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Profiling neuronal ion channelopathies with non-invasive brain imaging and dynamic causal models: Case studies of single gene mutations

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ABSTRACT

Clinical assessments of brain function rely upon visual inspection of electroencephalographic waveform abnormalities in tandem with functional magnetic resonance imaging. However, no current technology proffers in vivo assessments of activity at synapses, receptors and ion-channels, the basis of neuronal communication. Using dynamic causal modeling we compared electrophysiological responses from two patients with distinct monogenic ion channelopathies and a large cohort of healthy controls to demonstrate the feasibility of assaying synaptic-level channel communication non-invasively. Synaptic channel abnormality was identified in both patients (100% sensitivity) with assay specificity above 89%, furnishing estimates of neurotransmitter and voltage-gated ion throughput of sodium, calcium, chloride and potassium. This performance indicates a potential novel application as an adjunct for clinical assessments in neurological and psychiatric settings. More broadly, these findings indicate that biophysical models of synaptic channels can be estimated non-invasively, having important implications for advancing human neuroimaging to the level of non-invasive ion channel assays.

Introduction

The balanced flow of ions through synapses is integral to the stability and control of neuronal firing and information transmission in the brain. Abnormalities of ion channels and synaptic function are thought to underlie a range of neurological presentations including seizures, migraine and movement disorders (Catterall et al., 2008), and inform pharmacological treatment strategies (Yogeeswari et al., 2004). Furthermore, a growing body of evidence in psychiatry suggests alterations in simple mechanistic principles, like the ratio of neocortical excitation to inhibition or long-range to local synaptic transmission, could underlie complex disorders including social dysfunction (Yizhar et al., 2011), autism (Rubenstein and Merzenich, 2003) and schizophrenia (Jardri and Deneve, 2013). In animal models of these diseases, tools like optogenetics provide a means to manipulate synaptic transmission, providing a platform to test putative pathophysiological mechanisms in neural circuits (Tye and Deisseroth, 2012). However, there are no current technologies for non-invasively measuring brain function at this level in humans. While limited assessments of neurotransmitter and synaptic receptor levels are feasible with magnetic resonance spectroscopy (Dager et al., 2008) and positron emission tomography (Lee and Farde, 2006), these techniques do not directly measure neuronal function and can be applied only to a limited set of molecules. Here we describe how magnetic event-related fields (ERFs), measured at superconducting sensors around the head, can be fit to a biophysical model of neural circuits to recover potential probabilistic markers of an individual's synaptic function.

In this work, we utilize the specificity imparted by single-gene mutation neurological channelopathies (Catterall et al., 2008; Hanna, 2006; Kullmann, 2010) to assess the capability of our model-based assay in the context of magnetoencephalography (MEG). These signals are a close analogue of the electroencephalogram (EEG) and provide proof-of-principle for use in clinical settings, where EEG is widely available. Channelopathies, by virtue of their diverse clinical presentations (Catterall et al., 2008), illustrate how the functional consequence of particular ligand or voltage-gated ion channel dysfunction are neither easily predictable nor strictly amenable to diagnosis via clinical examination (Helbig et al., 2008). For example, patients with monogenic causes of epilepsy, such as generalized epilepsy with febrile seizures caused by mutations in neuronal sodium channels, can present with seizures of variable phenotypes and severities at different ages (Singh

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et al., 1999). In addition, genetic channel mutations can be partially penetrant, leading to differential interaction characteristics with various genes or with the environment (Kullmann, 2010). Outside of acquired (e.g., autoimmune) and single gene mutations, diagnosis of polygenic channel dysfunction (e.g., associated with idiopathic epilepsy (Cannon, 2006; Hanna, 2006)) using genome or exome sequencing suffers from a complex landscape of allelic risk; where non-affected individuals can harbor mutations in known or suspected epilepsy genes (Klassen et al., 2011). Therefore, patients with primary effectors from "mixed", as well as classical single-gene channelopathies could benefit diagnostically and prognostically from the in situ characterization of pre and postsynaptic neuronal cell dynamics. Indeed, in silico computational models of channel variation have been proposed as a crucial bridge between genetics and disease risk or drug responsivity (Klassen et al., 2011).

Our work – based on dynamic causal modeling (DCM) – goes a step further by providing a biophysical model of currents produced by interacting ion channels which are then matched to measurable electromagnetic signals. This means that empirical data can be used to test competing models — and the winning model can be optimized for a given individual. DCM was originally designed as an analysis framework for imaging network-level communication in functional magnetic resonance imaging (Friston et al., 2003) and has been developed to infer the synaptic basis of measured electrophysiological signals like those from MEG, EEG and intracranial local field potentials (David et al., 2006). Previously, DCM has been applied in healthy human participants to assess putative synaptic changes induced by pharmacological agents like L-DOPA (Moran et al., 2011c) and propofol (Boly et al., 2012). It has also been used in patients to test the contribution of long-range and regionally-specific connections to the vegetative state (Boly et al., 2011).

Here, we test sensitivity and specificity of the synaptic ion channel inferences available through electrophysiological DCM, utilizing data from two cases of single-gene mutation channelopathies. In order to test these particular patients we augmented a conductance-based neural mass model (Moran et al., 2011c) of regionally specific sources (Garrido et al., 2007) to include ligand-gated sodium, calcium, and chloride channels — as well as voltage-gated potassium and calcium channels (Fig. 1). This augmented model was used to explain auditory-evoked ERFs produced by 94 healthy control participants and 2 patients with known mutations causing loss-of-function in the inward-rectifying potassium channel gene KCNJ2 and in the voltage-gated presynaptic calcium channel gene CACNA1A. Our hope was to show a selective

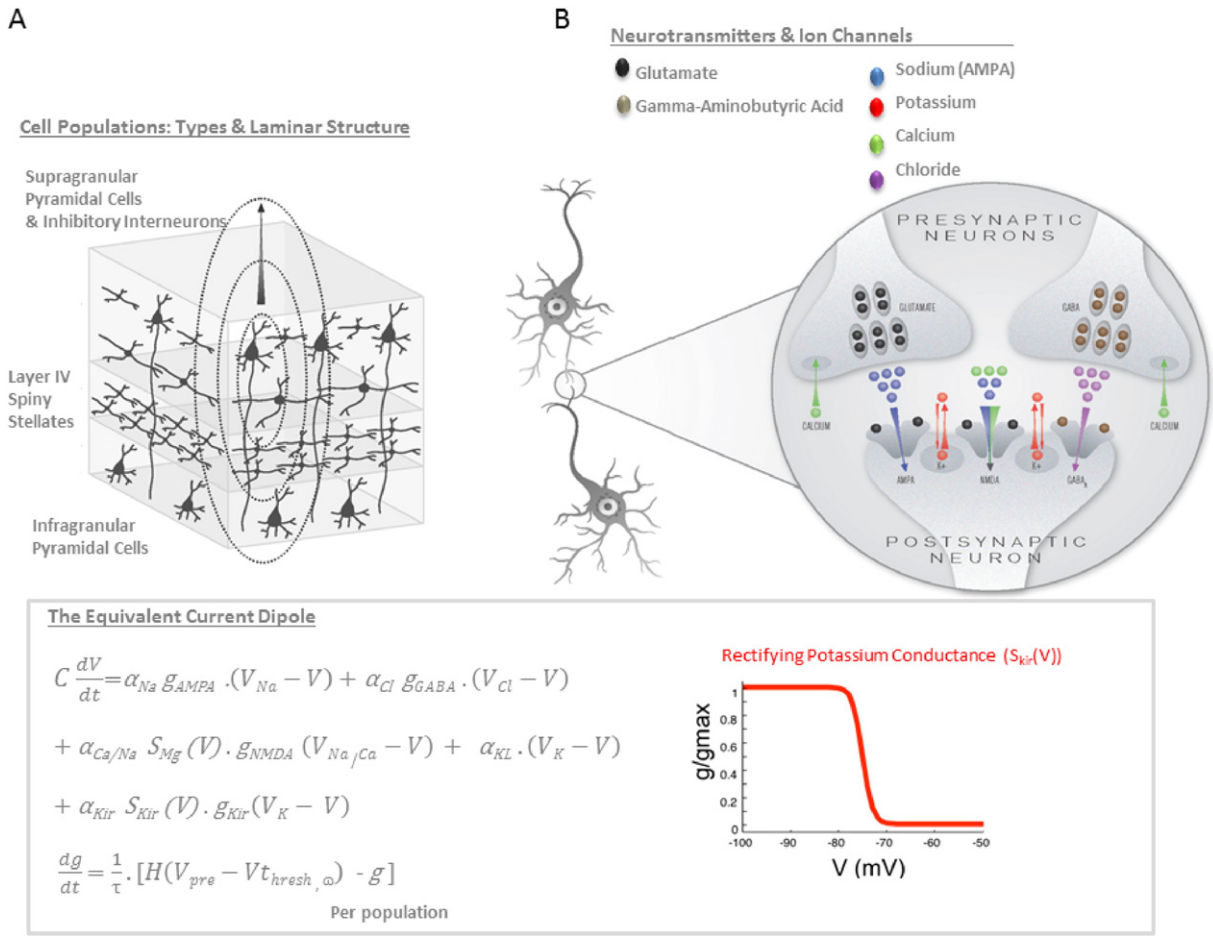

Fig. 1. Properties of the dynamic causal model. A. For the DCM, three populations of neurons are used to model the activity of a given source of electromagnetic signals. These populations, including spiny stellate cells, pyramidal cells and inhibitory interneurons, are associated with cortical layers by virtue of their intrinsic connectivity — where layer IV stellates receive forward inputs, and supra and infragranular pyramidal cells and inhibitory interneurons are the targets of backward connections. B. The population dynamics are approximated by a mean field reduction, where average channel properties control the synaptic activity at each population of cells (Marreiros et al., 2009). This synaptic activity represents neurotransmitter and voltage-gated ion channels with distinct dynamics. C. The channels include a glutamatergic AMPA-mediated sodium channel, a glutamatergic NMDA-mediated sodium and calcium channel, a $GABA_A$ mediated chloride channel, a leak potassium channel and an inward rectifying potassium channel. C. The dynamics at each population are formally described by a set of coupled differential equations where changes in postsynaptic depolarization (dV/dt) are governed by the dynamics of these channels with weights α and time constants τ. Reversal potential (V_{ion}) determines the direction of current flow. Channel conductance (g) have time constants τ, and are dependent on presynaptic firing H, which is a function of presynaptic membrane potential (V_{pre}) and the threshold potential (V_{thresh}). The inward rectifying potassium channel (right, in red) is gated to produce maximal conductance at hyperpolarized states.