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Project Title: Developing Neurophysiological Outcome Measures for Treatment Assessment in Niemann-Pick Disease Type C

LAY SUMMARY

Over the past 6 months our lab has been working on developing brain measures that can be used to track disease progression and treatment efficacy in Niemann-Pick Type C. We have been looking at tried-and-true cognitive neuroscience measures aimed at testing basic sensory processing and multisensory integration. To do this we use behavioral tasks and scalp-recorded electroencephalography (EEG). The EEG measures the brain's automatic response to sensory stimuli -- in our case, we use visual and auditory stimuli. Basic sensory processing is analyzed in the form of evoked potentials, which represent the brain's activity that is time locked to the sensory stimulus and filtered for noise/random activity. Multisensory integration represents the brain's ability to combine sensory information from different modalities to produce something that is above-and-beyond what either modality can do independently. This occurs, for instance, when we combine auditory signals from spoken words with visual signals from mouth and face movements to produce speech or when we combine visual and vestibular signals to achieve balance. The brain's ability to efficiently combine sensory signals from these far-away brain areas follows a strict developmental timecourse and necessarily relies on the integrity of connectivity within the brain. Based on behavioral and EEG data from 3 initial participants we hypothesized that: 1. Multisensory integration would be impaired in NPC, and 2. Basic auditory evoked potentials would be atypical in NPC (even in the absence of hearing loss).

Behavioral findings of multisensory integration showed an atypical pattern with 3 NPC boys failing to show an expected speeding up suggestive of multisensory integration in a reaction time task where the participant is asked to press a button to an auditory, a visual, or a multisensory (audio-visual) cue. Since this finding, we have collected EEG data from these 3 participants and an additional 8 participants while performing the same button-press task. These patients fall across a wide age spectrum, from barely 4 years of age to adulthood. We are currently compiling normative EEG data from age-matched controls to understand if, as in the behavioral findings, in this larger sample, using direct brain measures we see abnormal multisensory integration. Further testing and analysis is needed as participants in our sample are on differing medication, have varied disease onset, and length of diagnosis. We intend on collecting data from natural history participants to try and tease apart the effects of: 1. cyclodextrin, 2. age, and 3. Disease length on multisensory integration. We also have repeated EEG measures on 2 patients undergoing the cyclodextrin trial and 1 receiving cyclodextrin for compassionate use.

An interesting, and more developed, line of investigation concerns auditory processing in NPC. In EEG data collected from an initial 2, 14 year-old NPC males a prominent auditory response slowing down was noted in the patients, as compared to age and gender matched neurotypical controls. This delay in the auditory response might indicate compromised conduction in the brain. Such delays in brain responses representing simple sensory stimuli have also been noted in patients with disorders such as multiple sclerosis, where de-myelination of neurons is a prominent feature. Myelin insulates the axons of neurons and serves to speed up signal conduction. Cholesterol is an important component of myelin and myelination has been shown to be compromised in animal models of NPC. In our now larger more heterogeneous sample, we have found supporting evidence for the slowing of auditory cortical responses described above. It is important to note that this delay was present in all patient groups examined (4 year old, 9-11 year olds, 14 year olds, and adults). Importantly, the delay was noted even in patients not experiencing any clinical hearing loss or hearing deficits. A hearing screen was performed on the patients who visited our lab. Some data was acquired from patients at the NNPDF family conference where hearing accessed via self-report and/or parent/guardian report on a medical, developmental and psychiatric screener. Most family members report regular physician visits in which hearing is assessed. Further, even when hearing was not intact, no patient had reported any hearing loss for the frequency of the tones stimuli used in the experiment.

Questions still remain as to whether multisensory integration develops and then degrades in NPC or if the process never quite reaches healthy levels. Additionally, natural progression of altered cortical responses in NPC is still unclear, although the evidence seems to suggest an "auditory slowing" even in the youngest and less severely affected patients. The effects of cyclodextrin or other treatment on this measure and how this contributes to higher-order processes still requires further study. We will be on-site at NIH to collect follow-up data in June and July from 4 patients at various stages of the cyclodextrin trial -- 3 of which we have pre-cyclo data on. During this time we also intend on collecting follow-up data from an adult participant who, since her last session with us, has enrolled in the Vorinostat trial at NIH. We also hope to obtain disease severity measures for everyone in sample as well as full audiometry testing. Lastly, we intend on further exploring the relationship between our EEG measures, clinical measures, and neuropsychological measures (e.g. IQ and speech/language indices). The measures being examined in this project may provide important insight and have strong clinical implications as we directly assay brain function, in a quick and non-invasive way. This can provide an objective marker against which neurocognitive function can be compared. Most significantly though, changes in these measures would necessarily come "online" before changes in behavior or other clinical measures, as the any new/difference behavioral outcome follows learning/deterioration that occurs in the brain. As such, this experiment holds promise in aiding to develop markers for disease progression and against which to test treatment efficacy or toxicity, as they are closer to neural mechanisms which are being altered by disease and treatment agents.