Modelling impairment of evoked gamma range oscillations in schizophrenia

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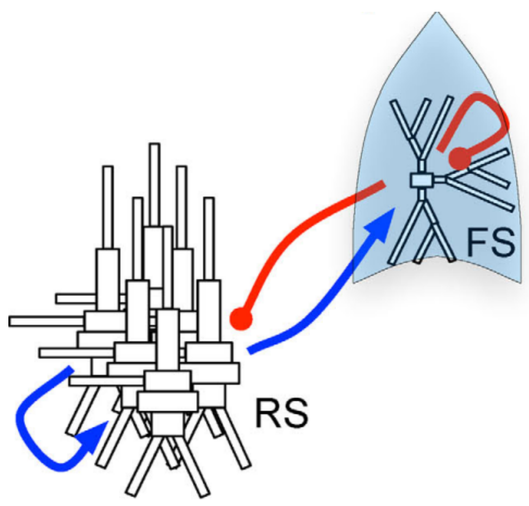
Introduction

Recent genome-wide association studies have identified more than 100 risk genes for schizophrenia [4]. Many among these are coding for ion channels and ion transporters. While their function has been well characterized the contributions of common variation in these channels to neurophysiological biomarkers and schizophrenia pathology remain elusive.

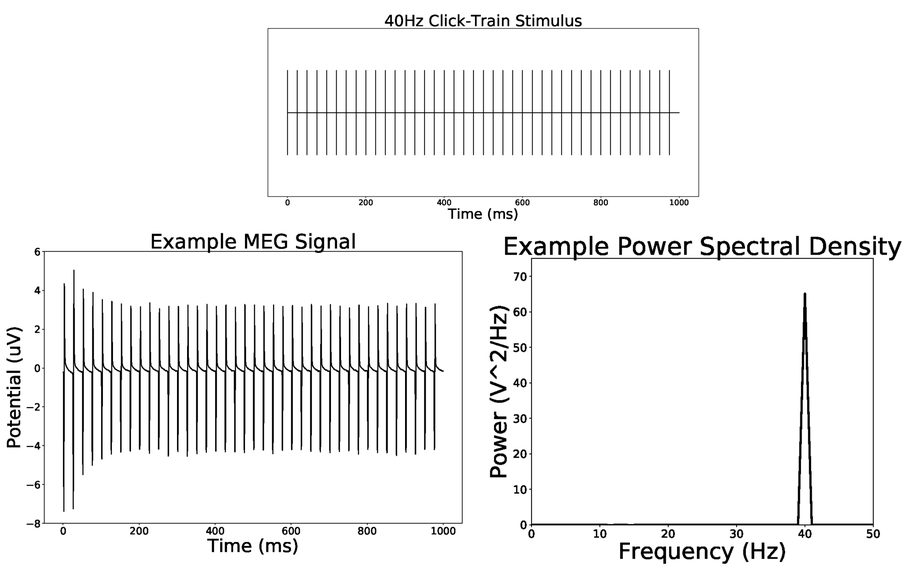
Here, we explore the effects of altered kinetics of voltage-gated ion channels on gamma range auditory steady-state response (ASSR) deficits, a common biomarker for schizophrenia [5].

Methods

We implemented a network model of primary auditory cortex based on [6] (see schematic below taken from [6]), however using a single cell model from a previous study [1] to implement the genetic variants.



Following earlier studies, we included a total of 86 variants of the following genes: CACNA1C, CACNA1D, CACNB2, SCN1A, and HCN1 [2, 3], coding for calcium, sodium and non-specific ion channels. To quantify ASSR deficits at gamma, we measured local-field potentials in response to 40 Hz click train stimuli, computed the power spectrum and extracted power at 40 Hz. The Figure below shows the 40 Hz click-train stimulus, an example LFP trace and the resulting power spectral density, demonstrating a clear oscillatory entrainment at the drive frequency similar to experiments [7].



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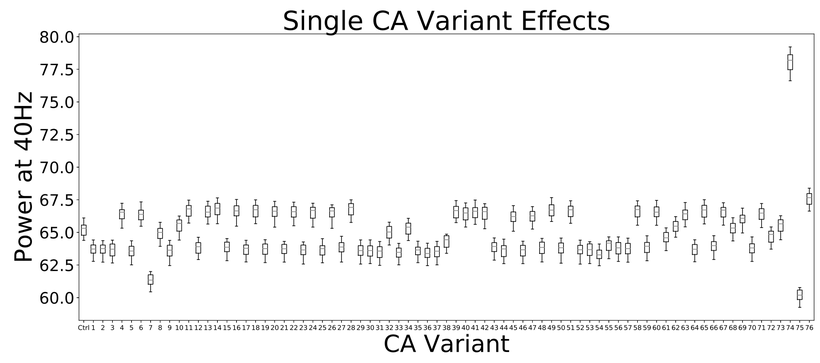
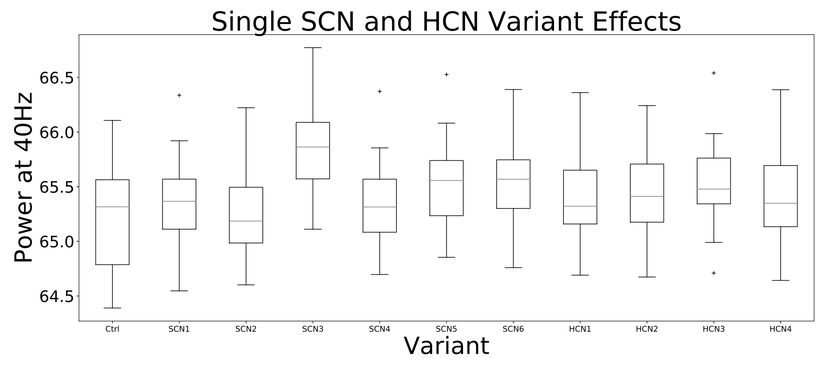
Results

Effects of single variants: First, we simulated the effect single variants of the genes had on the ability of the network to be driven at gamma frequency.

For the variants affecting genes coding for calcium channel subunits, we saw that most of the variants had a small effect on gamma power. However, a few variants were able to induce larger changes. Interestingly, we found a singificant correlation between changes in gamma power and changes in the offset of the activation parameter m of the high-voltage activated calcium channel affected by the variants ($r = 0.51, p > 0.001$).

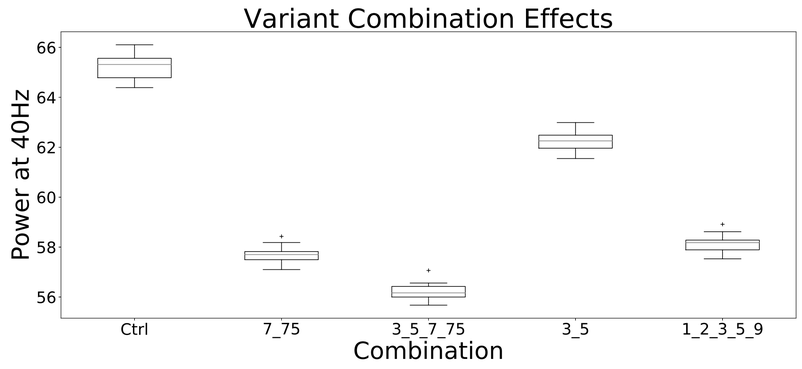


Variants affecting the SCN1A or HCN1 genes had hardly any effect on the networks ability to be driven at gamma.



Effects of combinations of variants: Ultimately, we explored the effects of combinations of variants:

- 7_75: the combination of the two variants shwoing the largest reduction of gamma power.
- 3_5_7_75: the two variants from above combined with two variants showing a moderate gamma reduction.
- 3_5: the two variants with moderate gamma reduction from above.
- 1_2_3_5_9: a combination of 5 variants with moderate reduction.



Overall, we found that the small changes for the single variants more or less linearly combined for the combinations. We also saw that the combination of variants with relatively small individual effects can lead to substantial alterations.

Conclusion

By simulating the effects of schizophrenia-associated alterations of genes coding for ion channels in a network model, we demonstrated their potential to alter gamma range oscillatory activity similar to deficits reported for patients with schizophrenia. Especially, we showed that the combination of several variants, each individually having a very small effect, can substantially reduce gamma entrainment. This highlights the relevance of cell-intrinsic mechanisms contributing to electrophysiological deficits in psychiatric disorder. Furthermore, the approach employed here shows how the fast growing body of evidence of alterations at the genetic level in psychiatric disorders can be translated into mechanistic insights on the cellular and, micro- and mesoscopic network level.