

Neural Functioning in Auditory and Visual Systems in Cystinosis: Linking Brain to Behavior

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The main goal of this project is to investigate the neural functioning of auditory and visual systems in children with cystinosis. By employing a non-invasive, children-friendly technique of event-related brain potentials (ERPs) we are examining auditory and visual perception, the strength and the breadth of auditory and visual spatial attention, and attentional orienting elicited by unexpected, novel events. All of the above-mentioned functions are important for the successful day-by-day functioning as well as academic performance in children and adults.

Our second main goal is to determine how, if at all, the observed neuro-functional abnormalities change with age. This information will help to understand the neural mechanisms of adult-onset cystinotic encephalopathy as well as will speak to the issue of early neuro-developmental insult vs. progressive brain injury as the pathogenesis of the disorder.

Our third main goal is to bridge the brain function and structure with cognitive and academic performance. We will correlate the ERP indices of brain function obtained in this project with structural brain measures obtained through an NIH grant awarded to Dr. Trauner, as well as cognitive measures obtained in the project "Academic Functioning in Cystinosis" funded by the Cystinosis Research Foundation.

The completed study will include 40 individuals diagnosed with infantile nephropathic cystinosis and 40 healthy age, gender, and SES matched control participants, age 6 years and above.

During funding period 03.16.07 - 03.05.08, the following progress has been made.

1. Subject recruitment

- We continue serious recruiting efforts of individuals with Cystinosis. To this end, a new collaboration regarding participant sharing has been established with Dr. R. Dohil's laboratory. We continue recruiting through the Cystinosis Research Network website as well as Dr. Trauner's laboratory. As a result, we are keeping with the projected timeline.

2. Data collection

- A group of young healthy adults comprising our normative data set has been collected and analyzed. The results show that our experimental design produces reliable indices of auditory and visual sensory, attentional, and executive functions.
- To date, we have collected data on auditory and visual ERP experiments from 14 individuals with Cystinosis, and by the end of March we will have tested 19 participants. This is roughly half of the proposed sample. This is 38 testing sessions.
- Data collection from typically developing control children is ongoing on an individual case-control matching basis. The controls are being matched on the

basis of gender, age, and SES. To date, we have tested 12 typical children and adults matched in this manner. This is 24 testing sessions. Five more, for the total of 17, will be tested by the end of March 2008.

3. Experimental Procedure and Data analysis

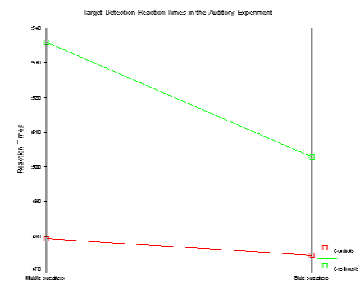
The study participants sat in a comfortable armchair while the EEG/ERP were recorded. Meanwhile, three types of stimuli were presented randomly at four different locations. In the visual experiment, those were four boxes drawn on the computer screen and in the auditory experiment, they were four speakers evenly spread out in front of a participant. The three stimulus types were frequent, “standard” stimuli, infrequent target stimuli, and varied, salient novel stimuli. The auditory stimuli were complex tones and the visual stimuli were shapes. Novels were more complex. The stimuli were presented in blocks of 400 stimuli. The participants had to attend to one pre-determined location during the duration of a block and to press a button in response to the target stimulus. They had to look directly in front of them at the fixation mark at all times. Attended location changed from block to block, for a total of 4 blocks per location. The EEG was cleaned from blink, motion, and electrical artifacts, segmented, and averaged by stimulus type. Behavioral response times to target stimuli and accuracy were also determined.

All behavioral and electrophysiological data that has been collected has been analyzed. The first preliminary results are illustrated in the figures below.

4. Results

Behavior. No group differences in Target Detection accuracy were found in the visual task. However, in the auditory task, the Cystinosis group performed significantly poorer than their controls ($p < .05$). Almost half of participants with Cystinosis had severe difficulty localizing sounds.

Interestingly, in both modalities, Reaction Times were longer for the central than peripheral targets, and there was a strong tendency for this to be more pronounced in the Cystinosis group (Group x Location interaction at the level of $p < .1$; see Chart).



Visual ERPs

Overall, ERP amplitudes were larger in the Cystinosis group than in the controls. This was entirely unexpected. However, this finding seems to be related to general changes in neural and extra-cerebral tissues rather than to be specific to brain function.

- At the level of visual *sensory processing*, we found enhanced P2 peak in the Cystinosis group (Figure 1, top panel). This finding is frequent in neuro-developmental populations. However, the Cystinosis group showed an appropriate enhancement of sensory response upon spatial attention as

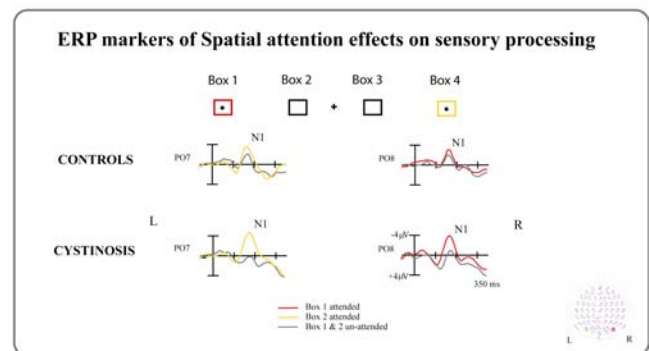
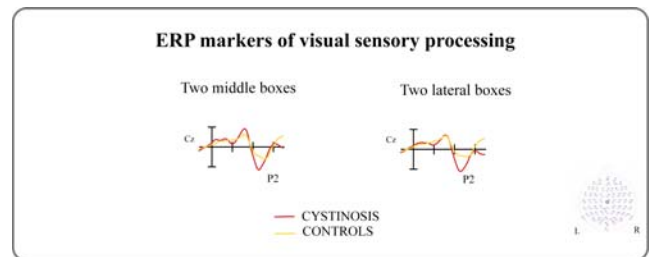


Figure 1

shown by the enhancement of the N1 peak at the attended locations (Figure 1, bottom panel).

- At the level of *target detection*, the Cystinosis group showed a broader spread of visuo-spatial attentional preference. While the controls showed a clear right-hemi-field facilitation (the target P300 response peaked earlier, and was larger in amplitude, for the stimuli that were presented on the right side), in the Cystinosis group this included right-sided as well as a left middle location (Figure 2).

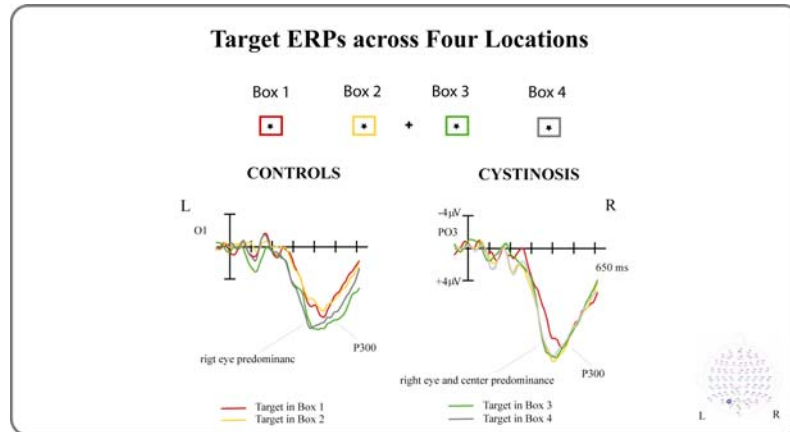


Figure 2

- Finally, response to novel stimuli, as indexed by the fronto-central Negative Component (Nc) was diminished in the Cystinosis group and, importantly, showed no spatial selectivity (Figure 3).

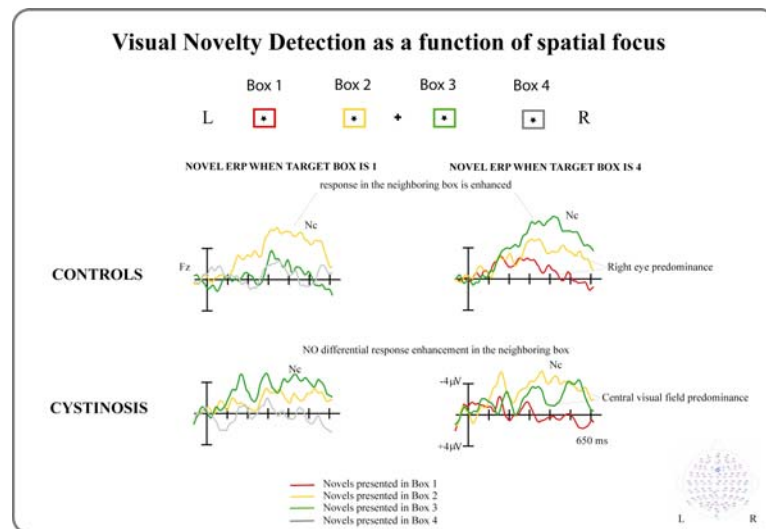
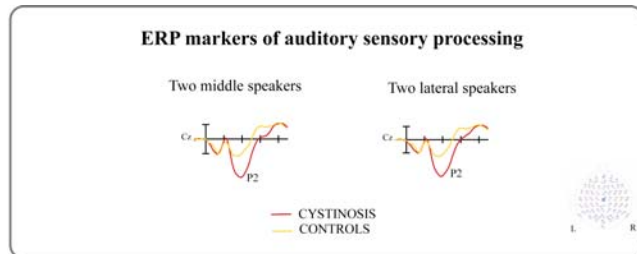


Figure 3

Auditory ERPs

- As in the visual modality, in the auditory modality the Cystinosis group showed strongly enhanced sensory P2 peak (Figure 4, top panel).
- As can be seen in the bottom panel of Figure 4, Spatial Attention effects differed substantially between the groups. PN is a Processing Negativity that indexes attention effects. It is assessed by comparing attended (but not responded to) and unattended stimuli. It has two components, the early component arising in the auditory cortex and the late component arising in the frontal cortex. Our data demonstrate that the early component is elicited in the Cystinosis group. However, the late PN component is either delayed, diminished in amplitude, or absent. These differences were more pronounced with attention to peripheral speakers.



- Due to the low *target detection* rate in the auditory modality, brain's responses to *targets* in the Cystinosis group were noisy and difficult to interpret. This should improve once more participants have been tested. However, an overall pattern of results seems to indicate that in this group, target detection is more efficient in the middle locations than in peripheral locations. No such differences were found in the control group.

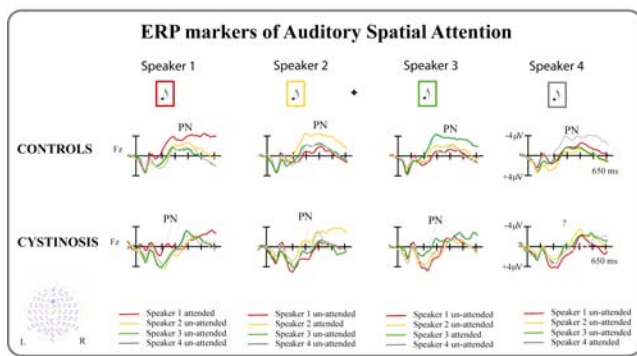


Figure 4

- The auditory *novelty responses* can manifest either as visual Nc (in younger children) or as a novelty P3 response. Novelty P3 reflects attentional orienting to potentially relevant sounds occurring outside the attentional focus while the Nc may reflect conscious processing of stimuli that triggered orienting. Novelty P3 was more consistent in our data. Further, it was elicited when the novel stimuli occurred in the peripheral speakers, indicating that they were more distracting when they occurred at locations more spatially distant from the attentional focus. In contrast to visual modality in which Cystinosis group showed abnormal novelty detection, in the auditory modality group differences were rather subtle (Figure 5). When the Nc was elicited, in the controls it showed location-dependent amplitude gradient. This pattern was less consistent in cystinosis

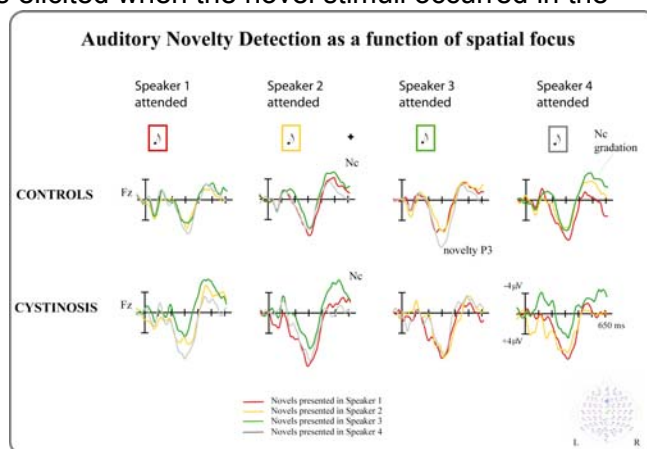


Figure 5

data.

5. Significance of findings.

Behavioral data indicate that, overall, individuals with Cystinosis have difficulties with perceptual localization. This is more severe in the auditory modality.

Electrophysiological finding of overall larger ERP amplitudes in the Cystinosis group may be caused by function non-specific factors such as increased water retention and/or thinner scalp bones due to renal osteodystrophy.

In addition, function-specific electrophysiological differences between the Cystinosis and control groups were found at all levels processing, with those at the attentional level predominating. The sensory differences were similar across the auditory and visual modalities and consisted of enlarged P2 peak, a frequent finding in neuro-developmental populations. Although the significance of this finding is not entirely clear, it has been associated with increased stimulus feature non-specific sensory arousal, potentially leading to disruption of stimulus feature specific encoding and excessive distractibility. Spatial attention effects differed between the auditory and visual modalities. In the Cystinosis group, spatial selection was intact in the visual modality and deviant in the auditory modality. In general, spatial attention and selection is more important in visual than auditory modality since we attend where we look at. In contrast, auditory localization abilities are often complemented by vision. Therefore, auditory localization might be a more challenging ability in general and, as evidenced by behavioral and ERP data, for the individuals with Cystinosis.

Voluntary stimulus parsing appears to be least affected in this disorder; however, subtle spatial attention differences are a possibility.

Finally, dampened response to visual novelty is striking. Although the neural generators of the Nc response are not known, its frontal predominance strongly suggests frontal lobe involvement. The auditory novelty P3 showed a more typical pattern. This response is strongly driven by afferent thalamo-cortical projections and has frontal, parietal, and temporal lobe generators.

Summarizing, our findings indicate that individuals with cystinosis have subtle electrophysiological deficits, with more challenging, higher-level functioning being affected the most. This includes auditory localization and visual novelty detection.

6. Plans for the next funding period.

- We will continue with data collection. We are hopeful that we will have recruited and tested 2/3 of projected participants by the end of the next funding period.
- We will continue analyzing visual and auditory behavioral and ERP data obtained from typical children as well as children and adults with Cystinosis. The focus will be to clarify how behavioral and brain responses change with age. Is there an age-related decline in cognitive functions due to cystinosis?
- We will attempt to identify individuals with late-onset cystinotic encephalopathy and examine their brain response pattern.
- In collaboration with Dr. Trauners' lab, we will begin compiling behavioral and structural MRI data sets of the participants tested with ERPs with the goal of examining relationships between behavior, brain function, and brain structure.