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Time perception in childhood absence epilepsy: Findings from a pilot study

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ABSTRACT

Objectives: With this explorative study, we aimed to examine time perception in children with childhood absence epilepsy (CAE) and to compare those children with a matched control group. The study also investigated the association between the neuropsychological performance of the group with CAE and time judgment. We hypothesize that children with CAE could fail in time perception and that this may be because of a common underlying substrate with executive impairments.
Methods: Thirteen children with CAE, aged 6–13 years, and 17 healthy children were recruited. All children performed the time bisection task; the children with CAE also performed a cognitive and neuropsychological assessment. We performed a univariate analysis using each parameter of the bisection task (bisection point [BP]) and Weber ratio (WR) as dependent variables, the group (patients vs. controls) as fixed factors and age at evaluation and vocabulary scores as covariates. In the subgroup of patients, we correlated bisection task parameters with neuropsychological tests using a nonparametric partial correlation; the analysis has corrected for age at evaluation.
Results: The BP and WR measures differed between controls and patients with CAE. In the subgroup of patients also performing a neuropsychological assessment, we found a correlation between the WR measure and performance on the inhibition test ($r = -0.641$, $p = .025$), coding test ($r = -0.815$, $p = .014$), and Trail Making Test B (TMT B) ($r = 0.72$, $p = .042$).
Conclusions: We found an altered time perception in a pilot study of a small group of children with CAE. A neurophysiological mechanism underlying CAE seems to influence cognitive and behavioral deficits and time sensibility.

1. Introduction

Time perception refers to the subjective experience of time flow, the adjustment of behavior to specific time frames, the ability to perceive and estimate time intervals and finally the ability to consider future consequences of behavior. Neurobiological research suggests that several brain areas might be involved in time perception, but no consensus exists on how and where in the brain time is processed [1,2]. The majority of researchers have agreed that time judgments do not result from a single brain region but from a distributed network of the frontostriatal systems, with different areas contributing to different tasks, depending on their demands [3].

From a neurofunctional point of view, timing functions are closely interlinked with other cognitive functions, in particular attention and executive functions, specifically working memory [4]. Timing, attention, and executive functions recruit prefrontal and subcortical areas, implying an underlying common neural basis [5]. However, in contrast to time perception, attention and executive functions are complex abilities widely studied in regard to and recognized as being affected by several neurodevelopmental diseases, particularly epileptic syndromes, including childhood absence epilepsy (CAE) [6,7].

Childhood absence epilepsy is a common pediatric epilepsy syndrome affecting 10% to 17% of all children with epilepsy. Several authors emphasized that even if CAE is considered a "benign" epilepsy syndrome that does not compromise the patient's global intelligence quotient (IQ), specific cognitive domains might be affected, particularly

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executive functions, the impairment of which could persist despite antiepileptic drug treatment [8]. In a previous study of estimation of time abilities in a small sample of patients with absence epilepsy, the authors [9] found that misperception of the time interval was linked to but not completely explained by paroxysms, suggesting that alterations may persist after the period of epileptic electroencephalography (EEG) phenomena.

With this pilot study, we aim to examine time perception in children with CAE and compare their performance to that of the healthy members of the control group. Furthermore, we aim to investigate the association between the neuropsychological performance of patients and their specific time perception abilities. We hypothesize that children with CAE could fail in time perception and that this may be associated with executive impairments.

2. Materials and methods

2.1. Participants

The primary study inclusion criteria for each CAE subject were a diagnosis of CAE according to the International League Against Epilepsy Classification of the Epilepsies (Position Paper of 2017) and at least one seizure recorded with video-EEG at onset. All patients with CAE had EEG evidence of 3-Hz spike-and-wave in addition to absence seizures induced by hyperventilation. We excluded patients with a mixed seizure disorder, atypical spike-and-wave complexes, juvenile myoclonic epilepsy, or a neurological illness other than epilepsy. At the time of evaluation, all subjects with CAE were under treatment with ethosuximide and were seizure-free.

The study included 13 children with CAE, aged 6–13 years, whose IQ scores were in the normal range (>85), and 17 healthy children.

Clinical characteristics of patients and controls are reported in Table 1.

Ethical approval was obtained by our institution; the caregivers of the children gave their informed consent.

2.2. Procedure

A child neuropsychologist assessed the patients. Children came to our clinic twice; for each assessment, we planned several breaks. On the first day, children performed cognitive assessment and neuropsychological tests. On the second day, when the children were more used to the setting, we recorded the bisection task and administered the remaining neuropsychological abilities tests.

2.2.1. Time bisection task

The experimental session started with a learning phase, in which we required participants to memorize two standard durations: 300 ms (short standard) and 900 ms (long standard). We presented both standard durations 10 times (first all short standards = 300 ms followed by all long standards = 900 ms). Stimuli were sound (pink noise).

Table 1
Characteristic of CAE and control children recruited for the study.

	CAE $N = 13$	Controls $N = 17$	p value
Age at evaluation, mean y (range)[a]	10.5 (6–13)	9 (8–10)	.028
Age at seizure onset mean y (range)[b]	6.5 (3–12)	–	–
Gender M (%)	7 (54%)	6 (35%)	.26
IQ	108 ± 16	n.p.	–
Seizures number at the first EEG (range)	2.8 (1–5)	–	–
Seizures pattern length mean sec (range)	11.4 (4–28)	–	–
Subjects seizures free at evaluation	13	–	–

Legend: n.p.: not performed.
[a] Mann–Whitney U test.
[b] Chi-square test.

After the learning phase, participants had to perform 4 blocks; in each block, we presented the stimuli 7 times for each of the comparison durations (300, 400, 500, 600, 700, 800, 900 ms; a total of 196 trials in each block). After the presentation of the comparison durations, the participants had to press the key labeled "C" (= short) if the duration presented was closer to the standard short or the key labeled with "L" (= long) if the duration presented was closer to the standard long. We asked the participants to respond with their left and right index fingers. A 1000-ms intertrial interval followed the response. Each experimental session lasted approximately 30 min.

2.2.2. Cognitive and neuropsychological assessment

Children with CAE performed the following cognitive and neuropsychological assessment.

2.2.3. Cognitive assessment

We used a short form of the Wechsler Intelligence Scale for Children IV (WISC-IV), standardized for an Italian sample, for an estimation of general cognitive functioning [10,11]. Subtests we selected were similarities, vocabulary, block design, and matrix reasoning.

2.2.4. Neuropsychological assessment

We used the following tests: visual and auditory attention tests of the NEPSY-II [12,13]; digit span forward, which evaluates short-term verbal memory [11]; digit span backward, which evaluates working memory [11]; Tower of London test, which evaluates planning and problem solving [14]; coding test of the WISC-IV [11,15], which evaluates visuomotor speed and working memory; inhibition test of the NEPSY-II, which evaluates inhibitory control [12,13]; phonemic verbal fluency test, which evaluates the ability to access the lexicon through a phonemic cue by setting up an adequate verbal search strategy [16]; Trail Making Test A, which evaluates scan and search speed; and Trail Making Test B (TMT B), which evaluates attention shifting [17]. We selected the tests based on the different executive subcomponents and independently to modality-specific characteristics of the tasks (i.e., verbal or visuospatial).

Children in the control group performed the WISC-IV subtests vocabulary and digit span. We chose the vocabulary subtest for its high correlation with the global IQ score and the digit span subtest for its specificity in measuring a fundamental executive component: working memory [11]. Furthermore, we chose the tasks following Zélanti and Droit-Volet, 2011 and 2012 [18,19].

2.3. Statistical analysis

Scores of the neuropsychological tests were age-corrected and converted into z scores, scaled, and equivalent scores, as appropriate, using published normative data.

Age at evaluation and gender were compared between the children with CAE and control group using the Mann–Whitney U test and a chi-square test. The scores obtained by the children with CAE and control group on the vocabulary and digit span tests were compared using the Mann–Whitney U test (Table 2).

For the bisection task, all trials were kept for the analysis. For each participant, a 7-point psychometric function was traced, plotting the

Table 2
Comparison and p value of mean and SD of the scores of vocabulary and digit span tests obtained by children with CAE and in the control group using the Mann–Whitney U test.

	Children with CAE	Control group	
Subtest WISC-IV	SS mean ± SD	SS mean ± SD	p value
Vocabulary	9.35 ± 3.12	13 ± 2.20	0.001
Digit Span	10.21 ± 3.23	12.05 ± 3.36	0.74

Legend: SS, scaled scores.

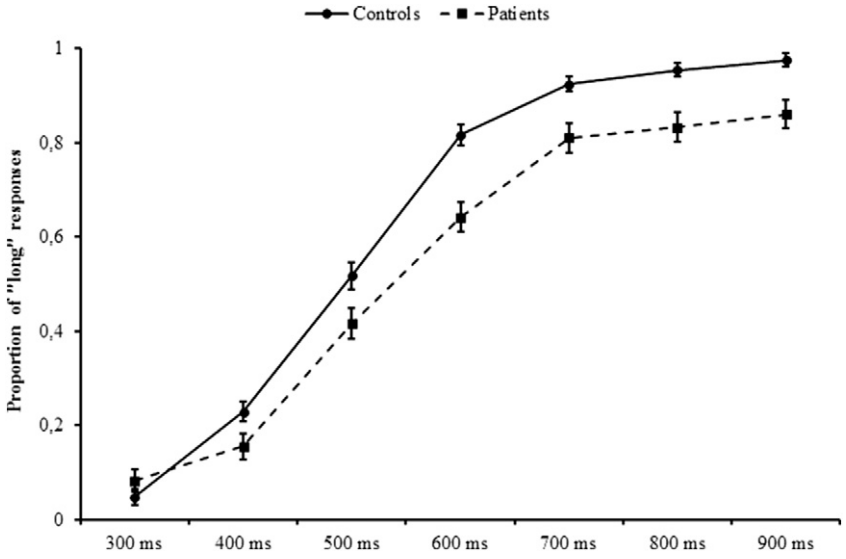

Fig. 1. Mean proportion of "long" responses for each group (patients and controls) as a function of Temporal intervals (300–900 ms).

seven comparison intervals on the x-axis and the probability of responding "long" on the y-axis (Fig. 1).

The cumulative normal function was fitted to the resulting curves. More specifically, we used a nonlinear least square analysis, with the Levenberg–Marquardt algorithm, and analyses were conducted with R. Temporal abilities with the time bisection task are expressed in term of perceived duration and temporal sensibility (no accuracy or reaction times are detected as explained by Kopec and colleagues [20] and Trevor and colleagues [21]). The perceived duration is tested with the temporal bisection point (BP), defined as the x value corresponding to the 0.50 probability of "long" responses on the y-axis. An observed shift of the BP can be interpreted as an indicator of perceived duration, with smaller BP values meaning longer perceived durations. Moreover, as an indicator of temporal sensitivity, we measured the Weber Ratio (WR). The WR is defined as the standard deviation (*SD*) divided by the actual midpoint between both standards; higher WR values denote poorer sensitivity.

We performed a univariate analysis using each parameter of the bisection task (BP and WR) as dependent variables, the group (patients vs. controls) as fixed factors and age at evaluation and scores obtained on the vocabulary subtest as covariates. Vocabulary scores were added to the analysis as covariate because they differed between groups (Table 2 in the results section).

Furthermore, in the subgroup of patients, we correlated bisection task parameters with neuropsychological tests using a nonparametric partial correlation. We used raw scores for both bisection parameters and neuropsychological tests, and we corrected the analysis for age at evaluation.

For the analysis, SPSS Statistics 21.0 (IBM Corp, Armonk, NY) and R studio were used [22].

3. Results

Age at evaluation and vocabulary scores differed between groups; therefore, we added these variables to the analyses as covariates.

We found differences in the bisection task parameters between patients and controls, as shown in Table 3. Patients showed temporal underestimation compared to controls (patients' BP mean = 564, *SD* = 65; controls mean = 501, *SD* = 46) (Fig. 2). Regarding WR, we observed higher variability in patients (mean = 0.20, *SD* = 0.09) compared to controls (mean = 0.34, *SD* = 0.19) (Fig. 3).

4. Discussion

Our aim with this pilot study was to explore time perception in children with CAE. We chose CAE for its pathophysiology and underlying neurobiological substrate.

By comparing the performance of the group with CAE to the healthy members of the control group, we found differences in both perceived duration and sensitivity, characterized for a temporal underestimation of patients compared to controls and a high variability in the responses. These results are not due to differences in cognitive functioning because we compared the group's performance to two WISC-IV subtests (selected for their high correlation with the global IQ score or with executive functioning), and we considered the performance differences in the analyses. Furthermore, in the subgroup of children with CAE, who performed an extensive cognitive and neuropsychological assessment, we found an association between executive functions and temporal parameters: worse performances on executive tests correlated to poor temporal sensitivity.

Impairment in the network of cortical–subcortical areas in patients with CAE has been widely established with functional magnetic resonance imaging (fMRI) studies [20,22]. In CAE pathophysiology, both cortical and subcortical areas with their interconnections are implicated

Table 3
The table reported *F* and *p* value of the univariate analysis of the variance including Group and age at evaluation and vocabulary scores as covariates of BP and WR.

BP (dependent)	*F*	*p*
Model 1 ($p = .043$)		
Intercept	34.90	.000
Group	6.56	.017
Age	0.000	.986
Vocabulary	0.259	.615
WR (dependent)	***F***	***p***
Model 2 ($p = .008$)		
Intercept	10.54	.003
Group	10.95	.003
Age	6.31	.019
Vocabulary	0.034	.85

In patients with CAE, after controlling for age at evaluation, we found a correlation between the WR measure and performance on the inhibition test ($r = -0.641$, $p = .025$), coding test ($r = -0.815$, $p = .014$), and TMT B ($r = 0.72$, $p = .042$).

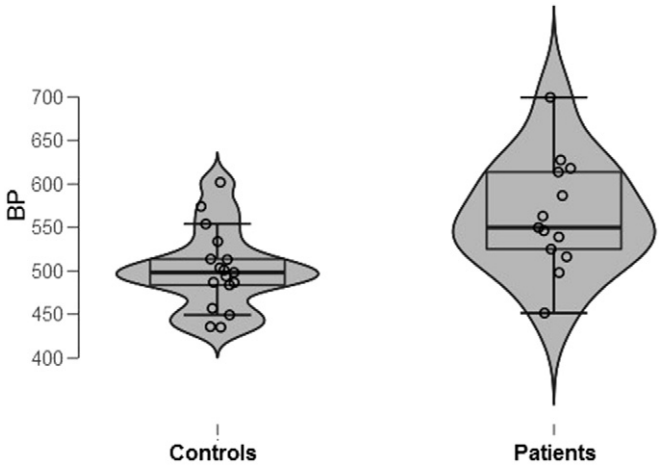

Fig. 2. Bisection point (BP) as e function of Group. Each dot represents a participant.

[23–25]; thalamicortical circuitry is required for the generation of typical spike–wave discharges [26], with consequent activation or inactivation of numerous cortical regions, particularly the frontal, parietal, and cingulate cortices [27–29]. The cerebral cortex and thalamus also communicate indirectly through an important intermediate bridge–basal ganglia [30]. Furthermore, an altered network connectivity in the anterior insula [6] and in low- and high-frequency bands even in the interictal period was found [31].

Circuitries underlying CAE share several structures involved in time perception, allowing us to hypothesize an overlap of structures and functions in the frontostriatal system, including striatum, prefrontal, and insular cortex [32–36].

Our suggestions are supported by the further correlation of timing processes and attention and executive functions, as previously reported in healthy subjects [32,37–39]. Deficits in attention and in executive functions are probably associated with the same basal ganglia-thalamicortical circuits involved in the pathogenesis of CAE [7,40,41]; attention and executive functions are reported as a core problem in CAE (for a review, see Verrotti and colleagues, 2015 [6]). Furthermore, patients with CAE exhibit a high rate of pretreatment cognitive and behavioral deficits, suggesting a distinct pattern of neurocognitive dysfunction [42]. However, other neural systems may also be involved, depending on the temporal task and the duration range used. A previous study found time perception alterations in patients with epilepsy with right or left medial temporal resections. In this study, the impaired duration productions are thought to be related to a distorted representation of time units in long-term memory [43].

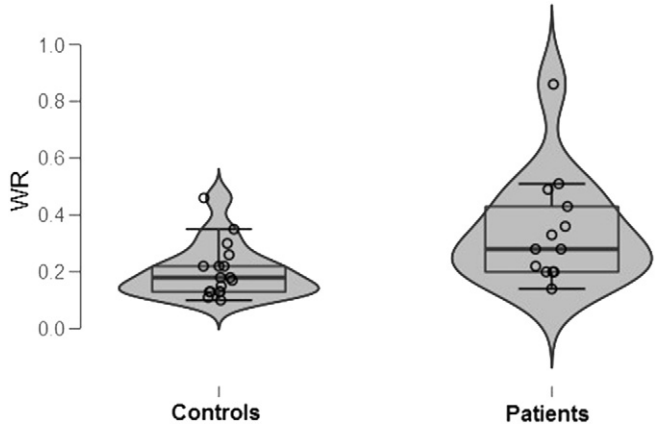

Fig. 3. Weber Ratio (WR) as e function of Group. Each dot represents a participant.

Time perception is a crucial ability underlying our ability to organize and plan our daily activities; for instance, accurate timing is needed to execute action at an optimal moment, to estimate the duration of events and to estimate future implications of immediate actions. Timing is functional for providing the most adaptive behavior [3,39,44–46] and for decision-making [47,48]. Impulsive decision-making has been found in several patient populations [2,48,49], such as impulsive borderline personality disorder patients [50] and alcohol and substance abuse [51]. Moreover, alteration in time perception has been found in patients with schizophrenia [52] and patients with depression [53]. In line with the hypothesis of a frontostriatal dysfunction, children with attention-deficit hyperactivity disorder (ADHD) have been found to exhibit significant timing deficits in different types of temporal tasks [54,55]; ADHD is a frequent comorbidity of CAE, appearing in about 40% of all patients [56], suggesting a common neural substrate of frontosubcortical systems among disturbances and time perception abilities.

The major limitation of the present study was that the small sample size reduced the generalizability of our results. However, our data provide first insight about the possibility of an alteration of time circuitries in CAE and of the contribution of different timing processes in the complex pattern of neuropsychological and psychological disturbances found in children with CAE. Children with CAE frequently experience functional difficulties in daily life and psychiatric disturbances, such as ADHD, the pathophysiology of which is actually not completely understood [23] but in which timing disturbances may have a role.

We tried to control our analyses for all factors that may have had an influence on our results and that effectively separated the group of patients from the control group. Therefore, we controlled for age at evaluation and for performance on the vocabulary subtest, variables differing significantly between the groups. These two variables did not seem to have an influence on temporal perception measures; however, differences in cognitive functioning may explain any problems found in the children affected by CAE and therefore should be considered. Further study with a wider group of children with CAE, naïve and treated subgroup, need to confirm the results of our pilot study and better define the relationship between cognitive and behavioral disorders and academic achievement in this population.

Furthermore, to explore preliminarily the association between executive and attentive functioning and time perception in children with CAE, we selected the tests based on the different executive subcomponents, including verbal working memory, and not on modality-specific characteristics of the tasks (i.e., verbal or visuospatial), because we did not focus on their effects on time perception. We selected the verbal working memory based on two previous studies conducted by Zélanti and Droit-Volet [18,19] in which the authors conducted timing tasks as well as neuropsychological tests to investigate which cognitive abilities explain age-related changes in time perception. However, the association that we found deserves in-depth examinations in a larger group of subjects.

Another limit of our study is that all children were under pharmacological treatment, and we did not exclude a possible confounding effect. However, research has previously showed that children with CAE have a high rate of pretreatment deficits that persist despite seizure freedom. Furthermore, rates are disproportionately higher for valproic acid treatment compared to ethosuximide or lamotrigine [42] use.

In conclusion, an altered time perception has showed in a small group of children with CAE. The neurophysiological mechanism underlying CAE seems to influence cognitive and behavioral deficits and time sensibility. Our findings could aid, with further studies, to elucidate the role of the underlying pathology and psychosocial variables in the comorbid behavioral and cognitive disorders of pediatric CAE.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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