Lay Summary

This project will use non-invasive electroencephalography (EEG) and behavioral tasks to examine the integrityof basic sensory transmission in the brain, connectivity between different rain areas, and the brain's ability to benefit from multi-sensory information. This will be the first study to examine multisensory integration in children with Niemann-Pick Type C disease (NPC) and we will monitor for changes in multisensory processing as patients undergo treatment in the cyclodextrin clinical trial. The brain's ability to benefit from multisensory information follows a fine tuned developmental time course and our lab has a large normative dataset tracking the development of multisensory integration in neurotypical children. This allows us to at any given age compare the EEG and behavioral data from NPC participants with those of age-matched controls.

In pilot work we have uncovered severe multisensory deficits and auditory transmission slowing at the individual patient level in three boys with NPC. The purpose of these studies is to develop an objective, easily obtainable, and inexpensive biomarker against which to examine the effectiveness of new therapeutic interventions. We have recently developed a successful collaboration with Dr. Forbes Porter's team at the Section on Molecular Dysmorhology, Division of Intramural Research at The Eunice Kennedy Shriver National Institute of Child Health and Human Development and are recruiting children from that site who are currently enrolled in or about to enroll in the NCATS-sponsored clinical trial for cyclodextrin. This will allow us to test these kids before and throughout the course of treatment to help quantify the effects of cyclodextrin on neural function. We intend on collecting EEG, behavioral, cognitive assessment, and genetic data from at least 15 NPC patients at three separate time points. This will allow us to begin to characterize basic sensory processing and multisensory facilitation (i.e. effective sensory transmission and neural connectivity) in NPC. By re-testing these children as they go through cyclodextrin treatment we will also be able to study the direct effects of the drug on the brain -- probing both for benefits and potential risks.

Objective neurobiological markers against which to test the efficacy of therapeutic interventions are sorely needed in NPC disease. These measures proposed here are considerably closer to effects of a given intervention in that they are directly measuring brain activity and are exquisitely sensitive to changes in the integrity of signal transmission through the cortical hierarchy. One would fully expect that changes in brain electrical activity would substantially precede measureable changes in behavior or the clinical phenotype. That is, new or improved behaviors can only be learned once there has been some rescue of neural function and this learning will likely proceed over a protracted timeframe, whereas the neural changes/rescue, if present, should be evident considerably more rapidly. On the other hand, this measure may also serve as an early direct neural-marker of potential adverse effects of novel pharmaceutical treatment. Only neural measures can effectively assess these possibilities and thus studying these processes in NPC patients before and after treatment could greatly benefit the community. Additionally, the portability of our EEG system and the low cost of our measures (in terms of time, money, and invasiveness) make it easily deployable at our lab and on the road, reducing the burden on patients and families. Although we will invite participants to our lab, we will also bring the lab to them -- at NIH and beyond. Further, this project will also clinically characterize the cognitive profile of all NPC participants through neuropsychological testing -- using measures of verbal intelligence, problem solving, abstract thinking, and vocabulary, as well as assessments of receptive and expressive language. This is of benefit to the community since these have not been comprehensively described in the literature.