AUDITORY- EVENT RELATED POTENTIALS IN MULTIPLE SCLEROSIS -A SYSTEMATIC REVIEW

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CERTIFICATE

This is to certify that this dissertation entitled **'Auditory- Event Related Potentials in Multiple Sclerosis-A systematic Review'** is a bonafide work submitted in part fulfilment for degree of Master of Science (Audiology) of the student Registration Number: P01II21S0076. This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru
September, 2023

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CERTIFICATE

This is to certify that this dissertation entitled **'Auditory- Event Related Potentials in Multiple Sclerosis-A systematic Review'** has been prepared under my supervision and guidance. It is also been certified that this dissertation has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled **'Auditory- Event Related Potentials in Multiple Sclerosis-A systematic Review'** is the result of my own study under the guidance of a faculty at All India Institute of Speech and Hearing, Mysuru, and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru,
September, 2023

Registration No. P01II21S0076

“யாதும் ஊரே யாவரும் கேளிர்”

“We have a sense of Belongings to everyplace and everyone is our own”

-Kaniyan Poongundranar

THIS DISSERTATION IS DEDICATED TO MY BELOVED AMMA, APPA, ANNA, THATHA, AND AAYA

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ABSTRACT

This systematic review aims to systematically review the research articles on event-related potentials in individuals with multiple sclerosis (MS)**.** The study used a detailed exploration of the major databases (e.g. Pubmed Central, Scopus, J Gate and Science Direct,) to archive the objectives of the systematic review.The retrieved articles were assessed in two stages: title and abstract screening, followedby a full-length article review. Twenty eight articles were selected after the full length review out of 40 shortlisted articles.

Multiple sclerosis (MS) is an auto-immune, demyelinating disease of the central nervous system. The demyelination process of the disease in the central nervous system can occur at any point in time which can exhibit various symptom. The disease usually presents with unilateral sensorineural hearing loss with sudden onset and fluctuating in nature (Atula et al., 2016; Fischer et al., 1985; Hellmann et al., 2011; Stach et al., 1990). Tinnitus and hearing loss are predominant symptoms of multiple sclerosis (Fischer et al., 1985). Cognitive impairment in MS was reported to have a varying prevalence of about 45% to 70% (Benedict et al., 2006; Kujala et al., 1997). Rate of information processing, attention, verbal fluency, and recent memory is the most impaired domains of cognition (Ivica et al., 2013). Working memory and information processing speed (IPS) are the most frequently impaired areas in MS, followed by learning, memory, and executive functions (Benedict et al., 2006; Rao et al., 1991; Sanfilipo et al., 2006). Therefore it is important to assess cognition, memory using Objective test (ERP) in individuals with multiple sclerosis.

Chapter 1

Introduction

Multiple sclerosis (MS) is an auto-immune, demyelinating disease of the central nervous system. The demyelination process of the disease in the central nervous system can occur at any point in time which can exhibit various symptoms. The most common type of multiple sclerosis is the relapsing-remitting (RR) which usually shifts to a secondary progressive (SP) fate (Compston et al., 2008) and Primary progressive (PP) MS is a third form which is considered to have a poor prognosis (Gajofatto et al., 2015; Segal et al., 2016). The disease may affect multiple systems out of which the auditory and vestibular systems can also be affected (Ghasemi et al., 2017).

The prevalence of hearing loss ranging from (1 to 23.3) % have been reported in individuals with multiple sclerosis. The disease usually presents with unilateral sensorineural hearing loss with sudden onset and fluctuating in nature (Atula et al., 2016; Fischer et al., 1985; Hellmann et al., 2011; Stach et al., 1990). Tinnitus and hearing loss are predominant symptoms of multiple sclerosis (Fischer et al., 1985). Patients with multiple sclerosis also manifested with vertigo around (37%) which has been evident in recent research (Stadio et al., 2019) advanced stage of the disease or rapid progressive condition of the disease could accompany by cognitive deficits (Lossef et al., 2009). The course of the disease can be heterogeneous, through which patients may develop sensorimotor, cerebellar, emotional, and cognitive symptoms (Compston et al., 2008). Usually, emotional lability, disinhibition, inattention, memory deficits and slowed thought processes are the cognitive impairment that is

seen in the disease whereas the language function is intact which has been correlated with cerebral atrophy (Lossef et al., 2009).

Cognitive impairment in MS was reported to have a varying prevalence of about 45% to 70% (Benedict et al., 2006; Kujala et al., 1997). Rate of information processing, attention, verbal fluency, and recent memory is the most impaired domains of cognition (Ivica et al., 2013). Working memory and information processing speed (IPS) are the most frequently impaired areas in MS, followed by learning, memory, and executive functions (Benedict et al., 2006; Rao et al., 1991; Sanfilipo et al., 2006). Multiple sclerosis patients typically show that their performance on tests of working (short-term) memory and free recall from long-term memory is worse than that of matched healthy controls (Beatty et al., 1988; Litvan et al., 1988; Rao et al., 1991; Grafman et al., 1991). Psychiatric comorbidity is common in the MS population, and this is particularly true for depression and anxiety, each of which affect more than 20% of the population (Marrie et al., 2015).

Magnetic resonance imaging (MRI) results in patients of multiple sclerosis with cognitive impairment shows lesion in white matter and grey matter (Hulst et al.,2013) in addition to atrophy of cortex and atrophy of certain structures of grey matter were also seen(Barista et al., 2012; Lorfice et al., 2020) and the loss of total longitudinal volume of brain is more when compared to the patients without cognitive impairment (Vollmer et al., 2016), though volumetric MRI gives structural information of cognitive impairment but cannot give information regarding functional aspect of cognition related to disconnection of cortical– cortical and cortical–subcortical. Hence, cognitive event-related potentials (ERPs) have been established as an electrophysiological biomarker that can be used to assess and monitor cognitive functioning (Leocani et al., 2010). Fatigue is also one of the major symptoms of multiple sclerosis and it affects cognitive

activities (Schinkel et al., 2002) and it affects 75% to 95% of MS patients (Samar et al., 2017). Exposure to stress for longer duration will lead to dysfunction of bioelectric activity of the brain and it will be mostly present in demyelinating disease (Rogan et al., 1997; Maes et al., 2001). Amato et al. (2008) reported inflammation and demyelination of the white matter tract will cause cognitive impairment. Physical disabilities, such as fine motor disabilities and reduction of visual acuity are the limitations for conducting neuropsychological testing in patients with multiple sclerosis so in this condition cognitive electrophysiological testing will be effective because it is not limited by physical disability (Basso et al., 1996; Beatty et al., 1990).

In Multiple Sclerosis patients, Event-related potentials (P300) were abnormal which indicates problem in the cortical regions and dysfunction in memory, attention, cognitive processing, and auditory discrimination (Sundgren et al., 2015). Incidence of P300 changes indicates cognitive dysfunction in multiple sclerosis. Hence, the early diagnosis of cognitive impairment using event-related potentials should be mandatory for the planning of additional supportive management(Ivica et al., 2013).A comparative study done by (Eshawaf et al., 2022) between normals and patients with MS reported that 20% of MS patients have absent MMN, indicating cognitive impairment, cognitive fatigue, or central processing disorders; and there was also no difference in latency and amplitude in the recorded MMN between the groups. So, they recommend the MMN test as a complementary diagnostic protocol and follow-up protocol for Multiple Sclerosis.

1.1 Need of the study

From the brief literature discussed above, it is clear that the event-related potential along with audiological evaluation will be critical in the cognition, attention, and auditory processing assessment in patients with multiple sclerosis. A study done by

Gur et al. (2022) showed a degenerative effect on tests like auditory brainstem responses (ABR), Cortical Evoked Potentials (CAEP), and Gap in Noise (GIN) whereas it was absent in the case of pure tone audiometry and otoacoustic emissions. This finding indicated that in MS the function of the peripheral auditory system is normal but the brainstem and the central auditory systems were affected. Thus, there is a need to gather collective information about the assessment protocol and findings of event-related potentials of individuals with multiple sclerosis. The findings of this systematic review will also help in generating awareness among audiologists regarding the importance of event-related potentials in the assessment of cognition, attention, auditory processing and rehabilitation of individuals with MS.

1.2 Aim of the study

The current study aims to systematically review the research articles on event-related potentials in individuals with multiple sclerosis.

1.3 Objective of the study

1. To study the effect of multiple sclerosis on cognition, attention and auditory processing.
2. To understand how the event-related potentials are important in the assessment, diagnosis, prognosis and management of multiple sclerosis.

1.4 Research questions

The following questions were addressed in the review

1. To study the effect of multiple sclerosis on cognition, attention and auditory processing.

2. To understand how the event-related potentials are important in the assessment, diagnosis, prognosis and management of multiple sclerosis.

Chapter 2

Methods

To aim of the study was to review the research articles on event-related potentials in individuals with multiple sclerosis, the articles were selected from the from the five databases “PubMed”, “Scopus”, “J-GATE”, “ScienceDirect” and “Pubmed Central” to achieve the objective of the study. The advanced search was conducted using key words and Boolean operations. The keywords are “audiological findings” AND “multiple sclerosis”, “cognitive function” OR “speech processing”, “evoked potentials”, “speech comprehension”, “cognitive deficit”, “dementia” AND “multiple sclerosis” etc.

To screen the articles, PRISMA guidelines (Page et al., 2021) was used. Before finalizing the articles that were taken for the systematic review from all the above mentioned databases were screened based on the following criteria.

2.1 Eligibility criteria

Eligibility criteria are inclusion and exclusion criteria that determine which articles are included and excluded from the systematic review. The following are the criteria for this review.

2.1.1 Inclusion criteria

- Participants of any age and gender.
- Articles published in English language.
- Articles that are published in the peer reviewed journals.
- Selection criteria were based on PICOS.
    - P–Population: Individuals diagnosed with Multiple sclerosis.

- I– Intervention: Drug therapy, central function training and auditory training.
- C–Comparison: Clinically normal comparison group.
- O–Outcome: Better outcomes measured using various subjective and objective tests.
- S–Study design: only case control, cross sectional, cohort and Longitudinal study will be considered.

2.1.2 Exclusion criteria

- Research articles involving animals were excluded.
- Case reports, case series, short communications, letters to the editor and review were excluded.
- Articles reporting pathologies other than MS.
- Articles having higher risk of bias or low methodological quality.
- Articles that aren't published in English.

2.2 Information sources

Articles from various peer reviewed journals were searched in different databases such as “PubMed”, “PubMed central”, “Scopus”, “J-GATE”, “and Science Direct”. The articles which are included in the systematic has taken only from these five databases.

2.3 Search strategies

The BOOLEAN operators such as AND, OR, and NOT was used for all the databases. The keywords “audiological findings” AND “multiple sclerosis”, “cognitive function” OR “speech processing”, “evoked potentials”, “speech comprehension” ,“cognitive deficit”, “dementia” AND “multiple sclerosis”, “event related potentials”, “cognitive processing”, “cognitive impairment”, “MMN”, “ N400”, “cognitive

assessment" AND "multiple sclerosis", "Progressive disorder", "Auto immune disorder", "Dementia" AND "multiple sclerosis", "Attention" AND "Multiple sclerosis", "Long Latency Potentials", "Autoimmune disorder" AND "Demyelination", "MMN"AND "Multiple sclerosis", "CAEP", "N400", "P600" were used.

2.4 Selection process

The articles for the review were selected only if it matches the inclusion and exclusion criteria as mentioned in the eligibility criteria. Each article has been verified with the review keywords and inclusion and exclusion criteria. The article which has not fallen under the eligibility criteria were excluded. The selection procedure was carried out by two authors separately and followed by third author when conflict was present. For the data selection process, the articles were title screened first, then abstract screened and finally full text screened. Duplicates detection was carried out using the reference management system 'Rayyan intelligent systematic review software' prior to the title screening followed by abstract screening. Again articles were shortlisted based on the abstract, with the articles meeting the inclusion criteria were selected for full text screening and the articles which did not satisfy the inclusion criteria were omitted from the systematic review process. Table 3.1 summarizes the articles that have been included in the review process which include methods, results and conclusions.

2.5 Data extraction

Initial search across all the above mentioned database were conducted by two authors independently using Boolean operators and keywords and the results from all the databases were combined using a reference management system. The articles from the PubMed database were selected and downloaded in the form of a bib file and the data from science direct was downloaded in the form of RIS file format created by

research information systems. The articles which were downloaded in the various form were being uploaded to the reference management system. Once the articles were uploaded in the reference management system, the selection process was carried out, starting with duplicate detection and the title screening, followed by abstract screening and full text screening, as mentioned in the selection process. PRISMA flow chart used in section process is shown in the Figure 3.1.

2.6 Methodological quality Appraisal

A methodological quality assessment was performed for all the studies which were included in the review. The national institute of Health (NIH) quality assessment tool for observational cohort and cross sectional studies was used to assess the risk of bias in the selected studies which assess research design, population, sample bias, information collecting, variables blinding, and important criteria for dropouts. The tool consists of various questions that can responded as ‘yes’ which indicates a low risk bias, and ‘no’, indicates a high risk of bias. However, when there was a disagreement or if there was a dilemma due insufficient information.it was considered as NR (not reported). Based on the above mentioned criteria, an overall grade of ‘good’, ‘ fair’, or ‘poor ‘was assigned. Each study was evaluated independently. The quality assessment tool for observation cohort and cross sectional studies is detailed in table 3.2.

Chapter 3

Results

The study was intended to conduct a systematic review on the research articles on event-related potentials in individuals with multiple sclerosis**.** The articles were finalized based on inclusion and exclusion criteria based on PICOS framework.

3.1 Search results

A total of 3125 articles were obtained after conducting the searches in all the database such as PubMed central, Scopus, and J-GATE, Science Direct, COCHRANE and Google scholar. Out of that 58 articles were removed as duplicates. Out of which, 58 were duplicates. After removing the duplicates, about 3027 articles underwent title and abstract screening. Following which 40 articles were selected for full text screening based on inclusion and exclusion criteria. Finally, 28 articles were eligible for the systematic review based on the eligibility criteria. Figure 3.1 demonstrates a complete PRISMA flowchart for the article selection.

Figure 3.1 PRISMA Flow chart for representation of the items screened, included and excluded in the systematic review.

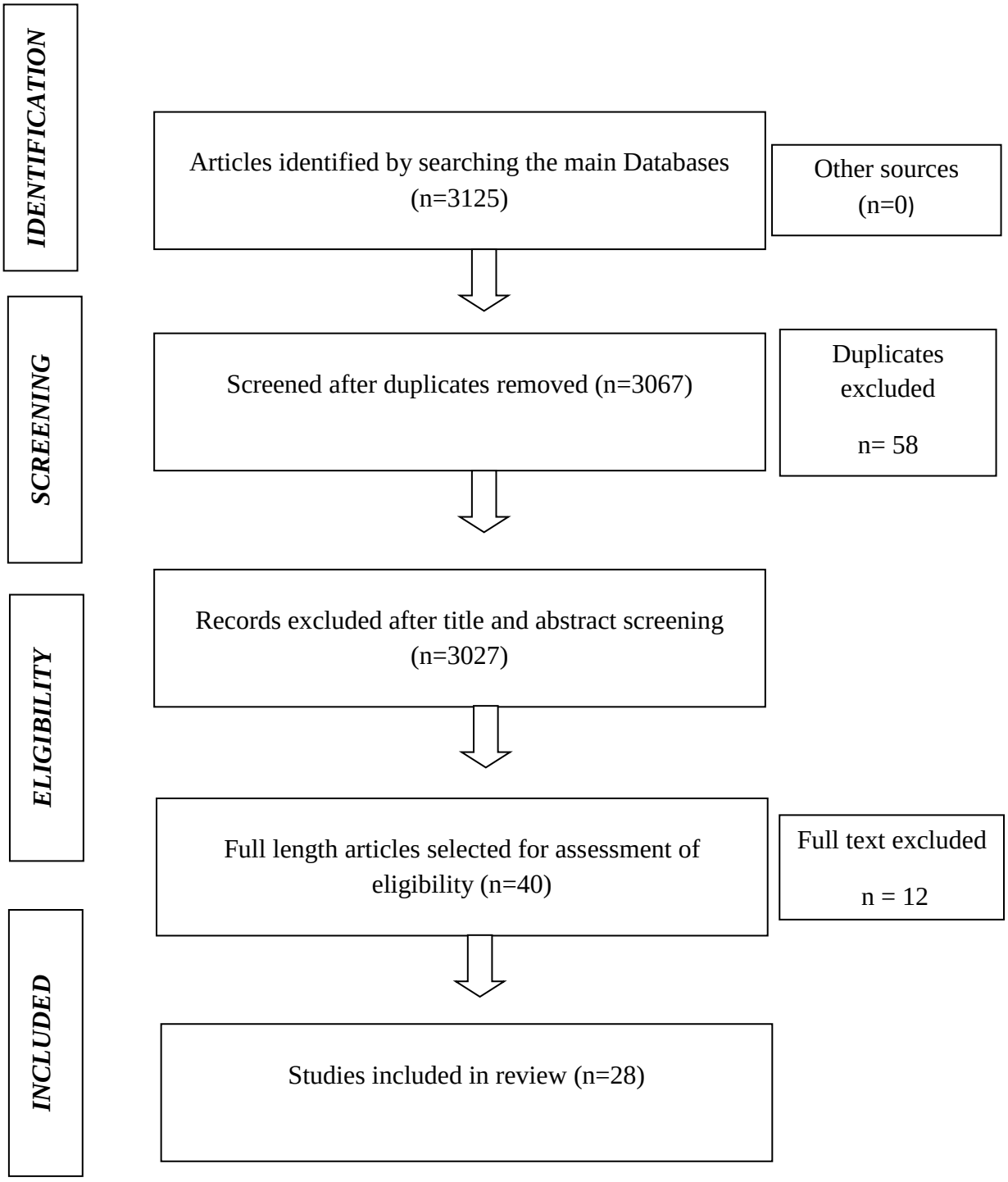

Table 3.1 An overview of the research article selected for the systematic review

Sl. No.	Author	Method	Event related potentials and other tests	Findings and conclusion
1	Ivica et al., (2013)	Study group : 14 Control group : 14 The inclusion criteria for the control group: normal hearing thresholds, history of normal neurological development, no complaints of tinnitus, no auditory processing disorders and absence of psychiatric problems The inclusion criteria for the experimental group: medical diagnosis of MS based McDonald et al.(2001) criteria and normal hearing thresholds	P300	**Findings** No significant difference was seen in the P300 target stimulus latency whereas the latency of frequent stimulus was prolonged across groups Out of the 14, 12 had abnormal frequent stimulus amplitude of P300. Whereas in control group only one had abnormal amplitude. Similarly, for target stimulus amplitude, seven had normal amplitude and seven had abnormal amplitude. **Conclusion** Patient with multiple sclerosis frequently will have cognitive dysfunction and P300 can be used to objectify the dysfunction.
2	Jung et al.,(2005)	Study group: 46 individuals with MS. Exclusion criteria : Emotional alteration Patient with history of other central nervous system diseases, hearing impairments, Control group: 46 healthy subjects without any	MMN	**Findings** MMN present mostly in controls than study group P3a was present mostly in controls. No difference was seen in the latency and amplitude of the P50 and N1 between controls and study group.

		neurological disease or hearing disease.		The amplitude of the N1P2 complex was reduced in the study group compared to controls **Conclusion** The changes in the MMN says auditory cortices dysfunction. So, in patients with cognitive dysfunction MMN provide indirect representation of neuropsychological deterioration.
3	Prosol et al., (2017)	**Type of multiple sclerosis:** Relapsing and remitting. study Group: 30 MS patients Controls: 26 healthy subjects Exclusion criteria: Severe cognitive impairment, progressive forms of MS ,mood disorders (such as depression), ,other neurological or Systemic disorders.	N200 and P300 The Symbol Digit Modalities Test (SDMT), The Perceived Stress Scale (PSS) and The D-type Scale (DS14) to assess cognition, stress and type D personality	**Findings** **Symbol digit modality test:** No significant correlation between SDMT and P300 and N200 latencies and amplitude. **N200 and DS4:** No significant correlation. **Perceived Stress Scale and D type Scale personality test result:** type D personality present in 7 individuals PSS was high in 13 individuals from test group **P300 and N200 between groups:** amplitude and latencies were higher than controls in MS patients **P300 and DS14:** No correlation **N200/P300 and PSS :** significant correlation for N200 amplitude and No correlation for P300 amplitude, N200 and P300 latencies **Conclusion** ERP were abnormal in the MS patients but without any decline in the cognition and correlations was seen between stress and negative affectivity (one of the dimensions of the D-type personality scale).

4	fpagos et al.,(2003)	**Type of multiple sclerosis:** Relapsing remitting form and progressive form of MS Study group:22 subjects with definite progressive multiple sclerosis without head injury, alcohol /drug abuse or stroke and 20 control group with no history of any neurological or hearing impairment	P600 Digit span test to assess short term memory	**Findings** Memory performance was poor in the study group than normals. **P600 and memory performance:** duration of illness was positively correlated with P600 latencies at F3 site and cerebellar clinical dimension was negatively related to P600 latencies at Fp1 site. **Conclusion:** MS patients poses abnormal aspects of "second pass parsing processes" of information similarly it was observed in P600 obtained during a WM test
5	Filipovic etal., (1997)	**Type of multiple sclerosis:** relapsing, remitting and secondary progressive MS Study group 44 patients with MS diagnosed based on poser's criteria study group : (HDMP, 1000 mg methylprednisolone, in 500 ml normal saline) Control group: (placebo, normal saline) Subjects not included who has history of taking corticosteroid ,anticholinergic or during investigation, other	P300 Expanded disability status scale (EDSS) was used to assess physical disability	**Findings** Significant difference was seen in the scores of EDSS and latency of event related potentials such as the latency was reduced in the study group who received methylprednisolone. **Conclusion:** The reduction in the latency of P3 after HDMP says that HDMP has effect on cognition of MS patient.

		immunosuppressive medication in the last six months, anti-depressive medication other central nervous system diseases, hearing impairment, strong emotional and behavior for cooperation.		
6	Pokryszko-Dragan et al., (2009)	**Type of multiple sclerosis** Relapsing, remitting MS Study group N=21 patients diagnosed with MS based on McDonald's criteria. Control group N=21 normal healthy individuals.	P3 and N2 **Neuropsychological tests (NT):** the Rey Auditory Verbal Learning Test (AVLT 1 and 2) with digit span, and the Trail Making Test (TMT) The Wechsler Adult Intelligence Scale (WAIS-r), to assess cognitive functioning, recent memory and sustained attention and cognitive flexibility respectively.	**Findings** The N2 and P3 latencies were longer in MS group than in control group whereas no difference was seen in the amplitude. Latencies of N2 positively correlated with the results of (TMT). No other significant correlation was seen between NT and ERP. After the initial assessment of (ERP and NT)16 patient took IFN beta -1a (44 microgram s.c. three times a week) for 1 year After 1 year of post treatment, No significant difference was seen in ERP values, WAIS-r and Digit Span. Whereas, improvement was seen in(AVLT 1 and 2)and TMT. **Conclusion** To monitor cognitive activity NPT (Neuro psychological test) is better than ERP.

7	Santos etal., (2006)	Study group N=40 MS patient diagnosed based on poser criteria. Control group: N=20 age matching MS group. Exclusion criteria: hearing thresholds should be below or equal to be 25dB HL,no problem in the otoscopic evaluation	MMN MSFC test, and the Paced Auditory Addition Test – PASAT- Paced Auditory Addition Test was used to assess cognition.	**Findings** 60 % MMN Present(duration variation) 45 % MMN was absent(frequency variation) No significant difference was seen between MMN negative amplitude between MS group and control group. Significant correlation between the absence of MMN wave with cognitive impairment measured using PASAT was seen. **Conclusion** When MMN is present in MS patient it can be used as a supratemporal auditory cortex functional index and its absence is related to cognitive impairment.
8	Jonathan et al., (2001)	**Type of multiple sclerosis** relapsing/remitting disease, secondarily progressive Control group of 10 normal and study group of 8subjects with MS	P300 MMSE (Mini mental state examination)was used to assess cognition	**Findings** Latency was prolonged more for N2 and P3 component than N1and P2. So, the interpeak latencies was also prolonged in MS when compare to normals. Amplitude of P3 was reduced, N2 was larger and P2 was slightly reduced in MS group when compare to controls. Significant correlation was seen between amplitude of N2 and P3, interpeak latencies with MMSE whereas latencies of N2 and P3were marginally correlated.

				No significant correlation was seen between amplitude of N1and MMSE. **Conclusion:** ERP can used to in the diagnosis and management of cognition in MS patients.
9	Sailer et al., (2001)	**Type of multiple sclerosis** relapsing, remitting or secondary progressive Study group 34 with definite MS The exclusion criteria were i) primary progressive multiple sclerosis; ii) severe depression; iii) acute MS relapse and / or treatment with steroids within the last 30 days; iv) treatment with central nervous active drugs such as anti-depressants, anti-psychotic or tranquilizer. The subjects divided into 3 groups (based on MRI) i) low lesion volume (LLV), ii) high lesion volume and a diffuse distribution of the MS plaques (HLV) and iii) high lesion volume with a predominantly frontal	Auditory task ERP- P300 Visual task ERP Neuropsychological test- WAIS R, digit span MRI - T2 weighted	**Findings** **ERP:** the reaction time was slower for the MS group when compare to the control group no significant difference was seen in N1 between 3 groups P3a (fronto temporal distribution) and P3b (parieto occipital) present in all subjects group. **Neuropsychological test:** No significant NPT score was obtained between lesion volumes. **Conclusion** ERP will give additional information to assess cognition with NPT. To assess cognitive dysfunction MRI can be used using new indices (magnetization transfer ratio, spectroscopy and diffusion weighted imaging) and ERP testing contribution can be enhanced by using specific working memory.

		distribution of the lesions (FLV)		
10	Sandorini et al., (1991)	Study Group: N=10 Selection criteria: intact cognition, minimal sensory loss in the upper extremities. Krupp fatigue severity scale indicates severe fatigue in all patients.	ERP: N1,P2,N2,P3b Motor evoked potentials Short term memory task	**Findings** **ERP for Task:** Target detection and short term memory- Reaction time was more for patients with MS(rest) when compared with controls and it is delayed further when MS in (fatigue) Accuracy- no significant difference when MS patient was in rest or fatigue. **ERP latency:** N1 and P3a: latency was significantly different for controls and MS and P3a latency was shorter for fatigued than rested in MS patients. Difference between N1 and P3a latency was not significantly different between controls and MS similarly for fatigued and rested MS. **Amplitude:** P3b amplitude is significantly different between controls and MS. P3a amplitude is larger for fatigued than rested. P3b unaffected by fatigue. **Motor evoked potentials:** No significant difference was observed between rested and fatigued MS for all the task. **Conclusion:** In MS patients, the time intervening between brain events subserving stimulus evaluation and those involved in the initiation of motor responses is prolonged for simple and complex auditory discriminations, and these periods become further prolonged with fatigue.

11	Lorfice et al., (2021)	**Type of multiple sclerosis:** Relapsing remitting type Study group: N=78 MS	Auditory: ERP(N100, P200, N200, and P300), Neuropsychological test(Brief Repeatable Battery of Neuropsychological Tests (BRBN), the symbol digit modalities test (SDMT), MRI the volumes of the whole-brain (WB), White Matter, and Grey Matter, including the cortex and Subcortical GM structures (putamen, caudate, pallidus, thalamus, hippocampus, amygdala, and nucleus accumbens)	**Findings:** **ERP with MRI:** significant difference in latency of P300 (prolonged) in MS who has cognitive impairment. Significant difference was seen in whole brain, grey matter, subcortical Grey Matter in patients with MS (CI). **ERP with NPT:** significant correlation was seen between failed NPT test and P300 latency and amplitude. **ERP with neuroradiological findings:** Significant correlation was seen between Grey Matter volume and shorter latencies and higher amplitude of N100, P200, N200, and P300. Cortex volume significantly correlated with amplitude of P300 while amygdale and hippocampus correlated with latency of P300. **Conclusion:** P300 is the indicator of cortical grey matter integrity. The volume of amygdala and hippocampus influence P300 latency. ERP Highlighting atrophy of deep GM.
12	Pokryszko et al.,(2016)	Type of multiple sclerosis: relapsing-remitting, and secondary progressive MS Study group: N=86 MS Diagnosed based on McDonald's criteria (2010).	ERP:P300 and N200 Fatigue: Fatigue Severity Scale (FSS) and Modified Fatigue Impact Scale (MFIS) subjects grouped	**Findings** **N100:** no significant difference in latency was scene between MS and controls **P300 N200:** latency was longer in MS than controls

		The exclusion criteria involved: concomitant diseases known to affect fatigue and/or cognitive functions, current immunosuppressive treatment or immunomodulation therapy Control group: 40	into 3 based on fatigue severity NPT: The Brief Repeatable Battery of Neuropsychological Tests (BRBNT)	Only at Pz amplitude of P300 and N100 was lower in MS No correlation was seen between fatigue measures and N200 Correlation was seen between P300 latency and fatigue measures. No difference was seen between subgroup of fatigue **Conclusion** Parameters of auditory ERP appeared to be electrophysiological biomarkers of cognitive function, but were not independently linked to fatigue.
13	Honig et al., (1991)	**Type of multiple sclerosis:** **Study group: N=**31 MS diagnosed based on Schumacher et al. (1965). **Control group:** 32 normals	ERP-300 MRI of brain Clinical examination-Expanded Disability Status Scale(EDSS), Mini-Mental State (MMS) cerebral functional scale (CFS), dementia scale (DS), information memory concentration test (IMCT)	**Findings** P300 (P3a and P3b) latency was longer and reduced amplitude in MS than controls. Prolonged latency was seen for the patients who has extensive demyelination in MRI and severe cognitive impairment (CFS). **Conclusions** Abnormal prolongation of P300 ERP latency correlates highly with cerebral white matter involvement and with impaired cognitive function.
14	Gil et al., (1992)	Study group : 101 MS diagnosed based on McAlpine's diagnostic criteria Control group : 71	N100, P200, N200 and P300	**Findings** P200, N200 and P300 latency were prolonged in MS when compared to controls but no significant difference in amplitude.

				P200, N200 and P300 latencies correlated with NPT test (ERFC) but no correlation for amplitude. The N200 and P300 latencies were increased in depressed MS but not significant. More increased latency was seen in the more severe group **Conclusion:** The progressive type lead to greater motor handicaps, to more marked cognitive deficit, and to greater latency abnormalities (P300) and(P200).
15	Giesser et al., (1991)	Study group: 6 demented and 6 non-demented MS patients diagnosed based on poser's criteria. Exclusion criteria: no psychoactive drugs Controls: 7 normals	ERP: N100, P200 and P300 Demetia - Minimal Record of Disability (MRD) NPT- Blessed Test, Benton Visual Retention Test, Buschke's Selective Reminding Test and the Category Retrieval Test	**Findings** The N100, P200 and P300 latencies were longer in dementia patients, and the N100-P300 interval was prolonged as well, compared to the non-dementia patients, whose ERP latencies did not differ from controls. Increased P300 latency was associated with poorer performance on the NP tests **Conclusion:** limited neuropsychological testing, the author failed to explain ERP latency and cognitive performance test.
16	Fiene et al.,(2018)	Type of multiple sclerosis: Relapsing and remitting, secondary Study group: 15 with MS diagnosed based on McDonald criteria (2001).	P300 TDCS stimulation (anodal and sham)	**Findings:** Anodal stimulation lead to increased P300 amplitude. Latency of P300 was increased which shows cognitive fatigue for prolonged stimulation of testing.

		Inclusion criteria: normal hearing, no severe depression, cognitive subscale of the Wurzburger Fatigue Inventory for MS (WEIMuS) min 9 score, no other pharmacological treatment except for MS.		During sham session fatigue was increased and it is associated with increase in latency and decrease in amplitude of P300 **Conclusion:** a single session of anodal tDCS over the left DLPFC can increase RT and P300 amplitude will be decreased which is associated with cognitive fatigue in MS patients.
17	Haimen et al., (2009)	**Type of multiple sclerosis:** Relapsing type Study group : N=6 MS with Pseudo Balbar Affect before and after Dextromethorphan/quinidine treatment Control group: N=6 healthy individuals, Inclusion criteria: pseudo Bulbar affect (PBA), score of more than 17 on center for Neurological study – Lability Scale (CNS - LS) Exclusion criteria: hearing complaints, had history of major psychiatric disturbance, had cognitive impairment, had steroid treatment within 6 months before examination, had substance abuse, or	Behavioral test ERP	**Findings:** PBA-preTx and PBA-DM/Q compared with controls which revealed effects on components of ERP. Treatment with DM/Q had a normalizing effect on the behavioral responses of PBA patients **Conclusion**: Administration of DM/Q resulted in normalization of behavioral and electrophysiological measurements.

		received psychopharmacological medication.		
18	Lazarevic et al., (2019)	**Type of multiple sclerosis:** Relapsing and remitting type Study group: N=81 Control group: N=32	Cognitive functions were assessed using a standard PASAT, the symbol digit modality test, and ERP (P300).	**Findings** **NPT test:** Fatigue and depression has negative effect on the cognitive function. **ERP:** the amplitude and latency of P300 was not influenced by depression and fatigue **Reaction time:** positively associated with depression and fatigue. **Conclusion:** Depression and fatigue have no effect on ERP amplitude and latency, so risk assessment for the development of cognitive impairment in patients with relapsing- remitting multiple sclerosis can't be participated.
19	Lori et al.,(2011)	Study group: N=6 children and adult (interferon beta-1a) Control group: N=9 (age matched)	Fatigue and depression were assessed by Beck Depression Inventory, the Fatigue Severity Scale, and the Fatigue Impact Scale. NPT: memory, IQ, attention, child depression Inventory ERP: P300	**Findings** **NPT:** cognition was deteriorated in 5 subjects after 2 years and no depression was seen in any of the children **ERP:** Amplitude was reduced and latency was increased in P300a and P300b of cognitively impaired MS subject. Whereas, it was normal in cognitively intact subject. As Cognition deteriorated and components of ERP also deteriorated.

				Conclusion: Neuropsychological functions in MS patient can be assessed and monitored over a time in MS subjects using ERP.
20	Szilasiova et al., (2022)	**Type of Multiple sclerosis:** relapsing-remitting MS, secondary progressive MS, and primary progressive MS **Cohort study** Study group : N=112 (2003) N=85 (2018) Inclusion criteria: diagnosed based Mc Donald's criteria (2001), > 18 years, informed consent) Exclusion criteria: Hyperacusis or deafness and relapse and/or corticosteroid use within 30 days before the evaluation.	ERP: P300 EDSS, disease phenotype	**Findings:** after 15years, phenotype was changed and EDSS score was increased for MS patient. ERP: prolonged latency of P300 **Conclusion:** P300 wave latency is a prognostic of long-term disability progress in patients with MS.
21	Kimiskidset al., (2016)	Study group : 59 MS Control group : 26	ERP-P300 NPT- Stroop Test and Trail Making Test, Wechsler Memory Scale Form II MRI- T1, T2	**Findings:** T1 lesion load predicts P300 and N200 latency more significantly. Other parameters of ERP such as amplitude of P300 and N200 were not correlated with MRI.

				ERP & T1, T2 MRI markers classified correctly 79.63% of patients in RR, PP and SP subgroups. **Conclusion:** The correlates of T1 lesion load and ERP is significant and types of multiple sclerosis can be differentiated using ERP and MRI.
22	Gedizlioglu et al., (2021)	**Type of multiple sclerosis: Relapsing and Remitting type** Study group: 35 MS diagnosed based on Mc Donald's criteria. Control group: 21 Inclusion criteria: have acute attack in the last 2 weeks,>18 years of age, EDSS score of less than % Exclusion criteria: No corticosteroids before, severe hearing loss and visual loss, no disease other than MS, no medication that influence cognition.	ERP (P300) Neuropsychometric test to assess cognition they used MOCA, MSFC, BRB-N, BDI-II, and MSQoL, Timed 25-Foot Walk test-leg function assessment were tested before and after giving corticosteroid treatment for 3 months	**Findings :** Latencies of P300 is prolonged and lower amplitude in relapse phase of MS than remission and controls. During relapse phase no Significant correlation was seen between the differences of BRB- N and MSFC During remission significant correlation was seen between subtest of BRB- N and MSFC score. **Conclusion :** Cognitive dysfunction is sustained and reversed during MS relapse phase. The P300 test was found to be practical, repeatable, and well correlated with the cognitive status of the patient with a relapse.
23	Papageorgiou et al.,(2006)	**Type of multiple sclerosis: relapsing remitting type**	Low-resolution brain electromagnetic tomography (LORETA)	**Findings** LORETA- significantly different patterns of current density activation seen at right frontal lobe

		Study group: N=18 of MS based on posers criteria and patients were given 1000 mg intravenous methylprednisolone (IVMP) for 3 days and then orally for 4 days Control group: N=16	ERP: P600 digit span Wechsler test were assessed for memory.	when compare to pre and post treatment (methylprednisolone). ERP: amplitude of P600 is increased and memory performance was also increased post treatment and it matching normals (controls). **Conclusion:** steroid treatment (methylprednisolone)as a treatment for relapsing remitting MS patients, may exert a beneficial effect of information processing
24	Barbosa et al.,(2022)	Study group: 40 Group I: 11 with MS Group II: 9 with NMOSD control group I: 11 and control group I I:9 Inclusion criteria: Absence of obstruction in the external acoustic meatus (EAM), presence of type-A tympanogram, normal hearing thresholds (equal or inferior to 15 dB HL at 500 - 4000 Hz).	BAEP, LAEP	**Findings:** CGI and SGI: significant difference in interpeak latencies III-V and I-V and latencies were prolonged in study group SGI and SGII: latencies were prolonged in SGI and significant differences in interpeak latencies III-V and I-V was seen. P2 and N2 amplitude were high in CGI SGI: p300 amplitude was high compare to SGII SGII: P2 and N2 amplitude was high compared to SGI Comparing with SG1, SG2 had a higher number of changes in LLAEP 80 % of MSor NMOSD were identified through BAEP and LLAEP. **Conclusion:** These tests were highly accurate to identify demyelinating diseases. These findings suggest that the AEP are important tools to help in the differential diagnosis of MS and NMOSD and valuable in the follow-up of the disease evolution.

25	Kiiski et al., (2012)	Study group: N=56 MS diagnosed based on MC Donald's criteria. Control group: N=39 Exclusion criteria: Current use of benzodiazepines or neuroleptics (minimum suspension period of 7 days), a history of alcohol, drug misuse, head injury, or stroke.	P3b visual and auditory NPT- PASAT(Paced Auditory Serial Addition Test), Hamilton rating scale for depression (HRSD-21) Event-related spectral perturbations (ERSPs) and inter-trial coherence (ITCs) superior method for visualizing ERP EEG	**Findings** MS patients had significantly reduced ERSP theta power when compare controls, and same was observed in CI vs. non CI MS patients. IC theta power was less for MS than controls in frontal, right temporal and central **Conclusion:** IC clustering is a reliable EEG method to aid the detection and monitoring of cognitive impairment in MS and therefor it complements general Neuropsychological test.
26	dijka et al., (1991)	study group :30 MS control group :19 MS patients were chosen with varies types and degree of handicap.	(BAEP), middle-latency AEP (MLAEP), and long-latency AEP (LLAEP). ERPs were investigated with two levels of difficulty for both the visual (VERP) and auditory (AERP) modalities. Measures of motor speed (tapping), Reaction time and EMG latency	**Findings** VERP N2 & N3 latencies were significantly longer in study group AERPS showed no significant difference in both the groups AERP latencies is proved to be insignificant related to any of the BAEP or MLAEP latencies for both the MS and control groups. Even though there was a difference between study group and control group for VEP and VERP latencies- no significant correlation Abnormal EMG, RT and tapping suggest decrease in motor aspects for MS Patients **Conclusion:** EP and ERP may be unrelated and the sensory disturbances revealed by EPs do not contribute to ERP abnormalities.

				ERP peak absent in ms population– not related to cognitive functioning This tells that ERPs as subtle indicators of cognitive impairment in MS
27	Matas et al.,(2010)	**Type of multiple sclerosis:** remittent recurrence type, Study group-25 (age=25 and 55) Inclusion criteria- diagnosed as MS ,Normal hearing sensitivity, no abnormalities for past 6 month before testing Control group-25 healthy Inclusion criteria-normal hearing and neurological development and no h/o tinnitus, auditory processing difficulties and psychiatric problems	BAEP, AMLR P300	**Findings:** BAEP- prolonged latencies values of wave I and III and between interpeak I-III and III-v were observed in MS population AMLR- No significant difference between the SG and CG for Pa or Na-Pa Amplitude. Study group had higher occurrence of abnormalities such as latency delay for Na and Pa wave. P300- latency delay was observed more in study group than control group **Conclusion:** BAEP, AMLR and P300 help in detection of changes in central auditory pathway in MS population since abnormalities was seen in patients with MS in all these tests
28	Newton et al., (1989)	Study group- 25 subjects with 24 subjects with definite MS and 1 with optic neuritis. Control group- 29 healthy subjects	ERP test was obtained in auditory 3 stimulus target detection test, visual modality task using odd ball paradigm along with reaction time by subjects	**Findings:** ERPS were almost normal for all patient but 10 showed problems in cognitive related components and another 3 subjects had a waveform with no cognitive component identified. These abnormalities were mainly noted in auditory task.

			tapping on the response button	For the 13 subjects, 11 of the subject had prolonged RT or decrease in target recognition task Abnormal EPR (N2 & P3 Latency)- longer duration of MS and higher MRI cerebellar score Correlation between MS and cognitive ERPS- decreased in P3 amplitude in depressed patients. 7/10 patients with h/o depression had abnormal ERPS mainly latency prolongation. The high MRI score reflects the extensive of the disease itself **Conclusion :** ERPs recorded using odd ball paradigm are useful in detecting cognitive function of MS patients

3.3 Quality Assessment

Quality assessment tool to determine the risk of bias in selected studies for the systematic review was done using the National Institute of Health (NIH) Quality assessment tool for case controlled, observational cohort and cross-Sectional studies which includes total 12 and 14 questions respectively. All of the included studies had well specified aims and objectives, and also the methodological quality varied from good to fair. The results of the studies included in this systematic review were qualitatively summarized to achieve the study's aims and objectives. The findings were further discussed in this systematic review's discussion chapter. Table 3.2 includes details on the quality assessment tool for case controlled, observational cohort and cross-sectional studies where "YES" indicating low risk of bias, "NO" indicating high risk of bias, and "NR, CD, NA" indicating unclear risk of bias.

Table 3.2 *Quality assessment of selected articles*

Authors/Year	Quality assessment tool for Observational Cohort and Cross-Sectional studies and case controlled studies														
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Rating
Ivica et al., (2013)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Jung et al., (2005)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Prosol et al., (2017)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
fpagos et al., (2003)	YES	YES	YES	YES	YES	YES	YES	NO	NA	YES	YES	NA	NO	YES	GOOD
Filipovic et al., (1997) (Case controlled study)	YES	YES	YES	YES	YES	YES	YES	YES	NA	YES	YES	YES	-	-	GOOD
Pokryszko-Dragan et al., (2009)	YES	YES	YES	YES	YES	YES	YES	NO	NA	YES	YES	YES	NO	YES	FAIR
Santos et al ., (2006)	YES	YES	YES	NO	YES	YES	YES	NO	NA	YES	YES	YES	NO	YES	GOOD
Jonathan et al., (2001)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Sailer et al., (2001)	YES	YES	YES	YES	YES	YES	YES	NO	NA	YES	YES	YES	NO	YES	FAIR
Sandorini et al., (1991)	YES	YES	YES	YES	YES	YES	YES	NO	NA	YES	YES	YES	NO	YES	FAIR
Lorfice et al ., (2021)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Pokryszko et al., (2016)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NA	NO	YES	GOOD
Honig et al., (1991)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Gil et al., (1992)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NA	NO	YES	FAIR

Giesser et al., (1991)	YES	YES	YES	YES	YES	YES	YES	YES	NA	YES	YES	YES	NO	YES	GOOD
Fiene et al.,(2018) (Case controlled study)	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	-	-	GOOD
Haimen et al., (2009) (Case controlled Study)	YES	YES	YES	NO	YES	YES	YES	NO	YES	YES	YES	YES	-	-	GOOD
Lazarevic et al., (2019)	YES	YES	YES	YES	YES	YES	YES	NO	NA	YES	YES	YES	NO	YES	FAIR
Lori et al., (2011)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Szilasiova et al., (2022)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Kimiskids et al., (2016)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Gedizlioglu et al., (2021)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Papageorgiou et al., (2006) (Case controlled study)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NA	-	-	GOOD
Barbosa et al., (2022)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	GOOD
Kiiski et al., (2012)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
dijka et al., (1991)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	NO	YES	GOOD
Matas et al., (2010)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES	YES	GOOD
Newton et al., (1989)	YES	YES	YES	YES	YES	YES	YES	NO	YES	YES	YES	NA	NO	YES	FAIR

Chapter 4

Discussion

This study aimed to systematically review the research articles on event related potentials in individuals with multiple sclerosis. Multiple sclerosis is an inflammatory progressive demyelinating disease caused by the destruction of myelin sheath by antibodies and immune cells (Rooper et al., 2005) and the symptoms are cognitive, motor and neuropsychiatric problem. Cognitive problem was present between one quarter and one half of the multiple sclerosis patient and has problem in recalling (Van den Burg et al.1987; Beatty et al. 1988) verbal fluency (Van den Burg et al. 1987; Litvan et al. 1988; Findley et al. 1989), conceptualization (Van den Burg et al. 1987) and attention (Findley et al. 1989). P300 elicited from frontal lobe, medial temporal lobe, cingulated gyrus, thalamus and structures of the limbic system (Ludowig et al., 2010) all these structures are involved in the reception and process of sensory information and selective attention. N200 is generated from sensory and frontal area which is responsible for the subconscious identification of the stimulus (Prosol et al., 2017)

In order to achieve the objectives 3125 articles were selected from all the databases that were mentioned in the method section. Based on the inclusion and exclusion criteria 28 articles were finalized for the review. In all the articles they have used at least any one of the event related potentials such as N100, N200, P300, N400 and MMN. To assess cognitive function in the neurophysiological test, the latency and the amplitude are the 2 important markers. latency indicates the time taken to process the information and prolonged latency shows that the time taken to process the information is more and

similarly reduced amplitude shows some disruption in the brain areas such as (frontal and parietal cortex, thalamus and temporo-mesial cortex) or temporal dispersion of information processing (Ivicaetal., 2013). Either prolonged latency or reduced amplitude of P300 is sufficient for the diagnosis of cognitive dysfunction (magnano et al., 2005). (Newton et al .,1989) has stated event related potential depends on white matter integrity also (Jonathan et al., 2001) reported changes in the ERP in multiple sclerosis patient is because of problem in the central demyelination and not because of damage in the primary afferent pathway. Latency of N1, P2 is better when compared to the latency of N2 and P3 which again indicates that the problem is more central and this findings correlated with mini mental state examination, a neuropsychological test. Cerebral white matter damage causes cognitive deficit and abnormal ERP in MS patient. Involvement of white matter damage which was showed in the MRI and degree of cognitive impairment was correlated (Newton et al., 1989; Honig et al., 1991). Prolongation in the latency of P300 correlated with severity of white matter damage (Jonathan et al., 2001) which indicates cognitive deficit in MS patients. Lori et al. (2011) reported that 3 to 10 % of MS patients are children and adults and also reported that in all the cognitively impaired MS patients the latency P300 is prolonged and amplitude is reduced.

The first objective of the study was to determine the effect of multiple sclerosis on cognition, attention and auditory processing. (Ivica et al., 2013; Giesser et al., 1991; Jonathan et al., 2001) observed changes in the P300 latency which was correlated with cognitive dysfunction such as visual verbal memory and storage and retrieval strategies in MS.(Jung et al., 2005) reported that in MS patients alterations in ERP by passive oddball task such as MMN and P3a and P3b was seen which shows that higher order auditory

cortices dysfunction which was associated to alterations in global cognition. Newton et al. (1989) reported 57% of MS has delayed cognitive potential which indicates cognitive dysfunction related to demyelination and also early components were normal in most of the MS patients such as (N1, P2and P100, N200 and P280). slowed speed of information processing is the one of the major features of cognitive impairment in MS and it was also seen in Neuropsychological test (Litvan et al., 1988; Ron et al., 1997) fpagos et al., (2003) and Pokryszko-Dragan et al. (2009) reported that MS is accompanied by working memory deficits**,** attention and verbal fluency alteration. Event related potential detects and predicts development of cognitive deficit (Giesser et al., 1991). Latency of P300 correlated with MRI lesion (cerebral white matter damage) and cognitive impairment. Which says that cognitive impairment is present in MS due to cerebral white matter (Honiget al., 1991). In relapsing remitting type of multiple sclerosis during the relapse phase cognition is significantly affected and it also correlated with neuropsychological test (Jung et al., 2005) found changes in MMN and P3a in cognitively impaired patients which states that MS patients has difficulty in information processing. (Gil et al., 1992; Newton et al., 1989; Sfasos et al., 2003) stated that increased P3b and P600 latency indicates information processing in MS (Jung et al., 2005) area of MMN is reduced in MS which pre attentive auditory automatic cognitive skill. Prosol et al., 2017 reported that More than 60% of the MS patients experienced moderate or severe stress and the amplitude of N200is high in MS patients with more stress. Dubayova et al., reported that Type D personality occurred much more commonly in MS patients (44.5%). Sfagos et al., (2003) reported the P600 amplitude is reduced in MS patients which indicates problem in reprocessing and it correlated with other psychological tests which indicates problem in working memory and

verbal memory in MS patients. Dragan et al. (2009) reported longer duration of the disease (MS) majorly affects memory. P300 prolongation correlated with depression in MS (Jonathan et al., 2001). In multiple sclerosis patient with dementia the N200 and P300 latency is prolonged when compared to the non dementia patient so the presence of dementia can be identified with event related potentials (Gil et al., 1992).

Relationship between cognitive impairment and lower grey matter volume was seen in MS patients which was indicated in MRI and event related potentials (Lorfice et al., 2001) the latency of P300 is affected by volume of amygdale and hippocampus therefore memory and other psychiatric disease was seen in MS patients. Lazarevic et al., (2019) reported depression was present in 29.6 % of MS patients in his study and after with the treatment of IFN beta- 1b, the depression and fatigue was reduced. Sandorini et al. (1991) reported that In P3a, shortened latency and increased amplitude was seen in patients with fatigue in MS and reaction time was prolonged for verbal short term memory and auditory discrimination also stated that fatigue affects attention hence problem in the performance was seen. In Relapsing remitting multiple sclerosis fatigue was present in 33 % of the MS population (Lazarevic et al., 2019) and also reported correlation between P300 and fatigue is evident for physical but not for cognitive. Dragan et al. (2009) stated fatigue can cause problem in the memory and attention. In patients of MS with dementia the latencies of N100, P200, P300 prolonged which shows that dementia is present in MS patients. (Jonathan et al., 2001; Filipovic et al., 1990; Verma et al., 1989) also reported changes in the ERP parameters was seen in other type of subcortical dementia. Giesser et al. (1991) stated that latency of N100, P200 and P300 were longer in dementia patients. So the increased latency of P300 correlated with neuropsychological test (NPT) and Reaction

time is also increased in Dementia patient. Hence the findings confirms dementia is presented in MS (Santos et al., 2006).

The second objective of the study was to understand how event related potential is important in the assessment, diagnosis, prognosis and management of multiple sclerosis. To diagnose cognitive dysfunction in MS P300 plays an important role (Newton et al., l989; Honig et al., 1991; Giesser et al., 1991). No correlation was observed between ERP and age, duration of the disease, degree of disability (Ivica et al., 2013; Jung et al., 2005; Prosol et al., 2017). It is not always possible to assess cognitive dysfunction by intellectual assessment tool in that case objective tests such as event related potentials will be very useful (Newton et al., l989). ERP is the useful test to assess attentional skills in MS (Jung et al., 2005). ERP can be used to monitor the effect of treatment (Haimen et al., 2009) used Dextromethorphan/quinidine as a treatment for MS changes in brain activity was observed post treatment and the amplitude of N100 and N400 were increased after the treatment. Transcranial direct current stimulation(tDCS) over the left dorsolateral prefrontal cortex (DLPFC) has done on MS patients with fatigue and post treatment the amplitude of P300 was increased which says that (tDCS) reduces fatigue related changes (Fiene et al., 2018). In MS patients after the treatment with high dose of methylprednisolone (HDMP) the latency so P3 has been reduced which states that P3 can be monitor changes post treatment in MS (Filipovic et al., 1997). In a study by Papageorgiou et al. (2006), P600 methylprednisolone was given as treatment to patients with relapsing remitting MS and the amplitude and latency of P600 was assessed during working memory task post treatment the amplitude of P600 was increased hence this drug was helpful for information processing in MS therefore ERP can be used to monitor the effect of treatment in MS. As

the disease progress the latency was prolonged and the amplitude was shortened in P300 which says that ERP can be used to assess prognosis of the disease (Sundrgren et al., 2010). Latency of more than 320 ms in P300 is considered as strong prognostic factor, P300 shows cognitive function, speed of processing and also assess any changes in pathogenesis of MS hence P300 can be used to assess prognosis of MS. Neuropsychological test is the gold standard test to assess cognitive dysfunction (Santos et al.,2006). Pokryszko-Dragan et al. (2009) reported that when monitor cognitive decline in MS, ERP is not a suitable test. Further, event related potential cannot indicate cognitive impairment in MS (Lazarevic et al., 2019).

Chapter 5

Summary and Conclusions

This goal of the study was to conduct a systematic review on the research articles on event-related potentials in individuals with multiple sclerosis**.** Articles were selected using specific keywords in five databases: J Gate, Pubmed Central, Scopus, Science Direct, and Pubmed. A total of 3125 articles were obtained after conducting the searches in all the five databases with 58 of them removed as duplicates remaining 3067 has undergone for title and abstract screening, after title and abstract screening 40 of the articles were eligible for full text screening remaining 2067 were not rejected based on the inclusion and exclusion criteria. While full text screening 12 were excluded because it did not full fill the eligibility criteria. Hence 28 articles were selected for systematic review.

The first objective of the study was to determine the effect of multiple sclerosis on cognition, attention and auditory processing. (Ivica et al., 2013; Giesser et al., 1991; Jonathan et al., 2001) observed changes in the P300 latency which was correlated with cognitive dysfunction such as visual verbal memory and storage and retrieval strategies in MS. Slowed speed of information processing is the one of the major features of cognitive impairment in MS and it was also seen in Neuropsychological test (Litvan et al., 1988; Ron et al., 1997; fpagos et al., 2003). Latency of P300 correlated with MRI lesion (cerebral white matter damage) and cognitive impairment. Which says that cognitive impairment is present in MS due to cerebral white matter (Honig et al., 1991). Prosol et al., (2017) reported that more than 60% of the MS patients experienced moderate or severe stress and the amplitude psychological tests which indicates problem in working memory and verbal

memory in MS patients. (Dragan et al., 2009) reported longer duration of the disease (MS) majorly affects memory. P300 prolongation correlated with depression in MS (Jonathan et al., 2001). Also, N200 is high in MS patients with more stress. In patients of MS with dementia the latencies of N100, P200, P300 was found to be prolonged, which shows that dementia is present in MS patients.

The second objective of the study was to understand how event related potential is important in the assessment, diagnosis, prognosis and management of multiple sclerosis. It is not always possible to assess cognitive dysfunction by intellectual assessment tool in that case objective tests such as event related potentials will be very useful (Newton et al., l989). ERP is the useful test to assess attentional skills in MS (Jung et al., 2005). ERP can be used to monitor the effect of treatment (Haimen et al., 2009) used Dextromethorphan/quinidine as a treatment for MS changes in brain activity was observed post treatment and the amplitude of N100&N400 were increased after the treatment. As the disease progress the latency was prolonged and the amplitude was shortened in P300 which says that ERP can be used to assess prognosis of the disease (Sundrgren et al., 2010). Latency of more than 320 ms in P300 is considered as strong prognostic factor a, P300 shows cognitive function; speed of processing and also assess any changes in pathogenisis of MS hence P300 can be used to assess prognosis of MS. Neuropsychological test is the gold standard test to assess cognitive dysfunction (Santos et al.,2006). Dragan et al. (2009) reported that to monitor cognitive decline in MS, ERP is not a suitable test.

It can be concluded that Event related potentials can be used in the assessment, management and to monitor the prognosis of the disease. It is also helpful to understand the effect of multiple sclerosis in an individual .since it is an objective test therefore it does

not require any cooperation of the subject. Hence, ERP is the most convenient way to assess cognition, memory, fatigue, stress, depression, attention and information processing in multiple sclerosis individuals. In addition, combination of structural MRI, neuropsychological and neurophysiological test (event related potential) will be the more reliable protocol for the assessment and management of multiple sclerosis.

5.1 Implications of the study

Majority of the study included in the systematic review reported that MS patients have problem in cognition, stress, fatigue memory and attention.

The impact of the systematic reviews are as follows.

- It is helpful in understanding cognition, attention and auditory processing deficit in individuals with multiple sclerosis and therefore helps in planning rehabilitation.

- It is helpful to understand the importance of auditory event related potential in addition to structural MRI and neuropsychological tests in individuals with multiple sclerosis for the assessment and management (to monitor the effect of the treatment)

5.2 Future directions

A standard protocol for the event related potential can be developed for the assessment and among the ERP which one has more value in the assessment of cognitive functions in MS patients.

5.3 Limitations of the study

The current systematic review has limitations that most of the studies are not the recent articles and most of the studies did not have control group who has MS. Further, none of the studies have mentioned that among the ERP which is the more reliable test for the assessment, hence such conclusion could not be drawn.

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APPENDIX

NIH Quality assessment questionnaire template used as quality analysis in the current systematic review study

Criteria	Yes	No	Other (CD, NA, NR)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome ifit existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to theoutcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently acrossall study participants?			
12. Were the outcome assessors blinded to the exposure statusof participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured andadjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

CD, cannot determine; NA, not applicable; NR, not reported *.

Criteria	Yes	No	Other (CD, NA, NR)*
1. Was the research question or objective in this paper clearly stated and appropriate?			
2. Was the study population clearly specified and defined?			
3. Did the authors include a sample size justification?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)?			
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			
6. Were the cases clearly defined and differentiated from controls?			
7 If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			
8. Was there use of concurrent controls?			
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			
11. Were the assessors of exposure/risk blinded to the case or control status of participants?			
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			

*CD, cannot determine; NA, not applicable; NR, not reported.