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

LAY SUMMARY

Over the past year 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.

In our first investigation we used a button-press task to uncover a previously unreported multisensory integration deficit in children with NPC (two 13 year olds and one 11 year old). Participants with NPC failed to show the expected multisensory speeding up, to an audio-visual cue, as compared to a unisensory cue (audio alone or visual alone). This provided us with behavioral evidence for altered connectivity in the brain. However, the patient age range in our original study posed a significant limitation on our ability to interpret these findings. This is because inter-sensory connections, such as those between auditory and visual areas of the brain, start developing very early in life, strengthen across childhood, and do not fully stabilize until late adolescence. Therefore one possible explanation for the absence of multisensory-facilitation in these younger patients could be a maturational delay. In this scenario, multisensory integration would be developing at a slower rate and would be seen in older patients. In this update we explore this alternative by examining data from NPC adults.

To do so we collected EEG and behavioral data from 9 adults diagnosed with NPC. Two of these adults were unable to consistently perform the behavioral task, and are subsequently excluded from the initial round of analyses. Following the same procedures employed in the younger patients we examined multisensory behavioral facilitation in these late-onset adult patients and compared them to a cohort of 34 neurotypical adults. Even though the adult

participants with NPC were able to perform our task much better than the children with NPC (i.e. more hits), they nonetheless showed the same multisensory integration deficits. In fact, the speeding of reaction times measured in 6 of the 7 patients who were able to perform the task fell outside of the normal spread of values reported in healthy adults. The single patient that did fall within the normative spread was far below the average gain in the control group and was also clinically the least severely affected in our sample. Overall, the behavioral results provide further evidence for altered connectivity in the brain in NPC.

Given these new findings, we may conclude that multisensory integration development in NPC is not simply lagging, as it does not “catch-up” given additional developmental time. Longitudinal follow-up of NPC children from a much earlier age than most of our pediatric sample would be needed to help to determine whether this lack of multisensory facilitation is the result of neurodegenation or a completely atypical development where the process never fully matures. Based on the age of our adult patient sample (19-35 years old), the fact that they were all late on-set NPC, and that clinically they are less severely impacted than the children showing deficits, we would hypothesize that the development of multisensory integration and connectivity in NPC does not follow the typical timecourse and never fully matures.

The EEG data, which provides us with a direct brain measure of sensory processing, was also atypical in the adults with NPC. Previously we suggested that auditory processing, in the form of auditory evoked potentials was altered in NPC across age and clinical severity. This new adult data shows altered processing in the evoked responses recorded across visual, auditory, and multisensory areas of the brain. Specifically we note decreased activation and a slight slowing down of visual and auditory responses. We also note an immature pattern of auditory activation in the NPC patients, similar to what is seen in younger neurotypical controls. Lastly, only in the adult control group do we see the expected increase in the brain’s response to the multisensory stimulus as compared to a modeled audio plus visual stimulus. Whereas for the NPC group the multisensory response itself is drastically attenuated and there is no noticeable difference in the size of multisensory responses as compared to the modeled audio+visual brain response.

An advantage of these EEG markers is that they represent the brain’s automatic processing of environmental stimuli and as such are present even if the participant cannot perform the task at hand. Furthermore, these measures are obtained non-invasively and relatively quickly. Next we will focus our attention to the EEG data from kids and those who were unable to perform the behavioral task. We will also continue to explore these sensory processing delays, with our next set of analysis closely characterizing the individual patient data (as opposed to group) as well as examining EEG data from a second experiment focusing exclusively on auditory processing. Additionally, we hope to explore any relationship between these brain measures and medication treatment, disease onset, and symptom severity.

To conclude, the measures being examined in this project may provide important insight and have strong clinical implications as we are directly assaying brain function. 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 any new behavior (be it adaptive or detrimental) must be preceded by a change in the brain (e.g. learning or deterioration). 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.