecond periods (Bean, 2007). Later, equipped with the knowledge that there are conductances that are active subthreshold and that dendrites possess ion channels, the role of voltage-gated ion channels in the *integration* module received attention (Magee, 2000; Sjostrom et al., 2008). For example, experimental and theoretical evidence is accumulating on how ion channels could contribute to integration of synaptic inputs with and without dendritic or backpropagating action potentials (Spruston, 2008).

In an exciting turn of events, especially for nonsensory neurons, a number of experimental and theoretical studies have

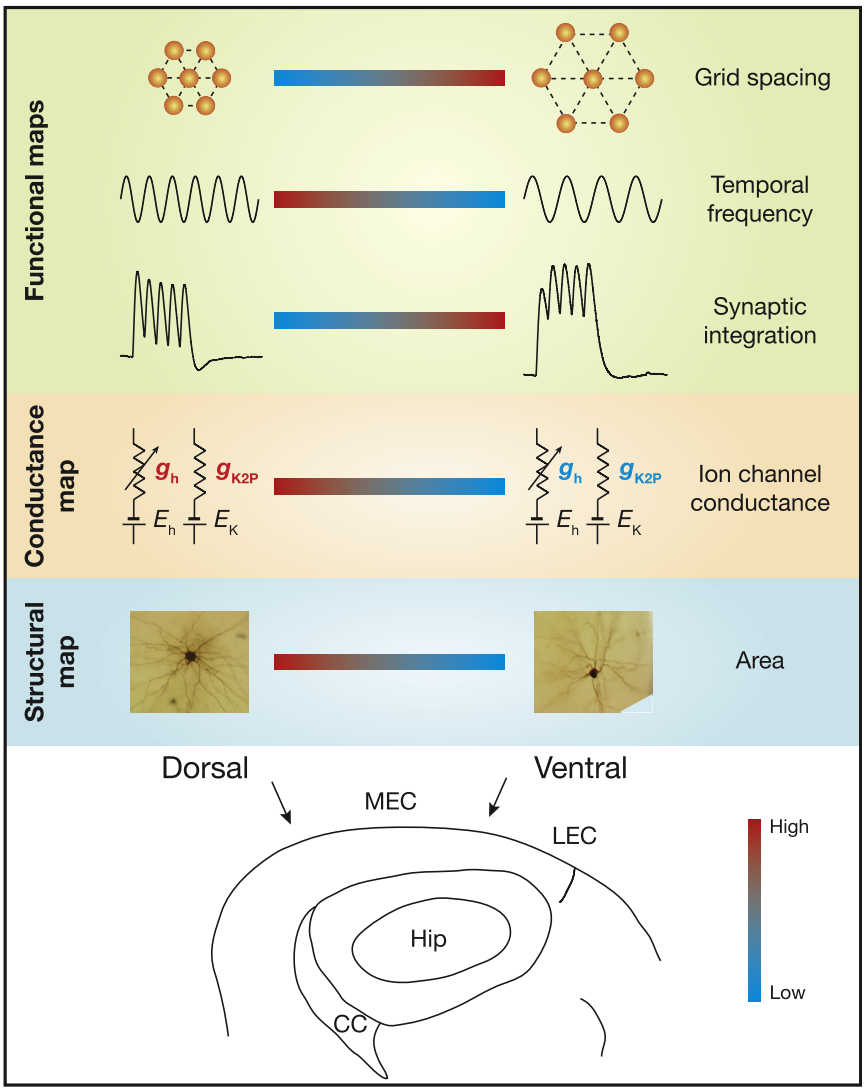

Figure 1. Stellate Cells in Layer II Entorhinal Cortex Have Been Reported to Express Maps of Various Properties along the Dorso-Ventral Axis

Specific functional attributes underlie maps of grid spacing (Moser et al., 2008), temporal oscillatory frequency of membrane potentials (Giocomo et al., 2007), and spatiotemporal summation of distinct inputs and temporal summation of the same synaptic inputs (Garden et al., 2008). Garden and colleagues also demonstrate that conductance maps of the *h* and two-pore K^+ channels could form the basis for these functional maps. They also report various structural maps, including a progressive reduction in somatic cross-sectional area and total dendritic surface area along the dorso-ventral axis (Garden et al., 2008). MEC, medial entorhinal cortex; LEC, lateral entorhinal cortex; Hip, hippocampus; CC, corpus callosum.

also started focusing on how voltage-gated ion channels could govern the *input* side of single-neuron information processing. A dominant theme of these studies has been the role of voltage-gated ion channels in tuning neuronal response properties to match specific aspects of the inputs that neurons receive. Topographic maps of frequency response properties (Giocomo et al., 2007), the role of ion channels in efficient information encoding by adapting to inputs (Stemmler and Koch, 1999), and activity-dependent plasticity of ion channels that can adapt response dynamics of single neurons at different dendritic locations (Frick et al., 2004; Losonczy et al., 2008; Narayanan and Johnston, 2008) are just a few of these new findings.

In this issue of *Neuron*, Garden and colleagues (Garden et al., 2008) show that integration of synaptic inputs in a layer II stellate neuron is tuned in accordance with its location along the dorso-ventral axis of the medial entorhinal cortex (MEC). The authors demonstrate that this functional map is accounted for by gradients in ion channel conductances (Figure 1) and argue for their putative role in efficient encoding of the spatiotemporal patterns of impinging synaptic inputs. This study, in conjunction with previous studies (Giocomo et al., 2007; Moser et al., 2008), provides rare insights into a nonsensory higher cortical region that has an anatomically well-defined structure executing a behaviorally relevant function. This combination offers wide-ranging opportunities for assessing the roles of voltage-gated ion channels in the aforementioned three modules of single-neuron information processing. Further, in conjunction with relevant network studies, this experimental preparation could also offer insights into the roles of voltage-gated ion channels in cortical microcircuit physiology to system-level analysis of learning and memory.

Functional Maps along the Dorso-Ventral Axis of the MEC

The stellate neurons of layer II MEC have sparked significant interest since the remarkable finding of their grid-like spatial firing fields (Moser et al., 2008). Specifically, when an animal wanders through its environment, the locations at which these neurons fire action potentials correspond to the corners of triangles arranged in a grid-like structure. More interestingly, Moser and colleagues (Moser et al., 2008) also discovered a topographic map of the distance between the grid's vertices, or the sides of the equilateral triangle. This distance increased progressively as a function of the neuron's location along the dorso-ventral axis, starting at around a foot at the dorsal border and increasing to several meters toward the ventral end of the MEC.

Later, Giocomo and colleagues (Giocomo et al., 2007) discovered a cellular correlate to this behavioral map, where they had reported a topographic map of intrinsic oscillatory frequency of these neurons along the same dorso-ventral

axis. They demonstrated a reduction in the intrinsic oscillatory frequency along the dorso-ventral axis, with the frequency reducing from around 6 Hz to 4 Hz along the axis. While the exact relationship between this cellular functional map to its behavioral counterpart is still not clear, several theories have been proposed based on computational models (Garden et al., 2008; Giocomo et al., 2007; Moser et al., 2008).

What does the topographic map of intrinsic oscillatory frequency mean to the response properties of single neurons to synaptic potentials? In exploring this aspect of dorso-ventral gradients, Garden and colleagues report a third functional map of synaptic integration, whereby the integrative ability of neurons progressively increase with their location along the dorso-ventral axis (Figure 1). Specifically, they demonstrate that the decay time of non-NMDA synaptic potentials, but not currents, increases along the dorso-ventral axis of MEC. This gradient in decay time of synaptic potentials progressively enhances both spatiotemporal summation of distinct inputs and temporal summation of the same inputs. Employing a range of experiments, Garden and colleagues argue that differences in synaptic properties are unlikely to account for this functional map of synaptic integration.

Basis for the Functional Maps

If the gradients in grid spacing, intrinsic oscillatory frequency, and synaptic integration are crucial "memories" of how neurons along the dorso-ventral axis should respond while navigating along a terrain, what aspects of a single neuron "stores" this memory? Theoretically, changes in resonance frequency (Giocomo et al., 2007) and synaptic integration (Garden et al., 2008) in the reported voltage range would point toward three possible "storage" locations: properties of the hyperpolarization-activated cation-nonspecific *h* channel (Magee, 2000; Narayanan and Johnston, 2008), leak channel properties (Narayanan and Johnston, 2008; Patel and Honore, 2001), and morphological differences (Sjostrom et al., 2008). Through the use of multiple experiments, Garden and colleagues report differences in each of these three properties and conclude that all three functional maps along the dorsoventral gradient could be attributed to conductance gradients in *h* channels and two-pore K^+ channels (Figure 1).

Evaluating intrinsic membrane properties of layer II MEC stellate neurons, Garden and colleagues demonstrate the following progressive changes along the dorso-ventral axis: increases in input resistance, membrane time constant, and rheobase current and a reduction in sag. Could these gradients in intrinsic properties be due to a gradient in cell morphology? Analyzing biocytin-filled reconstructions of layer II stellate neurons, Garden and colleagues uncover a progressive reduction in somatic cross-sectional area and total dendritic surface area along the dorso-ventral axis. While this would be consistent with the corresponding reduction in input resistance, Garden and colleagues employ computational modeling to argue that differences in morphology do not fully account for the dorsal-ventral gradient in input resistance. Finally, Garden and colleagues turn to channel pharmacology and demonstrate that the gradients in input resistance are fully accountable by conductance gradients in the *h* and two-pore K^+ channels.

In summary, Garden and colleagues conclude that conductance gradients in the *h* and two-pore K^+ channels could form the basis for the functional maps present along the dorso-ventral axis of layer II MEC. They also raise the interesting possibility of how neurons may encode information as efficiently as possible by tuning their integrative properties to the spatiotemporal organization of their synaptic inputs.

Future Directions and Conclusions

Given the interest that grid cells have evoked among neuroscientists working across the entire spectrum of molecular to systems neuroscience, a number of interesting questions arise from the findings of Garden and colleagues. At the molecular level, intriguing questions arise about what governs the formation and maintenance of these channel gradients (Vacher et al., 2008), with reference to early development (Moser et al., 2008) of these gradients and to their maintenance in spite of baseline channel turnover. At the cellular level, future studies could look for ion channel gradients within a stellate neuron and ask if there are similar dorso-ventral gradients in dendritic channel conductances (Magee, 2000; Sjostrom et al., 2008). Dendritic ion channels are important because they are closer to the input end of the neuron and hence could optimize response properties more locally, thus distinguishing between various inputs that reach the same neuron (Magee, 2000; Narayanan and Johnston, 2008). A related direction for exploration would be on whether these conductance densities are hard-wired or whether they undergo activity-dependent plasticity. If they do undergo such plasticity, how does it affect the grid-like patterns of firing and what signaling mechanisms are involved in the plasticity? Questions on how maps in layer II affect properties of neurons within the cortical microcircuit and of neurons that they project to (in the hippocampus) will help in understanding the micro- and macro-network implications of these maps. At the behavioral and systems level, it would be interesting to directly explore the role of voltage-gated ion channels in mediating the grid-like firing patterns and gradients in their spacing. For instance, it would be of interest to understand the role of *h* channels in mediating these properties and phenomena like phase precession using appropriate pharmacological agents and knockout mice. Finally, given that channelopathies in the medial temporal lobe have been reported with neurological disorders like epilepsy (Bernard et al., 2007), a study of the role of ion channels in mediating specific behavioral aspects can open up new therapeutic interventions for these disorders.

In conclusion, Garden and colleagues demonstrate that the "memory" of various functional maps in layer II mediate entorhinal cortex is "stored" in gradients of ion channel conductances. This study, in conjunction with previous studies (Giocomo et al., 2007; Moser et al., 2008), provides rare insights into a nonsensory higher cortical region that has an anatomically well-defined structure executing a behaviorally relevant function. This combination offers an ideal preparation with wide-ranging opportunities for assessing the roles of voltage-gated ion channels in various aspects of learning and memory.

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You Shouldn't Have: Your Brain on Others' Crimes

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Our legal system requires assigning responsibility for crimes and deciding on appropriate punishments. A new fMRI study by Buckholtz et al. in this issue of *Neuron* reveals that the right dorsolateral prefrontal cortex (rDLPFC) plays a key role in these cognitive processes. This finding sheds light on the neural mechanisms underlying moral judgment from a third-party perspective.

Much recent research documents people's willingness to punish norm violations and to enforce social norms. This willingness also exists if the punishers derive no material benefit themselves, but instead incur costs (Henrich et al., 2001). Even unaffected third parties who merely observe a norm violation engage in costly norm enforcement (Fehr and Fischbacher, 2004). Modern legal systems are probably based on these deep human instincts, aiming primarily at retribution: offenders are jailed or executed to *punish* them for their transgressions, and only in the second instance to prevent future harm to society (Kant, 1999; Whitman, 2003). Retributive punishment is thus a core element of contemporary justice. Judgment by third parties about punishment requires assigning responsibility for an offense that a perpetrator commits against a victim, judging the severity of that action, and finally selecting an appropriate punishment. Given the centrality of this process to the administration of justice, elucidating the cognitive and neural mechanisms underlying such judgments is of considerable interest.

In this issue of *Neuron*, Buckholtz and colleagues (Buckholtz et al., 2008) take a step in this direction: using functional magnetic resonance imaging (fMRI), they examine which brain regions are activated when humans make judgments regarding the appropriate punishments for various violations. Specifically, participants in their study read vignettes describing hypothetical transgressions that a fictitious agent, "John," commits against another person. The stories were divided into three conditions: in the first, the "responsibility" (R) condition, the perpetrator was responsible for the negative outcome of his action against the victim; in the "diminished responsibility" (DR) condition, mitigating circumstances were present that reduced the protagonist's responsibility; and finally, the "no crime" (NC) condition consisted of stories that did not describe crimes. The participants had to make judgments regarding the degree of punishment that the offender should receive, on a scale from 1 to 9.

The authors then proceeded to analyze the brain activation linked to these judgments. They contrasted activation in the "R" and "DR" conditions in order to identify neural correlates of responsibility. This contrast revealed a peak of activation in right doroslateral prefrontal cortex (rDLPFC). This activation did not simply reflect higher arousal resulting from reading the "R" compared to the "DR" stories, for two reasons: first, the stories were counterbalanced across subjects, so that the same stories appeared in the "R"