



Impaired auditory sensory memory in Cystinosis despite typical sensory processing: A high-density electrical mapping study of the mismatch negativity (MMN)

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ABSTRACT

Cystinosis, a genetic rare disease characterized by cystine accumulation and crystallization, results in significant damage in a multitude of tissues and organs, such as the kidney, thyroid, eye, and brain. While Cystinosis' impact on brain function is relatively mild compared to its effects on other organs, the increased lifespan of this population and thus potential for productive societal contributions have led to increased interest on the effects on brain function. Nevertheless, and despite some evidence of structural brain differences, the neural impact of the mutation is still not well characterized. Here, using a passive duration oddball paradigm (with different stimulus onset asynchronies (SOAs), representing different levels of demand on memory) and high-density electrophysiology, we tested basic auditory processing in a group of 22 children and adolescents diagnosed with Cystinosis (age range: 6-17 years old) and in neurotypical age-matched controls ($N = 24$). We examined whether the N1 and mismatch negativity (MMN) significantly differed between the groups and if those neural measures correlated with verbal and non-verbal IQ. Individuals diagnosed with Cystinosis presented *similar* N1 responses to their age-matched peers, indicating typical basic auditory processing in this population. However, whereas both groups showed similar MMN responses for the shortest (450 ms) SOA, suggesting intact change detection and sensory memory, individuals diagnosed with Cystinosis presented clearly reduced responses for the longer (900 ms and 1800 ms) SOAs. This could indicate reduced duration auditory sensory memory traces, and thus sensory memory impairment, in children and adolescents diagnosed with Cystinosis. Future work addressing other aspects of sensory and working memory is needed to understand the underlying bases of the differences described here, and their implication for higher order processing.

1. Introduction

Cystinosis, caused by bi-allelic mutations in the 17p13.2-located CTNS gene (Town et al., 1998), is an autosomal recessive disorder with an incidence of approximately one in 100,000 to 200,000 live births (Gahl et al., 2009). Though over 100 mutations have been identified, the most common is a 57-kb deletion (Levtchenko et al., 2014; Shotelersuk et al., 1998). CTNS encodes cystinosin, a lysosomal cystine-proton co-transporter. Its mutation results in excessive cellular cystine storage (Gahl et al., 1982; Jonas et al., 1982), which appears to cascade into deregulation of endocytosis and cell signaling processes (Ivanova et al., 2014). Moreover, intralysosomal cystine crystallizes, triggering significant damage in a multitude of tissues and organs

(Gahl and Kaiser-Kupfer, 1987).

The first manifestations of the disease emerge at around six months of age (Gahl, 1986), with typical development being described until then. Amid other possible complications, CTNS mutations often result in end-stage renal disease, hypothyroidism, and retinopathy (Vogel et al., 1990), at least in Infantile Nephropathic Cystinosis, the classic and more prevalent form of the disorder (Schneider et al., 1990), and the one addressed in the present study. Despite the undoubtedly multi-systemic nature of the disease (Elmonem et al., 2016), effectively treating the associated renal complications was the obvious focus until approximately 20 years ago. The emergence of renal replacement therapy and the development of cysteamine, a cystine-depleting agent which slows the progression of renal failure and protects extra-renal

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organs (van Rijssel et al., 2019), greatly increased life expectancy in this population (now above 50 years (Ivanova et al., 2014)), and allowed for a more prominent focus on the characterization of other aspects of the disease, such as the neurological, cognitive, and behavioral sequelae.

Human studies have since shown abnormally high levels of cystine in various brain regions (Levine and Paparo, 1982; Theodoropoulos et al., 1993; Vogel et al., 1990), and long-term adverse effects of Cystinosis on the central nervous system (Niemic et al., 2012). Furthermore, different neurological findings have been described, which include subcortical and cortical atrophy, Chiari I malformation, white matter abnormalities, and atypical electrophysiological (EEG) activity (Bava et al., 2010; Cochat et al., 1986; Ehrich et al., 1979; Fink et al., 1989; Rao et al., 2015). Cognitively, individuals diagnosed with Cystinosis often present intelligence quotients (IQ) in the typical range, but lower IQs have also been reported (Aly et al., 2014; Ulmer et al., 2009). A differential between non-verbal and verbal indices is consistently reported in this population, with the former being significantly lower than the latter (Frankel and Trauner, 2019; Spilkin et al., 2007; Ulmer et al., 2009). This pattern appears to emerge early in development and to persist throughout the lifespan (Scarvie et al., 1996; Trauner et al., 1988), regardless of age at treatment onset (Viltz and Trauner, 2013). Significant difficulties are observed in visual-motor, visual-spatial and visual memory skills, as well as executive function related abilities (Aly et al., 2014; Ballantyne et al., 2013; Besouw et al., 2010; Sathappan and Trauner, 2019; Viltz and Trauner, 2013), which may particularly hinder academic skills (Ballantyne et al., 1997). Motor deficits and fine motor incoordination have also been described (Trauner et al., 2007; Trauner et al., 2010; Ulmer et al., 2009). Some of these difficulties seem to be likewise present in unaffected heterozygous carriers of the cystinosis gene mutation (Sathappan and Trauner, 2019).

Despite compelling evidence that CTNS mutations are associated with structural brain differences and cognitive impairments, Cystinosis' impact on brain activity is still not well understood. High-density EEG, a non-invasive method that provides information at the millisecond scale, allows one to directly measure functional brain activity and thus reliably assess the integrity of neural function. The sparseness of studies in which EEG has been used to assess functional brain activity in Cystinosis is, thus, quite surprising. One case study looked at auditory and somatosensory evoked potentials in an adult female. Though no methodological details or specific result were included, typical neural activity was reported (Müller et al., 2008). A conference paper reported an enhanced auditory P2 for 14 individuals diagnosed with Cystinosis (age range: 6 to 52 years old), during a spatial localization task (Čeponiene et al., 2008). A more recent case study tested visual processing in two children with Cystinosis before and after kidney transplantation. Before transplantation (and during dialysis treatment), both children showed delayed and decreased early visual-evoked responses, when compared to their age-matched peers. Remarkably, both amplitude and latency measures normalized upon retest, two years after transplant (Ethier et al., 2012). In spite of the paucity of studies and the very small number of individuals tested to date, EEG measurements seem nonetheless to be sensitive to neuropathology in Cystinosis. Importantly, EEG and event-related potentials (ERPs) may be leveraged as outcome measures to assess the impact of treatment on brain function vis-à-vis neurophysiological integrity.

Therefore, here, to gain insight into potentially impaired neural function, we used high-density EEG to assay basic sensory processing in Cystinosis. We focused on early auditory sensory processing (the N1) and sensory memory (the mismatch negativity, MMN). The auditory N1 is the first prominent negative auditory-evoked potential (Näätänen and Picton, 1987), and reflects neural activity generated in and around primary auditory cortex (Giard et al., 1994; Leavitt et al., 2007). The MMN, in turn, operating at the sensory memory level, occurs when a repeating stimulus (the standard) in an auditory stream is replaced by a deviant stimulus: Regular aspects of consecutively presented standards

form a memory trace; violation of those regularities by a deviant induces the MMN (Näätänen and Winkler, 1999). Occurring 100 to 200 ms following the deviant event, the MMN is thought to reflect the neural processes underlying detection of a pattern violation and updating of a representation of a regularity in the auditory environment (Näätänen and Alho, 1995; Ritter et al., 1995; Ritter et al., 2002) (which is also consistent with a predictive coding interpretation of the MMN as described in (Stefanics et al., 2014)). To impose different levels of demand on the sensory memory system, the rate of presentation was parametrically varied. Additionally, we were interested in understanding how these neural measures related to cognitive function in Cystinosis. To this end and given the idiosyncratic pattern of IQ scores in Cystinosis, we queried the relationship between N1 and MMN and verbal and non-verbal IQ.

2. Materials and methods

2.1. Participants

Twenty-five participants diagnosed with Cystinosis (age range: 6-17 years old; $M = 11.08$; $SD = 2.55$) and twenty-eight neurotypical controls (NT) (age range: 6-17 years old; $M = 11.42$; $SD = 3.38$) were initially recruited. Exclusion criteria for the NT group included hearing problems, developmental and/or educational difficulties or delays, and neurological problems. Exclusionary criteria for the Cystinosis group included hearing difficulties and current neurological problems. Participants passed a hearing test (below 25dB HL for 500, 1000, 2000, 4000 Hz) performed on both ears using a Beltone Audiometer (Model 112). Four individuals diagnosed with Cystinosis were tested at an off-site location and, therefore, no hearing test was conducted. For these individuals, parents reported normal hearing and no history of hearing problems.

Four neurotypical controls presented high-average or superior verbal IQ scores, but borderline (≤ 80) non-verbal IQ scores and were therefore excluded from the final sample. Such discrepancies are, based on the Wechsler scales' critical values and index score discrepancies, statistically significant ($p < .05$) and occur in less than 5% of the neurotypical population. Due to illness on the scheduled day of testing, three individuals with Cystinosis were unable to perform the EEG tasks. Because those participants had traveled from out of town and, thus, could not be rescheduled, they were also excluded from the final sample. Twenty-two individuals diagnosed with Cystinosis and twenty-four neurotypical controls were part of the final sample.

All participants signed an informed consent approved by the Institutional Review Board of the Albert Einstein College of Medicine. Participants were monetarily compensated for their time. All aspects of the research conformed to the tenets of the Declaration of Helsinki.

2.2. Experimental Procedure and Stimuli

Testing occurred over a 2-day period and included a cognitive testing session (focused on measures of intelligence: Wechsler Abbreviated Scale of Intelligence (WASI-II); Wechsler, 1999) and an EEG recording session. The EEG paradigm reported here focused on auditory processing, utilizing a traditional duration-MMN oddball paradigm (Brima et al., 2019). Participants sat in a sound- and electrically-shielded booth (Industrial Acoustics Company Inc, Bronx, NY) and watched a muted movie of their choice on a laptop (Dell Latitude E6430 ATG or E5420M) while passively listening to regularly (85%) occurring standard tones interspersed with infrequently occurring deviant tones (15%). These tones had a frequency of 1000 Hz with a rise and fall time of 10 ms, and were presented at an intensity of 75dB SPL using a pair of Etymotic insert earphones (Etymotic Research, Inc., Elk Grove Village, IL, USA). Standard tones had a duration of 100 ms while deviant tones were 180 ms in duration. These tones were presented in a random oddball configuration (except that at least two standards

Table 1
Characterization of the NT and Cystinosis individuals included in the analyses: Age, gender, and IQ.

	NT	Cystinosis	t-test	MW/Wilcoxon	Cohen's d
Age	X = 11.71; SD = 3.38	X = 11.15; SD = 2.66	$t = 0.61, df = 41.89, p = .54$	$W = 262, p = 0.61$	$d = 0.18$
Gender	10 M, 14 F	9 M, 12 F	-	-	-
Verbal IQ	X = 111.54; SD = 9.85	X = 93.05; SD = 12.78	$t = 5.29, df = 35.33, p < .01$	$W = 425.5, p < .01$	$d = 1.62$
Perceptual Reasoning	X = 106.88; SD = 9.69	X = 86.70; SD = 12.40	$t = 5.92, df = 35.63, p < .01$	$W = 422, p < .01$	$d = 1.81$
IQ (full scale)	X = 109.92; SD = 7.49	X = 88.70; SD = 13.26	$t = 6.36, df = 28.78, p < .01$	$W = 445, p < .01$	$d = 1.97$
IQ: verbal vs p. reasoning					
NT			$t = -1.65, df = 23, p = .11$	$V = 72.5, p = .08$	$d = 0.48$
Cystinosis			$t = -2.75, df = 19, p < .05$	$V = 32.5, p < .05$	$d = 0.50$

preceded a deviant) to yield an MMN. In three blocked conditions, the stimulus onset asynchrony (SOA) was either 450 ms, 900 ms or 1800 ms. Each SOA was presented in blocks of 4 minutes long (counter-balanced across participants), composed of 500, 250 or 125 trials respectively. Participants were presented with 14 blocks (2*450 ms, 4*900 ms and 8*1800 ms), resulting in a possible 1000 trials (and 150 deviants) per SOA. For each of the SOA conditions, the presence and magnitude of the MMN was measured by comparing the event-related potentials (ERPs) to the standard and deviant stimuli. For the four individuals diagnosed with Cystinosis whose data were collected off-site, during a family meeting, the equipment was the same used for the remainder of the subjects, but cognitive and EEG data collections were carried out in two regular rooms. An attempt was made to keep the lighting and sound conditions identical to the ones experienced in the lab setting.

2.3. Data acquisition and analysis

EEG data were acquired continuously at a sampling rate of 512 Hz from 71 locations using 64 scalp electrodes mounted on an elastic cap and seven external channels (mastoids, temples, and nasion) (Active 2 system; Biosemi[™], The Netherlands; 10-20 montage). Preprocessing was done using the EEGLAB (version 14.1.1; Delorme & Makeig, 2004) toolbox for MATLAB (version 2017a; MathWorks, Natick, MA). Data were downsampled to 256 Hz, re-referenced to TP8 and filtered using a 1 Hz high pass filter (0.5 Hz transition bandwidth, filter order 1690) and a 45 Hz low pass filter (5 Hz transition bandwidth, filter order 152). Both were zero-phase Hamming windowed sinc FIR filters. Bad channels were automatically detected based on kurtosis measures and rejected after visual confirmation (number of channels excluded: NT: $M = 3.71, SD = 1.96$; CYS: $M = 4.76, SD = 2.19$). Artifacts were removed by running an Independent Component Analysis (ICA) to exclude components accounting for motor artifacts, eye blinks, saccades, and bad channels. After ICA, the previously excluded channels were interpolated, using the spherical spline method. Data were segmented into epochs of -100 ms to 400 ms using a baseline of -100 ms to 0 ms. These epochs went through an artifact detection algorithm (moving window peak-to-peak threshold at 120 μ V). Those subjects with trial rejection percentages above 30% were excluded, which was the case for one subject from the Cystinosis group. No significant differences were found between number of trials included in the analyses per group (Cystinosis group: trial rejection = 7.28%; NT group: trial rejection = 4.93%; $t = -1.16, df = 37.55, p = .25$).

The definition of the N1 and the MMN windows was based on the typical time of occurrence of the N1 and duration-MMN components, and on visual confirmation that amplitudes were maximal in these intervals. Mean amplitude for the N1 was measured between 80 and 130 ms. The MMN is the difference between deviants and standards and was here measured between 200 and 250 ms (100 to 150 ms post deviance onset). Using the *bin operator* function in ERPLAB (Lopez-Calderon and Luck, 2014), individual difference waves were created and then averaged per group. Amplitude measures were taken at FCz, where signal was at its maximum for both responses for both groups. These

amplitudes were used for between-groups statistics and correlations. Correlation analyses were computed across and between groups per component (N1 or MMN). Pearson correlations were performed, given that the distributions of the variables included in the analyses were not significantly different from the normal distribution, as tested by the *Shapiro-Wilks* Normality test (Royston, 1982), implemented using the *shapiro.test* function of the *stats* package in R (RCoreTeam, 2014) (N1 amplitude: $W = .96, p = .14$; MMN amplitude: $W = .99, p = .92$; verbal IQ: $W = .97, p = .42$; perceptual reasoning: $W = .96, p = .10$). All *p-values* (from *post-hoc* tests and correlations) were submitted to *Holm-Bonferroni* corrections for multiple comparisons (Holm, 1979), using the *p.adjust* of the *stats* package in R (RCoreTeam, 2014).

3. Results

Table 1 shows a summary of the included participants' demographics and performance on the WASI-II. Two-sample independent-means *t* tests were used to test for between-group differences. In cases in which the assumption of the homogeneity of variances was violated, *Welch* corrections were applied to adjust the degrees of freedom. Paired *t* tests were used to test for within-group differences. *Mann-Whitney U* and *Wilcoxon signed-rank* tests are also presented for comparison. The IQ statistical analyses revealed significant differences between the groups in all three sub-scales, with individuals diagnosed with Cystinosis showing lower IQ scores on verbal IQ (with five individuals with Cystinosis scoring lower than 85 points (one standard deviation from the normed mean of 100)), perceptual reasoning (with 13 individuals with Cystinosis scoring lower than 85 points and one lower than 70 points (two standard deviations from the normed mean) and full scale IQ (with 10 individuals with Cystinosis scoring lower than 85 points). The individuals diagnosed with Cystinosis ($M_{\text{difference}} = -7.86, SD_{\text{difference}} = 13.40$; 9 subjects with a point difference $\geq \pm 9$), but not the neurotypical controls ($M_{\text{difference}} = -3.71, SD_{\text{difference}} = 14.30$; 11 subjects with a point difference $\geq \pm 9$), presented significantly lower perceptual reasoning scores, when compared to verbal IQ.

Fig. 1 shows the averaged ERPs and topographies for the time windows of interest (N1 and MMN) per SOA and by group.

Mixed-effects models were implemented to analyze the EEG data, using the *lmer* function in the *lme4* package (Bates et al., 2014) in R (Version 3.1.2, (RCoreTeam, 2014)). The models were run separately for the N1 and the MMN time windows. Mean amplitude at FCz was the numeric dependent variable. For the N1, only standard amplitudes were considered. For the MMN, mean amplitude referred to amplitude of the difference between standards and deviants. Group (NT = -0.5, Cystinosis = 0.5) was a contrast-coded fixed factor, and SOA was a numeric fixed factor. Subject and SOA were random factors. While the inclusion of SOA as a fixed effect measures the overall effect of SOA on amplitude, its inclusion as a random effect aims to account for SOA variance and the impact of that variance on the fixed effects and on the fit of the model. Models were fit using the maximum likelihood criterion. *P* values were estimated using Satterthwaite approximations (Satterthwaite, 1946).

As expected, in the N1 time window there was a significant effect of

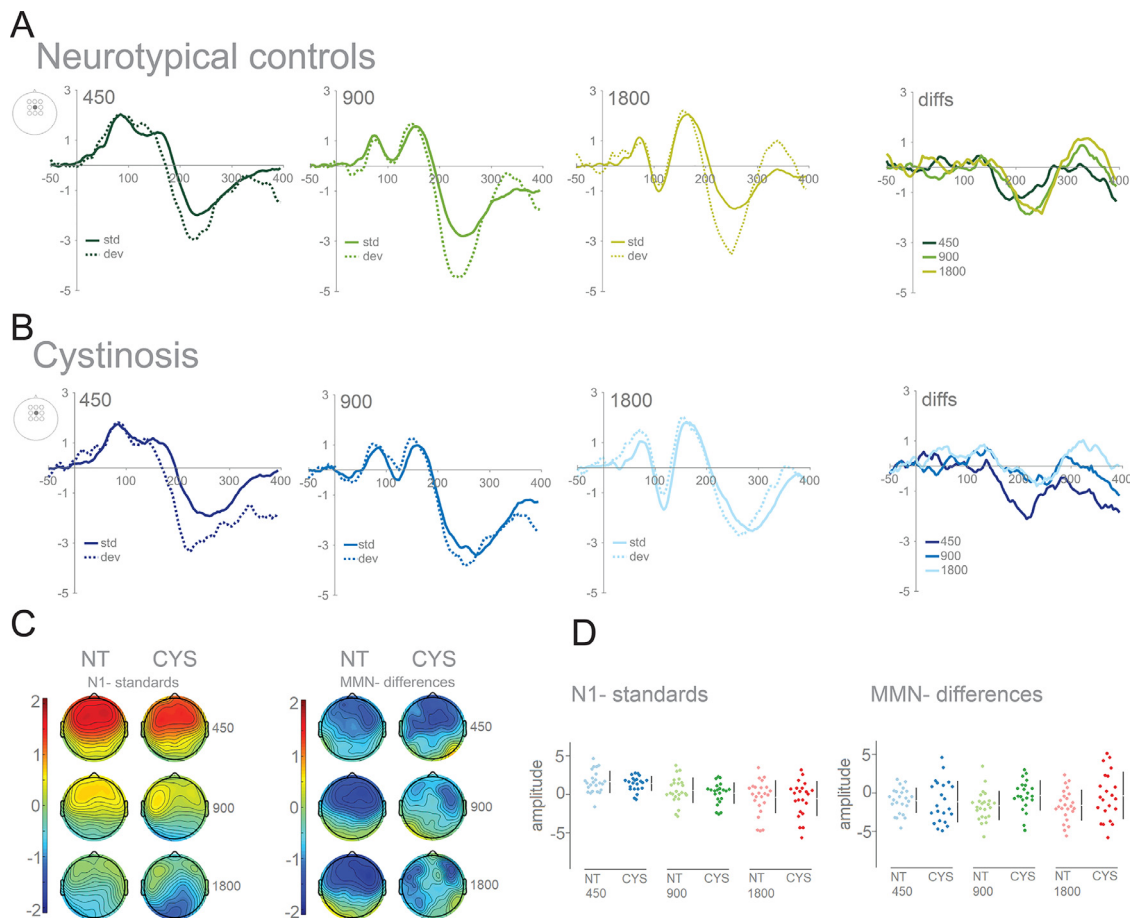


Fig. 1. Panel A: Averaged ERPs and topographies per SOA for the NT group at FCz (fourth plot labeled as *diffs* shows MMN, i.e., differences between standards and deviants); Panel B: Averaged ERPs and topographies per SOA for the Cystinosis group at FCz (fourth plot labeled as *diffs* shows MMN, i.e., differences between standards and deviants); Panel C: Topographies for the N1 (standards only) and the MMN time windows, organized from the shorter (450 ms) to the longer (1800 ms) SOA; Panel D: Raw amplitude values are plotted to show distribution. Summary measurements are displayed as gapped lines to the right of each plot: Mean is indicated as a gap in the lines, vertical lines represent standard deviation error bars.

SOA, with both 900 ms ($\beta = -1.20$, $SE = 0.07$, $p < .001$) and 1800 ms ($\beta = -2.02$, $SE = 0.07$, $p < .001$) conditions eliciting more negative responses than the shortest SOA (450 ms). No effect of group or interaction between group and SOA was found. As can be appreciated in [Figure 2](#), no significant correlations were found with either verbal IQ ($r = .24$, $p = .11$; NT: $r = .26$, $p = .22$; Cystinosis: $r = .25$, $p = .28$) ([Fig. 2A](#)) or perceptual reasoning ($r = .04$, $p = .82$; NT: $r = .03$, $p = .89$; Cystinosis: $r = -.07$, $p = .75$) ([Fig. 2B](#)).

In the MMN time window, there was a significant interaction between group and SOA, with the difference between 450 ms and 900 ms ($\beta = 1.86$, $SE = 0.18$, $p < .01$) and between 450 ms and 1800 ms ($\beta = 1.30$, $SE = 0.18$, $p < .01$) being larger for the individuals diagnosed with Cystinosis than for the neurotypical controls. *Post-hoc* analyses revealed that this was due to significantly decreased responses for the 900 ms and 1800 ms SOAs in individuals diagnosed with Cystinosis, when compared to the neurotypical controls ($t = -7.54$, $df = 567.04$, $p < .01$); ($t = -4.54$, $df = 481.59$, $p < .01$). As for N1, no significant correlations were found with either verbal IQ ($r = -.07$, $p = .64$; NT: $r = -.15$, $p = .48$; Cystinosis: $r = .24$, $p = .29$) ([Fig. 2C](#)) or perceptual reasoning ($r = -.19$, $p = .22$; NT: $r = -.26$, $p = .21$; Cystinosis: $r = .04$, $p = .87$) ([Fig. 2D](#)).

4. Discussion

We used high-density EEG and a passive oddball paradigm to characterize early auditory sensory processing and sensory memory in a

sample of children and adolescents with Cystinosis. Additionally, we measured the associations between auditory brain function and verbal and non-verbal IQ.

No differences were found between the groups in the auditory N1, suggesting that sensory transmission through the auditory system is largely intact in individuals with Cystinosis. This is in accordance with preliminary data from our lab showing maintained auditory processing in the context of a multisensory task in a modest sample of individuals with Cystinosis ([Andrade et al., 2016](#)). Though enhanced auditory potentials have been described for this population ([Čeponienc et al., 2008](#)), such differences were observed in a later, functionally distinct component (P2), in a sample with a significantly wider range of ages, and during a task focused on spatial selective attention. As can be appreciated in [Fig. 1](#), our data do not support the presence of an enhanced P2 in the current sample (450 ms- NT: $M = 1.22$, $SD = 0.89$; CYS: $M = 0.98$, $SD = 0.89$; $p = .74$; 900 ms- NT: $M = 1.33$, $SD = 1.13$; CYS: $M = 0.58$, $SD = 1.42$; $p = .18$; 1800 ms- NT: $M = 1.47$, $SD = 1.58$; CYS: $M = 1.04$, $SD = 1.61$; $p = .74$). Further, here, N1 was shown to modulate as a function of SOA in both Cystinosis and neurotypical control groups. This has been consistently described in the literature for the neurotypical population ([Teder et al., 1993](#)) and is often explained by one of two (non-exclusive) alternatives: habituation ([Özemesi et al., 2000](#); [Thompson and Spences, 1966](#)) or refractoriness ([Budd et al., 1998](#); [Tremblay et al., 2004](#)). Our findings therefore indicate highly typical auditory sensory response properties in Cystinosis.

In the MMN time window, significantly decreased responses were

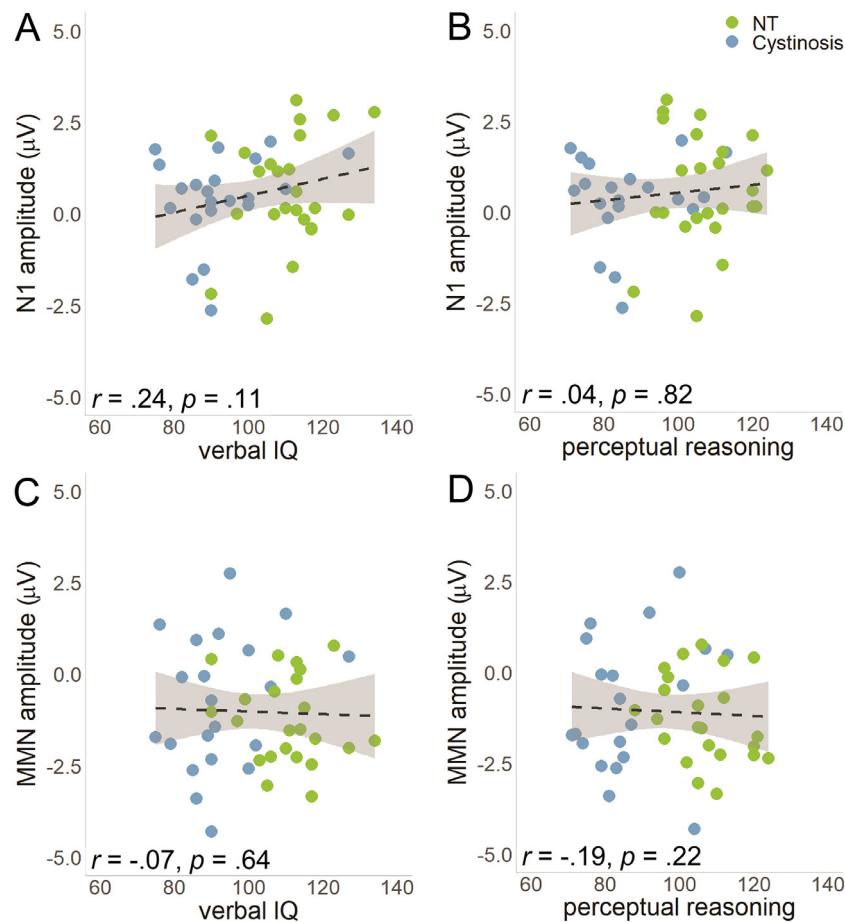


Fig. 2. Pearson correlations between N1 amplitude and verbal IQ (panel A) and perceptual reasoning (panel B) and between MMN amplitude and verbal IQ (panel C) and perceptual reasoning (panel D).

found in the Cystinosis group for the two longer SOAs, whereas a robust MMN was elicited for the shortest SOA. Previous work from our lab using this same MMN paradigm showed that increasing SOA similarly led to diminution of the MMN in Rett Syndrome (Brima et al., 2019), such that the MMN was no longer detectable at the longer SOAs. This was taken to index weakened maintenance of the memory trace in Rett. That differences between the groups were here, likewise, only observed for the longer SOAs, suggests that Cystinosis (at least during childhood and adolescence) might be characterized by deficits in the maintenance of short term auditory sensory memory (Bartha-Doering et al., 2015).

An impairment in auditory sensory memory (a preattentive memory system that allows an individual to retain traces of sensory information after the termination of the original stimulus (Cowan, 1999)) could impact subsequent processing in working memory (Bonetti et al., 2018), a conscious cognitive system responsible for the temporary holding, processing, and manipulation of information (Baddeley, 1992). Indeed, despite being somewhat separate processes with unique characteristics, auditory sensory memory and working memory seem to be associated in neurotypical controls, with those individuals who show better performance in working memory tasks, presenting enhanced MMN responses (Bonetti et al., 2018); and in clinical populations, with impaired auditory MMN being associated with deficits in working memory (Ahveninen et al., 1999; Javitt et al., 1995). Furthermore, they have been suggested to share neural bases (Pasternak and Greenlee, 2005). The deficit in auditory sensory memory reported here would thus be seemingly at odds with previous evidence of an enhanced auditory working memory in a modest sample of individuals with Cystinosis (Nichols et al., 1990). In a memory for sentences task (which asks the individual to recall sentences of increasing length and

complexity), children and adolescents diagnosed with Cystinosis performed better than in other subscales of the Stanford-Binet, which was argued as a potential compensatory mechanism for their poorer visual memory (Nichols et al., 1990). Nevertheless, no neurotypical controls were assessed and, therefore, though those with Cystinosis showed higher scores in the memory for sentences task than in the additional tasks, this finding does not allow one to draw conclusions about the typicality of such scores. And, indeed, in a study comparing children diagnosed with Cystinosis with their neurotypical peers, working memory, as assessed by a parent-completed questionnaire, appeared to be a problematic area in those with Cystinosis (Ballantyne et al., 2013).

Impaired auditory sensory memory could, ultimately, hamper language acquisition and processing (Čeponiene et al., 1999). Considering the average verbal performance in the individuals tested here and, generally, in Cystinosis, one might nevertheless argue that, in this population, despite the presence of early auditory sensory memory differences, the system appears to be resilient and to compensate for those differences at a later stage of processing. Future work addressing other aspects of sensory and working memory will be needed to better understand the underlying bases of the differences described here, and their implication for higher order processing.

Lastly, despite an average verbal IQ, individuals with Cystinosis presented low average non-verbal (perceptual) and full-scale IQ scores. Other studies have reported significantly lower IQs in this population, when compared to neurotypical controls (Aly et al., 2014; Ulmer et al., 2009). Although the exact cause of the cognitive deficits observed in Cystinosis is unknown, early cystine accumulation might be particularly detrimental to brain myelination through in utero damage to pre-oligodendroglial cells, which are susceptible to the type of oxidative stress

resulting from the metabolic impairment associated with CTNS mutations (Trauner et al., 2007). Myelination atypicalities could subsequently hinder the development of cortical projections crucial for complex cognitive processes (Trauner et al., 2007). The expected discrepancy between verbal and non-verbal indices (Frankel and Trauner, 2019; Spilkin et al., 2007; Ulmer et al., 2009) was also observed in the current study. Such a discrepancy could be explained by abnormal white matter microstructure in visual-related areas: In a diffusion tensor imaging study, children diagnosed with Cystinosis presented decreased fractional anisotropy and increased mean diffusivity in the dorsal visual pathway (Bava et al., 2010). Of note, however, IQ scores did not correlate significantly with our neural measures of interest (the N1 and MMN), suggesting that both basic auditory processing and sensory memory are not strongly associated with verbal and non-verbal abilities, at least as measured here. A dissociation between MMN and IQ has been previously shown in a study comparing neural responses of children with intellectual disability, developmental dysphasia, and neurotypical controls (Holopainen et al., 1998).

Several limitations to the present study should be addressed in future research. First, despite the substantial size of our sample considering the rare nature of Cystinosis, larger numbers would allow for more detailed analyses, particularly those looking at associations between neural, cognitive and behavioral outcomes. Furthermore, it will be important to characterize the developmental trajectory of auditory sensory memory and the potential impact of continued treatment-associated factors (dialysis, number of transplants) and/or of cystine accumulation in the brain, with a larger sample that includes adults and younger children. While identification of differences in sensory memory provide a potential biomarker of the effects of cysteamine on brain function to serve as secondary outcome measure for clinical trials, it will be critical to determine whether the deficit varies with other clinically significant symptoms. Furthermore, it will be interesting to determine if similar deficits are seen in unaffected carriers of the mutation, as shown for visual-spatial difficulties (Sathappan and Trauner, 2019), or if they are specific to the effects of cysteamine accumulation. As alluded to above, future work will need to be done to understand the implications of the auditory sensory memory deficit described here. For example, one would ideally have other auditory sensory and working memory measures supportive of these difficulties.

In summary, this study provides the first neural evidence of auditory sensory memory differences in children and adolescents diagnosed with Cystinosis, which has the potential to serve as a biomarker of the effects of treatment and of cysteamine on brain function.

Author Contributions

JJF and SM conceived the study and designed the original experiment. AAF and DJH collected and analyzed the data. AAF wrote the first draft of the manuscript. SM and JJF provided editorial input to AAF on the subsequent drafts.

Declaration of competing interest

The Authors declare no competing financial interests.

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