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HCN1-mediated interactions of ketamine and propofol in a mean field model of the EEG

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Ketamine and propofol, two popular anesthetic agents, are generally believed to operate via disparate primary mechanisms: ketamine through NMDA antagonism and propofol through the potentiation of $GABA_A$-gated receptor currents. However, surprisingly the effect of ketamine on the EEG is markedly altered in the presence of propofol. Specifically, while ketamine alone results in a downshift of the peak frequency of the alpha

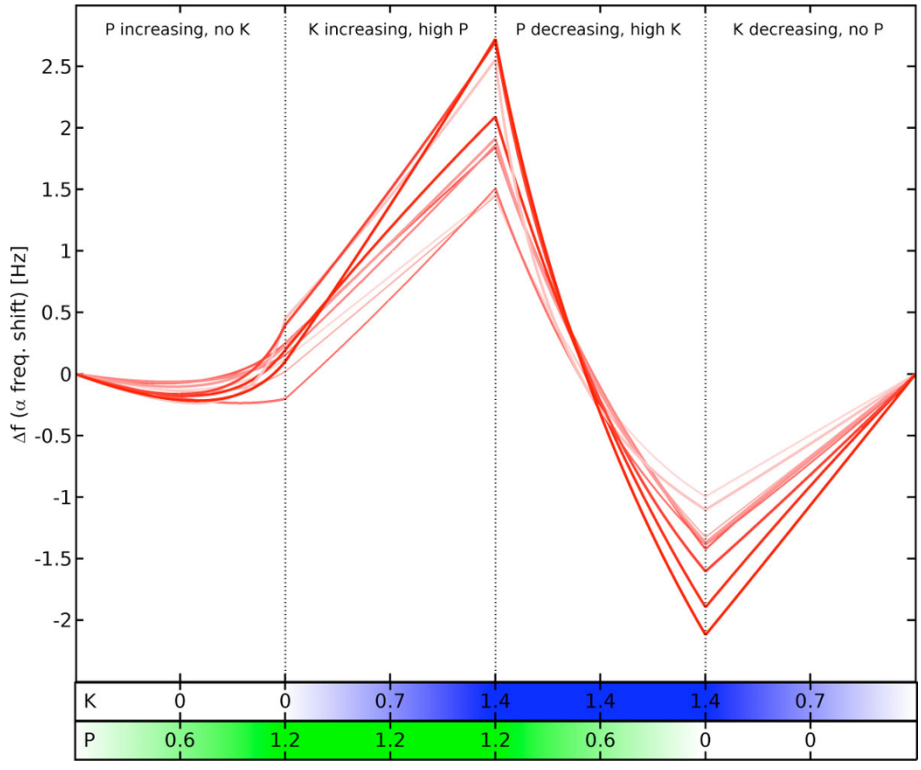

Figure 1 Predicted shift of the alpha peak frequency of ten parameter sets during four phases of linear change to the normalized ketamine (K) and propofol (P) concentrations, respectively.

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rhythm, and propofol keeps it roughly constant - when administered together, they increase the alpha peak frequency [1].

Recently it has been found that both ketamine and propofol inhibit the hyperpolarization-activated cyclic nucleotide-gated potassium channel form 1 (HCN1) subunits, which induces neuronal membrane hyperpolarization [2]. Furthermore, HCN1 knockout mice are significantly less susceptible to hypnosis with these agents; but equally affected by HCN1-neutral etomidate [2].

We show here [3] that an established mean field model of electrocortical activity can predict the EEG changes induced by combining ketamine and propofol by taking into account merely the HCN1-mediated hyperpolarisations, but neglecting their supposed main mechanisms of action (NMDA and $GABA_A$, respectively). See Figure 1.

Our results suggest that ketamine and propofol are infra-additive in their HCN1-mediated actions. This is consistent with independent experimental evidence [4]. We show here that the HCN1-mediated actions of ketamine and propofol, hitherto neglected by models of anaesthetic action, can not only explain a range of counterintuitive induced EEG changes but also predicts the infra-additivity of these drugs.

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