Auditory and Visual Oddball Paradigm Evaluated Through P300 in Five Girls with Rett Syndrome

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ABSTRACT

Few studies investigated information processing in genetic syndrome, such as Rett Syndrome, using ERPs. The main aim of this study was to examine visual and auditory processes in children with Rett Syndrome through the oddball paradigm. Five children with a diagnosis of Rett Syndrome, ranging from 7 to 11 age (M = 8, 8 years, SD = 4,36), matched for sex, age and mental age to typically developing children. Event-related potentials were recorded to an auditory and visual oddball task in all participants. The results showed that both auditory and visual P300 latencies were longer in the Rett group than the typically developing group. These findings suggest that children with Rett Syndrome need more time to process information.

Key Words: Rett Syndrome, ERP, oddball task, P300

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Introduction

The relationship between brain activity and cognitive processes has been extensively studied to understand the neurophysiological bases of many clinical disorders. For this purpose, brain activities can be estimated through EEG recordings during the execution of sensory, cognitive and motor tasks. Recordings are registered as a series of amplitude deflections in the EEG, in function of time (event-related potential, ERP) (Goffin and Zhou, 2012). The P300 is an ERP wave elicited by infrequent relevant stimuli. It is a large-amplitude positive ERP component (that depend on the level of attention and concentration of the subject) which peaks at ~ 300–600 ms after the presentation of the stimulus, and it is independent of the sensory modality of the stimulus (Nieuwenhuis *et al*., 2005; Nolan *et al*., 2012; Polich and Criado, 2006; Twomey *et al*., 2015). It is usually elicited using the oddball paradigm. Furthermore, its amplitude maximum is located in center parietal area at the median level and its latency is rather variable (Polich *et al*., 1997). The P300 is an endogenous potential because its presence is not recorded following a physical attribute of the stimulus, but due to a person's reaction to the stimulus. The wave would reflect a process of evaluation and classification of a stimulus. In fact, while its amplitude is directly proportional to the rarity of stimulus, to the irregularity of the pattern of stimuli presented, to the inter-stimulus and at the distance between a target stimulus and the previous one, its latency results in direct relation with the complexity of discernment of stimuli (Polich, 2007).

Recently the interest in this component has increased because of its importance in many cognitive operations and its abnormalities in vary brain disorder, such as schizophrenia, Attention deficit hyperactivity disorder (ADHD) and Autism Spectrum Disorder (ASD) (Caprì *et al*., 2019; Cui *et al*., 2017; Donkers *et al*., 2015; Fabio, 2012; 2017; Fabio and Antonietti, 2012; Fabio and Caprì, 2015; 2017; 2019; Fabio and Towey, 2018; Fabio and Urso, 2014; Fabio

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et al., 2015; 2018b; 2019c; Lin *et al*., 2018; Ludyga *et al*., 2017; Sokhadze *et al*., 2017; Martino *et al*., 2017; Twomey *et al*., 2015). For example, many studies have been conducted on the P300 in the ASD, in order to discover the pathological mechanism of ASD (Donkers *et al*., 2015; Ishikawa *et al*., 2017; MacLean *et al*., 2015). ASD patients present perception and sensory reactivity abnormalities, which reflect their difficulty to effectively process information (Gomes *et al*., 2008). Furthermore, ASD children shown an atypical way of elaborating distracters and orienting attention to novelty, suggesting a low selectivity in pre-processing of distractors and influencing the elaboration processing in the further phases. This suggests a decrease in the discrimination capacity in the ASD patients (Sokhadze *et al*., 2017). A recent meta-analysis (Cui *et al*., 2017) indicates that deficits in cognition, in attention orientation and in working memory processing in ASD patients can be the result of the abnormalities encountered in P300 component. In particular, these abnormalities were found in the decision-making processing condition.

Few studies investigated information processing in genetic syndrome, such as Rett Syndrome (RTT), using ERPs (Goffin *et al*., 2014; Goffin *et al*., 2012; LeBlanc *et al*., 2015; Stauder *et al*., 2006; Bader *et al*., 1989).

RTT is a neurodevelopmental disorder, with genetic aetiology (APA, 2013), that mainly affecting females than males (Leonard *et al*., 2001; Moretti and Zoghbi, 2006). RTT is characterized by an evolutionary regression after a seemingly normal development period, usually diagnosed around 3 years of age (Falzone *et al*., 2015; Fabio, 2019; Fabio *et al*., 2011; 2018a; 2018c; 2018d; 2018e; Tarquinio, 2016). Features as intellectual disability, autistic behaviour, stereotypies, progressive motor deterioration, deceleration of head growth, ataxia, breathing dysfunction, and epilepsy are common in RTT (Antonietti *et al.,* 2005; Castelli *et al*., 2013; Fabio *et al*., 2009a; 2009b; Fabio *et al*., 2013; 2014; 2016; Vignoli *et al*., 2010).

As mentioned above, ERP studies of auditory processing in RTT are limited. A recent study (Key *et al*., 2016) has examined auditory ERP to evaluate spoken word processing during passive listening in girls with RTT. The auditory stimuli were English words that are typically among the first learned by young children and pronounceable nonwords. The results indicated that subjects with RTT differentiated known words from novel nonwords. This study demonstrated the feasibility and utility of an auditory listening ERP paradigm as a measure of higher-order processing of socially relevant stimuli evidenced in recognition of familiar voices among novel distractors in RTT. Others studies (Peters *et al*., 2015; 2017) investigating auditory ERP in RTT have relieved that individuals with RTT can discriminate familiar voices from novel distractors, but no evidence of recognizing own name, suggesting general attention to auditory inputs and reduced speech content processing.

With reference to P300, using auditory and visual evoked potential paradigms Bader *et al*. (1989) used passive oddball task, in which the subject is not asked to identify the infrequent stimulus; their results showed P300 activity in patients with RTT indicating residual perceptual and discrimination properties. Moreover, in the work of McCulloch *et al*. (2001) visual event-event related potentials were studied. Three subjects with RTT participated in a face discrimination paradigm and four subjects with RTT in a face recognition paradigm but the authors could not identify any ERP components. In another study Stauder *et al*. (2006) examined seventeen subjects with RTT from 2 to 60-years-old. The authors present a life span approach to study the development of auditory and visual processing using passive oddball paradigm. Results indicated that patients with RTT showed longer ERP latencies and smaller ERP amplitudes in both the visual- and auditory modality than the control group. Moreover, while in RTT children, some ERP components were detected, adults with RTT show some ERP activity in the auditory oddball task and aberrant ERPs in novel and unexpected stimulation in the visual task. Overall, these results suggest a reduction in the speed of information processing and lower brain activation, with a deterioration during adulthood (Stauder *et al*., 2006). Similar results were obtained by LeBlanc *et al*. (2015) which show a reduction in visually evoked potential (VEP) amplitude and increases in latency in RTT patients.

Overall, the P300 wave is an ERP elicited by infrequent, task-relevant stimuli and appeared at about 300 ms, represents higher cognitive function of information processing, working memory or stimulus categorization (Thakur *et al*., 2011). In RTT literature, ERP studies focused primarily on visual processing and the use of eye gaze while participants attend to stimuli on a screen (Djukic *et al*., 2012) because individual with RTT are able to direct the gaze to communicate (Fabio *et al.*, 2019a; 2019b; Julien *et al*., 2015). Given the aforementioned results and the complexity of RTT, ERP method can be a valid measure to evaluate the cortical processing without the need for overt behavioral responses.

The purpose of the present study is to examine visual and auditory processes in children with RTT through oddball paradigms. Oddball paradigm is commonly used to elicit the P300 component and to study the effects of perceptual novelty on information processing. In this paradigm two different stimuli are presented, using a random order of presentation. The stimuli were visual and auditory. The task consists of discriminating the rare oddball target from the frequent and repetitive standard stimulus. Stimuli novelty refers to both infrequent or rare stimuli and unfamiliar stimuli (in terms of absence of exposure) (Ferrari *et al*., 2010).

More precisely, we hypothesized that the visual and auditory latency P300 parameter would be longer in RTT than in control group and the amplitude P300 parameter would be lower in RTT than in control group.

Methods

Participants

Five children with a diagnosis of RTT, ranging from age 7 to 11 (M = 8, 8 years, SD = 4,36), were recruited from "Gaetano Martino" University Hospital and compared with five typically developing children (TD) matched for sex, age and mental age. They were severely mentally retarded and were not able to use verbal speech. All showed pervasive hand stereotypies. Ambulation was preserved only in two children. All attended schools or socio-educational centres. A general assessment was carried out by a psychologist through the Vineland Adaptive Behavior Scale (VABS) and the Rett Assessment Rating Scales (RARS) (Fabio *et al.*, 2005). Table 1 shows the characteristics of the RTT participants.

The two TD groups were recruited from a public school in a town of the Southern Italy. They were not diagnosed as affected by behavioural, neurological, emotional and/or relational problems by the specialised psychologists. The TDA ranged from 7 to 11 years age (M = 8,2 years, SD = 3,8). While the TDMA ranged age between 2 and 4 (M= 3,5 years, SD = 4,32).

Materials

Functional Scales. The VABS are designed to support the diagnosis of intellectual and developmental disabilities. The Scales are organized into four domains: communication; daily living; socialization; and motor skills. The interviewer asks general questions pertaining to the subject's functioning in each subdomain and uses the responses to rate the examinee on each critical behaviour item (2: always present, 1: sometimes present, 0: seldom or never present). Typical interviews require approximately one hour. A total score is computed by summing the individual ratings for each scale. The reliability of the Scales was established as follows: split-half, 0.73–0.93 for the communication domain, 0.83–0.92

Table 1. Characteristics of the participants.

	RTT group					TD group				
	1	2	3	4	5	1	2	3	4	5
Age (years)	10	10	7	8	9	10	10	7	8	9
MECP2 mutation type	R294X	R168X	R270X	R255X	R255X					
VABS subscales										
Communication	22	23	3	8	10	208	206	203	200	199
Daily ability	12	21	3	8	12	380	380	378	370	373
Socialization	14	20	3	8	10	24	22	24	24	22
Motor ability	10	21	3	7	10	144	140	140	142	144
VABS total score	58	85	12	31	42	756	752	745	736	738
RARS subscales										
Cognitive	14	12	15	8	12					
Sensory	14	10	13	5	14					
Emotional	12	13	11	7	14					
Autonomies	15	15	16	12	16					
Behavior	14	10	14	9	12					
Motor	16	9	16	7	15					
RARS total score	85	69	85	48	83					

for daily living skills, 0.78–0.94 for socialization, 0.70–0.95 for motor skills, 0.84–0.98 for adaptive behaviour composite, 0.77–0.88 for maladaptive behaviour (survey form) (0.80 and 0.90 for the Survey Form). The interrater reliability coefficients for the survey and expanded forms ranged from 0.62 to 0.75. Standard error of measurement ranged from 3.4 to 8.2 over the four domains, and from 2.2 to 4.9 for the Adaptive Behaviour Composite, on the survey form.

The RARS is a standardized scale used to evaluate subjects with Rett syndrome (Fabio *et al*., 2005). RARS is organized into seven domains: cognitive, sensorial, motory, emotional, autonomy, typical characteristics of the disease and of behaviour. The cognitive area consists of evaluations of attention, spatial orientation, temporal orientation, memory, eye contact, replying by smiling, shared attention, verbal and non-verbal communication; the sensorial area consists of eyesight and hearing; the motor area consists of position and movement of the body, movement of hands, scoliosis, problems in the feet; the emotional area refers to understanding emotions and the expression of emotions; the autonomy area refers to excretive control, feeding, ability to wash and dress; the typical characteristics of the disease and behaviour area refers to mood changes, convulsions, breathing problems, hyperactivity, anxiety, aggressiveness, bruxism, rolling of the eyes, epilepsy, aerophagia, muscular tension, feeding habits; the overall impression area refers to the general evaluation of the symptoms of RTT (from no symptoms (1) to all the symptoms (4). The items in RARS were constructed following the diagnostic criteria for RTT proposed by the Diagnostic and statistical manual of mental disorders, 4th ed. (DSM-IV-TR, American Psychiatric Association, 2000) and recent research and clinical experience. A total of 31 items was generated as representative of the profile of RTT. Each item is provided with a brief glossary explaining its meaning in a few words. Each item is rated on a 4-point scale, where 1 = within normal limits, 2 = infrequent or low abnormality, 3 = frequent or medium-high abnormality, and 4 = strong abnormality. Intermediate ratings are possible; for example, an answer between 2 and 3 points is rated as 2.5. For each item, the evaluator circles the number corresponding to the best description of the patient. After a patient has been rated on all 31 items, a total score is computed by summing the individual ratings. This total score allows the evaluator to identify the level of severity of RTT, conceptualized as a continuum ranging from mild symptoms to heavy deficits. Skewness and kurtosis values, calculated for the distribution of the total score, were 0.110 and 0.352, respectively. The distribution was found to be normal. Cronbach's alpha was used to determine the internal consistency for the whole scale and subscales. Total alpha was 0.912, and the internal consistency of the subscales was high (from 0.811 to 0.934).

Oddball tasks

The P300 was evoked with a visual and an auditory oddball task. The method complied with the oddball procedure of previous studies using this paradigm in subjects with RTT and children with intellectual disabilities (Stauder *et al*., 2006; Key *et al*., 2016).

The visual oddball task consisted of 80 target visual stimuli and 20 rare visual stimuli. They were a red apple on a white background (target stimulus) and a yellow and gray bike (rare stimulus) on a white background. They were presented in a session during 1000 ms with an inter-stimulus interval of 1500 ms. The stimuli were binaurally delivered in a predictable sequence (a rare stimulus after five targets stimuli for the first 40 trials) and a random stimulus sequence (for the last 60 trials) (Fig. 1 and 2). Subjects were required to maintain gaze at the fixation point while looking the stimuli presented.

The auditory oddball task consisted of 100 auditory stimuli: 80 target tones (1000 HZ) and 20 rare tones (2000 Hz). The auditory target stimulus was a pure tone with a clearly distinguishable pitch of an Italian name, respectively "Elena". The rare stimulus was a pure tone with a clear reproduction of the bomb explosion sound. All stimuli (50 ms; 5 ms rise and fall time) were presented binaurally at a volume of 75dB SPL with an inter-stimulus interval of 1500 ms. The stimulus sequence was the same of the visual oddball task (Fig. 3 and 4). Subjects were required to maintain gaze at the fixation point while listening the tones presented.

ERP quantification

For electrophysiological recordings, 20 Ag/AgCl electrodes were used, positioned on the scalp according to the international 10-20 convention. The earth was applied in frontal position; the reference electrodes (M1 / M2) on both mastoids and shortes together. The interelectrode resistance has been reduced to 5 kΩ for all electrodes. The bandwidth

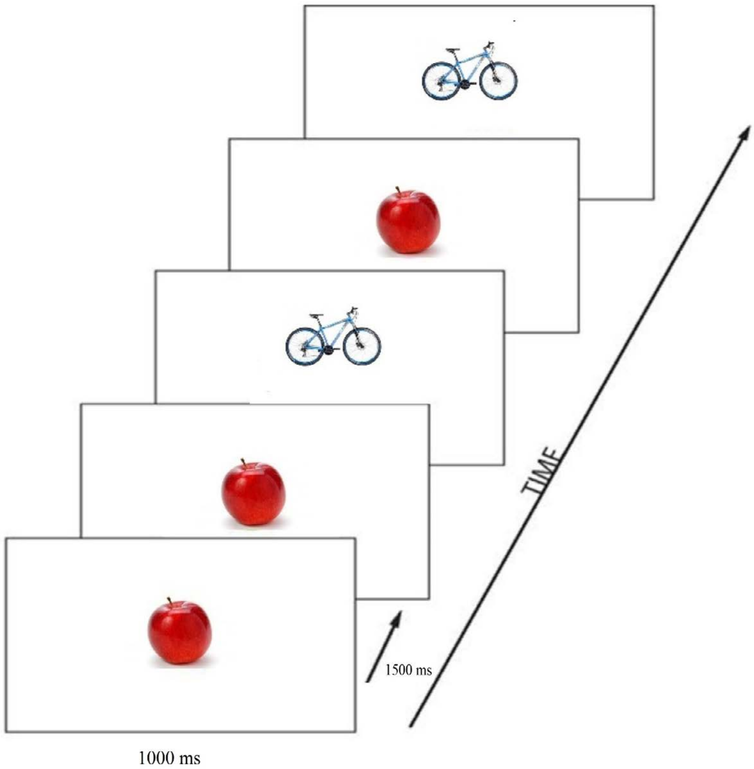

Figure 1. Example of a sequence of the visual oddball paradigm (with the bike as rare stimulus).

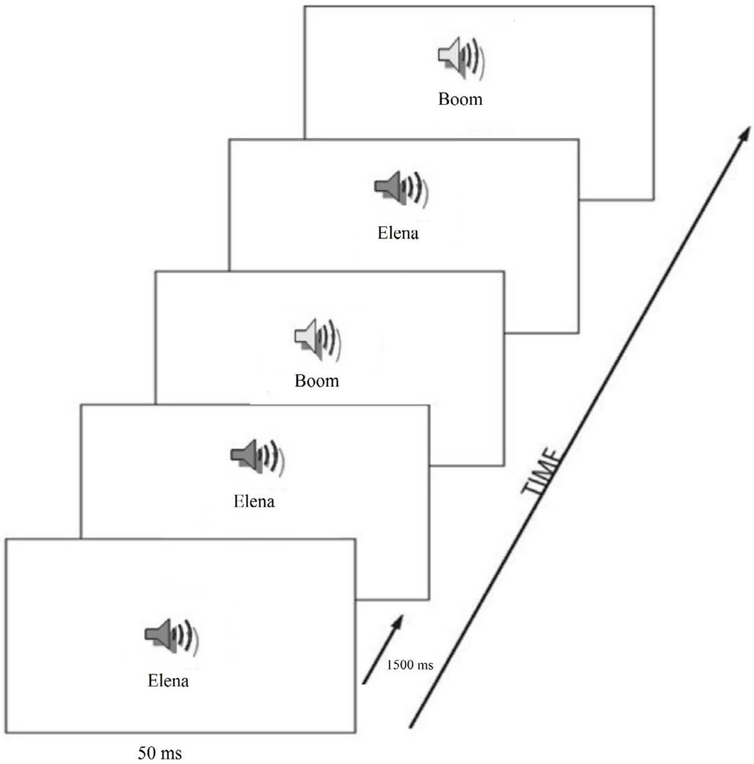

Figure 2. Example of a sequence of the auditory oddball paradigm (with “Boom”as rare stimulus).

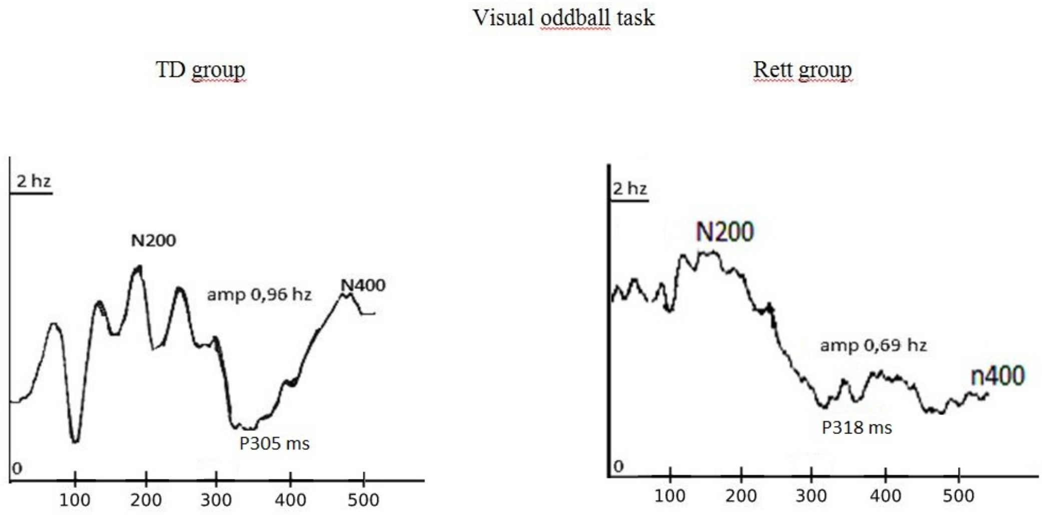

Figure 3. Visual ERPs in Rett group and TD group.

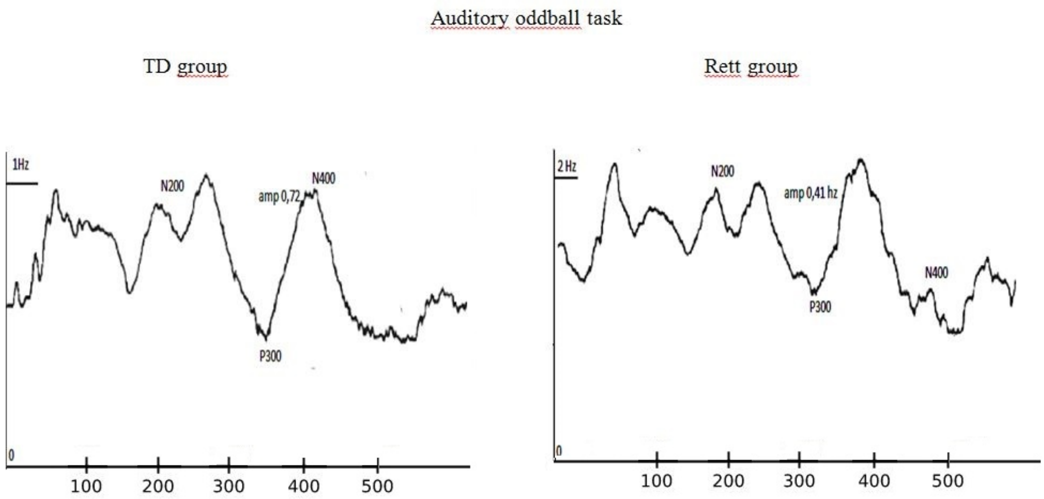

Figure 4. Auditory ERPs in Rett group and TD group.

was between 0.1 Hz and 30 Hz. The EEG was divided into epochs between -200 and +800 ms in standard mode and between -100 and +400 ms in fast mode. The average of the activity evoked by averaging was then extracted, subdividing the ERPs according to the generator stimulus. The Large Averages according to the type of generator stimulus. Averages of evocated activity and topographic propagation of both groups were subsequently obtained. The average of the activity reflects 4 epochs: the mean of the first serie concerns the first 5 odd stimuli, the mean of the second is from the 6^{th} to the 10^{th}, the third from the 11^{st} to the 15^{th} and the fourth from the 16^{th} to the 20^{th}. The potential P300s were analyzed by the electrodes Fz, Cz, Pz, T3, T5. For all the potentials the latencies (at peak) were analyzed. The electrical potentials from all 19 electrodes were used to construct the topographic maps of evocated activity.

EEG analysis

EOG artifacts were removed from the EEG by means of linear regression (Neuroscan 4.2). Next the EEG data were epoched and baseline corrected using a 100 ms prestimulus and 1000 ms post-stimulus period. EEG epochs containing data of which the absolute voltage in any channel

exceeded ±350 lV for children with RTT and ±250 lV for typically developing subjects were omitted from the ERP averages for each stimulus condition. ERP peaks were scored within a given time window resulting in an (peak-) amplitude and (peak-) latency after stimulus onset.

Procedure

The parents or the caregivers received instructions while the electro-cap and EOG electrodes were installed. During EEG recording a visual and an auditory oddball task was presented. The visual stimuli were presented on a 15 in. CRT monitor and the participants sat 50 cm from the monitor. The auditory stimuli were presented via headphones. In both oddball tasks there was no instruction and for the visual oddball task the experimenter checked constantly whether the participant focused at the center of the screen. The visual oddball task was always presented first because focusing on the screen implies more effort than passive listening to tone sequences. Between tasks there were short breaks. During task performance two experimenters stayed in the same room as the participant. One observed the participant and the other monitored the EEG signal on the laptop computer. The entire recording lasted about one and a half hour.

Statistical analysis

The data were analysed using SPSS Version 22.0 for Windows. The descriptive statistics of the dependent variables were tabulated and examined. The alpha level was set to 0.05 for all statistical tests. In case of significant effects, the effect size of the test was reported. The effect sizes were computed and categorized according to Cohen (1988). The Greenhouse–Geisser adjustment for nonsphericity was applied to probability values for repeated measures.

Results

Tables 2 and 3 show the means and standard deviations related to the auditory P300 and visual P300 into 4 epochs for RTT group and TD group. Differences between groups for both auditory and visual oddball were assessed using Kruskall–Wallis tests.

Table 2. Means (M) and standard deviations (SD) related to the auditory P300 into 4 epochs for RTT group and TD group.

Epochs	RTT Group	TD Group
	M (SD)	M (SD)
1	315.42 (4.15)	306.60 (2.19)
2	321.20 (7.15)	302.80 (3.83)
3	316.40 (3.57)	309.00 (5.47)
4	322.00 (5.56)	310.40 (0.58)

Table 3. Means (M) and standard deviations (SD) related to the visual P300 into 4 epochs for RTT group and TD group.

Epochs	RTT Group	TD Group
	M (SD)	M (SD)
1	315.80 (3.56)	300.00 (0.55)
2	317.20 (7.15)	300.00 (0.45)
3	302.00 (12.51)	305.00 (2.73)
4	322.40 (6.95)	307.20 (6.57)

The Kruskal-Wallis test indicates that the level of latency of the two groups differed significantly both with reference to auditory and visual oddball tasks (respectively, χ^2= 3,27, p<.01 and χ^2= 2,41, p<.01).

This result indicates that both visual and auditory P300 latency was higher in the RTT group than in the TD group, as shown in Fig. 3 and 4. This difference is more evident in the trend of auditory P300, because the occurrence of P300 related to the rare stimulus is higher compared to the visual rare stimulus.

With reference to amplitude, the same analysis was conducted. We found that the level of amplitude of the two groups differed significantly both with reference to auditory and visual oddball tasks (respectively, χ^2= 2,11, p<.01 and χ^2= 1,98, p<.01). These results suggest higher latencies and smaller ERP amplitudes than the Control group, suggesting slowed information processing and reduced brain activation.

Discussion

The aim of the present work was to study whether the visual and auditory latency P300 parameter would be longer and the amplitude P300 parameter would be lower in subjects with RTT than in TD group. The results indicated that both auditory and visual P300 latency was longer in the RTT group than in the TD group. These results are in accordance with previous research (LeBlanc *et al*., 2015; Stauder *et al*., 2006), suggesting that children with RTT need more time to process information, resulting in increased latency both for auditory and visual stimuli. Indeed, P300 latency reflects both the time spent post-stimulus for information processing before activation and executive function (attention, memory) (Howe *et al*., 2014). The RTT group highlights the reactions, albeit slowly, to the rare stimulus, while this result is not consistent with previous studies (McCulloch *et al*., 2001; Stauder *et al*., 2006) probably because these studies analysed adults with RTT.

In the study of Stauder *et al*. (2006) the results showed that in RTT children the sensitivity to the rare stimulus is preserved, while it is absent in RTT adults, probably due to the chronicity of the disease with age.

Furthermore, even if significant differences appear in the latency and in the amplitude between the RTT group and the control group, the response of the subjects to the auditory stimuli was different from that to the visual stimuli. In fact, the differences in latency between the two groups was not large. Probably this is due to the fact that the rare auditory stimulus, such as the bomb, produced a greater physiological reactivity and immediately activated automatic attention in the subjects. Generally, a loud noise activates the sympathetic and parasympathetic nervous system, responsible for activation and mobilisation of the body to facilitate attention and for recovery and restoration, respectively (Lydon *et al*., 2016). This result is consistent with previous studies (Ford *et al*, 1997; Roth, 1984) which indicated that loud noises elicited shorter latency P300s, caused by a general increase in arousal or activation. Several factors affect the reaction time to a stimulus, such as intensity and duration of the stimulus. Future studies could use rare auditory stimuli of varying intensity and duration in order to broaden the knowledge in this area.

Conclusion

Although this study contributes to the study of cognitive processes in subjects with RTT, the results cannot be generalized, due to the small sample size. Future research should include a larger sample with different ages in order to investigate the development of auditory and visual information processing and increase knowledge in this field of study. This would permit the planning of appropriate cognitive training to reduce the effects that chronic disease can have on RTT patients.

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