Evoked responses and transient beta events reveal the frontal microcircuit dynamics of inhibitory control during response inhibition.

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Abstract:

Frontocentral event-related potentials (FC-ERPs) from human scalp EEG are often used as proxy measures of cognition, but the multiscale mechanisms producing them are poorly understood. To address this gap in the context of response inhibition (RI) in the stop-signal task (SST), we used Human Neocortical Neurosolver's (HNN) biophysical model of a cortical column under external drive to simulate the microcircuit mechanisms that produce the successful (SS) and failed Stop (FS) FC-ERP, including condition differences in the P2, N2, and P3. Using modeling constrained by empirical ERPs, we predict that the strength and timing of thalamocortical drives at early and late timepoints, respectively, are essential mechanisms underlying SS. Predictions about drive timing align with a theoretical "horse-race model" conceptualization; predictions about drive strength do not. Regulation of early movement-associated activity in SS may be accomplished in part due to GABAb-ergic activity following high-power beta transients known to be increased during SS. These simulations make novel predictions about cortical dynamics of RI, which may generalize to mechanisms of control across contexts.

Keywords: inhibitory control; response inhibition; stop-signal; cortical microcircuit; event-related potential

Introduction

Frontocentral event-related potentials (FC-ERPs) from human electroencephalography (EEG) are proxy signatures of cognition, including in the Stop-Signal task (SST), in which they index inhibitory control processes (Kok et al., 2004). In the SST, the P3 component of the FC-ERP onsets earlier in successful (SS) compared to failed Stops (FS; Wessel and Aron, 2015). A behavioral "horse-race model" of SST behavior predicts SS results from an underlying Stop process outpacing a Go process and that SS entails a faster (but not stronger) Stop process than FS (Logan and Cowan, 1984). Thus, the P3 has characteristics expected of a neural proxy of the Stop process.

Despite theories associating the FC-ERP's components with the Stop process, the mechanisms that generate them remain poorly understood, and we do not know whether these align as well with behavioral-cognitive theory. Here, we address this limitation using the Human Neocortical Neurosolver (HNN; Neymotin et al., 2020) – a biophysical model of the canonical neocortical column under external thalamocortical drive designed to interpret the multiscale origin of human M/EEG signals. Applying HNN, we predict the multiscale dynamics producing the FC-ERP during SS and FS in the SST.

Methods

Stop-Signal locked FC-ERPs were extracted from an open-source dataset of EEG recordings collected during the SST (N = 234, Wessel, 2020).

HNN includes individual compartmental pyramidal and inhibitory point cells arranged in a laminar structure of a cortical column under external thalamocortical and cortical drive. (See Neymotin et al. (2020) for more details and empirical support for this model.) Users simulate ERPs with HNN by determining a sequence of proximal (delivered to pyramidal basal dendrites) and distal (delivered to pyramidal apical tufts) drives that generate a simulated dipole with the same shape and polarity as an empirical ERP. The precise timing and

strength (i.e., synaptic conductance) of these drives are tuned with algorithmic optimization of RMSE between the simulated current dipole and the empirical ERP. The timing of these drives was adjusted from the default HNN parameters developed for S1 ERPs (Jones et al 2007) to account for the longer ERPs in frontal cortex, and the number of spikes increased for the proximal drive associated with the high-amplitude P3 in FC-ERPs (ref. **Fig. 1A**). The timing and synaptic weights of these external drives were optimized using COBYLA to find a good fit to the empirical SS FC-ERP. Once we established our HNN model for the SS FC-ERP, testing the differences between FS and SS conditions was accomplished by tuning the timing and synaptic weights of external drives in a hypothesis driven manner.

Results

HNN was first applied to study the mechanisms that underlie the SS FC-ERP. We found that a sequence of proximal, distal, and a final proximal (Proximal 2) drive could reproduce the SS FC-ERP (see **Fig. 1A**). Next, to test the race model-derived hypothesis that a difference in P3 onset could be accounted for by Proximal 2 drive that arrives later but is not weaker in FS, we tested what exact changes were required to the SS FC-ERP HNN parameters to recapitulate the FS FC-ERP. We first optimized the simulated dipole to the FS FC-ERP with synaptic weights for Proximal 2 drive *fixed* (i.e., only timing could change). We found that a timing change in Proximal 2 could account for a later FS P3 (see **Fig 1B**). In contrast, testing the alterative hypothesis that strength changes could account for the later FS P3 did not result in simulations that matched the data.

Our simulations also predicted that increases in spiking at the time of P2 in FS trials produces a higher-amplitude P2 (see Fig. 1B); regulation of this spiking, which could be associated with erroneous responding, may be critical for stopping. This is remarkable because there are early increases in FC transient beta rates during SS (Wessel, 2020), and these beta events have been hypothesized to recruit GABAb-ergic inhibition (Law et al., 2022) that could facilitate regulation of early spiking. As in previous work, delineating the impact of beta mechanisms on ERPs will be critical to a full understanding of the dynamics supporting RI.

Discussion

While a horse-race model conceptualization of the P3 is compatible with cortical mechanisms of the FC-ERP, our simulations predict earlier differences in the P2 and N2 require changes in the strength of underlying processes not accounted for by timing changes alone.

These HNN simulations reveal novel, testable predictions about microcircuit mechanisms supporting RI. These open-source models provide a starting point from which the field can begin to further test the mechanisms of inhibitory control that manifest in these and other similar FC-ERPs, such as in error-processing or salience detection.

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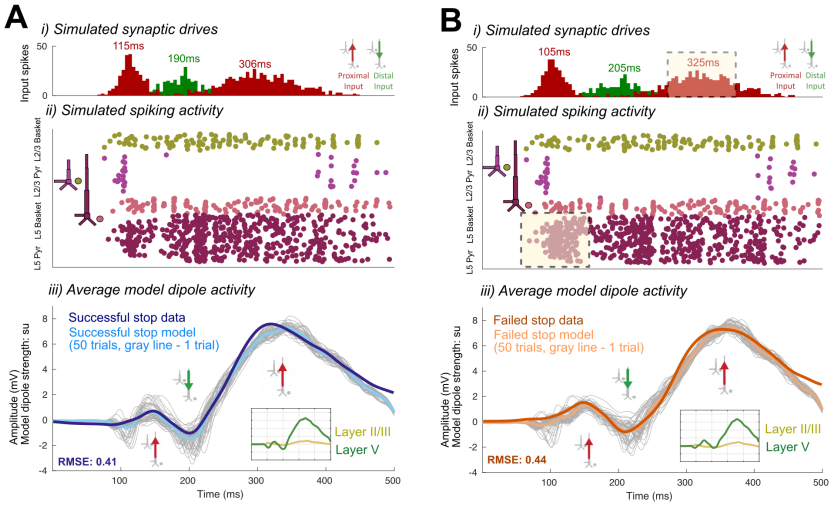

Figure 1: HNN models dipoles fit to the SS **(A)** and FS **(B)** FC-ERP. Boxes are included to highlight differences of interest, including later Proximal 2 drive and increased early spiking in FS.

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