Identifying G1D disease locus in Large Animal Brain of Pig

GLUT1 DEFICIENCY SUMMIT 2024

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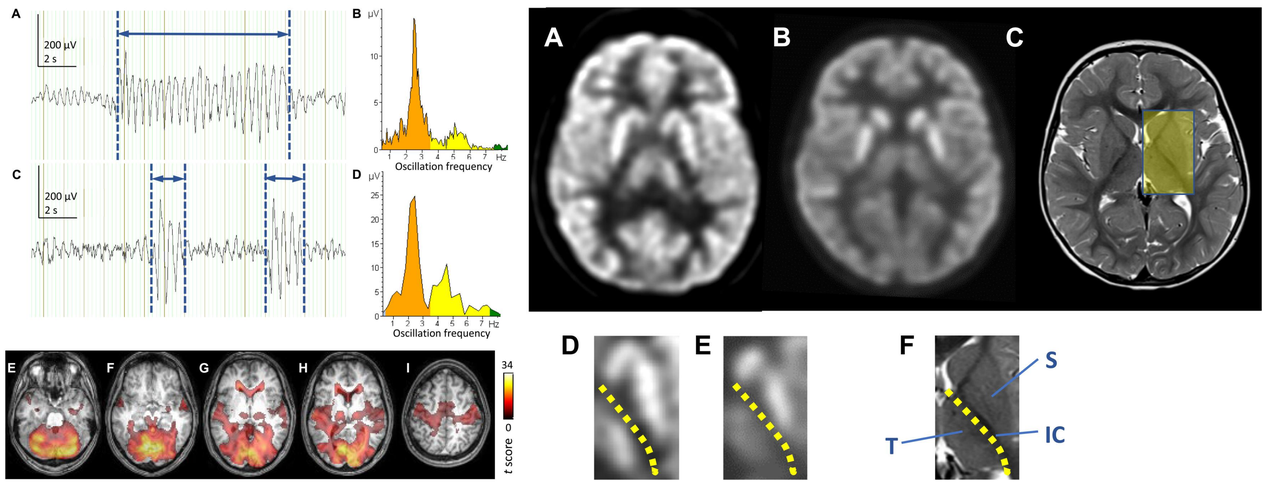
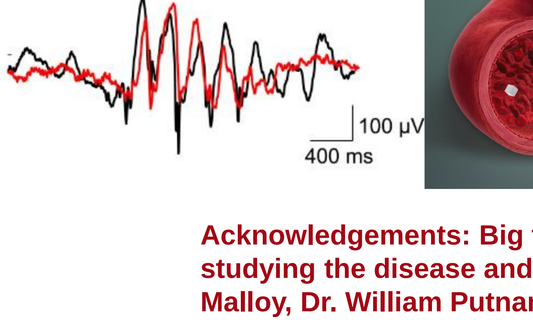
ABSTRACT

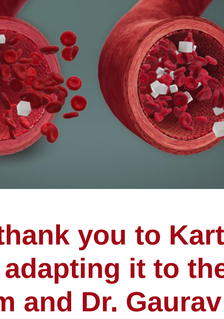
- Patient EEGs, fMRI and 18-FDG PET have greatly enhanced our understanding of disease locus for G1D and guided us to approach the detailed scientific experiments in animal models primarily mice so far.
- Mouse experiments with some limitations ranging from the longitudinal aspects to methodic limitations have helped us understand that seizure locus could very well be layer V parvalbumin positive inhibitory neurons that projects to thalamus leading us to slow oscillatory activity in conjunction with behavioral phenotype observed in mice.
- We are unsure of how adult mice results may differ from the developing mice since G1D is primarily occurs during development.
- Aside from their limited temporal resolution, fMRI and 18FDG-PET are only at best indirect correlates of glucose absorption.
- Pig model of G1D can answer several key questions and overcome almost all the limitations of small animal brain model.
- G1D Pig will allow simultaneous measurement of in-vivo neurophysiology and metabolism from multiple brain regions to accurately identify the disease locus.

INTRODUCTION



- 18-FDG-PET requires accumulation of radioactive label and, it is not a direct measure of glucose uptake and additionally temporal scans were acquired over 60 minutes timeframe following 30 min injections, which makes it hard to tell when the tracer exactly reached and accumulated in response to rapid neurophysiological changes. We can only get steady state changes in tracer accumulation, which is used clinically to get epileptic seizure foci.
- BOLD signal increase as paper suggests shows changes in signal for adult who could keep awake and immobilize them during these events. Also, small seizure could not be correlated since it would not be synchronized accurately to BOLD signal.





- Mice Mass spectrometry could only allow measurement of 13C glucose enrichment of whole brain since the size of the organ limits the access to required amount of tissue for data.
- This limitation along with other discussed for patients could be overcome from studying metabolism in conjunction with neurophysiology regional for getting disease locus required to target treatment options augmenting the reduced Glut1 transporters.

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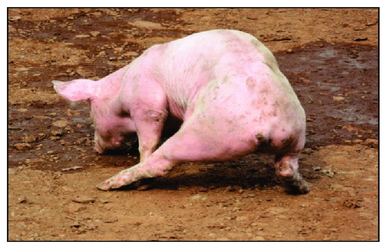
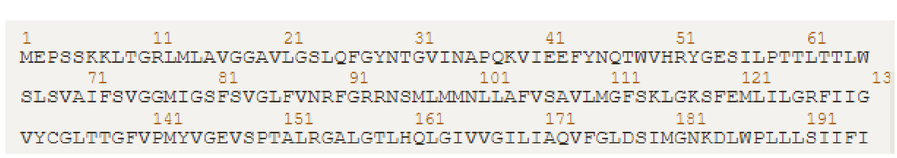
- Primary Aims:

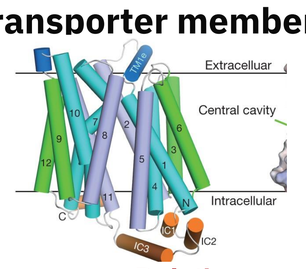
1. Developing genetically modified pig to exhibit the Glut1 Phenotypes such as paradoxical periodic hyperexcitability resulting in seizures, hypoglycemia of brain cells and ataxic gait.
2. Overcome limitations of Human and mice Glut1 research by using Glut1 model of pig for ex-vivo region-specific NMR spectroscopy, high density electrocorticography with high sampling rate extracellular activity from Layer 5 of Somatosensory cortex.

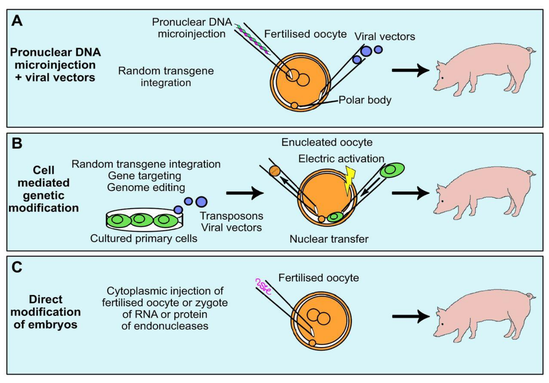


METHODOLOGY

SLC2A1 - Solute carrier family 2, facilitated glucose transporter member 1

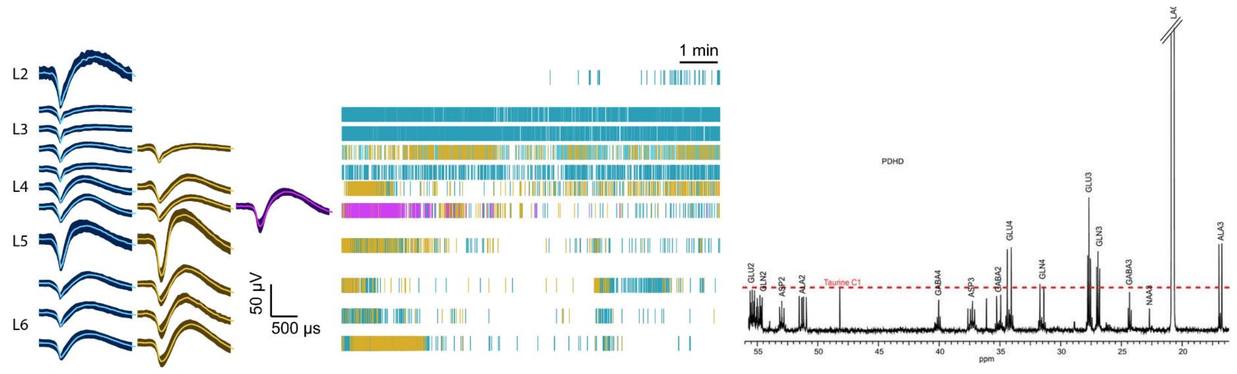


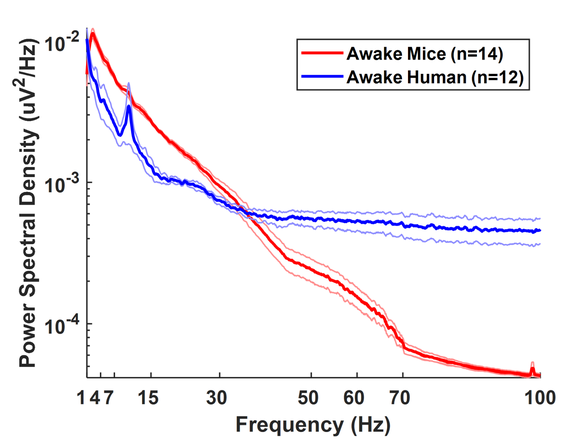


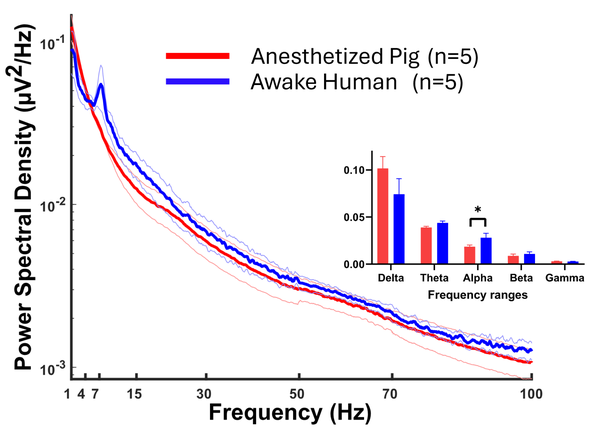


- Missense, Frameshift, Nonsense or Deletion would directly impact the translation of protein required for Glut1 Transporters.
- Craniotomy with complete access to the cerebral cortex for ECoG and extracellular recording.
- 13C ex-vivo NMR spectroscopy would allow us to investigate metabolic profile including metabolites that are otherwise invisible with required spatial resolution in in-vivo NMR.
- Experiment in pig model at various blood glucose levels will simulate human condition to study the effects thoroughly.

RESULTS & CONCLUSION







- Somatosensory cortical 13C metabolism spectra would inform us about the correlation of presence of glucose and its impact on metabolites along with how layer 5 cortical activity changes impacting the thalamic activity as a result.
- The result derived from published data should resemble patient-based research rather than mouse activity.
- With large animal brain model, we overcome many limitations that small animal such as mice introduce due to developmental issues and restricted longitudinal study access.
- We cannot for ethical reasons have human research as detailed and as distressing as we can within the guideline in animals.

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