**Neurophysiological explorations of basic sensory and higher-order cognitive processing in children and adults with Cystinosis (CTNS gene mutations).**

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In this talk, I will describe a series of studies performed in both children and adults with Cystinosis, where high-density electrophysiological (EEG) scalp recordings were used to assess the neurophysiology of basic auditory and visual sensory function, auditory sensory memory functioning, and higher-order cognitive control processes. Cognitive processes specifically addressed were response inhibition and error processing. **A)** In the first of these studies, we presented simple auditory tone pips through headphones to children with cystinosis (N=22) and age-matched controls (N=24) while they watched a silent movie and ignored these sounds. Occasionally, the simple series of regularly repeating tones was interrupted by a tone that was slightly longer in duration. Even when people ignore these auditory inputs, the brain produces neurophysiological responses, and whenever one of the occasional longer duration tones occurs, the auditory cortex produces a differential response known as the mismatch negativity (MMN), which shows that the system is sensitive to these auditory deviations. This is a very simple way to assess the integrity of neural processing for auditory inputs and to see if the auditory sensory memory system is functioning normally. The results showed that the neural responses to the basic tone stimuli were highly typical in children with cystinosis, but we did see a weakness in generating the MMN response to the deviant tones under conditions that were designed to tax the auditory sensory memory system, suggesting mild-to-moderate sensory memory impairment in children and adolescents diagnosed with Cystinosis 1. **B)** We conducted a near-identical study in adults with cystinosis (N=15) with highly similar results to those we observed in children. That is, adults with cystinosis produced highly similar neurophysiological responses to the regularly repeating tones to those we observed in controls, suggesting intact early auditory cortical processing. However, significantly reduced MMNs were again seen under conditions where the auditory sensory memory system was taxed, suggesting mild-to-moderate changes in auditory sensory memory and attentional processing. Parallel cognitive testing also revealed lower scores on verbal IQ and perceptual reasoning in cystinosis 2. **C)** In this ongoing study, participants with cystinosis, both children and adults (N=37) engaged in a so-called response inhibition task whereby they were instructed to press a button upon presentation of novel pictorial stimuli (“Go” trials), but to withhold/inhibit the button press if the same stimulus was presented twice in a row (“NoGo” trials). Using this paradigm, we can assess the basic visual sensory processing of the pictorial stimuli as well as the neural responses associated with response inhibitions and with the making of errors (i.e. pressing the button to a NoGo stimulus). A number of interesting findings were observed. First, individuals with cystinosis showed a surprising increase in the amplitude of their early visual sensory responses, which may be an indication of some hypersensitivity to visual inputs. They also found it more difficult to perform this task, making more errors while also responding more slowly, and this was accompanied by clear differences in response-inhibition related neurophysiological responses. Lastly, individuals with cystinosis showed a reduction in neural responses associated with awareness of making an error – that is, they did not register the occasions they made errors as effectively as controls 3.

Overall, electrophysiological assessments of sensory and cognitive functioning in cystinosis across the age span, revealed mild-to-moderate deficits in this population. These electrophysiological techniques provide objective measures of neural functioning that may have excellent utility as biomarkers against which to test the efficacy of both pharmacological and other therapeutic interventions.

Works Cited

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3 Francisco, A. A., Foxe, J. J., Berruti, A. S., Horsthuis, D. J. & Molholm, S. (in preparation).