Talaat *et al.*
The Egyptian Journal of Otolaryngology (2023) 39:151
https://doi.org/10.1186/s43163-023-00512-1

The Egyptian Journal of Otolaryngology

ORIGINAL ARTICLE Open Access

Assessment of cognitive function in children with temporal lobe epilepsy using mismatch negativity

Hossam Sanyelbhaa Talaat[1], Asmaa Salah Moaty[1], Sameh A. Abd El Naby[2], Hadeer M. Elgammal[3] and Ahmed Mahmoud Zein-Elabedein[1*]

Abstract

Objectives This study aimed to assess cognitive function in children with temporal lobe epilepsy (TLE) using mismatch negativity (MMN) potentials.

Background Temporal lobe epilepsy (TLE) is a neurological condition that causes cognitive and behavioral problems. These complications were found to be affected by many factors including underlying neuropathology, age of onset, psychological issues, and therapeutic side effects that exacerbate pathophysiology of the condition.

Subject and method In this case–control study, 44 children were involved and were divided into two groups: the study group involved 22 children with TLE, while the control group involved 22 normal children. Pure-tone audiometry, immittancemetry, and measurement of mismatch negativity (MMN) test were done for all subjects in this study.

Results Latency of MMN was significantly increased, while the amplitude was significantly decreased in the study group compared to the control group. Abnormal MMN test was obtained in TLE patients.

Conclusion Prolonged MMN latencies and decreased amplitudes in patients indicate impaired cognitive function in children with TLE compared with controls.

Keywords Temporal lobe, Epilepsy, Cognitive function, MMN

Background

Epilepsy is a brain disorder characterized by different types of seizures brought on by brief, recurrent disturbances in the brain's normal electrical activity [1–3]. Cognitive and behavioral deficits are more common in epilepsy patients. Several factors, including underlying neuropathology, seizure type, age of onset, psychological issues, and treatment side effects, can cause or exacerbate an underlying cognitive impairment in people with epilepsy [4]. Temporal lobe epilepsy (TLE) is frequently linked to memory loss due to damage to the hippocampus and nearby structures. It has been repeatedly demonstrated that TLE causes problems with both short- and long-term memory [4].

Mismatch negativity (MMN) is an auditory event-related potential (ERP) which is produced when an uncommon ("deviant") tone appears after a series of frequent ("standard") tones [5]. According to one theory, MMN develops on its own if there is a discrepancy between the physical characteristics of an aberrant stimulus and the neurosensory memory traces left behind by

*Correspondence:
Ahmed Mahmoud Zein-Elabedein
ahmed.mahmoud@med.menofia.edu.eg
[1] Audiology Unit, Faculty of Medicine, Menoufia University, Menoufia Governorate, Shibin El-Kom, Egypt
[2] Pediatrics, Faculty of Medicine, Menoufia , University, Shibin El-Kom, Egypt
[3] Audiology Quesna Central Hospital, Quweisna, Egypt

repeated conventional stimuli [6]. The first cortical activities in the cognitive processing of auditory information are assumed to be reflected by MMN [7] and are thus part of auditory pre-attentive memory [8]. MMN can be induced without attention and has minimal motivational effects [9].

The primary auditory cortices and the superior temporal cortices are assumed to be home to the main MMN generators. The MMN can be elicited irrespective of the subject's attentional state, which makes this ERP particularly suitable for clinical groups with low cooperation, such as children [10]. Several studies have shown that the MMN is an effective instrument for assessing central hearing impairment, cognitive decline, and functional decline [9–18]. There are few studies that look at mismatch-negativity results in patients with temporal lobe epilepsy; this study seeks to examine these findings to assess cognitive function in such patients by evaluating the auditory processing dysfunction using MMN test [9–18].

Methods

This case–control study was conducted in Menoufia University hospitals in the audiology unit (ENT department) in cooperation with the department of pediatric neurology in the period from April 2021 to October 2022. Ethical approval was obtained through the ethical committee with approval number (7/2021ENT35). Consent was taken from all the parents of the children to participate in the study. Subjects included in this study were divided into 2 groups; control group consisted of 22 normal children in the age range of (4–12 years), selected from the relatives of the children in the study group living within the same regions. However, the study group consisted of 22 children recruited from the pediatric neurology clinic diagnosed by pediatric neurologist as temporal lobe epilepsy of the complex partial subtype in the age range of (4–12 years). Children were controlled; if the children were not controlled, the test was done after at least 1 week from the last attack with the following exclusion criteria: children suffering from other neurological or systemic disorders and children suffering from otological problems. The Stanford-Binet IQ test was done for all children before they entered the study, and those who had a score below the normal scores were excluded. Complete history was taken from all subjects in this study including age, sex, types of epilepsy, its duration, frequency of attack, control of epilepsy, medications, EEG finding, and MRI finding. Physical and neurological assessments were done for all subjects.

Audiological evaluation was done including otoscopic examination, pure-tone audiometry using r37a clinical audiometer (either conventional or play audiometry which was done in only 4 cases), speech recognition threshold test for children as well as the word discrimination score (WD) [19] using sound-treated room model amplisilence S.P.A-10070, and acoustic immittance using middle ear analyzer (GSI 38-Auto TYMP).

MMN was done using Interacoustic, Eclipse 25. Children were awake during the recording, watching cartoons. The skin was cleaned by cotton soaked in alcohol, the ground electrode was placed on the forehead, the reference electrodes were placed over the mastoid, and the active electrode was placed over FZ. A standard stimuli (1 kHz) and deviant stimuli (2 kHz) were delivered to the children in oddball paradigm (15% deviation from the normal) at a rate of 0.7 per second using insert phones, 200 sweeps pure tones that were delivered at 70 dBHL, the filter was adjusted at 100 Hz for low-pass filter and 1 Hz 6/oct for high-pass filter, and analysis time was pre stimuli 90 ms and 630 ms for post stimuli [20].

MMN was identified as the largest negative excursion range from 100 to 250 ms occurring after the P2 response (positive peak of late-latency auditory-evoked potentials (LLAEP) occurring at approximately 160 ms). The response parameters of MMN were determined as the duration between the start of the stimulation and the lowest peak was determined to be the MMN latency (peak latency). From the trace's zero voltage to its deepest dip, MMN amplitude was recorded (baseline to peak amplitude). It is measured by deducting the reaction to normal stimuli from the response to abnormal stimuli.

Sample size estimation

Sample size was calculated by statistics doctor in the Community Department, Faculty of Medicine, Menoufia University [21]. Minimum sample size calculated is 40 subjects according to the following formula:

$$n \geq \frac{\left[\frac{z_{1-\alpha}}{2} + z_{1-\beta}\right]^2 + \left[\sigma_1^2 + \sigma_2^2/r\right]}{\left[\mu_1 - \mu_2\right]^2} \quad (1)$$

where

n: sample size.

$z_{1-\alpha}$: *z*-score for CI 95% and equals 1.96.

$z_{1-\beta}$: *z*-score for power of the study 80% and equals 0.84.

σ: estimated standard deviation.

μ: estimated mean.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 28 (SPSS Inc. Released 2020) was used for analysis of the results. Qualitative data were expressed as

number (N), percentage (%), and quantitative data as mean (x), standard deviation (SD), and range (minimum–maximum); analytic statistics, where Student's *t*-test (t), a test of significance, was used to compare quantitative variables between two groups of normally distributed data, and Mann-test Whitney's (U), which was used to compare qualitative data. Spearman correlation was employed for variables that were not normally distributed.

Results

Demographic characteristics are demonstrated in Table 1; there was no significant difference between the two groups regarding age and sex. Clinical data of children with temporal lobe epilepsy including their mean disease duration was 2.93 ± 2.05 years, number of attacks was 5.64 ± 4.62, the mean duration from the last attack was 3.98 ± 4.07 months, and these children were treated with benzodiazepine (45.5%), levetiracetam (0.9%), and benzodiazepine and levetiracetam (45.5%). All subjects had normal tympanometry results, normal hearing in both ears, normal MRI results, and temporal lobe epilepsy in EEG test. There is a statistically significant difference in MMN latency and amplitude between both groups as shown in Table 2.

According to ROC curve, it is found that in the latency cut-off value ≥ 1.81 and the amplitude cut-off value ≥ −3.28, the MMN latency and amplitude show a sensitivity of 90.9% and a specificity of 60% for both with an AUC value of (0.510–0.847) and (0.649–0.947), respectively, as shown in Fig. 1.

MMN abnormalities in TLE children included prolonged latency in 90.9% and low amplitude in 90.9%. There were no statistically significant correlations regarding the age, sex, duration of epilepsy, duration from the last attack, frequency of attacks, and the treatment as shown in Table 3.

Table 1 Demographic characteristics of the studied groups

	Control group (*N* = 22)	Study group (*N* = 22)	Test of significance	*p*-value
Age (years)			*t*-test	
Mean ± SD	6.65 ± 1.69	7.27 ± 1.80	1.150	0.257
Range	4–10	4–10		
Sex				
Male	11 (50%)	12 (54.5%)	X^2	0.768
Female	11 (50%)	10 (45.5%)	0.087	

t Student *t*-test, χ^2 chi-square test

Discussion

Temporal lobe epilepsy (TLE) is a chronic neurological disorder characterized by recurrent attacks of seizures arising from electrical abnormality of temporal lobe origin. TLE is the most common type of focal epilepsy [22]. Temporal lobe epilepsy is associated with impairment of cognitive functions; memory affection is the most common important due to damage in hippocampus surrounding structures [23].

Both short-term and long-term memories are compromised in TLE, as has been consistently demonstrated [24, 25]. TLE in children is a neurological condition that affects the central auditory system's cortical regions directly. To explore topographic and functional facets of auditory processing as well as underlying neurodevelopment, TLE appears to be a useful model. The use of event-related potentials (ERPs) may help researchers to better understand the learning difficulties in children with TLE as well as how epilepsy affects neural plasticity [26]. Cognitive function includes memory and attention [27]. Working memory disorder is recognized as the key cause in learning disabilities which can be assessed using MMN [28].

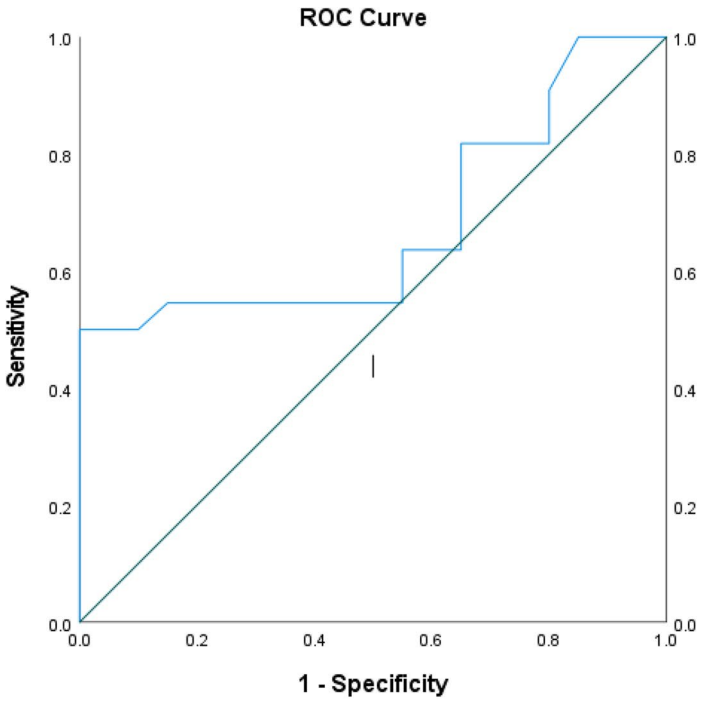
Mismatch negativity (MMN) indicates the initial cortical event in the cognitive processing of auditory information, and it is an auditory event-related potential (ERP). MMN can be elicited in the absence of attention. MMN test can be used to find the relationship between the auditory processing and temporal lobe epilepsy in children [29].

In the current study, results from 22 children with temporal lobe epilepsy (aged 8–12 years) and 22 healthy children were compared using MMN. Regarding age and sex, there was no statistically significant difference between the two groups.

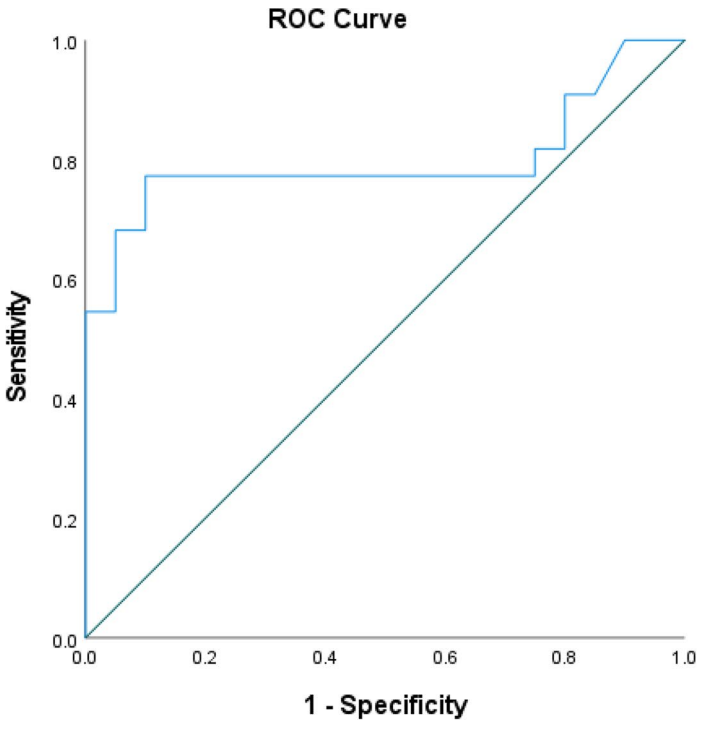
Table 2 Comparison between the studied groups regarding MMN results

	Control group (*N* = 22)		Study group (*N* = 22)		Test of sig	*p*-value
	Mean ± SD	Range	Mean ± SD	Range		
Latency	215.65 ± 33.16	134–250	277.27 ± 85.92	180–424	*t* = 3.118	**0.004**
Amplitude	−2.29 ± 0.75	−3.83–1.27	−1.35 ± 1.01	−3.4–0.2	*U* = 3.303	**< 0.001**

t Student *t*-test, *U* Mann–Whitney test



Roc curve for latency in TLE patients



ROC curve for amplitude in TLE patients

Fig. 1 ROC curves for amplitude and latency in the study group

Table 3 Relation between latency and amplitude of MMN and clinical data of study group

		Latency		Amplitude	
		Test of sig	***p*-value**	**Test of sig**	***p*-value**
Socio-demographic	**Age (years)**	$r = 0.140$	0.536	$r = -0.193$	0.390
	Sex				
	Male	$t = 0.374$	0.712	$U = 0.763$	
	Female				0.446
Clinical data of TLE	**Duration of epilepsy (years)**	$r_{rho} = -0.025$	0.911	$r_{rho} = -0.286$	0.197
	Last attack (months)	$r_{rho} = -0.225$	0.314	$r_{rho} = 0.057$	0.801
	Number of attacks	$r_{rho} = 0.003$	0.988	$r_{rho} = -0.348$	0.112
	Treatment				
	Depakine				
	Tiratam	*ANOVA* = 2.395	0.118	K-W = 1.491	0.475
	Depakine, tiratam				

r_{rho} Spearman correlation coefficient, *t* Student *t*-test

There were statistically significant differences between both groups regarding MMN latency and amplitude. MMN latency in TLE group was found to be more prolonged compared to that of the control group. Also, MMN amplitude was found to be reduced in almost all TLE patients when compared to the control group. Abnormal MMN tests (either prolonged latency or low amplitude) were obtained in almost all TLE patients. These results demonstrated that there was auditory processing dysfunction in TLE cases which was proved by abnormalities in the MMN test.

According to ROC curve in the current study, the auditory processing dysfunction in TLE cases can be predicted by using MMN test.

Prolonged MMN duration may be due to difficulty in the closure mechanism of MMN process explaining that there was a dysfunction of information processing observed in TLE patients due to concentration and memory difficulties, given that these patients may take more time for detecting the stimulus compared to controls. In TLE patients, developmental delay, original brain damage, and dynamic variables all have an impact on memory dysfunction (e.g., seizure frequency and medication) [30]. Also, in previous research, the MMN amplitude was affected differently by different areas of the temporal lobe [31]. For instance, although lesions in the medial area of the temporal lobe generated a pathological increase in MMN amplitude, lesions in the superior temporal lobe decreased MMN amplitude [32]. However, the TLE children in the current study had low MMN amplitude despite the normal MRI. Our results agreed with Metz-Lutz et al. who attempted to correlate neurophysiology dysfunction and various neurophysiological aspects of focal epileptic activity in benign childhood epilepsy with centro-temporal spikes (BCECTS) which reported lower amplitude in the cases compared to controls [31]. Also, the results agreed with Honbolygó et al. that assessed the cognitive function and speech perception skills in children with temporal lobe epilepsy using MMN (speech stimuli); the study revealed low score for language and memory functions in epileptic children in comparison to control group [33].

In the current study, MMN test abnormalities were obtained in children with TLE. Therefore, MMN test is suggested to detect cognitive dysfunction in these patients and can help in the design of rehabilitation programs for improving cognitive function, e.g., memory exercises, problem-solving games, and mental exercises. MMN can be used in the follow-up of the rehabilitation program with comparison of MMN results before and after the training program to determine the improvement in the cognitive function [34].

Some memory functions improve after surgery for epileptic lesions. The greater potential for cerebral plasticity in children may be the cause of the improvement in memory observed in some studies following surgery. In children with temporal lobe epilepsy, younger age and early surgery have been found to predict positive memory outcomes [35].

Limitation of the study

It is important to note that usage of anti-epileptic drugs (AEDs) may have an impact on both latencies and amplitude, given that all patients were receiving treatment with AEDs at the time of data collection. For instance, it has been demonstrated that anti-epileptic drugs can affect motor response times, latencies, and amplitudes generally [36]. It has been discovered that benzodiazepines, which are also used as AEDs, decrease MMN amplitude [37]. Benzodiazepines may alter sensory memory and

prolong the time it takes to evaluate an input. To further understand how AEDs affect TLE patients, so further studies to compare the changes in the MMN in children with TLE without treatment versus TLE with treatment will be needed.

Conclusion

Abnormalities in MMN test reflect cognitive impairment in children with TLE. It can be used to determine any cognitive dysfunction in these children, helping us to perform rehabilitation programs for improving cognitive function and follow-up of these patients.

Acknowledgements
The authors would like to thank members of Audiology Units, and Department of Pediatric Neurology, Menoufia University hospitals for research support.

Authors' contributions
HS selected the topic. AZ designed the plan of the research. SA diagnosed temporal lobe epilepsy and selected children of the study group. HA performed the test under supervision of AS and AZ. The data was collected and revised by all research group before analysis. AS analyzed the data. HA write the article, and A and A revised it. All authors read and approved the final manuscript.

Funding
The authors declare no financial or other conflicts of interest related to this work.

Availability of data and materials
The datasets analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was carried out according to the guidelines and roles prescribed by the Research Ethics Committee, Menoufia University, Faculty of Medicine. Ethical approval was obtained through the ethical committee with approval number (7/2021ENT35). A consent was taken from all the parents of the children to participate in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 15 June 2023 Accepted: 8 September 2023
Published online: 04 October 2023

References

1. Wiebe S, Blume WT, Girvin JP, Eliasziw M (2001) A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med 345:311–318
2. Engel J Jr (1996) Surgery for seizures. N Engl J Med 334:647–652
3. Williamson PD, French JA, Thadani VM, Kim JH, Novelly RA, Spencer SS, Spencer DD, Mattson RH (1993) Characteristics of medial temporal lobe epilepsy: II. Interictal and ictal scalp electroencephalography, neuropsychological testing, neuroimaging, surgical results, and pathology. Ann Neurol 34:781–7
4. Ballaban-Gil K (1995) Language disorders and epilepsy. In: Pedley TA, Meldrum BS (eds) Recent Advances in Epilepsy. Churchill Livingstone, Edinburgh, pp 205–220
5. Näätänen R, Gaillard AW, Mäntysalo S (1978) Early electiveattention effect on evoked potential reinterpreted. Acta Psychol (Amst) 42:313–329
6. Näätänen R, Paavilainen P, Alho K, Reinikainen K, Sams M (1989) Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain? Neurosci Lett 98:217–221
7. Näätänen R, Alho K (1995) Mismatch negativity—–a unique measure of sensory processing in audition. Int J Neurosci 80:317–337
8. Näätänen R, Winkler I (1999) The concept of auditory stimulus representation in cognitive neuroscience. Psychol Bull 125:826–859
9. Näätänen R (2000) Mismatch negativity (MMN): perspectives for application. Int J Psychophysiol 37:3–10
10. Ajmore MC, Zivin LS (1970) Factors related to the occurrence of typicalparoxysmal abnormalities in the EEG records of epileptic patients. Epilepsia 11:361–381
11. Lopes R, Simões MR, Ferraz L, Leal AJ (2014) The mismatch negativity (MMN) potential as a tool for the functional mapping of temporal lobe epilepsies. Epilepsy Behav 33:87–93. https://doi.org/10.1016/j.yebeh.2014.02.017
12. Alho K, Woods DL, Algazi A, Knight RT, Näätänen R (1994) Lesions of frontal cortex diminish the auditory mismatch negativity. Electroencephalogr Clin Neurophysiol 91:353–362
13. Annett M (1970) A classification of hand preference by association analysis. Br J Psychol 61:303–321
14. Beck AT, Ward CN, Mendelson M et al (1961) An inventory for measuring depression. Arch Gen Psychiatry 4:561–571
15. Betts T, Boden S (1992) Diagnosis, management, and prognosis of a group of 128 patients with non-epileptic attack disorder. Part I Seizure 1:19–26
16. Betts T (1998) Psychiatric aspects of nonepileptic seizures. In: Engel J, Pedley TA (eds) Epilepsy: a Comprehensive Textbook. Lippincott-Raven, Philadelphia, pp 2101–2116
17. Carpenter WT, Heinrichs DW, Wagman AM (1988) Deficits and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 145:578–583
18. Cartmill A, Betts T (1992) Seizure behaviour in a patient with posttraumatic stress disorder following rape. Notes on the aetiology of "pseudoseizures." Seizure 1:33–6
19. Soliman S, EL-Mahallawy T, Simple speech test material as a predictor for speech reception threshold (SRT) in preschool children. Master Dissertation: Audiology Unit, Ain Shams, Egypt, 1984.
20. https://www.manualslib.com/manual/2411925/Interacoustics-Eclipse-Ep15.html?page=65#manual
21. Miyajima M, Ohta K, Hara K, Iino H, Maehara T, Hara M, Matsuura M, Matsushima E (2011) Abnormal mismatch negativity for pure-tone sounds in temporal lobe epilepsy. Epilepsy Res 94(3):149–157. https://doi.org/10.1016/j.eplepsyres.2011.01.009. (Epub 2011 Mar 1 PMID: 21367585)
22. NINDS, The epilepsies and seizures: hope through research, National Institute of Neurological Disorders and Stroke (NINDS), U.S. National Institutes of Health (NIH), archived from the original on 27 July 2018, retrieved 8 August 2018.
23. Engel J (2001) A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 42(6):796–803. https://doi.org/10.1046/j.1528-1157.2001.10401.x
24. Butler CR, Zeman AZ (2008) Recent insights into the impairment of memory in epilepsy: transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment. Brain 131(Pt.9):2243–63
25. McCagh J, Fisk JE, Baker GA (2009) Epilepsy, psychosocial and cognitive functioning. Epilepsy Res 86:1–14
26. Tomé D, Jesus E, Esteves M (2011) Auditory middle latency responsein epilepsy. Sinapse 11:5–11
27. Roberts, A. C., Robbins, T. W., & Weiskrantz, L. (Eds.). (1998). The prefrontal cortex: executive and cognitive functions. Oxford University Press. https://doi.org/10.1093/acprof:oso/9780198524410.001.0001
28. Zhang H, Chang L, Chen X, Ma L, Zhou R (2018) Working memory updating training improves mathematics performance in middle school students with learning difficulties. Front Hum Neurosci 12:154. https://doi.org/10.3389/fnhum.2018.00154

29. Duncan CC, Barry RJ, Connolly JF, Fischer C, Michie PT, Näätänen R, Polich J, Reinvang I, VanPetten C (2009) Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clin Neurophysiol 120(11):1883–1908
30. Hoppe C, Elger CE, Helmstaedter C (2007) Long-term memory impairment in patients with focal epilepsy. Epilepsia 48:26–29. https://doi.org/10.1111/j.1528-1167.2007.01397.x
31. Metz-Lutz M-N, Filippini M (2006) neuropsychological findings in rolandic epilepsy and Landau-Kleffner syndrome. Epilepsia 47:71–75. https://doi.org/10.1111/j.1528-1167.2006.00695.x
32. Escera C, Corral MJ, Yago E (2002) An electrophysiological and behavioral investigation of involuntary attention towards auditory frequency, duration and intensity changes. Cogn BrainRes 14:325–332
33. Honbolygó F et al (2006) Converging evidences on language impairment in Landau–Kleffner syndrome revealed by behavioral and brain activity measures: a case study. Clin Neurophysiol 117(2):295–305
34. Irazoki E, Contreras-Somoza LM, Toribio-Guzmán JM, Jenaro-Río C, van der Roest H, Franco-Martín MA (2020) Technologies for cognitive training and cognitive rehabilitation for people with mild cognitive impairment and dementia A systematic review. Front Psychol 9(11):648. https://doi.org/10.3389/fpsyg.2020.00648.PMID:32373018;PMCID:PMC7179695
35. Menlove L, Reilly C (2015) Memory in children with epilepsy: a systematic review. Seizure 25:126–135
36. Rosburg T, Trautner P, Dietl T, Korzyukov OA, Boutros NN, Schaller C (2005) Christian Erich Elger, Martin Kurthen, Subdural recordings of the mismatch negativity (MMN) in patients with focal epilepsy. Brain 128(4):819–828. https://doi.org/10.1093/brain/awh4421
37. Rosburg T et al (2004) Effects of lorazepam on the neuromagnetic mismatch negativity (MMNm) and auditory evoked field component N100m. Neuropsychopharmacology 29(9):1723–1733

Publisher's Note