Title:

Auditory Processing in Patients with Temporal Lobe Epilepsy: a systematic review and meta-analysis

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Highlights

- Deficient auditory processing in Temporal Epilepsy Patients is evidenced by psychoacoustic and electrophysiological evaluation
- Lack of hearing sensitivity assessment is documented in electrophysiological studies

Abstract

Background: Hearing efficiency is known to influence and interact with communication and mental health. Hearing impairment may be hidden when co-occurring with neurological disorders.

Purpose: We performed a systematic review and meta-analysis in order to address the following questions: 1) which specific tools of auditory processing show clear deficits, separating Temporal Lobe Epilepsy (TLE) patients from normal controls,2) How well is TLE evaluated in terms of hearing and auditory processing?

Methods: The study inclusion criteria were: 1) patients diagnosed with temporal lobe epilepsy, 2) presence of a normal control group, 3) auditory processing assessment using auditory stimuli with behavioral tests and/or P300 or Mitch Match Negativity (MMN) latency and/or amplitude, 4) publications written in English, 5) publication date

after 2000. 132 articles were retrieved and based on PRISMA & PICO criteria 23 articles were analyzed.

Results: Temporal resolution and processing as measured by the behavioral tests of Gaps-In-Noise (GIN) and Duration Pattern Test (DPT) document deficiencies in TLE patients and separate them from normal controls. Electrophysiology as measured by MMN & P300 shows statistically significant differences in TLE patients compared to controls with patients showing deficient auditory processing. A clear difference between studies with psychoacoustic assessment as opposed to electrophysiology ones may be due to lacking or incomplete evaluation of peripheral hearing by gold standard tools (76.9% in electrophysiology studies).

Conclusion: Auditory processing is deficient in patients with TLE. There is a clear need to evaluate hearing efficiency before proceeding to auditory processing evaluation with behavioral or electrophysiological tests.

Key words: hearing, temporal lobe epilepsy, auditory processing, time resolution, duration pattern recognition

Abbreviations: TLE: temporal lobe epilepsy, MMN: Mitch Match Negativity, GIN: Gaps-In-Noise, DPT: Duration Pattern Test

1. Introduction

Hearing efficiency is known to influence and interact with communication, learning, social aspects of life, cognition and mental health [1,2]. Understanding the connection of hearing with all these elements of life is a prerequisite to establishing a better approach to when, how and why to evaluate hearing capacity. To answer the question when to evaluate an individual for hearing, one must take under consideration that hearing impairment may be hidden when co-occurring with a neurological disorder [3]. This refers to the characteristic “invisible disability” of hearing impairment [4].

Symptoms may extend beyond constantly asking people to repeat phrases, saying "sorry, what did you say?" or similar behavior. Instead, individuals with hearing impairment may have frequent headaches due to their constant struggle to hear accurately or seem like being inattentive or avoid communication all together leading to social isolation. Such symptoms should lead to hearing evaluation [5]. Common clinical practice does not comply with this leading to undiagnosed hearing impairment in adults [6].

To answer the question how to evaluate hearing one should start with pure tone audiometry and extend to speech in noise evaluation as a first step of an auditory processing assessment. Hearing evaluation in the presence of a neurological disorder is usually either absent or not elaborate enough [7]. In a clinical setting it might be difficult to evaluate every patient and the need to gather reliable information about patients that may be requiring a detailed evaluation is essential. A recent exploratory study [3] showed that despite current recommendation to include a full functional ability and communication assessment in patients with stroke, hearing is not specifically included in the assessment. This reveals the need for transferring published research knowledge into clinical practice and might be the result of limited multidisciplinary communication in the medical community. Lastly, to answer the question why there is a need to evaluate hearing as described above one should refer to the importance and frequency of occurrence of hearing impairment. Hearing impairment is the third leading cause of years lived in disability at a global level [8] and middle life untreated hearing loss is the biggest modifiable cause of dementia [9].

Amongst neurological disorders potentially associated with deficits in auditory processing Temporal Lobe Epilepsy (TLE) is particularly relevant. Auditory function may be affected in TLE as the epileptogenic foci in the temporal lobe may affect auditory processing through temporary neural dysfunction. Temporal lobe may be considered as the last stop of bottom-up auditory processing while encompassing primary and secondary auditory areas to fully perceive and interpret incoming auditory signals [10]. Accordingly, this systematic review and meta-analysis aims to address the following two questions: 1) which specific tools of auditory processing show clear deficits separating TLE patients from normal controls and 2) to what

extent does the evaluation of auditory perception in patients with Temporal Lobe Epilepsy (TLE) align with established gold standard assessment tools?

2.Material & Methods

The study was registered with PROSPERO database (registration number CDR42024526181) for the International Prospective Register of Systematic Reviews. Two databases, Scopus and PubMed were systematically searched with the following key words for papers between January 2000 to December 2023:(“auditory processing”) AND (“temporal lobe epilepsy”), (“auditory processing”) AND (“temporal lobe epilepsy”) AND (“P300”), (“auditory processing”) AND (“temporal lobe epilepsy”) AND (“MMN”), (“temporal processing”) AND (“temporal lobe epilepsy”), (“temporal processing”) AND (“temporal lobe epilepsy”) AND (“P300”), (“temporal processing”) AND (“temporal lobe epilepsy”) AND (“MMN”), (“dichotic listening”) AND (“temporal lobe epilepsy”), (“dichotic listening”) AND (“temporal lobe epilepsy”) AND (“P300”), (“dichotic listening”) AND (“temporal lobe epilepsy”) AND (“MMN”), (“temporal lobe epilepsy”) AND (“P300”), (“temporal lobe epilepsy”) AND (“MMN”). The databases were chosen as the most relevant material is included as well as due to ease of access.

The study inclusion criteria were: 1) patients diagnosed with temporal lobe epilepsy, 2) presence of a normal control group, 3) auditory processing assessment using auditory stimuli with behavioral tests and/or electrophysiological methods, focused on P300 or Mitch Match Negativity (MMN) latency and/or amplitude, 4) publications written in English, 5) publication date after 2000. Studies that didn’t fulfill the above criteria were excluded.

After searching the electronic databases with keywords and filters, the records found were screened by title and abstract by two independent review authors and those unrelated to the study subject were rejected. In case of disagreement a third senior reviewer provided input to resolve the conflict. Full text was sought and assessed for the remaining records and they were either accepted or rejected based on the inclusion

criteria. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed [11].

The research was structured and organized according to the PICO model [12], which is an acronym for Target Population, Intervention, Comparison, Outcomes and Study type. The population of interest or health problem (P) corresponds to patients with temporal lobe epilepsy, (I) to behavioral and /or electrophysiological evaluation (P300 or MMN) of auditory processing, C) corresponds to comparison of results for each test between clinical and control groups and O) refers to the auditory processing evaluation outcomes.

2.1 Meta-analysis

As the systematic review revealed abnormal auditory processing in both behavioral and electrophysiological studies and in order to perform a comprehensive evaluation of auditory dysfunction in TLE, a meta-analysis was conducted for all tests that were used in at least four different publications. The meta-analysis was conducted using the "metafor" packages from R software (version 4.3.2) [13]. Due to the fact that a variety of measurements from the same population were reported (e.g. left ear/ right ear, multiple measurements from each participant), a multilevel model of meta-analysis was used to account for the nested structure of the data, including non-independent effect sizes in a single model [14, 15]. Additionally, in this model, using the "dmetar" and "esc" packages, I^2 values estimating heterogeneity variance both within and between study [16,17] can be reported. The Knapp-Hartung method was applied to account for heterogeneity in regression coefficients [18] while variability between and within studies was also assumed through the use of a random effects model [16]. For the normalization of the effect sizes of all the studies that were included, the Standardized Mean Difference (SMD) was calculated. Hedge's g adjustment [19] for small sample bias was used in order to correct the effect sizes and avoid skewing the results, as the studies involved a relatively small number of participants.

In order to create a conceptually and visually meaningful comparison of the data, the signs of some of the measurements were changed. Thus, regardless of the test that is

reported, a positive sign and/or a higher value, indicates higher performance in hearing evaluation. A total of three models will be presented. The first one presents only the behavioral data, the second presents all the electrophysiological data together and the last model includes all measures together.

3.Results

3.1 Data extraction and quality assessment

Literature review resulted in one hundred and thirty-two (132) publications, seventy-four (74) in Scopus and fifty-eight (58) in PubMed. When the seventy-one (71) duplicates were removed, sixty-one (61) articles remained. Following the title and abstract evaluation twenty-nine (29) publications were excluded as irrelevant to the population of interest. For the thirty-two (32) remaining reports, the full text was retrieved and assessed. Sixteen (16) studies were excluded, five (5) because a healthy control group was not included in the study, (3) three studies were review papers, two (2) due to lack of clearly description of the behavioral test that was used, and (3) three studies because P300 data were lacking. Three (3) studies were conducted in Benign epilepsy with Centro-temporal spikes (BECTS) patients thus not considered acceptable. Seven (7) additional studies were found following citation searching from the already included seventeen (17) articles. The last step was to evaluate the accepted articles following the guidelines proposed by the Cochrane's tool for assessing risk of bias (RoB2) [19], which did not lead to the exclusion of any studies. This was evaluated by all authors and includes five domains with an overall RoB judgment domain. The five domains that were judged according to high, low or some concerns included randomization process, deviation from intended evaluations, missing data, outcome measure and selection of the reported results.

3.2 Overview

A total of twenty-three (23) studies were finally included. (Fig.1)

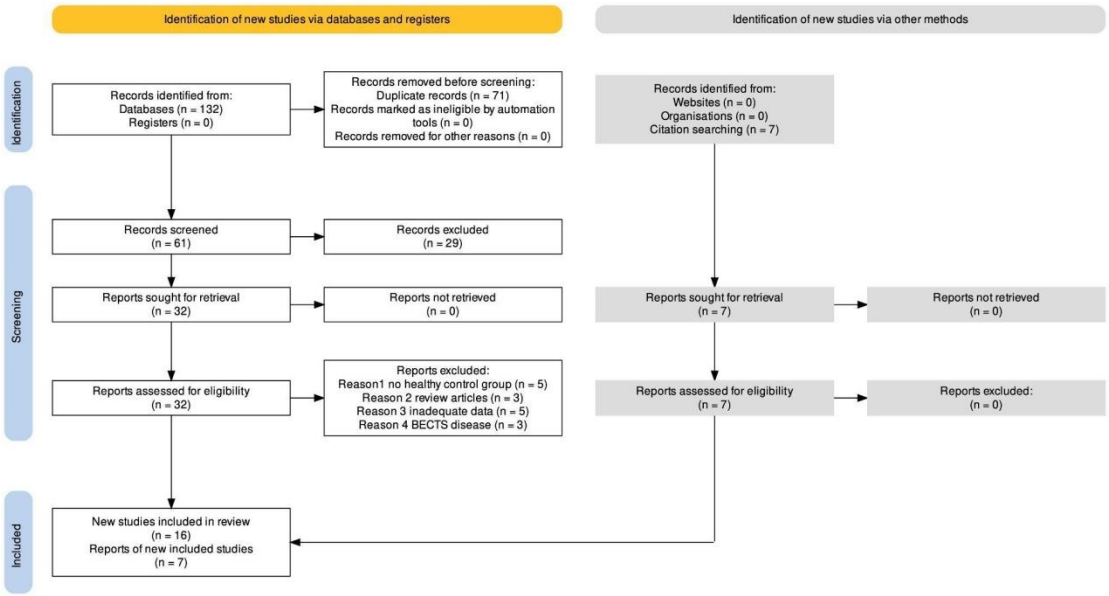

Fig. 1. PRISMA 2020 flow diagram of study selection.

Peripheral hearing: Pure tone audiometry, the gold standard evaluation of hearing sensitivity was present with specific cut-off thresholds in 8 [20-27] out of 10 behavioral studies[20,21,22,23,24,25,26,27,28,29], 1[34] in 6 of P300 studies [30,31,32,33,34,35], 1[39] out of 5 studies using MMN [36,37,38,39,40] and 1[42]out of 2 studies [41,42] combining electrophysiology and behavioral auditory processing assessment (see table 1 for details).

Table 1.

no	**Author**	Peripheral hearing evaluation
	Behavioral studies	
1	Lavasani, A.N, et.al (2016)	pure tone thrs. ≤20 dBHL, SRTs, tympanometry, acoustic reflex
2	Aravindkumar, R., et.al (2012)	pure tone thrs. ≤25 dBHL
3	Aravindkumar, R., et.al (2014)	pure tone thrs. ≤25 dBHL
4	Rajasekaran, A.K., et.al (2021)	pure tone thrs. ≤25 dBHL
5	Ismail, N. M., et.al (2019)	pure tone thrs. ≤20 dBHL, tympanometry, acoustic reflex
6	Rabelo, C. M., et.al 2015	pure tone thrs. ≤20 dBHL
7	Meneguello, J., et.al (2006)	pure tone audiogram (no specified cut-off threshold), SRTs, tympanometry, acoustic reflex
8	Shahbazi, S., et.al (2016)	pure tone thrs. ≤25 dBHL, tympanometry
9	Ehrlé, N., et.al 2001	no data
10	Bidet-Caulet, A., et.al (2009)	self-report
	MMN studies	

1	Hara, K., et.al (2012)	self-report
2	Miyajima, M., et.al (2011)	self-report
3	Hirose, Y., et.al (2014)	self-report
4	Zhao, L., et.al (2017)	pure-tone audiogram, tympanometry
5	Lopes, R., et.al (2014)	no data
	P300 studies	
1	Chen, R-C., et.al (2001)	no data
2	Mudabbir, M.M., et.al (2021)	self-report
3	Chayasirisobhon, W. V., et.al 2017	no data
4	Artemiadis, A.K., et.al 2014	no data
5	Casali, R., et.al (2016)	pure tone thrs. ≤15 dBHL, tympanometry
6	Gökçay, F., &Gökçay, A. (2005)	no data
	Combined studies	
1	Rocha, C. N., et.al (2010)	history of auditory problems
2	Boscariol, M., et.al (2015)	pure tone thrs. ≤15 dBHL, tympanometry

Table 1. Peripheral hearing assessment in the included studies. Abbreviations & Acronyms: thrs: threshold, SRTs: speech recognition thresholds, no data: no referral to hearing status or no description of the method used for peripheral hearing evaluation.

Behavioral evaluation of auditory stimuli process requires evaluation of different domains such as monaural low redundancy, dichotic- binaural interaction and temporal aspects of hearing. Literature review resulted in ten studies [20-29] assessing auditory processing with behavioral tests (Table 2), with temporal processing being the most studied aspect.

Table 2.

Behavioral studies	**Adults**		
Author	**Sample (age range)**	**Behavioral test**	**Results**

1. Lavasani. A.N, et.al (2016)	HC n=18 (20-50 y) Pat. n=25 (20-50 y) RTLE n=11 LTLE n=14	**GIN** th. (ms) Mean (SD)-PCI % mean (SD). RE: 4.77 (0.54) - 70.7% (6.4) LE: 5.10 (0.83) - 69.2% (8.3) RE:7.09(2.2) – 59.20% (2.8) LE: 7.18(2.3) – 57.90% (1.3) RE:6.64(2.9) – 61.06% (1.3) LE:7.20(2.6) – 58.30% (1.3)	**DPT %** mean (SD) RE: 94.99(4.9) LE: 92.60 (5.5) RE:93.6(6.04) LE:93.6(6.2) RE:63.08 (2.2) LE:63.50 (2.34)	-Mean GIN thr. ss better in HC vs RTLE (p=0.01 RE & p=0.02 LE) - Mean GIN th.ss better in HC vs LTLE (p=0.03 RE & p=0.012 LE -Mean DPT ss better in HC vs LTLE (p=0.000 RE & p=0.000 LE) -Mean DPT ss better in RTLE vs LTLE (p=0.00RE & p=0.00 LE)
2. Aravindkumar, R., et.al (2012)	HC n=50 26.3y(SD=5.17) RTLE n=13 31y(SD=7.67) LTLE n=13 25.76y(SD=8.26)	**GIN** th. (ms) Mean (SD)-PCI % mean (SD) RE 5.22(1.11) - 69.77(8.98) LE 5.06 (1.00) - 71.10(8.89) RE 8.15 (2.34) - 55.13(14.47) LE 7.85 (3.00) - 51.92 (17.96) RE 9.54 (5.67) - 47.82 (12.70) LE 10.15(4.06) - 48.72 (12.49)		-mean GIN thr. Ss better in HC vs RTLE & LTLE (p=0.000 in both ears) - mean PCI ss better in HC vs RTLE & LTLE (p= 0.000 in both ears) -no ss difference between RTLE vs LTLE
3.Aravindkumar, R., et.al (2014) not included in the meta-analysis as the test used was not used by at least 4 studies in total	HC n=50 27.16y(SD=4.95) Pat. n=100 MTLE+HS n=50 26.62y(SD=7.56) MTLE-HS n=50 27.36y(SD=9.42)	**DDT** % mean (SD) FR right ear: 98.00 (3.13) FR left ear: 96.70 (3.70) DR right ear:99.90 (0.70) DR left ear: 99.80 (1.10) FR right ear: 80.55 (14.18) FR left ear: 71.25 (16.60) DR right ear: 89.95 (16.13) DR left ear: 83.00 (22.58) FR right ear: 73.10 (21.75) FR left ear: 65.05 (22.18) DR right ear: 81.95 (24.03) DR left ear: 77.20 (23.55)		-ss difference better HC vs MTLE +HS & MTLE-HS in all conditions (p< 0.001) -ss difference MTLE+HS vs MTLE-HS on FR-right ear condition (p=0.046)
4.Rajasekaran, A.K., et.al (2021)	HC n=50 (15-50y) Pat. n=100	**DPT %** mean (SD) RE: 93.10 (9.99) LE: 93.70 (9.08)		-mean percentage of correct response ss better in HC vs all patients' groups (p<0.001) -no ss difference between clinical groups

	MTLE+HS n=50 (15-50y) MTLE-HS n=50 (15-50y)	RE:55.90(25.96) LE:56.20(28.38) RE:49.10(32.15) LE:46.30(32.46)	
5. Ismail, N. M., et.al (2019)	HC n=10 (12-16 y) 14.3(SD=1.2) TLE n=30 (12-16 y) 13.8(SD=1.5)	**GIN ap (ms).** thr. Mean (SD)-**total GIN score%** mean (SD) RE 4.8 (0.8) - 74.3 (4.3) LE 4.8 (0.8) - 73.0 (4.6) RE 8.8 (1.7) - 49.2 (7.3) LE 8.5 (1.6) - 49.9 (7.4)	-mean approx. GIN th.& total GIN score (%) ss better in HC vs TLE (p<0.001) -ss negative correlation between total GIN % & GIN total correct score and disease duration -ss positive correlation between approx. GIN th. and disease duration
6. Rabelo, C. M., et.al 2015	HC n=30 24.9(SD=3.3) Pat. n=16 38.9(SD=9.3)	**GIN** thr(ms) Mean (SD)-PCI % mean (SD) RE 4.7 (1.0) - 75.6 (7.6) LE 4.6 (1.0) - 76.1 (7.6) RE 7.4 (2.9) - 57.6 (13.0) LE 8.1 (1.7) - 52.7 (13.1)	-ss lower (better) GIN thr.in HC vs TLE (p<0.001) -ss poorer performance in PCI in TLE vs HC
7.Meneguello, J., et.al (2006)	HC n= 10 (16-48 y) TLE n=8 (22-51 y)	**DPT %** (average) RE: 85.2%. LE: 85.7% RE: 53.3% LE: 56.6% **DDT %** (average) RE: 99.2% LE: 98.7% RE:94.6% LE: 91.5% **Non-verbal dichotic test** % (average) F.A RGH LGH RE: 11.1. 11.8. - LE: 12.8 - 11.9 RE: 11.3 11.5. - LE: 12.3 - 11.5	-HC similar performance to TLE to sound source discrimination -TLE lower performance vs HC in DPT -TLE lower performance in verbal & non -verbal dichotic tests
8.Shahbazi, S., et.al (2016) not included in the meta-analysis as the test used was not used by at least 4 studies in total	HC n=25 (18-59 y) LTLE n=25 (18-59 y)	**SSW** Right non-competing condition 2.16(2.86) Right Competing condition 3.32(3.11) Left non-competing condition 2.69(4.31) Left Competing condition 3.96(3.82) RE 3.64(3.27) LE. 4.24(3.73) Total 3.92(3.20) Right non-competing condition. 10.98(8.35) Right Competing condition 15.16(17.07) Left non-competing condition 12.68(9.61) Left Competing condition 20.00(14.44) RE 11.04(7.12) LE 13.48(7.61 Total 12.04(6.50)	-ss difference (p<0.001) in all conditions, TLE higher vs HC -poor direct relationship btw duration of epilepsy and total score (p=0.04) -ss higher score in TLE vs HC I order effect (p=0.048), ear effect (p<0.001) and reversals (p=0.008)
9.Ehrlé, N., et.al 2001 not included in the meta-analysis as the test used was not used by at least 4 studies in total	HC n= 6 (22-55 y) RTLE n=8 (17-52 y)	anisochrony discrimination thresholds % (tempo 80 msec) 16.4% (mean) 17.7% (mean)	-ss higher threshold LTLE vs RTLE (P<0.01) and vs HC (P<0.01) at 80 msec tempo -threshold obtained with 80msec tempo ss different from other tempos (P<0.01)

	LTLE n=10 (25-44 y)	27.5% (mean)	
10.Bidet-Caulet, A., et.al (2009) not included in the meta-analysis as the test used was not used by at least 4 studies in total	HC n=18 TLE n=26	**7 Non-verbal tests** -auditory modulation detection tests -auditory short-memory tests -acoustic short-term memorization of pure tones -acoustic short-term memorization of environmental sounds -auditory object short-term memorization -short -term memorization and extraction of an environmental sound within a sound mixture -auditory semantic identifications	-ss worse correct response rate in patients pre- and post-surgery vs HC in: acoustic short-term memorization of pure tones (pre: P=0.008, post: P=0.005) acoustic short-term memorization of environmental sounds (pre: P=0.028, post: P=0.014) auditory object short-term memorization (pre: P=0.016, post: P=0.036) short -term memorization and extraction of an environmental sound within a sound mixture (pre: P<0.001, post: P<0.001) auditory semantic identifications (pre: P<0.001, post: P<0.001) -ss worse accuracy after larger resection vs smaller resection surgery in acoustic short-term memorization of pure tones(P=0.047)

Table 2 Studies assessing auditory processing with behavioral tests. Abbreviations & Acronyms: HC: healthy control, Pat.: patients, n: number, RE: right ear, LE: left ear, TLE: temporal lobe epilepsy, RTLE: right temporal lobe epilepsy LTLE: left temporal lobe epilepsy, MTLE: mesial temporal lobe epilepsy, HS: hippocampal sclerosis, GIN: gaps in noise, DPT: duration pattern test, DDT: dichotic digit test, SSW: staggered spondaic word, Thr.: Threshold, PCI: percent of correct identification, Ap.: approximate , SD: standard deviation, F.A: free attention, RGH: right guided hearing, LGH:left guided hearing, ms:millisecond, SD: standard deviation, y:year

A total of eleven papers [30-40] conducted an electrophysiological study in TLE patients by measuring latency and/or amplitude of P300 event related component (ERP) or MMN. (Table 3).

Table 3.

MMN studies	**adults**				
Author/year	**Sample** **Age range**	**Electrophysiology test**		**Stimuli**	**Result**
MMN studies	**adults**				
1. Hara, K., et.al (2012)	HC n=22 (20-50 y)	**MMN latency (ms)** mean (SD) Consonant vowel stimuli Fz 144.1 (28.5) Cz 138.0 (29.6) Mast. R. 139.9 (30.5) Mast. L. 149.5 (36.7)	**MMN amplitude (μV)** mean (SD) Consonant vowel stimuli Fz. - 1.23 (1.6) Cz. -0.96 (1.42) Mast.R. 1.19 (1.11) Mast. L. 1.36 (1.20)	Consonant vowel (90dB SPL)	-difference btw standard & deviant stimuli (MMN) mean amplitudes was ss smaller in TLE vs HC in mastoid sites (P<0.05)

	TLE n=19 (20-50 y)	Fz. 150.1 (26.7) Cz. 143.3 (28) Mast.R. 130.7 (35.6 Mast.L. 141.5 (36.9	Fz -2.19 (1.86) Cz -2.33 (1.60) Mast.R. 0.32 (1.38) Mast.L. 0.26 (1.32		
2.Miyajima, M., et.al (2011)	HC n=20 (23-50 y) 34y(SD=7.8) TLE n=20 (20-50 y) 33.9y(SD=10.0)	**MMN latency (ms)** mean (SD) Frequency stimuli Fz. 133 (28) Cz. 141 (42) Mast R 150(33) Mast L 145 (31) Fz. 179 (36) Cz. 171 (41) Mast.R 185 (39) Mast L 157 (53)	**MMN amplitude (μV)** mean (SD) Frequency stimuli Fz. -0.05 (0.73) Cz. -0.10 (1.19) Mast R 0.47 (0.58) Mast L 0.35 (0.51) Fz. -0.75(0.84) Cz. -0.64(0.93) Mast R 0.02(0.63) Mast.L 0.06(0.91	Tonal freq. changes (90 dB SPL)	-mean MMN amplitudes ss higher in TLE vs HC in frontocentral sites (P<0.05) -mean MMN latency was ss longer in TLE vs HC in both sites (P<0.05) - TLE greater standard waveform amplitudes vs HC (P<0.001) at mastoids
3. Hirose, Y., et.al (2014)	HC n=15 (22-48 y) 32.4y(SD=9.1) TLE n=15 (20-50 y) 33.2y(SD=9.8)	**MMN latency (ms)** mean (SD) Duration stimuli Fz. 224 (19.1) Cz. 214 (17.4) Mast R 221 (25.6) Mast L 223 (26.9) Frequency stimuli Fz. 150 (23.6) Cz. 152 (24.7) Mast. R 146 (19.9) Mast. L 144 (19.8) Duration stimuli Fz 219 (21.7) Cz 219 (23.3) Mast. R 228 (22.3) Mast. L 219 (24.9) Frequency stimuli Fz 156 (25.6) Cz 155 (25.0) Mast.R 144 (22.1) Mast.L 135 (20.4)	**MMN amplitude (μV)** mean (SD) Duration stimuli Fz. -1.28 (0.98) Cz. -1.08 (1.15) Mast. R 0.68 (0.45) Mast. L 0.67 (0.51) Frequency stimuli Fz. −1.20 (0.58) Cz. −0.87 (0.74) Mast. R 0.50 (0.40) Mast.L. 0.68 (0.55) Duration stimuli Fz. -1.51 (0.71) Cz -1.53 (0.72) Mast. R 0.17(0.50) Mast. L 0.37(0.63) Frequency stimuli Fz - 0.49 (1.08) Cz. - 0.40 (1.22) Mast.R 0.26 (0.47) Mast.L 0.47 ((0.65)	Tonal duration changes Tonal freq. changes 90dB SPL)	-mean MMN amplitudes were ss lower in TLE vs HC at mastoids (Duration stimuli) (P<0.05
4.Zhao, L., et.al (2017)	HC n=30 44.27(SD=9.61) TLE n=30 37.74y(SD=13.74)	**MMN latency (ms)** mean (SD) Frequency stimuli Fz. 176.09 (27.23) Cz. 177.40 (26.44) Mast.R 174.90 (23.67) Mast.L 174.36 (24.37) Fz. 196.83 (11.54) Cz 196.29 (13.14) Mastoid Mast.R 198.58 (15.77) Mast.L 196.95 (16.27)	**MMN amplitude (μV)** mean (SD) Frequency stimuli Fz. -1.93(-0.93) Cz. -2.26 (-1.07) Mast.R 2.14 (1.48) Mast.L 2.04 (1.30) Fz -1.94(-1.37) Cz. -1.93(-1.35) Mastoid Mast.R 2.28(1.34) Mast.L 2.27(1.34)	Tonal freq. changes (70dB SPL)	-Mean MMN latency was ss longer in TLE vs HC at both frontocentral (P<0.05) and mastoid (P<0.001) sites.
MMN studies	**children**				

5.Lopes, R., et.al (2014) **This study was not included in the metaanalysis due to no reported sd**	HC n=10 (4-16 y) Pat. n=17 (4-17y)	**MMN latency (ms)** Duration stimuli 110-162 (range). 149 (average).		Tonal duration changes (60dB HL)	-MMN latency abnormal 6/17 pat. -MMN amplitudes abnormal 7/17 pat. all TLE
P300 studies	**adults**				
6.Chen, R-C., et.al (2001)	HC n= 60-44.2y (SD=16.7) Pat. n=40 IGE n=27-30.59y (SD=12.50) TLE n=13 40.91y (SD=15.11)	**P300-age corrected P300 latency (ms)** mean (SD) Frequency stimuli RE 342.0 (23.1) – 0.2(20.2) LE 342.1 (22.1) – 0.1(18.9) RE 350.0 (40.5)- 13.8(40.4) LE 350.7 (38.0) – 15.0(37.2)	**P300 amplitude (μV)** mean (SD) Frequency stimuli RE 14.1 (6.4) LE 14.0 (6.7) RE 12.6 (6.5) LE 11.8 (5.9)	Tonal freq. changes (70 dB)	-age corrected P300 latencies in patients ss longer vs HC (P<0.001) -TLE pat. mean age corrected P300 latency ss longer vs HC (P<0.05) -high frequency seizures (>400) group age corrected P300 latency ss longer vs HC (P<0.05)
7.Mudabbir, M.M., et.al (2021)	HC n=15 28.13y(SD=4.76) RTLE n=15 29.2y(SD=5.84) LTLE n=15 26.20y (SD = 6.25)	**P300 latency (ms)** mean (SD) Frequency stimuli 323.93(40.28) 351.06(47.23) 328.80(36.03)	**P300 amplitude (μV)** mean (SD) Frequency stimuli 2.304((1.46) 2.77(1.19) 2.68(1.78)	Tonal freq. changes (- dB)	-no ss difference of P300 amplitude & latency btw TLE and HC or btw patient subgroups - correlations of auditory P300 latency & amplitude of LTLE with cognitive scales
8.Chayasirisobhon, W. V., et.al 2017	HC n=30 Age matched TLE n=3 (11-78y) 39.8y(SD=18)	**P300 latency (ms)** mean (SD Frequency stimuli Fz 319.1 (18.9) Cz 315.4 (17.6) Pz 323.8 (23.3) Fz. 324.7 (41.8) Cz. 327.4 (31.5) Pz. 324.1 (32.2)	**P300 amplitude (μV)** mean (SD) Frequency stimuli Fz 10,1(4,9) Cz 11.05 (5.8) Pz 11.2 (5.6) Fz 14,0 (6.7)) Cz 15.0 (7.0) Pz 13.4 (6.9)	Tonal freq. changes (60 dB HL)	-no ss difference in P300 amplitude & latency btw TLE and HC
9.Artemiadis, A.K., et.al 2014		**P300 latency (ms)** median(range) Frequency stimuli		Tonal freq. changes (40 dB)	-TLE longer latency and lower amplitude vs HC -P300 latency & amplitude are good predictors of TLE

This study was not included in the metaanalysis due to no reported sd	HC n=16 (19-61y) Median 35y TLE n=43 (17-57y) Median 32.5y	346 (288-408) 377 (320-448)			
P300 studies	**children**				
10.Casali, R., et.al (2016)	 HC n=16 10.5 y(SD=1.9) BECTS n=13 11.6 y(SD=1.8) TLE n=7 11.5 y(SD=1.8)	**P300 latency (ms)** mean (SD) Frequency stimuli 318(27.7) 324.1 (4.8) 336.3 (23.5)	**P300 amplitude (µV)** mean (SD) Frequency stimuli 5.77 (2.37) 4.8 (3.2) 4.65 (2.45)	Tonal freq. changes 75dB HL monoaurally	-TLE group P300 latencies ss longer vs HC (P=0.037))
11. Gökçay, F., &Gökçay, A. (2005) **This study was not included in the metaanalysis due to no reported sd**	 HC n=2 (9-18) y Mean=13.5y Part. epilepsy n=55 (9-18) y Mean =13.1y Gen. epilepsy n=45 (9-18) Mean=14.4y Intr. epilepsy n=20 (8-20) Mean=14.9y	**P300 latency (ms)** mean Frequency stimuli 337 335 360 333		Tonal freq. changes (95dB SPL)	-P300 latency longer in partial epilepsy group (P=0.043) and intractable group (P=0.005) vs HC -ss lower repeated words in auditory number assay test in patient groups vs HC

Table 3. Studies assessing auditory processing with electrophysiological methods (MMN or P300). Abbreviations & Acronyms: HC: healthy control, Pat.: patients, n: number, SD: standard deviation, TLE: temporal lobe epilepsy, RTLE: right temporal lobe epilepsy, LTLE: left temporal lobe epilepsy, BECTS: Benign epilepsy with Centro-temporal spikes, MMN: mitch match negativity, Fz: frontal lobe midline sagittal plane electrode placed, Cz: central midline sagittal plane electrode places, Pz: parietal lobe midline sagittal plane electrode placed, ms: millisecond, µV: microvolt, part.: partial, gen: generalized, Intr.: intractable, year, SD: standard deviation, freq: frequency

The concurrent use of both behavioral and electrophysiological tests was employed only in two studies (Table 4). Boscariol et al [42] reported temporal processing deficits in TLE patients indicated by pathological results in both GIN and DPT but no statistically significant difference in P300 latency and amplitude compared to healthy controls. Rocha et.al [41] evaluated dichotic listening and documented lower performance in both ears of left TLE patients and concurrently a trend to P300 longer latency and lower amplitude in study group. In addition, P300 was not recorded in half patients.

Table 4.

	CHILDREN				
Author	**Sample**	**Behavioral test**	**Electrophysiological test**	**Stimuli**	**Results**
1.Boscariol, M., et.al (2015)	HC n=16 10.52y(SD=1.92) Pat. n=19 11.56y(SD= 1.79)	**GIN**thr. (ms) mean (SD)-PCI % mean (SD) RE: 4.75 (2.37) - 77.81(6.05) LE: 4.38 (0.62) - 78.96(7.52) **DPT**% mean (SD) Naming Humming RE:83.83(6.69) - 88.04(12.28) LE:82.00(11.57) - 86.20(10.24) **GIN**thr. (ms) mean (SD)-PCI % mean (SD) RE:8.21(2.37) - 62.89(13.37) LE: 7.47(2.01) - 59.91(10.58) **DPT** % mean (SD Naming Humming RE:61.19(24.94) - 65.77(22.29) LE:54.89(26.44) - 65.94(23.85)	**P300 latency(ms) - amplitude(μV) mean (SD)** <u>Frequency stimuli</u> RE:317.5(28.17) - 5.88(2.18) LE:318.5(28.13) - 5.67(2.61) **P300 latency**(ms)**- amplitude** (μV) mean (SD) RE:330.84(30.18) - 4.63(2.99) LE: 323.05(29.37) - 4.90(2.78)	Tonal freq. changes 75dB HL	-ss higher GIN thr. in TLE vs HC (p<0.001) -ss lower PCI in TLE vs HC (p<0,001) - ss lower performance in DPT test in TLE vs HC both naming & humming (p=0.002) -no ss difference btw groups in latency (p=0.34) and amplitude (p= 0.19)
	ADULTS				
2.Rocha, C. N., et.al (2010)	HC n=12 (20-25y) 22.83y(SD=1.14)	**DDT % mean (SD)** RE: 97.71 (1.67) LE: 99.1 (1.23)	**P300 latency(ms)-amplitude** (μV) mean (SD) <u>Frequency stimuli</u> C3RE:309.33(28.38) – 8.92(5.10) C3LE:291.50(37.53) – 9.85(5.18) C4RE:307.33(37.46) – 9.00(4.03) C4LE:298.00(37.03) – 6.92(3.29)	Tonal freq. changes 75dB HL	-HC performed ss better vs LTLE in DDT both ears (p= 0.0238 RE, p= 0.0226 LE) -P300 not recorded in 6 individuals of LTLE group -P300 ss longer latency LTLE vs HC in sites C3LE & C4RE (p= 0.0326 & p =0.0526 respectively) -P300 ss lower amplitude in LTLE

	LTLE n=12 (20-50y) 35.8y(SD=8.12)	RE:81.67 (22.01) LE:83.75 (20.16)	**P300 latency(ms)-amplitude**(μV) mean (SD) C3RE:321.17(40.36) - 7.51(4.85) C3LE:327.08(38.37) - 5.92(4.43) C4RE:343.58(48.37) - 5.26(5.06) C4LE:328.67(45.56) - 7.59(4.18)		vs HC in sites C3LE & C4RE (p= 0.0583 & p= 0.0580 respectively)

Table 4. Studies assessing auditory processing with both electrophysiological and behavioral tests. Abbreviations & Acronyms: HC: healthy controls, Pat.: patients, TLE: temporal lobe epilepsy, RE: right ear, LE: left ear RTLE: right temporal lobe epilepsy, LTLE: left temporal lobe epilepsy, BECTS: benign epilepsy with Centro-temporal spikes, GIN: gaps in noise, DPT: duration pattern test, DDT: dichotic digit test, Thr.: Threshold, PCI: percent of correct identification, PPS: pitch pattern sequence, MMN: Mitch Match Negativity, ms: millisecond, μV: microvolt, SD: standard deviation, y: year, freq: frequency

3.3 Meta-analysis

The first meta-analysis model (fig.2) presents all the studies (k = 38) including a behavioral assessment of the two groups (DPT, GIN%, GINms). The overall effect size as revealed in the forest plot, is negative and statistically significant (estimate = -1.7905, SE = 0.1738, p<0.000, CI -2.1427to -1.4383). This finding indicates that TLE patients have overall lower auditory processing performance, as assessed by behavioral tests. The Q test for heterogeneity (Q (df = 37) = 154.6195, p. < 0.0001) is significant indicating heterogeneity in the effect sizes as a variety of factors seems to affect the outcome (e.g. test, study, ear). The estimated variance components are τ^2 (level 3) = 0.029 and τ^2 (level2) $^{=}$ 0.2. Thus, I^2 = 7.78% heterogeneity is due to the employment of different tests, while I^2 = 54.05% of the total heterogeneity is due to study level variation.

An ANOVA was conducted to compare the efficiency of a three and a two-level model. Findings indicated that a two-level model could also be employed as the AIC number of the two models was very close but it was preferred, following the relevant literature [16], to keep the three-level model as it better describes the nested and non-independent nature of the dataset. This approach was also preferred for all the other models that are presented.

Following the funnel plot (fig.3) and the significant findings of Egger's Test ($F(1, 36) = 84.8606$, $p < 0.0001$), a leave-one-out sensitivity analysis was conducted. A total of six studies were removed using the threshold of two standard deviations. The meta-analysis was repeated but findings did not reveal a substantial change as both models had highly significant overall effects ($p < 0.001$), while the heterogeneity of the model after removing the six studies increased from $I^2 = 61.84\%$ to $I^2 = 76.5\%$.

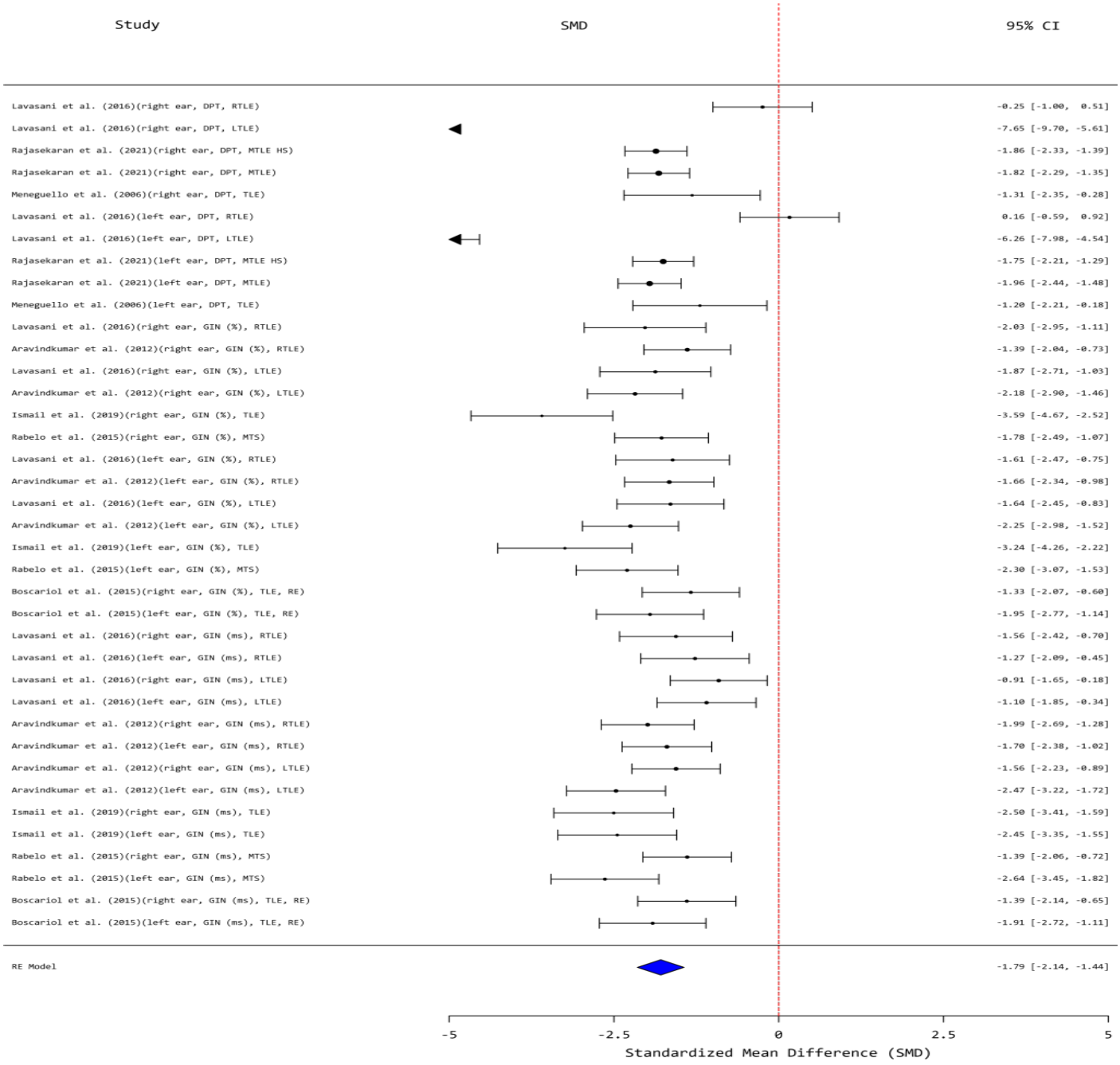

Fig.2: Meta analysis forest plot comparing the performance in psychoacoustic/behavioral tests of the TLE patients with the control groups. The studies are presented according to ear measurements (left ear, right ear, both ears), behavioral test conducted (DPT, GIN), unit of measurement (percentage for DPT, ms and percentage for GIN), type of temporal lobe epilepsy (TLE, RTLE, LTLE).

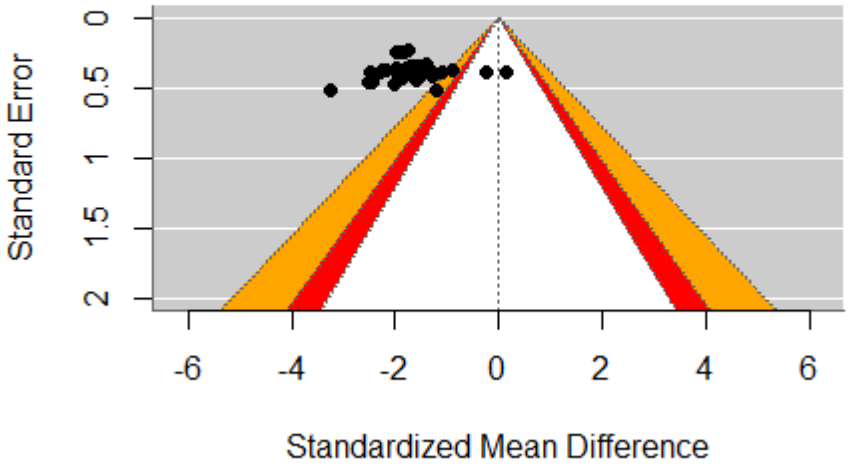

Fig. 3: Funnel plot of the behavioral studies after the sensitivity analysis

The second model that is presented (fig.4) presents the electrophysiological studies (MMN and P300), (k = 69). The overall effect size was found to be significant (estimate = -0.3489, SE=0.1532, p=0.0259, CI -0.6546 to -0.0431), indicating that the two participant groups differ significantly in their performance. The Q test for heterogeneity (Q(df=68)= 196.8676, p.<0.0001) was significant implying heterogeneity of the effect sizes. The estimated variance components were τ^2 (level 3)= 0.1820and τ^2 (level2)=0.1517. This means that heterogeneity is not due to test differences but due to study level differences (I^2 (level 2) = 34.65%). Overall, total I^2 was 76.24% revealing significant study heterogeneity. The Egger's test indicated potential publication bias (intercept = -2.0360, SE = 0.6003, p = 0.0012). However, the leave-one-out sensitivity analysis did not indicate any outliers in any of the effect sizes that could potentially affect the conclusions presented above. The forest plot (fig.4) presents a pooled effect size of -0.35 with a 95% confidence interval ranging from -0.65 to 0.04 indicating a marginally statistically significant difference between the two populations.

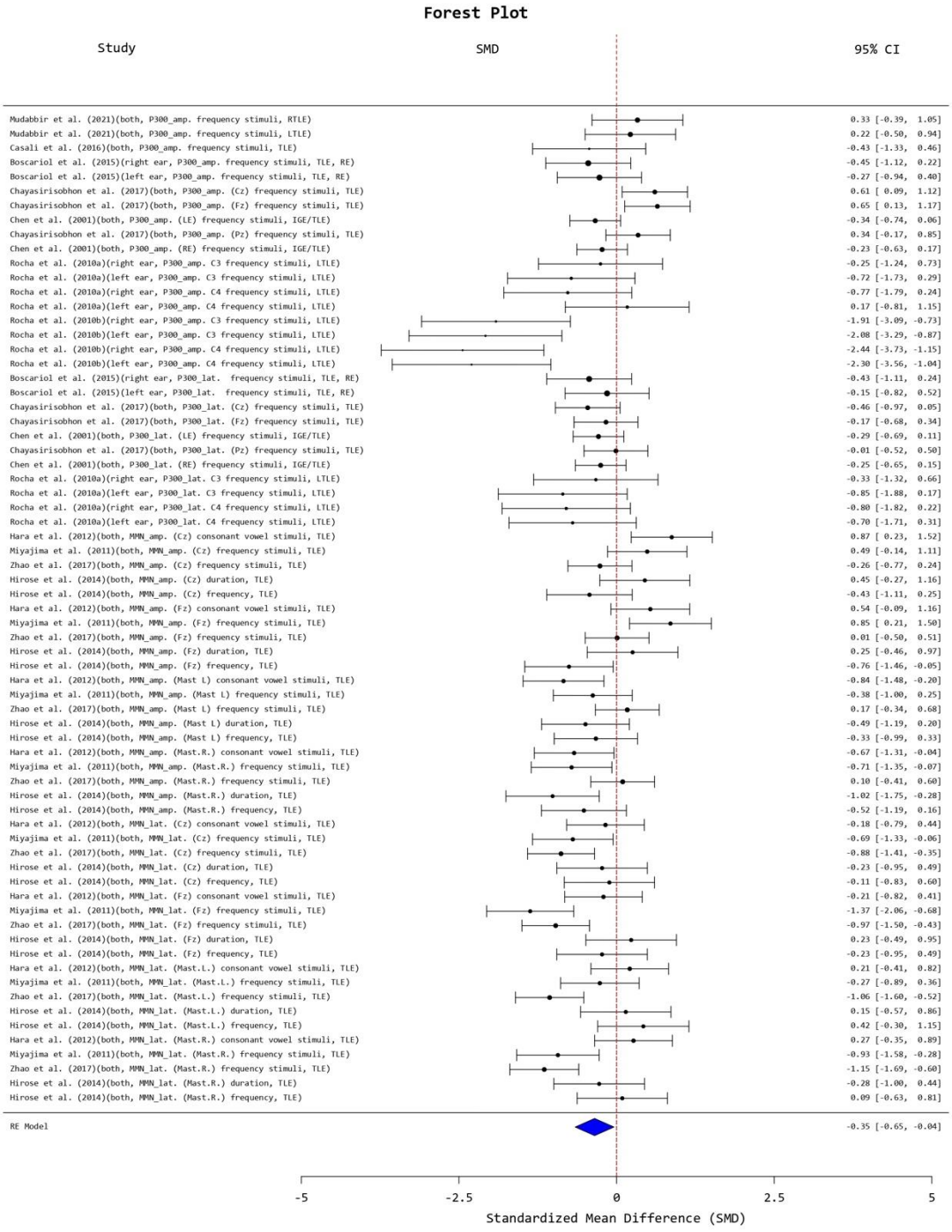

Fig.4: Meta analysis forest plot comparing the performance of the TLE patients with the control groups in electrophysiological tests. The studies are presented according to ear measurements (left ear, right ear, both ears), electrophysiology test conducted MMN (amplitude and latency), P300 (amplitude and latency), type of temporal lobe epilepsy (TLE, RTLE, LTLE).

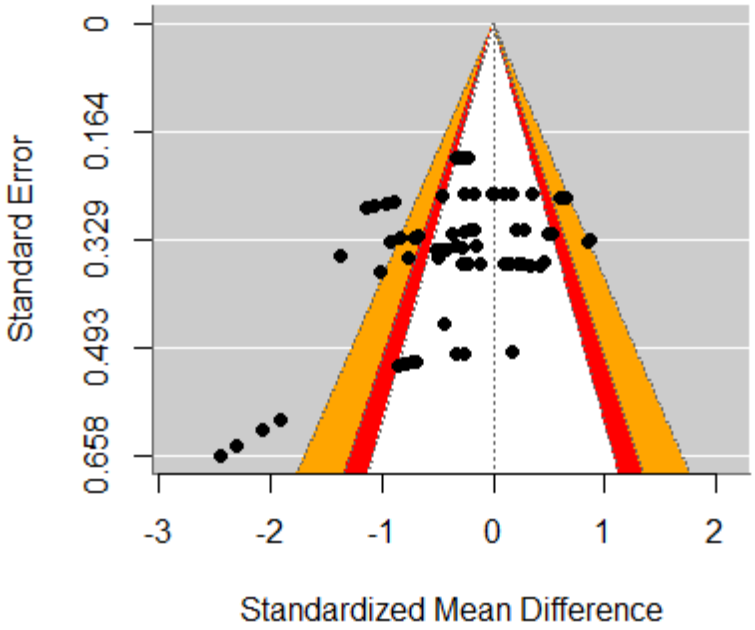

Fig. 5: Funnel plot of electrophysiological studies

The next model (fig. 6) presents the data for both behavioral and electrophysiological studies (k = 107). The overall effect size was found to be significant (estimate = -1.1832, SE = 0.3681, p<0.01, CI -1.9131 to -0.4534) revealing that the two groups had significant differences in their performance. The Q test for heterogeneity (Q(df=106) = 803.3295, p<.0001) was significant implying heterogeneity of the effect sizes. The estimated variance components were τ^2 level 3 = 0.6063 and τ^2 level 2 = 0.2673. This means that I^2 level 3 = 72.57% variance is due to variation caused by the different tests while I^2 level 2 = 16.16% is due to study level variation. Overall, findings indicate that TLE patients have overall lower auditory processing performance, as assessed by both behavioral and electrophysiological tests.

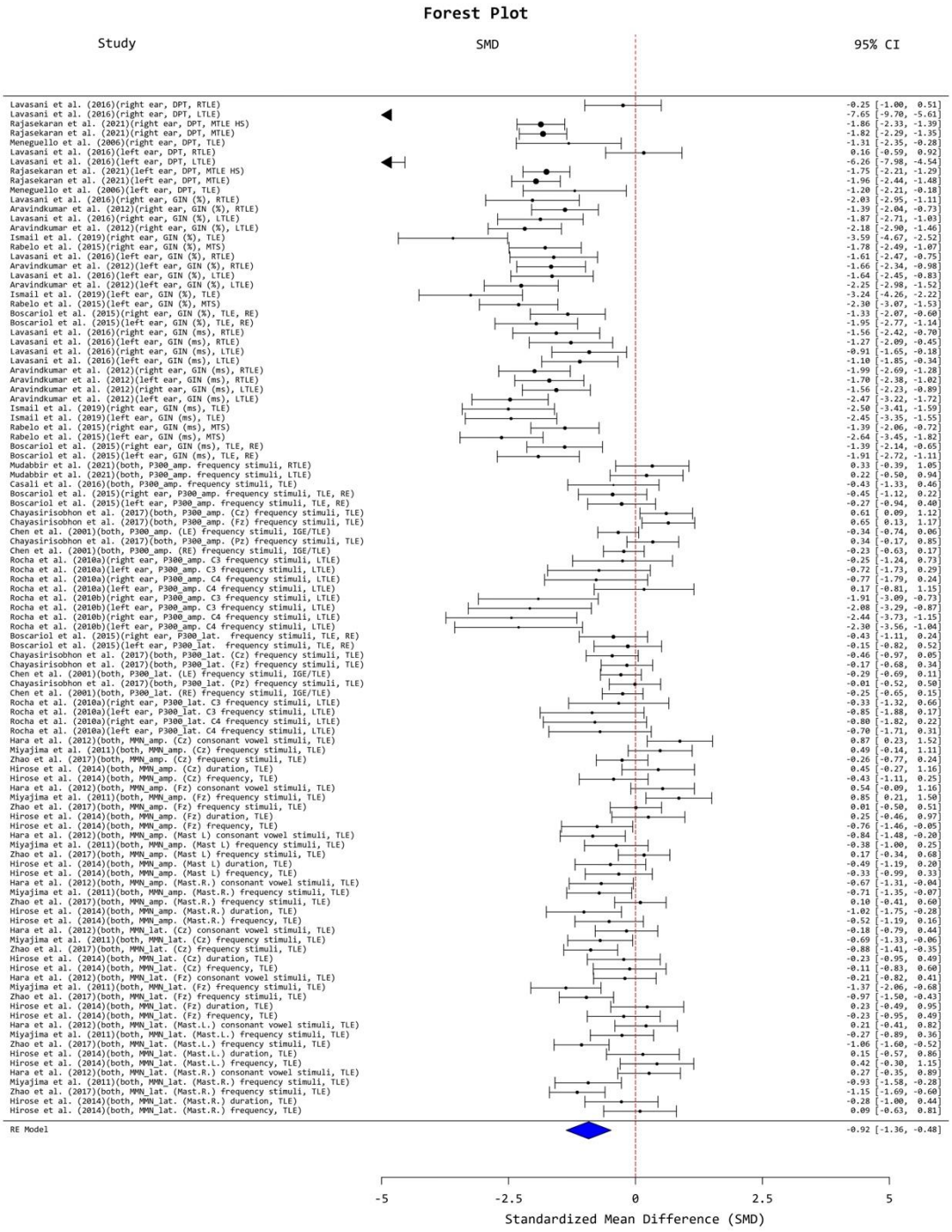

Fig. 6: Meta analysis forest plot comparing the performance of the TLE patients with the control groups. The studies are presented according to ear measurements (left ear, right ear, both ears), behavioral test conducted (DPT, GIN), electrophysiology test conducted MMN (amplitude and

latency), P300 (amplitude and latency), test details, unit of measurement (percentage for DPT, ms for GIN), type of temporal lobe epilepsy (TLE, RTLE, LTLE).

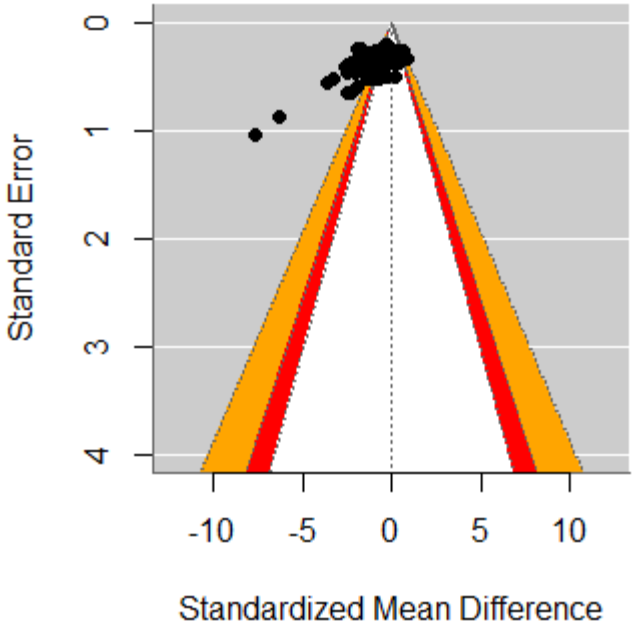

Fig. 7: Funnel plot of behavioral and electrophysiological studies

4.Discussion

The current systematic review and meta-analysis shows that TLE patients have reduced hearing capacity, due to reduced auditory processing rather than hearing sensitivity performance. This is the case for behavioral psychoacoustic tests assessing temporal processing, such as the Duration Pattern sequence Test and Gaps-In-Noise. Electrophysiology, reported by MMN & P300, alone or combined to behavioral tests, also shows statistically significant worse performance for TLE patients compared to normal controls. The meta-analysis conducted shows that the auditory processing deficits are statistically significant, separating TLE patients from normal controls, with psychoacoustic tests showing a more robust result that could be due to the optimal peripheral hearing testing in behavioral studies compared to electrophysiology studies.

The limited number of papers with a combined behavioral and electrophysiologic approach all show that TLE patients have abnormal auditory processing in different domains. Rocha et al [41] evaluated auditory processing in adults with mesial temporal sclerosis and found that patients underperformed in the dichotic listening task compared to healthy controls. P300 recordings were absent in half of the patients, while there was a tendency towards P300 wave longer latency and lower amplitude Researchers concluded that patients presented with both impaired binaural integration ability and a high incidence of unrecorded P300. In another study, Boscariol et.al [42] documented abnormalities in the temporal processing domain, when they performed Gap In Noise (GIN) and Duration Pattern (DPT) tests in children with epilepsy, but no P300 alterations were found when these patients were compared to healthy controls. The abnormal results in GIN and DPT, tasks that require corpus callosum and primary auditory cortex optimal functioning, could be due to temporal and extratemporal regions dysfunction caused by epilepsy. There is some argument whether GIN is only a temporal processing test or involves cognition as well, especially attention and decision making. Papesh A., et.al [43] tried to correlate GIN to both endogenous (P300) and exogenous (P200, N100) electrophysiological components in blast-exposed veterans. They reported a significant association between GIN and P300, as expected, suggesting that both tasks share common neural pathways and that GIN depends on attention and memory too. Interestingly, GIN was found to correlate with exogenous potentials as well. The relation between GIN and N1 wave indicates that gap detection ability is associated with the strength of the acoustic stimuli represented in the acoustic cortex.

Auditory event related potentials, particularlyP300 and MMN, are objective ways to evaluate the processing of auditory information through the Central Auditory Nervous System (CANS). They reflect the electrical activity of generators located in various cortical and subcortical loci, including the auditory cortex and thalamus, produced by acoustic stimuli [44]. Both are elicited by auditory stimuli in the so-called oddball paradigm, and the registered potentials are the result of the individual's ability to discriminate between different auditory stimuli. MMN is a negative polarity ERP component that does not require the subjects' attention. It is evoked when, in a series of stimuli, a deviant stimulus mismatches with the anticipated standard one. The generators of MMN lie in frontal and mastoid areas bilaterally [45]. It measures

auditory sensory memory, processing, and auditory discrimination and is a sensitive index of discrimination deficits [45]. On the contrary, P300 is an endogenous positive late potential produced when the patient has to identify, attend to, and report the rare (odd-ball) stimuli. Although P300 implicates cognitive functions, it is also related, at least at a first level, to auditory perception ability [46]. Based on the reviewed literature, MMN absence could be interpreted as brain inadequacy to maintain an echoic memory trace due to pathological discrimination of sound characteristics. On the other hand, P300 absence seems to correlate with the presence of brain pathology and could indicate abnormal cognitive processing. [47,48]

The reviewed research shows abnormalities in most of the studies assessing P300 and MMN in TLE patients. Only two studies [31,32] reported no difference in P300 latency between TLE patients and healthy controls. Three [30,34,35] of the six P300 studies confirmed significant latency prolongation, indicating slower neural processing speed in TLE [48]. One study [33] found significantly prolonged P300 and, at the same time, lower amplitude in patients, but it should be pointed out that they presented with both hippocampal and extrahippocampal impairments. As for the five studies [36-40] assessing MMN, differences in amplitude and/or in latency were reported depending on the site used to record it, suggesting that epilepsy has different effects at the two sites that are thought to be MMN generators. Two researchers [36,38] found amplitude reduction in TLE only in the mastoid area, whereas the fronto-central recording didn't differ between patients and controls. Interestingly, this change in amplitude was reported when the MMN was elicited by speech sound [36] and duration deviant oddball paradigms [38]. Two studies [37,39] found latency prolongation in both mastoid and frontocentral sites when pure tones, differing in frequency, were employed to elicit the MMN. One study [40] demonstrated MMN amplitude abnormalities in temporal generators of TLE patients that related to lesion location.

It should be mentioned that the MMN studies have heterogeneity in the type of the acoustic stimuli used to elicit the electrophysiological component. In two studies [37,39] the deviant stimulus differed in frequency, while in one study, [40] the difference was in stimuli duration. Hirose et.al [38] used tonal stimuli that differed in both frequency and duration for MMN production and reported amplitude reduction in mastoid areas only by duration deviants. There is also a study by Hara et.al [36] in

which MMN was elicited by vowel speech sounds, and reduced amplitude was also documented in mastoids. Stimuli intensity also varies from 60dBHL in Lopes [40] study, 70 dB SPL in Zhao et al [39], and 90 dB SPL in the remaining three studies [36--38]. Studies assessing the P300 wave all use tonal stimuli that differ in frequency, while the stimuli intensity varies between 40 dB [33], 60 dB [32],70 dB [30], 75 dB [34,] and 95 dB [35]. This great methodological heterogeneity may explain the less robust but still significant ability of electrophysiological tests to differentiate TLE from controls. Psychoacoustic tests used in behavioral evaluation studies have more homogeneous methodology and a more robust ability to differentiate of TLE patients from controls.

Behavioral assessment revealed temporal processing deficits in all studies. Temporal processing refers to the ability of CANS to perceive sound in time and is crucial for many processing skills [50]. In two studies [20,28] patients with left TLE performed worse compared to right TLE patients in tests assessing temporal aspects of auditory processing, in agreement with research suggesting that the left hemisphere is specialized for temporal processing. Dichotic perception was abnormal in the three studies [22,26,27] that evaluated this auditory processing domain. Worse performance of patient groups compared to healthy controls and bilateral deficits were documented in these studies as well. Sound source localization ability was normal in the one study that evaluated it [26]. Only one researcher [29] evaluated patients before and after anterior temporal lobectomy and reported underachievement in auditory short-term memory and identification tasks, but surgery didn't alter their performance. The lack of laterization could reflect the fact that processing of sound presupposes the anatomical and functional integrity of both brain hemispheres and the corpus callosum. [50,51] This finding is also in line with studies reporting that epilepsy, even when unilateral, provokes damage in an extensive neuronal network in both hemispheres [52].

It should be noted that testing of hearing sensitivity is either incomplete or lacking in 13 out of 23 studies found by this systematic review. This translates into 56.5% of studies not properly testing for hearing sensitivity while trying to assess auditory processing. This reflects limited awareness of hearing evaluation guidelines, as hearing sensitivity evaluation should precede auditory processing assessment. The majority of published papers on TLE patients evaluating auditory processing uses either

psychoacoustic/behavioral tests or electrophysiology tests, thus limiting their usefulness for clinical practice. In clinical practice, the question to be answered is: Does a person has difficulty hearing in everyday life situations. To answer this, one must keep in mind that hearing threshold evaluation is based on the audiogram as a gold standard test, which is a behavioral test. Auditory Processing evaluation is the next step, with a minimum of a speech in noise/babble, dichotic digit, and temporal resolution tests. This clinical approach provides all essential elements of hearing sensitivity and auditory processing, with electrophysiology adding to the assessment by addressing the integrity of the auditory system. The fact that this approach is not used in most studies lead to a poorer representation of hearing as a whole, even though specific tests show deficits in patients clearly differentiating them from normal controls.

Even though pure tone audiometry is the gold standard test for hearing evaluation and hearing loss is known to affect P300 recordings [53,54], ten of the thirteen studies that assessed an ERP component excluded patients based on self-reported hearing problems or did not present hearing evaluation data at all. Only three [34,39,42] studies (23.1%), two of them [34,42] involving children, conducted pure tone audiometry. These findings are in agreement with the van der Merwe, J., et al [55] review study. They reported that only 36% of the studies assessing P300 in neurological patients describe their hearing status, and 70% of them rely on patients' self-reports about their hearing difficulties. They concluded that peripheral hearing evaluation should be included in P300 studies.

This systematic review and meta-analysis revealed a lack of evaluation of hearing sensitivity in the majority of studies using electrophysiology to evaluate auditory processing and/or cognition in Temporal Lobe Epilepsy (TLE) patients. The main issue with the absence of proper hearing sensitivity evaluation is the high possibility of undiagnosed hearing loss. TLE patients are selectively being evaluated by specific auditory processing tests, with limited studies providing a broad assessment of auditory processing. However, individual auditory processing tests are consistently showing deficits that are in accordance with electrophysiology results based on P300 and MMN with respect to latency and amplitude. To answer the first research question regarding which specific tools of auditory processing show clear deficits separating patients from normal controls, the Gaps-In-Noise test, Duration Pattern test, MMN & P300 are

showing a clear deficit for patients. To answer the second research question of this review, there is either a lack of or a partial evaluation of hearing sensitivity and auditory processing in TLE patients. There are certain limitations to this study. It should be noted that the number of studies is small. The auditory processing tests administered do not cover the full range in clinical practice, and the psychoacoustic/behavioral ones (GIN, DPT) are showing a clearer discriminatory power than the electrophysiological ones (P300, MMN), possibly due to more consistent methodology protocols.

5.Conclusion

Both behavioral and electrophysiological tests indicate disturbed auditory processing in TLE patients. Prior to any auditory processing assessment, it will be important to evaluate hearing sensitivity in adults and children with temporal lobe epilepsy.

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CRediT authorship contribution statement

D. Aggeli: Conceptualization,Writing – review & editing**,** Writing – original draft**,** Investigation, Data curation **E. Kelmali** Writing, Methodology, Investigation**. V. M. Illiadou:** Conceptualization, Writing – review & editing, Project administration, Methodology, Investigation, Data curation **V.K. Kimiskidis:** Review & editing, Project administration, Data curation**. D-E. Bamiou,** Project administration, Conceptualization, Writing – review & editing**.** All authors: Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1.] Tsimpida, D., Kontopantelis, E., Ashcroft, D., &Panagioti, M. (2020). Comparison of self-reported measures of hearing with an objective audiometric measure in adults in the English longitudinal study of aging. JAMA Network Open, 3(8) doi:10.1001/jamanetworkopen.2020.15009

[2.] Iliadou, V., Moschopoulos, N., Sidiras, C., Eleftheriadou, A., &Nimatoudis, I. (2018). Over-diagnosis of cognitive deficits in psychiatric patients may be the result of not controlling for hearing sensitivity and auditory processing. Psychiatry and Clinical Neurosciences, 72(9), 742. doi:10.1111/pcn.12768

[3.] Koohi, N., Vickers, D. A., Utoomprurkporn, N., Werring, D. J., &Bamiou, D. E. (2019). A hearing screening protocol for stroke patients: an exploratory study. Frontiers in neurology, 10, 842.

[4.] World report on hearing. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

[5.] Bamiou DE, Iliadou VV, Zanchetta S, Spyridakou C. What Can We Learn about Auditory Processing from Adult Hearing Questionnaires? J Am AcadAudiol. 2015 Nov-Dec;26(10):824-37. doi: 10.3766/jaaa.15009. PMID: 26554488.

[6.] Tang D, Tran Y, McMahon C, Turner J, Amin J, Sinha K, Alam MN, Wuthrich V, Sherman KA, Garcia P, Mitchell R, Braithwaite J, Leigh G, Lim S, Shekhawat GS, Rapport F, Ferguson M, Gopinath B. A protocol for the Hearing impairment in Adults: A Longitudinal Outcomes Study (HALOS). PLoS One. 2023 Mar 16;18(3):e0283171. doi: 10.1371/journal.pone.0283171. PMID: 36928424; PMCID: PMC10019733.

[7.] Edwards DF, Hahn MG, Baum CM, Perlmutter MS, Sheedy C, Dromerick AW. Screening patients with stroke for rehabilitation needs: validation of the post-stroke rehabilitation guidelines. Neurorehab Neural Repair. (2006) 20:42–8. doi: 10.1177/1545968305283038

[8.] Haile LM, Kamenov K, Briant PS, Orji AU, Steinmetz JD, Abdoli A, et al. Hearing loss prevalence and years lived with disability, 1990–2019: findings

from the Global Burden of Disease Study 2019. *The Lancet*2021;397:996–1009. doi: 10.1016/S0140-6736(21)00516-X

[9.] Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*2020;396:413. doi: 10.1016/S0140-6736(20)30367-6

[10.] Chowsilpa, S., Bamiou, D. E., &Koohi, N. (2021). Effectiveness of the auditory temporal ordering and resolution tests to detect central auditory processing disorder in adults with evidence of brain pathology: a systematic review and meta-analysis. *Frontiers in Neurology*, *12*, 656117.

[11.] Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *International journal of surgery*, *88*, 105906.

[12.] Richardson, W. S., Wilson, M. C., Nishikawa, J., & Hayward, R. S. (1995). The well-built clinical question: a key to evidence-based decisions. *ACP journal club*, *123*(3), A12-A13.

[13.] Viechtbauer, W. (2010). Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software, 36(3), 1–48. https://doi.org/10.18637/jss.v036.i03.

[14.] Konstantopoulos, S. (2011). Fixed effects and variance components estimation in three-level meta-analysis. Res. Synth. Methods 2, 61–76. doi: 10.1002/jrsm.35

[15.] Harrer, M., Cuijpers, P., Furukawa, T.A., & Ebert, D.D. (2021). Doing Meta-Analysis with R: A Hands-On Guide. Boca Raton, FL and London: Chapman & Hall/CRC Press. ISBN 978-0-367-61007-4.

[16.] Cheung, 2014. "Modeling Dependent Effect Sizes with Three-Level Meta-Analyses: A Structural Equation Modeling Approach." Psychological Methods 19 (2): 211.

[17.] Hartung, J., and Knapp, G. (2001). Predictive distributions for betweenstudy heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat. Med. 20, 1771–1782. doi: 10.1002/sim. 6381

[18.] Morris, S.B., 2008. Estimating effect sizes from pretest-posttest-control group designs. Organ. Res. Methods 11 (2), 364–386. https://doi.org/10.1177/1094428106291059.

[19.] (Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.)

[20.] Lavasani, A. N., Mohammadkhani, G., Motamedi, M., Karimi, L. J., Jalaei, S., Shojaei, F. S., ... &Azimi, H. (2016). Auditory temporal processing in patients with temporal lobe epilepsy. Epilepsy & Behavior, 60, 81-85.

[21.] Aravindkumar, R., Shivashankar, N., Satishchandra, P., Sinha, S., Saini, J., &Subbakrishna, D. K. (2012). Temporal resolution deficits in patients with refractory complex partial seizures and mesial temporal sclerosis (MTS). Epilepsy & Behavior, 24(1), 126-130.

[22.] Aravindkumar, R., Shivashankar, N., Satish Chandra, P., Sinha, S., Saini, J., &Subbakrishna, D. K. (2014). Dichotic perception in patients with and without medial temporal sclerosis. Speech, Language and Hearing, 17(3), 153-159.

[23.] Rajasekaran, A. K., Shivashankar, N., Sinha, S., Saini, J., Subbakrishna, D. K., &Satishchandra, P. (2021). Auditory Temporal Ordering in Patients with Medial Temporal Lobe Epilepsy with and without Hippocampal Sclerosis. Neurology India, 69(2), 414

[24.] Ismail, N. M., Shalaby, A. A., Abdel Azim, G. S., &Abd-Ellatif, E. I. (2019). Impact of Temporal Lobe Epilepsy on Central Auditory Processing in Children. The Egyptian Journal of Hospital Medicine, 77(2), 4956-4963.

[25.] Rabelo, C. M., Weihing, J. A., &Schochat, E. (2015). Temporal resolution in individuals with neurological disorders. Clinics, 70, 606-611.

[26.] Meneguello, J., Leonhardt, F. D., & Pereira, L. D. (2006). Auditory processing in patients with temporal lobe epilepsy. Brazilian journal of otorhinolaryngology, 72(4), 496-504

[27.] Shahbazi, S., Hajiabolhassan, F., Mohammadkhani, G., Jalaie, S., Taheri, T., &Tafakhori, A. (2016). Evaluation and comparison of auditory processing problems in temporal lobe epileptic patients and normal subjects with Persian staggered spondaic word test.

[28.] Ehrlé, N., Samson, S., &Baulac, M. (2001). Processing of rapid auditory information in epileptic patients with left temporal lobe damage. Neuropsychologia, 39(5), 525-531.

[29.] Bidet-Caulet, A., Ye, X. L., Bouchet, P., Guénot, M., Fischer, C., & Bertrand, O. (2009). Non-verbal auditory cognition in patients with temporal epilepsy before and after anterior temporal lobectomy. Frontiers in human neuroscience, 42.

[30.] Chen, R. C., Tsai, S. Y., Chang, Y. C., &Liou, H. H. (2001). Seizure frequency affects event-related potentials (P300) in epilepsy. Journal of clinical neuroscience, 8(5), 442-446.

[31.] Mudabbir, M. M., Mundlamuri, R. C., Mariyappa, N., Kumar, R. A., Velmurugan, J., Bhargava, G. K., ... & Sinha, S. (2021). P300 in mesial temporal lobe epilepsy and its correlation with cognition–A MEG based prospective case-control study. Epilepsy & Behavior, 114, 107619.

[32.] Chayasirisobhon, W. V., Chayasirisobhon, S., Tin, S. N., Leu, N., Tehrani, K., &McGuckin, J. S. (2007). Scalp-recorded auditory P300 event-related potentials in new-onset untreated temporal lobe epilepsy. Clinical EEG and neuroscience, 38(3), 168-171.

[33.] Artemiadis, A. K., Fili, M., Papadopoulos, G., Christidi, F., Gatzonis, S., Zalonis, I., ... &Triantafyllou, N. (2014). Auditory event-related potentials (P300) and mesial temporal sclerosis in temporal lobe epilepsy patients. Epileptic disorders, 16(1), 67-73.

[34.] Casali, R. L., do Amaral, M. I. R., Boscariol, M., Lunardi, L. L., Guerreiro, M. M., Matas, C. G., & Colella-Santos, M. F. (2016). Comparison of auditory event-related potentials between children with benign childhood epilepsy with centrotemporal spikes and children with temporal lobe epilepsy. Epilepsy & Behavior, 59, 111-116

[35.] Gökçay, F., &Gökçay, A. (2005). Evaluating cognitive functions with visual and auditory number assays and P300 in children with epilepsy. Brain and Development, 27(4), 253-258.

[36.] Hara, K., Ohta, K., Miyajima, M., Hara, M., Iino, H., Matsuda, A., ... & Matsuura, M. (2012). Mismatch negativity for speech sounds in temporal lobe epilepsy. Epilepsy & Behavior, 23(3), 335-341.

[37.] Miyajima, M., Ohta, K., Hara, K., Iino, H., Maehara, T., Hara, M., ... & Matsushima, E. (2011). Abnormal mismatch negativity for pure-tone sounds in temporal lobe epilepsy. Epilepsy research, 94(3), 149-157.

[38.] Hirose, Y., Hara, K., Miyajima, M., Matsuda, A., Maehara, T., Hara, M., ... & Matsuura, M. (2014). Changes in the duration and frequency of deviant stimuli engender different mismatch negativity patterns in temporal lobe epilepsy. Epilepsy & Behavior, 31, 136-142.

[39.] Zhao, L., An, D., Mao, L., Tang, X., He, L., & Zhou, D. (2017). Mismatch negativity is abnormal but not lateralizing in temporal lobe epilepsy. Epilepsy & Behavior, 68, 35-40.

[40.] Lopes, R., Simões, M. R., Ferraz, L., & Leal, A. J. (2014). The mismatch negativity (MMN) potential as a tool for the functional mapping of temporal lobe epilepsies. Epilepsy & Behavior, 33, 87-93.

[41.] Rocha, C. N., Miziara, C. S. M. G., Manreza, M. L. G. D., &Schochat, E. (2010). Electrophysiological and auditory behavioral evaluation of individuals with left temporal lobe epilepsy. Arquivos de neuro-psiquiatria, 68, 18-24.

[42.] Boscariol, M., Casali, R. L., Amaral, M. I. R., Lunardi, L. L., Matas, C. G., Collela-Santos, M. F., &Guerreiro, M. M. (2015). Language and central temporal auditory processing in childhood epilepsies. Epilepsy & Behavior, 53, 180-183.

[43.] Papesh, M. A., &Koerner, T. (2023, August). Clinical Gaps-in-Noise Measures in Blast-Exposed Veterans: Associations with Electrophysiological and Behavioral Responses. In *Seminars in Hearing*. 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA: Thieme Medical Publishers, Inc..

[44.] Parthasarathy, Teralandur K. Electrophysiologic assessment of CAPD: A review of the basics. The Hearing Journal 53(4): p 52, 54, 56-58, April 2000.

[45.] Näätänen, R., Kujala, T., Escera, C., Baldeweg, T., Kreegipuu, K., Carlson, S., &Ponton, C. (2012). The mismatch negativity (MMN)–a unique window to disturbed central auditory processing in ageing and different clinical conditions. Clinical neurophysiology, 123(3), 424-458.

[46.] Alain, C., Roye, A., & Arnott, S. R. (2013). Middle-and long-latency auditory evoked potentials: what are they telling us on central auditory disorders. Handbook of clinical neurophysiology: disorders of peripheral and central auditory processing, 10, 177-199.

[47.] Duncan-Johnson, C. C., &Donchin, E. (1982). The P300 component of the event-related brain potential as an index of information processing. Biological psychology, 14(1-2), 1-52.

[48.] Rik van Dinteren, R., Arns, M., Jongsma, M. L., &Kessels, R. P. (2014). P300 development across the lifespan: a systematic review and meta-analysis. *PloS one*, *9*(2), e87347.

[49.] Shinn, J. B. (2003). Temporal processing: the basics. *The Hearing Journal*, *56*(7), 52.

[50.] Jerger J, Musiek F. Report of the consensus conference on the diagnosis of auditory processing disorders in school-aged children. J Am AcadAudiol 2000;11(9): 467–74.

[51.] Musiek, F. E., Shinn, J. B., Jirsa, R., Bamiou, D. E., Baran, J. A., &Zaida, E. (2005). GIN (Gaps-In-Noise) test performance in subjects with confirmed central auditory nervous system involvement. *Ear and hearing*, *26*(6), 608-618.

[52.] Riley, J. D., Franklin, D. L., Choi, V., Kim, R. C., Binder, D. K., Cramer, S. C., & Lin, J. J. (2010). Altered white matter integrity in temporal lobe epilepsy: association with cognitive and clinical profiles. *Epilepsia*, *51*(4), 536-545.

[53.] Reis, A. C. M. B., Frizzo, A. C. F., de Lima Isaac, M., Garcia, C. F. D., Funayama, C. A. R., &Iório, M. C. M. (2015). P300 in individuals with sensorineural hearing loss. Brazilian Journal of Otorhino- laryngology, 81(2), 126–132. https://doi.org/10.1016/j. bjorl.2014.10.001

[54.] Miranda EC, Pinheiro MM, Pereira LD, Iorio MC. Correlation of the P300 evoked potential in depressive and cognitive aspects of aging. Braz J Otorhinolaryngol. 2012 Oct;78(5):83-9. doi: 10.5935/1808-8694.20120013

[55.] van der Merwe, J., Biagio-de Jager, L., Mahomed-Asmail, F., & Hall III, J. W. (2022). Documentation of peripheral auditory function in studies of the auditory P300 response: A critical review. *Journal of Psychophysiology*