In Vivo Sensory Cortex Dysfunction in Pyruvate Dehydrogenase Deficient Mice

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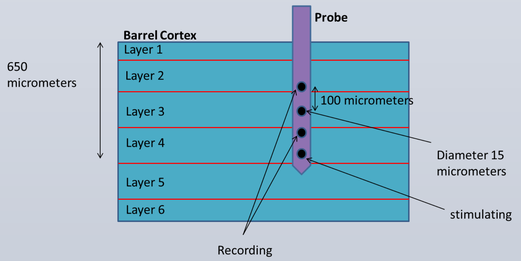
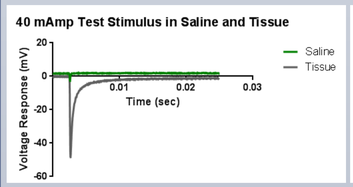
Introduction

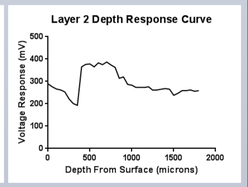
Pyruvate Dehydrogenase (PDH) is a critical enzyme in the pathway to metabolize glucose for the Krebs cycle. The cycle is the source of the principal brain neurotransmitters glutamate and GABA and of ATP. PDH deficiency manifests in patients as severe lactic acidosis, multiple neurological deficits, and intellectual disability. The disease is X-linked, and almost always prenatally deadly to males and causes shortened lifespan and debilitating developmental problems in females. Processing of sensory information in the cerebral cortex is crucial for intellectual function and is an aspect of the disease that is poorly understood. We hypothesize that cortical thinning in these patients contributes to aberrant sensory processing and resulting intellectual disability. Specifically, we hypothesize that there exists a deficit in neurotransmission within the primary somatosensory cortex that can be tested in a novel mouse model of PDH deficiency that replicates the cardinal features of the human disorder, including seizure-like activity and decreased brain mass.

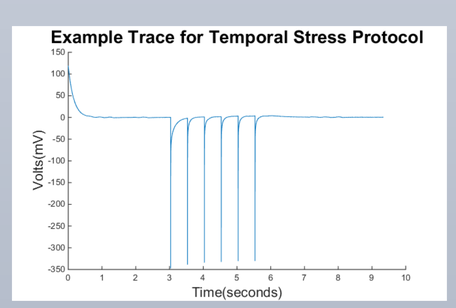
Methods

We used a single linear array of electrodes to stimulate the cortex in layer IV and record in both layer IV and II as shown below. Using different filters we were able to examine LFP and slow wave activity at the same time we measured action potentials. In each mouse, we examined spontaneous activity in layer II and IV, evoked response in layer II from stimulation in layer IV, and synchronized spontaneous activity between the two layers.



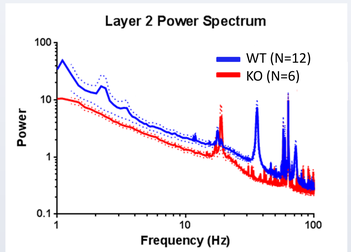


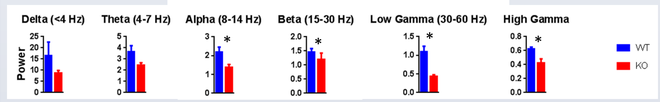


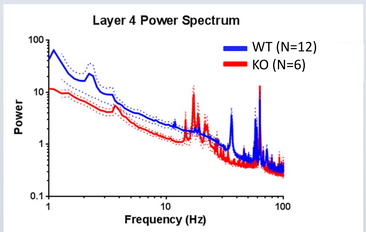


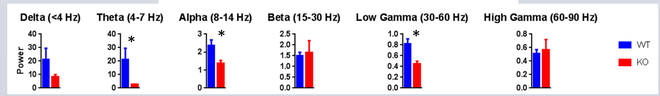
Neurotransmission and Processing

Decreased Slow Wave Oscillations in the Cortex

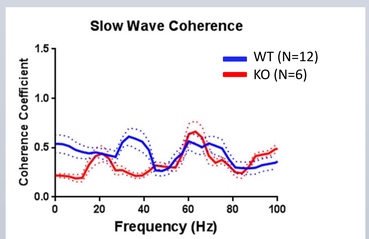


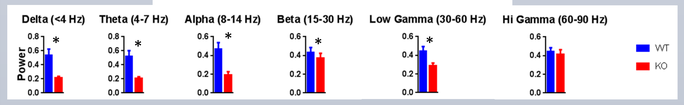




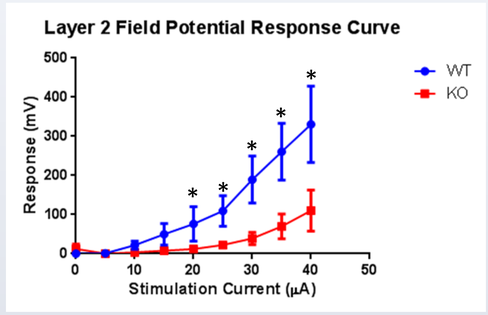


Decreased Synchronicity in a Global Network

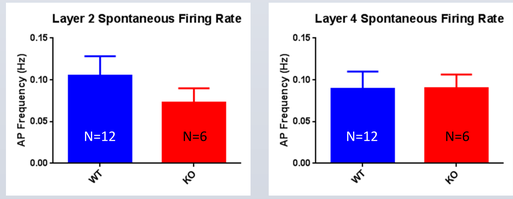


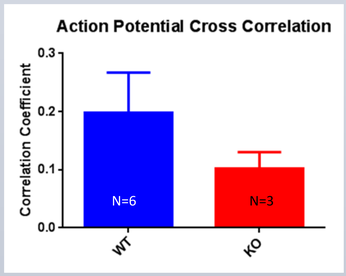


Decreased Neurotransmission Between Cortical Layers

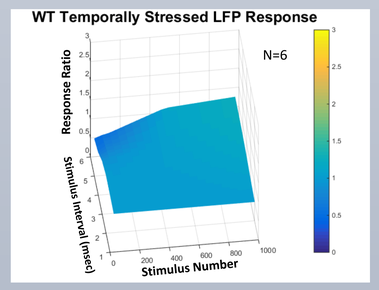


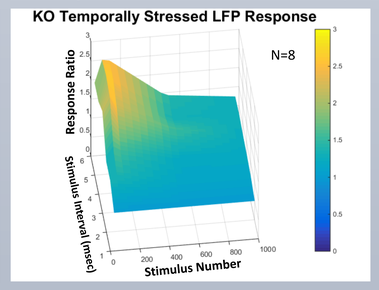
Information Output from Layers II/IV

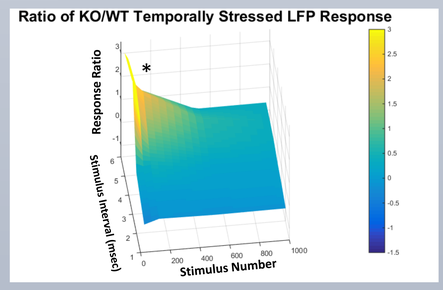




Gating Dysfunction in Sensory Cortex

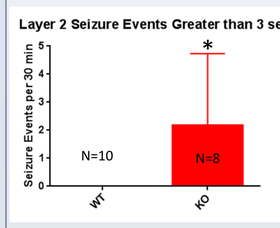


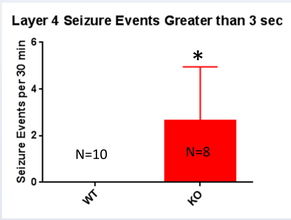


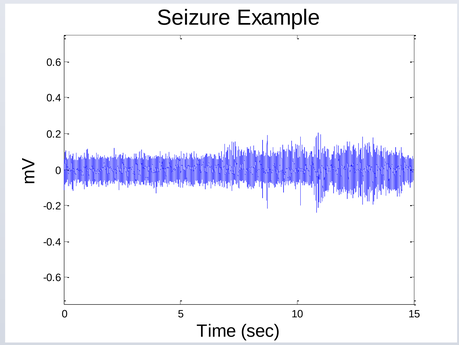


Seizures

We defined seizure-like activity as a train of action potentials lasting at least 3 seconds with a frequency of 5Hz.







Conclusions

We have observed a significant loss of slow wave electrical input, evoked response in neurotransmission, spontaneous output, and synchronicity of slow wave oscillations in the PDH mutant mice. This implies cortical dysfunction in sensory processing that could contribute to intellectual disability. In addition, the dysfunctions in gating suggest inability to properly filter incoming stimuli, and the seizure like activity lends to the credence of global neurological deficits similar to human patients with cortical thinning. In addition to identifying sensory processing deficits, treatments targeting this phenotype could be beneficial to PDH-deficient patients and may inform therapies for other neurodevelopmental disorders of energy metabolism that manifest with sensory processing deficits.

Acknowledgements

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