BEHAVIORAL AND ELECTROPHYSIOLOGICAL (P300) CORRELATES FOR VISUAL AND AUDITORY PROCESS IN ALZHEIMER'S DISEASE

Project under AIISH Research Fund [ARF]
Sanction No.: SH/CDN/ARF-14/2019-20
Total grants: Rs. 4.88.000

Project duration: 12 months

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Acknowledgments

This project report is the outcome of the study conducted with financial support from the AIISH Research fund. The Principal Investigator and the Research Officer extend their gratitude to the Director, All India Institute of Speech and Hearing, Mysore for extending the necessary support for the conduct of the project. Our thanks are also due to all participants for their timely cooperation.

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Abstract

Working memory deficits are a recognized feature of Alzheimer's disease (AD). The current study aimed to examine the visual and auditory processes of working memory capacity in individuals with dementia (IWD) and neurotypical individuals (NTI) through the use of behavioral and electrophysiological measures. The behavioral task employed in the present study was a visual n-back (4-back) task for five different stimuli categories, viz., common objects, fruits, vehicles, numbers, and alphabets using the E-Prime 2.0 software. The outcomes of the behavioral task in terms of reaction time and threshold of performance for each category of the stimulus were extracted and was subjected for analysis. The auditory electrophysiological measures were obtained using Electrical Geodesics Inc. (EGI) NetStation 5.4 and were further subjected to post-processing and analysis using the EEGLAB plugin on the MATLAB software. The primary auditory electrophysiological measure was the P300 elicited using both speech (/da/-frequent and /ga/- infrequent) and tone (1kHz pure tone-frequent and 2kHz- infrequent) stimuli. An oddball paradigm (80:20) was employed to elicit P300 from the participants. Further, the P1-N1-P2 complex was also obtained and subjected to analysis. The latency and amplitude of these evoked potentials were considered for further analysis. NTI group demonstrated shorter reaction times and higher thresholds compared to the IWD group for various categories of stimuli. The threshold of performance of the NTI group was observed to be 4-back level for various categories of stimuli whereas the performance of the IWD group was scattered at different levels. The majority of the participants of the IWD group could only reach a threshold of 2-back level for various categories of stimuli. In general, the performance of the IWD group was more variable and scattered compared to the NTI group which was more consistent and stable. Significant between-group differences were noted at almost all levels of the n-back task for all categories of stimuli. Comparison of reaction time at the threshold level of performance also revealed significant differences across the groups with superior performance by the NTI group.

The performance of the NTI group was superior to the IWD group in the electrophysiological measures as well. Prolonged latencies and diminished amplitudes were observed for the IWD group for both speech and tone stimuli with some exceptions. Between-group differences revealed that P300 elicited using both speech and tone stimuli from various cortical regions were different in terms of their latency and amplitude, especially at the parietal region. Within-group differences were also observed in the NTI group for P300 elicited using both speech and tone stimuli. In contrast, within-group differences were minimal in the IWD group. Statistically, it was observed that shorter latencies and higher amplitudes were present for speech evoked P300 compared to tone evoked P300 at the majority of cortical regions. Further, the P1-N1-P2 complex was examined for both tone and speech stimuli. These also revealed a superior performance by the NTI group than the IWD group.

Latencies and amplitude of P300 elicited from various cortical regions showed a fair to moderate correlation with a threshold reaction time of the n-back task in the NTI group. Whereas, the IWD group demonstrated strong to perfect negative correlations across the latencies and amplitudes of P300 elicited from different cortical regions with the threshold

reaction time of the n-back task. Further studies are warranted to validate the findings of the current study.

Keywords: *Working memory, n-back, E-Prime, Latency, Amplitude.*

CHAPTER 1

INTRODUCTION

Dementia is usually a disease of the elderly and is characterized by progressive loss of memory and other mental faculties such as language, judgment, and planning, impairment of daily activities, and deficiency in social interaction. Dementia impacts personal, family, and societal life (Das et al., 2012). Dementia is caused due to Alzheimer's disease, Cerebrovascular disease, Lewy Body disease, Frontotemporal lobar degeneration (FTLD), Parkinson's disease, and mixed pathologies (Wilson et al., 2012). Less common dementias include progressive supranuclear palsy, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, and inherited metabolic disorders, most of which are extremely rare (Morris, 1996).

Alzheimer's Disease (AD), with or without comorbid conditions, is the leading cause of dementia (Barker et al., 2002; Wilson et al., 2012) and accounts for 75% or more of all pathological diagnoses of dementing disorder (Jellinger et al., 1990). The World Health Organization (WHO) (World Health Organization, 2002), predicted that by 2025, about 75% of the estimated 1.2 billion people aged 60 years and older will reside in developing countries. It is estimated that nearly 35.6 million persons worldwide were living with dementia in 2010 (Prince et al., 2013). It is also expected that the number of people living with dementia will almost double every 20 years to 42.3 million in 2020 and 81.1 million in 2040 (Ferri et al., 2005).

Alzheimer's disease is thought to begin 20 years or more before symptoms arise (Gaugler, Joseph, et al., 2019), with small changes in the brain that are unnoticeable to the person affected. Only after years of brain changes do individuals experience noticeable symptoms, such as memory loss and language problems. Symptoms occur because nerve cells (neurons) in parts of the brain involved in thinking, learning, and memory (cognitive function)

have been damaged or destroyed. Individuals typically live with Alzheimer's symptoms for years. Over time, symptoms tend to increase and start interfering with individuals' ability to perform everyday activities. At this point, the individual is said to have dementia due to Alzheimer's disease, or Alzheimer's dementia.

Current research identifies three stages of Alzheimer's disease: preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and dementia due to Alzheimer's disease (Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011).

1.1 Preclinical Alzheimer's Disease

In this stage, which is still under investigation, individuals have measurable changes in the brain, cerebrospinal fluid, and blood that indicate the earliest signs of Alzheimer's disease (biomarkers), but they have not yet developed symptoms such as memory loss. While research settings have the tools and expertise to identify some of the early brain changes of Alzheimer's, additional research is needed to fine-tune the tools' accuracy before they become available for widespread use in hospitals, doctor's offices, and other clinical settings. It's important to note that not all individuals with an Alzheimer's biomarker go on to develop MCI or dementia (Bennett et al., 2006; Knopman et al., 2003), although many do.

1.2 MCI Due to Alzheimer's Disease

MCI has been described as a transitional diagnostic condition between normal cognitive aging and dementia (Holsinger et al., 2007). A meta-analysis of studies in cognitive impairment in Alzheimer's disease revealed that episodic memory or the ability to recall the explicit past events or experiences is presumed to be the first and most severely affected cognitive domain in these individuals (Bäckman et al., 2005). Episodic memory deficits are a key indicator of

the prodromal stage of dementia where the symptoms may not be very specific or severe, specifically for amnestic MCI and they are thought to represent the effect of early neuropathological changes in the hippocampal and entohinal cortices (De Jager & Budge, 2005; Ganguli et al., 2004; Kavé & Heinik, 2004). People with MCI due to Alzheimer's disease have biomarker evidence of an Alzheimer's-related brain change (for example, elevated levels of β-amyloid) and show cognitive decline greater than expected for their age, but this decline does not significantly interfere with everyday activities (Roberts & Knopman, 2013).

In MCI, changes in thinking abilities may be noticeable to family members and friends, but may not be noticeable to others. People with MCI, especially MCI involving memory problems, are more likely to develop Alzheimer's or another dementia than people without MCI (Kantarci et al., 2009; Mitchell & Shiri-Feshki, 2009). A recent analysis found that after 2 years' follow-up, 15 percent of individuals older than 65 with MCI had developed dementia (Petersen et al., 2018). A systematic review, in which data from multiple studies are pooled and summarized, found that 32 percent of individuals with MCI developed Alzheimer's dementia within 5 years' follow-up (Ward et al., 2013).

1.3 Dementia Due to Alzheimer's Disease

Dementia due to Alzheimer's disease is characterized by noticeable memory, thinking, and behavioral symptoms that impair a person's ability to function in daily life, along with evidence of an Alzheimer- related brain change.

Individuals with Alzheimer's dementia experience multiple symptoms that change over a period of years. These symptoms reflect the degree of damage to nerve cells in different parts of the brain. The pace at which symptoms of dementia advance from mild to moderate to severe differs from person to person.

In the mild stage of Alzheimer's dementia, most people can function independently in many areas but are likely to require assistance with some activities to maximize independence and remain safe. They may still be able to drive, work and participate in favorite activities.

In the moderate stage of Alzheimer's dementia, which is often the longest stage, individuals may have difficulties communicating and performing routine tasks, including activities of daily living (such as bathing and dressing); become incontinent at times; and start having personality and behavioral changes, including suspiciousness and agitation. In the severe stage of Alzheimer's dementia, individuals need help with activities of daily living and are likely to require around-the-clock care.

1.4 Biomarkers for Alzheimer's Disease

As mentioned earlier, MCI appears to be at an increased risk of developing Alzheimer's disease, they experience memory loss that is significantly diverse from normal aging individuals. Additionally, these individuals do not fall into the criteria of dementia specifically due to their usually preserved overall cognitive functions and Activities of Daily Living (ALDs). But, studies report episodic memory deficits as a preclinical sign anywhere between 3 to 8 years earlier than a formal diagnosis of AD. Therefore, early detection of cognitive-linguistic changes may aid in faster recognition of Mild Cognitive Impairment or Alzheimer's Disease (Fleming & Harris, 2008; Harris et al., 2008). Presently, the accepted criteria include the following: (a) reported change in cognition (preferably corroborated by an informant), (b) one or more impaired cognitive domains for age and education, (c) not normal, not demented (i.e., does not meet criteria for dementia syndrome according to *Diagnostic and Statistical Manual of Mental Disorders-4* (American Psychiatric Association, 1994), ICD 10, and (d) intact activities of daily living (Albert et al., 2011).

Among several factors being studied as biomarkers for Alzheimer's are the amounts of beta-amyloid and abnormal tau in the brain as shown on Positron Emission Tomography (PET) imaging, levels of certain proteins in fluid (for example, levels of beta-amyloid; t-tau, p-tau181, p-tau199, p-tau231, and VILIP-1 in cerebrospinal fluid (CSF) and levels of particular groups of proteins in the blood), and level of glucose metabolism in the brain as shown on PET imaging using the radiotracer fluorodeoxyglucose.

Even though there is an emergence of presumed biomarkers for AD (Jack et al., 2010), the clinical diagnostic accuracy of this condition is sub-optimal (Beach et al., 2012). Thus, a sensitive and reliable physiological measure of the cognitive deficits associated with AD could provide insight into the cognitive physiology of the disease, and help with diagnosis, and assessment of severity and progression. The brain responses for any sensory, motor and cognitive events are reflected and well-characterized in Event-Related Potentials (ERP). The fact is ERP methods are suitable for detecting and quantifying the cognitive deficits associated with AD. Event-related potentials (ERP) measured non-invasively by electroencephalography have shown diagnostic potential in AD (Leko et al., 2018).

In individuals with MCI, ERP has shown its potential utility in marking the disease progression, and subsequent conversion to the condition called dementia. For example, a study has shown discriminative information in the ERP responses to the auditory stimuli for patients with MCI who is likely to progress to AD (Bennys et al., 2011). The other findings by another set of authors are the patients with amnestic MCI showing abnormal ERP for a word repetition task are noted to be at high risk to progress to AD (Olichney et al., 2008). It has been suggested that the diagnostic efficiency of CSF protein biomarkers t-tau, p-tau181, p-tau199, p-tau231, and VILIP-1 could be supported by adding ERP in clinical practice (Leko et al., 2018). Thus, ERP has been shown to reliably tract the cognitive decline associated with AD progression.

To explain in brief, ERPs are well suited to study perception and attention of cognitive aspects. The most important aspect of ERPs is the temporal resolution which permits to measure the activities of the brain from one millisecond to the next, and cognitive aspects of attention and perception will operate in this temporal measurement scale of tens of milliseconds. The electrophysiological recording is provided as a direct measure since the brain is a wet electrical device. And for any nature of the electrical activity and the tissue in which ERPs are generated and propagated, there is no measurable conduction delay between the brain activity generated inside the head and the potentials recorded from the scalp (Nunez & Srinivasan, 2006). The averaged ERPs are measuring electrical potentials generated in the extracellular fluid as ions flow across cell membranes and neurons talk to one another via neurotransmitters.

Therefore, ERPs are voltage changes time-locked to some physical or mental occurrence in the ongoing electrical brain activity (recorded as EEG). The advantage of using electrophysiological measures is that they are sensitive to potential changes in functional aspects of speech perception that are manifested at the neural level and may be seen before any behavioral manifestation occurs (Tremblay et al., 1998). In auditory ERP studies, perhaps the most commonly used experimental approach is the active oddball paradigm. In this paradigm, typically two classes of stimuli are presented, one occurring frequently (standard) and the other occurring infrequently (target), and the subject is required to distinguish between the two stimuli and to respond to the stimuli that are predesignated as targets.

P300, an auditory event-related potential has been used in studying auditory linguistic processing (Henkin et al., 2002). It is also suggested that P300 reflects stimulus encoding, recognition, and classification (Kutas & Dale, 1997). In addition, P300 is associated with extended stimulus processing and memory retrieval functions (Polich & Kok, 1995). In particular, the P300 component of the ERP has been widely applied in the scientific study of

age-related cognitive dysfunction, because it reflects attentional and memory processes. This ERP is most commonly elicited in an active oddball paradigm when a subject detects an occasional target stimulus in a regular train of standard stimuli. In the novelty oddball paradigm, in turn, deviant or unexpected tones elicit a frontal subcomponent of P300, namely, the P3a, which is considered as an electrophysiological marker of the orienting response (Squires et al., 1975). Hence, P300 has the potential to be used as an electrophysiological correlate to directly reflect the cortical neuronal activity of the auditory stimuli.

Although this technique is well known, it is not yet fully realized through the wide adoption of ERP in the clinical use of cognitive communicative disordered populations. The possible reason could be the lack of standardization of ERP acquisition and data analysis techniques and impracticality of conducting ERP tests in clinical setup on actual clinical population. Hence, there is a need to validate event-related potential markers of Alzheimer's disease on a clinical trial in association with a behavioral method that assesses the cognitive-linguistic processing.

The best example of a behavioral task that assesses cognitive-linguistic processing, is the discourse task. With reference to discourse tasks in individuals with Dementia, there is an exact relationship between discourse and cognition. According to Ralph et al., (2001) the degradation of semantic networks is the main characteristic of individuals with Dementia. Where they exhibit difficulty in confrontation naming and show a poor score on semantic verbal fluency on standardized testing (Zakzanis et al., 1999). Similar to the loss of language in individuals with aphasia, a general deterioration in language skills is often associated with a decline in several cognitive skills as well (Almor et al., 1999). However, the discourse task could be time-consuming and can be cumbersome with respect to the analysis. The n-back task can be used as a substitute to probe into the specific cognitive-linguistic processing aspects.

The n-back task is a novel behavioral approach to measure the cognitive aspects of an individual. In recent studies, many researchers proved that the n-back task can assess and index Working Memory (WM) in individuals with cognitive communicative disorders (aphasia) in comparison with the neuro-typical individuals (Wright & Fergadiotis, 2012). N- back being a parametric task, aids in deciding if a current stimulus matches with prior stimulus sequentially which comes in 'n' place. It is thus considered to have a strong idea which helps in validity and its structure is consensus with the definition of WM, wherein it requires temporary storage and manipulation of stored information along with continuously revising WM components (Wright & Fergadiotis, 2012). Few functional neuroimaging studies suggested stimulation of frontal and other cortical areas implicated in the WM network constantly through a performance of n-back tasks by healthy adults (Temporal Dynamics of Brain Activation during a Working Memory Task, 1997), and have evidenced that this task is answerable for the central executive component of WM (Smith et al., 1998). Electrophysiological studies involving P300 and the theta frequency band power, have indicated that the n-back task exceptionally demands working memory processing compared to the other tasks (Scharinger et al., 2017).

1.5 ERP and Cognitive Processing

There are only a few studies published about P3a in AD and the findings have been to some extent inconsistent. AD patients are characterized by longer P3a latency than control subjects suggesting delayed orientation to deviant stimuli (Key et al., 2005). Furthermore, these authors suggested that the separation of P3 subcomponents (P3a and P300) by dipole source analysis may increase sensitivity and specificity and correctly detect AD patients from healthy subjects. On the other hand, some authors found no difference in the P3a between AD patients and controls but instead showed that the P3a was different in AD patients compared with patients with vascular dementia whereas the P300 was similar in these patients.

There are ERP studies done on bilingual persons with Broca's aphasia to check for the semantic processing and syntactic processing of language functions. Results of the electrophysiological findings showed that irregular variation and poor wave morphology was seen in persons with Broca's aphasia, the N400 component was elicited in neuro-typicals. Bilinguals obtained more negativity than monolinguals. More reaction time and poorer accuracy of response were observed in persons with Broca's aphasia compared to neuro-typicals in all the three linguistic categories; no differences were observed between monolinguals and bilinguals for reaction time measures (Kumar & Goswami, 2013). No reported Indian studies are using ERPs to find the clinical markers in the AD population by assessing cognitive processes like working memory and attention specifically meant for individuals with dementia.

However, with reference to western context, for example, when a deviant stimulus is associated with a task of ERP features there is an update in working memory, and P3a is associated with detecting the involvement of attention and processing of novelty according to (Polich, 2007). When working memory is updated by utilizing the attentional resources the P3b amplitude varies (Donchin & Coles, 1988). Whereas, the P3b latency reflects stimulus evaluation and classification speed (Duncan-Johnson & Donchin, 1982). Therefore the majority of findings are P3b amplitude typically being smaller and P3b latency being longer for individuals with AD in comparison with neuro-typical individuals (Polich & Corey-Bloom, 2005).

In contrast to the P3b, the findings related to the amplitude and latency of P3a are scarce and the results are inconsistent. The peak amplitude of P3a is a measure of focal attention and shows a positive correlation with executive function (Juckel et al., 2012). With specific to the AD population it has been shown that reduction in P3a amplitude is in association with the decreased attention and executive functions of neurophysiological testing (Cecchi et al., 2015).

Thus, the group difference with reference to healthy control suggests a clinical implication to use ERP features to measure cognitive deficits in the preclinical stage of individuals with AD.

The expected declines in various cognitive processes like perception/sensory acuity, speed of processing, and executive function, remain unclear to differentiate between MCI, AD, and normal aging. With this need, there is an attempt to validate the existing behavioral and electrophysiological method (ERPs) as a clinical marker to identify, diagnose and treat AD.

1.6 Aim

The aim of this study is to validate the behavioral and event-related potentials as a clinical marker for individuals with Alzheimer's disease.

1.7 Objectives

1. To investigate the behavioural measures of cognitive functions using the n-back task (visual stimuli) as a clinical marker for individuals with Alzheimer's disease.

2. To investigate the event-related potentials (P300) using auditory stimuli (tonal and speech stimuli) as a clinical marker for individuals with Alzheimer's disease.

3. To correlate the behavioural and ERP measures as a clinical marker to process visual and auditory stimuli in Alzheimer's disease.

CHAPTER II

REVIEW OF LITERATURE

Alarmingly increasing prevalence of Alzheimer's disease (AD) due to the aging population in developing countries, combined with lack of standardized and conclusive diagnostic procedures, make an accurate diagnosis of Alzheimer's disease, especially for its early-stage also known as amnestic mild cognitive impairment (MCI), a major public health concern (Vecchio & Määttä, 2011). While no current medical treatment exists to stop or reverse this disease, recent dementia-specific pharmacological advances can slow its progression, making early diagnosis all the more important. Approximately 10 percent of MCI adults progress to AD (Mitchell & Shiri-Feshki, 2009). Behaviourally, both AD and MCI are traditionally diagnosed in relation to abnormalities in brain functions such as memory, cognition, perception, and language. Furthermore, the differentiation of probable AD from other dementing illnesses is generally obtained by excluding alternative causes for cognitive dysfunction. It is important therefore to determine whether AD and MCI can be characterized by functional deficits other than high-level abnormalities already described and whether, with further development, they are specific and sensitive enough to contribute to the search of early markers of the disease process.

Among several factors being studied as biomarkers for Alzheimer's are the amounts of beta-amyloid and abnormal tau in the brain as shown on positron emission tomography (PET) imaging, levels of certain proteins in fluid (for example, levels of beta-amyloid; t-tau, p-tau181, p-tau199, p-tau231 and VILIP-1 in cerebrospinal fluid and levels of particular groups of proteins in blood), and level of glucose metabolism in the brain as shown on PET imaging using the radiotracer fluorodeoxyglucose. Due to the high costs involved, small availability and the need for invasive procedures sometimes make these biomarkers of limited usefulness

(Cintra et al., 2014). In an attempt to facilitate the diagnosis of AD, several non-invasive biomarkers have been proposed, including event-related potentials (ERPs). Within evoked potentials, P300 has been proposed as a biomarker for Alzheimer's disease owing to its advantages of being a less cost involved and being non-invasive.

Event-related potentials (ERP) has been widely used as a cognitive measurement tool for diagnosis and prognosis of many neuropsychiatric diseases (Emek et al., 2013). ERPs are voltage changes time-locked to some physical or mental occurrence in the ongoing electrical brain activity (recorded as EEG). In auditory ERP studies, perhaps the most commonly used experimental approach is the active oddball paradigm. In this paradigm, typically two classes of stimuli are presented, one occurring frequently (standard) and the other occurring infrequently (target), and the subject is required to distinguish between the two stimuli and to respond to the stimuli that are predesignated as targets. Variations of this paradigm include the passive oddball paradigm, in which the subject is instructed to ignore the stimuli, and so-called novelty oddball paradigm, in which a third class of stimuli (novelty) are also presented intermixed with the standard and target stimuli.

2.1 P300 as a biomarker

Auditory P300, a positive deflection occurring at about 300ms from stimulus onset, is one of the most widely studied components of the ERP. The component P300 is defined as the highest positive peak occurring between 250 and 500 milliseconds after a rare (occasional relevant-'target') stimuli, occurring after the two negatives components N100 and N200 and the positive component P200 (Linden et al., 1999; Polich & Criado, 2006). It is generated by the activation of multiple neocortical and limbic regions, and has two functionally different components: the earlier P3a that is maximal over frontocentral regions, and the later P3b that is maximal at posterior scalp locations (Squires et al., 1975).

The P300 is parietocentral positivity that occurs when a subject detects an informative task relevant stimulus(Sutton et al., 1965). It is most commonly elicited in an active oddball paradigm when a subject detects an occasional target stimulus in a regular train of standard stimuli. The P300 probably represent concurrent activity in multiple regions of the brain, including temporoparietal neocortical areas and higher limbic structures(Halgren et al., 1980; Halgren, Baudena, Clarke, Heit, Liégeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995; Horn et al., 2003; Johnson, 1989; Mccarthy et al., 1997; Menon et al., 1997; Opitz, 1999; Stevens et al., 2000; Verleger et al., 1994).

The P300 is generated in many areas of the cortex, mainly in the temporoparietal cortex, and reflects cognitive processes as attention, recognizing and classification of stimulus, and also work memory and decision making(Pedroso et al., 2012). Therefore, it is supposed that P300 is more useful than N200 in the diagnoses and monitoring cognitive deficit.

The major theoretical interpretation of the P300 component is that it indexes updating of activity in corticolimbic circuits in processes requiring attention and working memory (Donchin, 1981; Donchin & Coles, 1988). This context updating theory has its roots in Sokolov's model of the orienting response, which has been postulated to result from a change in the organism's neural representation of the stimulus(Polich, 1989). P300 amplitude is also proportional to the amount of attentional resources devoted to a given task (Gonsalvez & Polich, 2002; Kramer & Strayer, 1988; Wickens et al., 1983) and has been associated with superior memory performance(Fabiani et al., 1990).

P300 is associated with attention and working memory processes, particularly in tasks of sustained attention demanding vigilance(Portin et al., 2000). P300 amplitude can therefore be viewed as a measure of central nervous system (CNS) activity that reflects the processing of incoming information when it is incorporated into memory representations of the stimulus

and the context in which the stimulus occurs. Variation in P300 amplitude is, therefore, assumed to reflect the degree or quality with which that information is processed. The P300 has a latency to peak of anywhere from 300 to 1000ms, depending on task complexity and the clinical sample tested. A frequently observed phenomenon is that the P300 latency increases when categorization of the stimulus becomes more difficult. A general consensus seems to be that P300 is evoked after the stimulus has been evaluated(Kok, 2001). Thus, the latency of P300 has been regarded as a measure of stimulus evaluation time (Kutas et al., 1977; Polich, 1986) and is generally unrelated to response selection processes (McCarthy & Donchin, 1981; Pfefferbaum et al., 1986). It is therefore independent of behavioral reaction time (Duncan-Johnson, 1981; Verleger, 1997). Indeed, it is just these properties that make the P300 a valuable tool for assessing cognitive function: because P300 latency is an index of the processing time required before response generation, it is a sensitive temporal measure of the neural activity underlying the processes of attention allocation and immediate memory. In addition, P300 latency is negatively correlated with mental functions in normal subjects, with shorter latencies associated with superior cognitive performance (Emmerson et al., 1989; Polich et al., 1983, 1990; Polich & Martin, 1992).

The P300 latency is the most common aspect of the P300 wave analyzed in studies of dementia and cognitive decline(Howe et al., 2014). P300 latency is thought to reflect post-stimulus information processing (Goodin et al., 1978; Pfefferbaum et al., 1984; Updating P300: An Integrative Theory of P3a and P3b, 2007) and executive function (memory, attention, integration of complex stimuli)(Bennys et al., 2007; Johnson et al., 1985).

The P300 wave has also been classified into two subcomponents known as P3a and P3b, but the relationship of the P3a to the P300 wave has not been fully elucidated(Updating P300: An Integrative Theory of P3a and P3b, 2007; N. K. Squires et al., 1975). P3a appears to reflect orientation to an incongruent stimulus while P3b reflects the discrimination of a

congruent and incongruent tone(Updating P300: An Integrative Theory of P3a and P3b, 2007). Prolongation of the P300 latency has been hypothesized to be associated with the subtle, but progressive cognitive decline seen in AD(Lee et al., 2013).

P300 amplitude is related to working memory, and the P300 amplitude correlates positively with memory ability in healthy controls, (Ally et al., 2006) whereas decreases in P300 amplitude are associated with decreased brain activation (Magnano et al., 2006) and cognitive dysfunction(Polich, 1986). The P300 amplitude also decreases with age, an effect that appears exaggerated in Alzheimer's disease(Saito et al., 2001).

2.2 Studies supporting the use of P300 as a biomarker

Literature related to the relationship between neurodegeneration and P300 components is quite extensive. Although P300 has been shown to consistently discriminate between patients with AD (and even mild AD) (Bennys et al., 2007; Juckel et al., 2008), patients with MCI (V. Papaliagkas et al., 2008; V. T. Papaliagkas et al., 2011), and unaffected controls; the usefulness of P300 in the diagnosis of early dementia have been a subject of debate across researchers in the recent past. Studies that are in support of the use of P300 as a biomarker for MCI as well as AD and studies that are against the use of P300 are discussed below.

Ally et al. (2006), elicited P300 from an AD group, their biological children, and two age and gender matched control groups using the auditory oddball paradigm. Each group consisted of 20 subjects each. ERPs recorded from sites Fz, Cz, and Pz were analysed using analysis of variance. Results suggested that the amplitude, but not the latency, of the cognitive event-related potential P300 differs between patients with AD who are taking cholinesterase inhibitors and healthy older control participants. The most important finding suggested that P300 may identify preclinical changes in participants who are at relatively high risk for the disease because of genetic predisposition. The results suggested possible early 'precursor'

changes in these cognitive abilities for biological children of patients with AD. However, these at risk participants with abnormal P300 amplitude and latency times did not show deficits in cognitive abilities measured by the MMSE. Thus, they concluded that, clinical evidence of the disease may first be evident in very mild deficits in sustained attention and vigilance (as reflected in reduced amplitude of P300), leading to future memory impairment.

Farina, Rodriguez, Rosenfeld, Maineri, and Kaefer (2006), aimed to evaluate if there was a correlation between P300 latencies and CDR scores. 28 consecutive patients (45 to 84 years old with a mean age of 61.1 years) attending a memory clinic for diagnostic test of cognitive dysfunction were subjected to an auditory event related potential study involving the odd-ball paradigm. As the latencies of P300 correlate with age, a Z score was calculated for each patient in relation to the mean expected for the age which was then compared to their CDR score. A battery of tests and some questionnaires as well as Quantitative EEG were also applied as part of their diagnostic workup. CDR scores were 0 to 3 (mean 0.7). The mean of the Z score to P300 was 3.77 (±3.1). A moderate correlation was found for P300 latencies Z-scores and CDR (r 0.493; p 0.009). They concluded P300 latencies to be a valuable method when a more objective test is needed in the evaluation of patients with cognitive dysfunction.

Jackson and Snyder (2008), suggested that quantitative EEG offers a non-invasive, rapid, and replicable method for assessing age-related and disease-related neurophysiologic change as a neuroimaging tool that is relatively inexpensive, potentially portable, and capable of providing high-density spatial mapping. They identified quantitative EEG as a reliable and sensitive biomarker of MCI & early AD.

Vecchio and Määttä (2011), in a followup study, showed that the abnormalities in P300 in AD and MCI latency correlated with the severity of cognitive impairment. Upon one year followup, after the baseline study, the P300 latencies demonstrated significantly more

prolongation than their baseline measures in AD and MCI patients, although their neurophysiological evaluation showed no statistical decline, suggesting that the P300 latency may reflect cognitive decline more sensitively than neuropsychological tests in the longitudinal followup of AD patients.

Emek et al. (2013), aimed to investigate changing brain dynamics in de novo Alzheimer's Disease (AD) patients, Mild Cognitive Impairment (MCI) patients and healthy elderly by implying auditory ERPs. 15 de novo AD patients (mean age 70.53 years) according to NINCDS-ADRDA criteria, 15 MCI patients (mean age 71.93 years) according to Petersen's criteria and 15 healthy elderly (mean age 70.80 years) participated in their study. The groups did not differ in terms of age and gender. A classical auditory oddball paradigm was used for the experiments. The EEG was recorded from F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, Oz and O2 locations. The maximum amplitudes for each subject's averaged P300 response (0.5-25 Hz) were measured. The maximum amplitudes of auditory P300 for target tones between groups differed significantly on all electrode sites. Post-hoc comparisons revealed that P300 amplitudes of MCI group were significantly lower than in healthy controls and significantly higher than in AD group over the right and left parietal and occipital electrodes. On all the other electrode sites, P300 amplitudes of MCI subjects were significantly lower than the healthy controls and didn't differ between AD patients. P300 amplitudes of healthy controls were significantly larger than AD patients in all regions. They reported of a statistically significant difference in P300 amplitude between the groups. They concluded that, P300 responses are considered to be related to attention and memory processes, lower amplitudes of P300 in AD and MCI patients are an electrophysiological reflection of attention and memory deficits.

Lee et al. (2013), carried out a study involving 31 AD patients and 31 elderly normal control subjects. Age and education level were matched between the two groups. The

relationship between the P300 and the Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K) assessment packet (including 11 neuropsychological tests) were examined in AD patients. Their results revealed that, when compared to the control subjects, the AD patients exhibited significantly decreased P300 amplitudes; however, there was no significant difference between the two groups in terms of P300 latency. After a permutation-based correction for multiple tests, P300 amplitudes at the Cz and Pz electrodes were significantly correlated with performance on the word list recognition, constructional praxis, and word fluency neuropsychological tests in the AD patients. Additionally, P300 latencies at the Pz and C6 electrodes were also significantly correlated with performance on the Mini-Mental State Examination, CERAD-K version (MMSE-K), and Trail Making Test part A (TMT-A) neuropsychological tests in the AD patients. Their results suggested that the P300 is responsive to the deterioration of language, memory, and executive functions observed in AD patients. Although there was no significant difference between the AD patients and control subjects in the P300 latency, P300 latency has been shown to reflect impaired global cognition and attention deficits associated with AD. They concluded that P300 indices could be used as biological markers that indicate impaired neuropsychological functions in AD patients.

Howe et al. (2014), investigated the clinical utility of the auditory P300 latency event-related potential in differentiating patients with Alzheimer's disease (AD), patients with mild cognitive impairment (MCI), and unaffected controls using meta-analysis of 48 studies. Studies were carried out between 1970 and 2013. Effect size estimates were computed from mean P300 latency measurements at midline electrodes between patients and unaffected controls using the random effects restricted maximum likelihood model. Also, the effects of clinical and ERP/EEG methodological variables were assessed in a moderator analysis. P300 latency was found to be significantly prolonged in patients with AD (and MCI) compared to unaffected

controls. Shortened P300 latencies were observed when comparing patients with MCI to patients with AD. Clinically relevant differences in P300 latency effect sizes were associated with mean age, interstimulus interval, stimulus difference, target frequency, reference electrode, and sampling rate. Their meta-analytic findings provided robust statistical evidence for the use of the auditory P300 latency subcomponent as a biological marker of prodromal AD.

Cintra et al. (2014), investigated whether the P300 evoked potential can estimate the risk of MCI progression to Alzheimer's dementia (AD). They reviewed the PubMed database and selected eight among 929 articles after applying the exclusion criteria. From the articles they concluded that the electrode placed at the parietal region is the most effective and that the latency increase and amplitude decrease of the electrode reading are related to the higher risk of progression from MCI to a diagnosis of AD. Most of the selected studies sustain P300 to estimate the progression risk from MCI to AD. They also pointed out, the low number of studies, small sample size and heterogeneous results as important limitations. They concluded that P300 represents a promising method to estimate the likelihood of the MCI progression to AD. However, more studies are needed to support P300 for daily clinical practice.

Cecchi et al., (2015) investigated whether event-related potentials can provide a sensitive and reliable measure of the cognitive deficits associated with early Alzheimer's disease. A total of 103 subjects with probable mild AD and 101 healthy controls were recruited at seven clinical study sites and were tested using an auditory oddball ERP paradigm. They found that subjects with mild AD showed lower amplitude and increased latency for ERP features associated with attention, working memory, and executive function. These subjects also had decreased accuracy and longer reaction time in the target detection task associated with the ERP test. Analysis of ERP data showed significant changes in subjects with mild AD that are consistent with the cognitive deficits found in this population.

Evidence exists also for age-related modulation of the P300 deflection, i.e., reduction in amplitude and increase of latency, correlated with age-related changes in cognition across various tasks and populations (Polich, 1996). These P300 age related changes may reflect the degeneration of brain cortex and the dysfunctional cortical interconnection that occur with age (Bashore & Ridderinkhof, 2002; Reuter-Lorenz, 2002).

Wang, Zhang, Han, and Zhou, (2016) aimed to identify the differences in the cognition and motor cortex excitability between 27 AD and 30 bvFTD patients. Cognitive event-related potentials (P300) were recorded during an auditory oddball task. Followed by the assessment of the excitability of the motor cortex, including the resting, facilitated motor threshold (RMT and FMT) and cortical silent period (CSP), during transcranial magnetic stimulation (TMS). They found that, the bvFTD patients exhibited significantly longer P300 latencies compared with AD patients. There was a significant negative correlation between cognition and P300 latency in the bvFTD group. The results also showed that bvFTD patients displayed a significantly longer P300 latency compared with AD patients. Simultaneously, AD patients displayed a hyperexcitability of the motor cortex, which may be a compensatory mechanism for the execution of voluntary movements. The AD patients showed significantly reduced RMT and FMT values compared to the bvFTD group; however, no significant correlation was found between AD severity and the excitability of the motor cortex. The authors concluded that cognition and motor cortical functions are different between AD and bvFTD patients. They also suggested that non-invasive electrophysiological examinations have the potential to identify unique pathophysiological features that can be used to differentially diagnose AD and bvFTD patients.

Papadaniil et al. (2016), carried out a study on 21 healthy volunteers, 21 MCI patients and 21 AD patients. The grand average ERP waveforms of both the target and standard tones were extracted for each group and the voltages were transformed into reference-independent

values by average referencing using the EGI 300 Geodesic EEG system. They found that the ERP components are modulated as the neurodegeneration progresses, with the latencies being longer to a statistically significant degree and the amplitudes being attenuated.

Hedges et al. (2016), investigated the possible association between P300 amplitude and Alzheimer's disease and the need for biomarkers in early Alzheimer's disease. The main purpose of their meta-analysis and meta-regression was to characterize P300 amplitude in probable Alzheimer's disease compared to healthy controls. Twenty articles containing a total of 646 subjects met inclusion and exclusion criteria. The overall effect size from all electrode locations was 1.079 (95% confidence interval = 0.745-1.412, $P < .001$). The pooled effect sizes for the Cz, Fz, and Pz locations were 1.226 ($P < .001$), 0.724 ($P = .0007$), and 1.430 ($P < .001$), respectively. Meta-regression showed an association between amplitude and educational attainment, but no association between amplitude and age, sex, and dementia severity. They concluded that, P300 amplitude is smaller in subjects with Alzheimer's disease than in healthy controls.

Tsolaki et al. (2017), investigated P300 as well as MMN in 21 healthy elderlies, 21 mild cognitive impairment (MCI) and 21 mild AD patients. Their results revealed longer latencies of both mismatch negativity (MMN) and P300 and slower and far less accurate responses as neurodegeneration progressed.

From the above studies, it is clear that the P300 (P3b subcomponent) is the most studied ERP component related to dementia and cognitive decline. Properties of P300 are affected by the nature of the stimulus including presentation probability, stimulus sequence, stimulus quality, the inter-stimuli intervals (ISIs)(Duncan et al., 2009), the target-to-target time interval (TTI)(Updating P300: An Integrative Theory of P3a and P3b, 2007), attention, and task relevance of the stimulus(Patel & Azzam, 2005). Additionally, P300 characteristics seem to

change due to subject related factors, such as age (van Dinteren et al., 2014), gender, and handedness (Polich & Hoffman, 1998). The methodological variables are the reason why there are not fully comparable data in the literature about normal and abnormal P300 values. As discussed above, various studies show the impact of neurodegeneration on P300 latency(Caravaglios et al., 2008; Lai et al., 2010) and a few present the impact on P300 amplitude, as well(Bennys et al., 2007; Juckel et al., 2008; Medvidovic et al., 2013).

Frontal lobe contribution to the identification of the target tone in the present oddball task and the elicitation of the ERP components have been suggested in the past. Recent studies have found hypometabolism of the middle frontal gyrus in AD due to disconnectivity (Klupp et al., 2014), while others report decreased volumes of frontal lobe early in MCI and AD (Zhao et al., 2016). Thus, there is now sufficient evidence to suggest that the latency and amplitude of the P300 are altered in AD (Ally et al., 2006; Caravaglios et al., 2008; Lai et al., 2010; Pokryszko-Dragan et al., 2003; Polich, 1989; Polich & Corey-Bloom, 2005). Furthermore, studies also evidence that that characteristics of the P300 wave are also compromised in individuals with MCI(Bennys et al., 2007; Lai et al., 2010). Recent studies suggest that the latency and amplitude of the P300 wave might serve as a marker for monitoring the process through which MCI becomes AD(Fraga et al., 2018; E. J. Golob et al., 2009; V. Papaliagkas et al., 2008; V. T. Papaliagkas et al., 2011). Changes in the P300 parameters have been identified in carriers of gene mutations that lead to familial AD almost 10 years before the disease onset (E. J. Golob et al., 2009). Taken together these results suggest that the P300 could contribute to the assessment of AD.

2.3 Studies against use of P300 as a biomarker

Even though, the component P300 has an increased latency in AD patients compared to those with preserved cognition, especially in the analysis of the frontal and parietal electrode

responses (Pedroso et al., 2012), there is no consensus on the value of P300 for diagnosis of MCI and on its application to determine the risk of MCI progression to AD(Jiang et al., 2015).

A major reason against the use of P300 as a biomarker in individuals with AD is that reduction in P300 amplitude has been reported in a variety of conditions, such as traumatic brain injury(Duncan et al., 2003; Nandrajog et al., 2017) cigarette smoking(Hedges & Bennett, 2014) and schizophrenia(Jeon & Polich, 2003). This suggests that P300 amplitude reduction is not specific for probable Alzheimer's disease and that further investigation into differences in event-related potentials between neuropsychiatric conditions is required.

According to Golob, Irimajiri, and Starr(2007), P300 latency does not seem to be capable of predicting which MCI patients will convert to AD, and therefore seems to have no predictive value for AD diagnosis. Vecchio and Määttä(2011), also questioned the diagnostic utility of P300, even though it is clinically useful as an index of cognitive function.

Pokryszko-Dragan et al., (2003) attempted to evaluate parameters of auditory and visual P300 in patients with mild and moderate dementia of the Alzheimer type (DAT) and to correlate these with neuropsychological test results. Their study group comprised 13 patients with DAT (6 mild & 7 moderate) and 13 healthy, age-matched controls. Auditory and visual event-related potentials were evoked using a basic oddball paradigm. P300 latency and amplitude were compared in patients with DAT and controls and between subgroups of patients with mild and moderate DAT. Correlations between P300 parameters and the results of the Mini-Mental State Examination (MMSE), the Global Deterioration Score (GDS), and the Alzheimer's Disease Assessment Scale (ADAS-cog) were also analyzed. They found that the mean latency of auditory P300 was significantly prolonged, and the mean amplitude of visual P300 was significantly lower in the DAT patients. 4 patients with DAT (31%) had a prolonged latency of auditory P300. No significant differences in P300 parameters were found between

mildly demented and controls or between mildly and moderately demented. A positive correlation was found between MMSE score and auditory P300 latency in Fz and visual P300 amplitude in Cz. The results obtained in mildly demented patients were neither significantly different from those of healthy controls, nor from the results of the moderately demented group. They suggested that, P300 parameters undergo significant, modality-specific changes in patients with DAT; however, they are not sensitive enough to differentiate early dementia from normal aging. The P300, an additional ERP whose change is associated with cognitive decline, also shows abnormal latency and amplitude in individuals with mild AD. Specifically, in an auditory oddball paradigm, individuals with mild AD had a longer latency of the auditory P300, whereas in a visual oddball paradigm, these individuals showed a smaller visual P300 amplitude when compared with healthy controls.

However, application of the auditory ERPs to the study of dementing illness and AD have produced majorly positive findings than negative findings. The P300 response, in particular, has become popular in studies of dementia. Because the P300 response is related to fundamental aspects of cognitive function in normals, it should be useful in the diagnosis of dementia especially that of the Alzheimer's type. In general, this assertion is supported by a wide variety of previous findings that include the spectrum of dementias. Although the P300 does not appear to differentiate between types of cortical dementias (except for the findings of Wang et al., 2016), it does accurately reflect the level of cognitive dysfunction caused by these disorders.

2.4 Need to combine P300 with neuropsychological measures

As only a small proportion of individuals with Mild Cognitive Impairment (MCI) will convert to dementia; methods currently available to identify risk for conversion do not combine enough sensitivity and specificity, which is even more problematic in low-educated

populations. Current guidelines suggest the use of combined markers for dementia to enhance the prediction accuracy of assessment methods. Therefore, Parra et al., (2013) investigated the sensitivity and specificity of the electrophysiological component P300 and standard neuropsychological tests to assess patients with Alzheimer's disease (AD) and MCI. The neuropsychological battery comprised tests of memory, attention, language, praxis, and executive functions. The P300 was recorded using a classical visual odd-ball paradigm. They found that P300 amplitude in Fz was smaller in both MCI and AD patients than in healthy controls. No significant differences were found between groups in Pz. Three variables were found to achieve sensitivity and specificity values above 80% (Immediate and Delayed recall of word list - CERAD - and the latency of P300) for both MCI and AD. When they entered the model together (i.e., combined approach) the sensitivity for MCI increased to 96% and the specificity remained high (80%). Their findings suggest that the combined use of sensitive neuropsychological tasks and the analysis of the P300 may offer a very useful method for the preclinical assessment of AD, particularly in populations with low socioeconomic and educational attainment.

2.4.1 N-Back task

The N-back task of working memory (WM) assessment assesses memory components and the ability to process the memorized component simultaneously. This task was developed by Kirchner, (1958), and is a continuous performance task that helps in assessing a part of working memory and its capacity. There is variant form of this "n-back" procedure (Gevins & Cutillo, 1993) which is employed with human studies. The participants have to attend to a series of stimuli and have to respond whenever a stimulus matches the one presented 'n' trials previously (where 'n' is a pre-specified integer, usually one, two, or three). This task require on-line monitoring, updating, and manipulation of remembered information and is presumed to place higher demands on several key processes within WM.

In recent studies, many researchers proved that n-back task has a capability to assess and index working memory in individuals with cognitive communicative disorders (aphasia) in comparison with the neuro-typical individuals(Wright & Fergadiotis, 2012). It is thus considered to have strong idea which helps in validity and its structure is consensus with the definition of WM, wherein it requires temporary storage and manipulation of stored information along with continuously revising WM components(Wright & Fergadiotis, 2012). Few functional neuroimaging studies suggested stimulation of frontal and other cortical areas implicated in the WM network constantly through performance of n-back tasks by healthy adults(Temporal Dynamics of Brain Activation during a Working Memory Task, 1997), and have evidenced that this task is answerable for the central executive component of WM (Smith et al., 1998).

The additional information is that, there are numerous cognitive functions which is relevant to the n-back task with the impression of dorsolateral frontal cortex (approximately Brodman areas 9/45) being responsible for certain functions. To list few are, holding spatial information on-line, monitoring and manipulation within WM, response selection, memory facilitated by implementation of strategies, organization of material before encoding and verification and evaluation of representations that have been retrieved from long-term memory. With reference to mid-ventrolateral frontal cortex (BA45,47), the distinct set of cognitive processes that is relevant to the n-back task is the selection, comparison and judgement of stimuli held in short-term and long-term memory, holding nonspatial information on-line, stimulus selection, the specification of retrieval cues and elaborated encoding of information into episodic memory. The other cognitive function like stimulus response mapping or the buffer for perceptual attributes and storage of working memory content is related to the parietal lobe. The error detection and response correction in relation to increased effort, complexity or attention involved in a cognitive task is controlled be anterior cingulate cortex.

The stimuli for this n-back task can be from various input modalities like visuo-spatial, auditory and olfactory which create demands on different processing systems. In addition, the manner of stimuli presentation could be verbal stimuli (ex: letters and words) and non-verbal stimuli (ex: shapes, faces, and pictures) along with the type of monitoring that is required for any n-back task (ex: identity of a same face) is also important. Finally, with reference to the working memory load, it is often varied up to 3-back even though the validation of results with respect to poor performance of some individuals is reported(Callicott et al., 1999) and the 0-back condition does not require the manipulation of information within working memory. In spite the huge amount of review; however, there is little agreement on various issues pertaining to the assessment of WM in individuals with Dementia. The issues are, (1). The consecutive presentation of stimuli, each requiring a decision of matching with previous or the second to last etc, (2). Use of single probe stimulus requiring decision to say whether probe was part of set of multiple stimuli. (3). Delayed simple matching tasks is the presentation of single stimulus that should be compared to a second, subsequently presented one. However, the recent review suggests the use of lexical categories at word level assessing semantics and at sentence level assessing syntactic aspects as a stimulus to measure a person's working memory capacity. This task was developed by Kirchner (1958) and is a continuous performance task that helps in assessing a part of working memory and its capacity. Therefore, to assess WM capacity in individuals with dementia, n-back task with different types of stimulus either linguistic or non-linguistic may be suitable and suitably used one.

Several studies have addressed the neural activation patterns relating to WM functions using functional neuroimaging. The n-back task has face validity as a WM task as it requires maintaining, continuous updating, and processing of information (Kane et al., 2007). It has moderate to good correlation with other measures such as Stroop task, measures of fluid intelligence, and measures of short-term memory (Gajewski et al., 2018). Oberauer (2005),

suggested weak-to-modest relations between n-back and complex WM tasks, however a strong relation between n-back and RAPM was also demonstrated (Gray et al., 2003). In their fMRI study, Gray et al., (2003) found not only that 3-back performance correlated with RAPM scores but also that 3-back lure performance accounted for variance in RAPM after controlling for 3-back control performance.

Kirova, Bays, and Lagalwar (2015), stated that episodic deficits during Alzheimer's disease progression which have been widely studied are the benchmark of a probable AD diagnosis. However, WM and executive function decline during mild cognitive impairment (MCI), or the preclinical stage of AD as well. This executive function decline (in addition to episodic memory deficits) during MCI has been suggested as a sign of progression to AD.

There are already a few experimental methodologies to study the neural correlates of WM. The diversity is further enhanced by uncommon paradigms, as well as the fact that researchers utilize an array of stimuli (e.g., verbal material, natural objects, or abstract symbols) and incorporate several experimental manipulations (e.g., varying load, retention interval or distraction). Discussed below are some studies wherein n-back task has been investigated in the past in elderly population.

Bragin et al., (2008) carried out the assessment of working memory profile (words, numbers, shapes, pictures, and textures) in 32 elderly patients with depression utilizing the N-Back task. They found that, working memory networks were different for various types of visual stimuli. They suggested that N-back is a useful tool for rapid assessment of working memory profile in the elderly.

Kane et al., (2007) replicated the works of Oberauer, (2005) and Roberts and Gibson, (2002), and found that complex WM span and n-back were weakly associated. Surprisingly, these tasks did not appear to be measures of the same construct. They also reported that they

are unaware of any theory that would predict n-back and complex span to be unrelated, or that these measures would independently account for individual differences in intelligence. They explained with the findings of Oberauer, (2005) that, as n-back and similar recognition tasks simultaneously tap both familiarity- and recollection-based processes, familiarity would have obscured the relation to recall-based complex span tasks.

Behavioral performance on the n-back has been shown to discriminate between patients with dorsolateral prefrontal cortex dysfunction (e.g., schizophrenic patients) and healthy controls(Perlstein et al., 2001). This suggests that n-back performance may be sensitive to the integrity of the frontal lobes, with greater working memory loads placing greater demand upon frontally mediated cognitive functions. If so, the n-back may be a useful task for assessment of working memory ability within the context of clinical neuropsychological evaluation.

Huntley & Howard, (2010) reviewed the studies done on working memory in early Alzheimer's disease. They suggested that, as the N back task has also been used in fMRI studies as a test of WM, and activations have been found in a range of areas including dorsolateral PFC, inferior frontal cortex, anterior cingulate and posterior parietal cortex (Temporal Dynamics of Brain Activation during a Working Memory Task, 1997; Owen et al., 2005); and suggested that the function of the CES as measured by alphabet span, dual task and N back tasks involves a network of prefrontal, frontal and parietal areas.

Bragin et al., (2015) incorporated the N-back task testing and training protocol for different stimuli (words, 3-digit numbers, pictures, geometrical figures and textures) for 2 patients with mild and moderate dementia respectively as a part of the rehabilitation model. After 24 months of treatment, brain speed on all WM tasks did not decline, but it did significantly improve only on the word targets for both patients and for numbers and people in patient 1. Both patients demonstrated stability on most of cognitive tasks including MMSE,

Clock Drawing Test etc., by 24 months of combined treatment. Performance for patient 1 stayed stable at the maximum on the word and numbers targets, with improvement on the shapes and texture targets, and a decline in performance with the people targets. For patient 2, performance with the word targets stayed at the maximum while it decreased on the numbers, shapes, people and texture targets. They concluded that, cognitive training together with other components of an integrative rehabilitation program may help stabilize or improve specific markers of brain functioning (reaction time as measured within n-back task) and arrest cognitive decline in select patients with dementia for 24 months.

Kensinger, Shearer, Locascio, Growdon, and Corkin, (2003) compared the performance of 22 patients with mild AD, 20 patients with early PD and without dementia, and 112 control participants on tests of inhibition, short-term memory, and 2 commonly administered tests of WM. The results suggest that although mild AD and early PD both impair WM, the deficits may be related to the interruption of different processes that contribute to WM performance. Early PD disrupted inhibitory processes, whereas mild AD did not. The group with AD showed no deficit on the 2-back task. The WM deficits seen in patients with AD were suggested to be secondary to deficits in other cognitive capacities, including semantic memory.

Miller, Price, Okun, Montijo, and Bowers, (2009) examined the convergent validity of the n-back with an established measure of working memory viz., backward digit span. The relationship between n-back performance and scores on measures of processing speed was also examined, as was the ability of the n-back to detect potential between-groups differences in control and Parkinson's disease (PD) groups. Results revealed no correlation between n-back performance and digit span backward. N-back accuracy significantly correlated with a measure of processing speed (Trail Making Test Part A) at the 2-back load. Relative to controls, PD patients performed less accurately on the n-back and showed a trend toward slower reaction times, but did not differ on any of the neuropsychological measures. Results suggest the n-back

is not a pure measure of working memory, but may be able to detect subtle differences in cognitive functioning between PD patients and controls. They also suggested that n-back accuracy may rely more on information processing speed or motor speed than on working memory in a PD sample, as evidenced by a correlational relationship with TMT A (albeit at the 2-back load only). Their study argued against using the n-back as a measure of working memory in a PD population; however, their results suggested that n-back accuracy scores may be useful in detecting subtle differences in cognitive functioning between control and PD groups.

Benoy, Hema, and Devi, (2020) investigated the distinct semantic processing ability in individuals with dementia using n-back task. Their study investigated the distinct semantic processing ability through n-back task in ten neurotypical individuals and seven individuals with Dementia. They also probed into the effect of various stimuli categories (three groups of lexical items, alphabets and numbers) on working memory. The findings of the study revealed that individuals with dementia significantly differ in their working memory capacity when compared to neurotypical individuals. This was attributed to the impaired ability to access semantic information and slow processing speed. Differences were also found with respect to the processing of various stimuli categories within both the groups under the study. These differences are attributed to the varied processing load put forth by different stimuli within the working memory and to some extrinsic factors such as familiarity with the stimulus. They suggested that an objective testing procedure like an n-back task can aid in faster recognition of MCI and Dementia following the routine subjective assessment of Dementia.

2.4.2 N-Back P300 combined

Fraga, Ferreira, Falk, Johns, and Phillips, (2017) investigated whether or not event-related (de)synchronisation (ERD/ERS) can be used to differentiate between 27 healthy

elderly, 21 subjects diagnosed with amnestic mild cognitive impairment (aMCI) and 16 mild Alzheimer's disease (AD) patients. Using 32-channel EEG recordings, they measured ERD responses to a three-level visual N-back task (N = 0; 1; 2) on the well-known delta, theta, alpha, beta and gamma bands. Their findings revealed that healthy elderly (HE) elicited consistently greater beta and alpha ERD responses than MCI and AD patients at many scalp electrodes, most of them located at fronto-central and temporal-parietal areas. Additionally, significant ERD differences were found on the gamma band in the MCI vs. AD comparison. Based on the findings, they concluded that ERD responses to N-back task could be useful for early MCI diagnosis or for improved AD diagnosis, and also for assessing the likelihood of MCI progression to AD.

Scharinger et al., (2017) compared an n-back task, a complex operation span task, and a simple digit span task by means of typical WM load-related measures of the Electroencephalogram (EEG) like the parietal alpha and beta frequency band power, the frontal theta frequency band power, and the P300 amplitude. Their objective was to examine whether these tasks would show commonalities or differences in WM processing-load. The N-back and the complex operation span task showed timely more prolonged alpha frequency band power effects as compared to the simple digit span task. This indicated higher demands on WM processing in the former two tasks. The theta frequency band power and the P300 amplitude were most pronounced in the N-back task as compared to both span tasks. They also identified a strong positive deflection that was maximally over parietal electrodes between 300 and 500 ms during the n-back task. This indicated specific demands on cognitive control in the N-back task.

The neuropsychological tests that are best correlated with P300 latency are those that assess how rapidly subjects can allocate and maintain attentional resources(Vecchio & Määttä, 2011). This association is also supported by results indicating that P300 latency increases as

cognitive capability decreases from dementing illness (Polich, 1986; Squires, Goodin, & Starr, 1979). N-back being a cognitively demanding neuropsychological task; if combined with the P300 as a biomarker can bring about improvement in the sensitivity and specificity than the tools being used independently.

Hence, this study aims to identify and correlate the various auditory processes (using electrophysiological-P300) and visual processes (using behavioural- n-back task) in individuals with Alzheimer's disease.

CHAPTER III

METHOD

This study was carried out with the aim of assessing the working memory capacity in individuals with dementia (IWD) and neurotypical individuals (NTI) through the use of behavioral and electrophysiological measures. Hence two experiments were involved in this study. The first experiment consisted of the behavioral experimental paradigm, the n-back, task, and the second experiment consisted of the electrophysiological experimental paradigm, the P300 for tone and speech stimuli.

3.1 Research design

The present study was a standard group comparison, wherein the individuals with dementia (IWD) formed the clinical group and neuro-typical individuals (NTI) formed the control group for the purpose of comparison.

3.2 Tools used

3.2.1 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA)(Nasreddine et al., 2005) is a brief 30-question test that takes around 10 to 12 minutes to complete and helps assess people for dementia. The MoCA evaluates different types of cognitive abilities. These include orientation, short-term memory/delayed recall, executive function/visuospatial ability, language abilities, abstraction, animal naming, attention, and clock-drawing test. Scores on the MoCA range from zero to 30, with a score of 26 and higher generally considered normal(Nasreddine et al., 2005). The Kannada version of MoCA was utilized for screening individuals with dementia in this study.

A disadvantage of the MoCA is that it takes a little longer to administer, and like many other screenings, it should be paired with multiple other screenings and tests to accurately identify and diagnose dementia. Hence, the current study also used Clinical Dementia Rating Scale.

3.2.2 Clinical Dementia Rating Scale

The Clinical Dementia Rating Scale (CDR) (Morris, 1993) is a rating scale for the clinician to characterize the degree of severity of dementia (from 0 = "no dementia" to 3 = "severe dementia"); it is based upon semi-structured interviews with (a) the patient thought to suffer from dementia and (b) with a knowledgeable informant (usually spouse or child). The interview with the patient includes among others cognitive tasks, e.g., concerning memory and orientation.

3.3 Participants

Participants considered were '16' individuals with dementia (IWD) under clinical group (Mean age of 72.25 ± 7.18 years) and '34' neuro-typical individuals (NTI) (Mean age of 54.76 ± 18.43 years) matched to the clinical group based on age, gender, and education forming the control group (NTI). All the participants were native speakers of the Kannada language and were obtained from in and around the city of Mysore in Karnataka.

The inclusionary criteria for Individuals with dementia were as follows:

- IWD were diagnosed as having dementia by a neurologist and were also evaluated by a Speech-Language Pathologist using the Kannada version of Montreal Cognitive Assessment (MoCA- Nasreddine et al., 2005) as well as Clinical Dementia Rating Scale (CDR- Morris, 1993).
- All the IWD were having a severity of very mild to mild dementia as per CDR Scale.

- All the IWD obtained a score of 16 to 22 on MoCA-Kannada.
- Individuals with dementia had no other associated clinically significant neurologic disorders other than dementia.
- Participants with a diagnosis of Dementia of Alzheimer's Type by the neurologist only were included in the study. Participants with other types of dementia such as Vascular Dementia; dementia due to Pick's Disease; dementia associated with Parkinson's disease and so on were not included in the study.

The inclusionary criteria which were common for Individuals with dementia, as well as neurotypical individuals, were as follows:

- Handedness was checked using Edinburgh handedness inventory - Revised (Williams, 2010), and the individuals with similar (right) handedness only were considered for the present study.
- All participants demonstrated hearing and visual acuity to the normal limit on screening (after correction, if needed).
- Participants were monolingual, bilingual, or multilingual, and the languages known by the individuals were noted down.
- The participants had no complaint of any otological problems or ototoxicity. In order to identify any such issues, a detailed general case history was taken.
- The participants a routine audiological evaluation before participating in the study. Air conduction thresholds were less than or equal to 30 dBHL in both the ears on Pure Tone Audiometry. (Clinical audiometer-Madsen OB922, (Version 2.64) with TDH 39 earphones enclosed in MX-41/AR supra oral ear cushions used to estimate the air-conduction thresholds, and Radio Ear B-71 bone vibrator)

- Participants, if taking any sedatives and memory dietary supplements, were asked to suspend them for 72 hours before testing.

The demographic details of individuals with dementia are tabulated in table 3.1 below.

Table 3.1: Demographic details of individuals with dementia

Subject No.	Age	Gender	Language status	Education	MOCA score	CDR score
1	65	Female	Monolingual	Degree	23	0.5
2	68	Male	Multilingual	Degree	21	1
3	69	Female	Monolingual	Secondary	19	1
4	75	Female	Bilingual	Secondary	20	1
5	79	Female	Monolingual	Secondary	18	1
6	64	Male	Multilingual	Degree	22	0.5
7	77	Male	Bilingual	Diploma	21	1
8	68	Female	Monolingual	Secondary	18	2
9	74	Male	Multilingual	Post Graduate	17	2
10	72	Male	Multilingual	Degree	18	1
11	65	Male	Multilingual	Post Graduate	22	0.5
12	67	Male	Multilingual	Degree	19	1
13	68	Male	Multilingual	Post Graduate	17	2
14	75	Female	Monolingual	Secondary	15	2
15	78	Female	Monolingual	Diploma	18	2
16	92	Female	Monolingual	Primary	17	2

Among these participants, 13 completed both behavioral and electrophysiological experiments whereas three (Subjects 14, 15, and 16) could complete only the behavioral task of n-back. Similarly, the demographic details of neurotypical individuals are tabulated in table 3.2. Among the 34 Neurotypical Individuals, 30 completed both the behavioral and the electrophysiological experiments whereas four (subjects 31-34) could complete only the behavioral task of n-back. Even though the study was planned for subjects aged greater than 60 years, due to the COVID-19 pandemic and subsequent lockdown, data was also collected from 12 individuals who were of a younger age group based on availability.

Table 3.2: Demographic details of neurotypical individuals

Subject No.	Age	Gender	Language status	Education	Subject No.	Age	Gender	Language status	Education
1	60	Male	Bilingual	Diploma	18	65	Male	Monolingual	Diploma
2	77	Male	Monolingual	Secondary	19	30	Male	Multilingual	Post Graduate
3	67	Male	Bilingual	Post Graduate	20	29	Male	Multilingual	Post Graduate
4	69	Male	Multilingual	Degree	21	29	Male	Multilingual	Post Graduate
5	65	Male	Multilingual	Post Graduate	22	28	Male	Multilingual	Post Graduate
6	67	Female	Monolingual	Degree	23	34	Male	Multilingual	Post Graduate
7	70	Male	Bilingual	Diploma	24	35	Male	Multilingual	Post Graduate
8	74	Female	Monolingual	Secondary	25	28	Male	Multilingual	Post Graduate
9	72	Male	Bilingual	Degree	26	27	Male	Multilingual	Post Graduate
10	70	Male	Monolingual	Degree	27	28	Female	Multilingual	Post Graduate
11	61	Male	Monolingual	Primary	28	39	Male	Multilingual	Degree
12	63	Male	Multilingual	Degree	29	38	Male	Multilingual	Post Graduate
13	62	Male	Multilingual	Diploma	30	26	Male	Multilingual	Post Graduate
14	70	Female	Monolingual	Secondary	31	74	Male	Multilingual	Degree
15	72	Male	Multilingual	Degree	32	68	Male	Bilingual	Diploma
16	64	Male	Multilingual	Post Graduate	33	72	Male	Monolingual	Diploma
17	65	Female	Bilingual	Secondary	34	64	Male	Bilingual	Post Graduate

3.4 Data collection

Data was collected after finalizing the behavioral and electrophysiological protocols from December 2019 to June 2020. Data acquisition was carried out at the Recording Room in the Department of Speech-Language Sciences, All India Institute of Speech and Hearing, Mysuru. Data collection was impacted by the lockdown due to the COVID-19 pandemic.

3.4.1 Experiment 1: Behavioural experimental paradigm: N-back task

To perform the N back task the participants had to store the 'n' number of information in their working memory and update the content of working memory by leaving the unwanted information and adding the new information.

3.4.1.1 Stimulus

With reference to the study of Wright et al. (2007), the sem-back task was created which replicated the N-Back using lexical items as the stimuli (Figure 3.1). These semantic lexical categories were lexical items like 'common objects', 'fruits' and 'vehicles', 'alphabets' and 'single digits' considered as stimuli and termed this task as Sem-back task. These stimuli were obtained from the Kannada version of the Western Aphasia Battery (WAB-K) (Shyamala & Kumar, 2008). This was carried out in order to obtain culturally appropriate as well as familiar stimuli for the participants. Each category contained 10 stimuli which were randomly arranged to form the sequence for 1-back, 2-back, 3-back, and 4-back tasks. The details of stimuli in each category have been tabulated in Table 3.3.

Table 3.3: Details of stimulus used for n-back task.

Common Objects	**Fruits**	**Vehicles**	**Alphabets**	**Single Digits**
Cup	Apple	Aeroplane	ತ (/t̪a/)	0
Pencil	Pineapple	Autorickshaw	ಕ (/ka/)	1
Comb	Banana	Bike	ಪ (/pa/)	2
Knife	Mango	Bus	ಬ (/ba/)	3
Flower	Pomegranate	Car	ಟ (/ʈa/)	4
Matchstick	Watermelon	Cycle	ಮ (/ma/)	5
Chair	Grapes	Truck	ಗ (/ga/)	6
Table	Pear	Train	ಡ (/ɖa/)	7
Fan	Orange	Jeep	ಚ (/ʧa/)	8
Television	Papaya	Scooter	ನ (/na/)	9

Once the stimuli were identified; images corresponding to the stimuli were obtained from the internet for lexical categories of “common objects”, “fruits” and “vehicles”. Images which were large in size (More than 2 MegaPixels) and which were not copyright protected were obtained. These pictures were placed in slides within the software Microsoft PowerPoint 2013 so as to obtain uniformity of the stimuli. Each picture was centered and was placed with maximum resolution within each slide. For the category of “alphabet”, a text box was inserted in the center of the slide, and each alphabet was manually typed (Font: Tunga; Font size: 96; Bold). For the category of “single-digit”, a text box was inserted in the center of the slide, and each digit was manually typed (Font: Arial; Font size: 108; Bold). These slides were exported into .jpg format and were saved in a folder. These pictures served as stimuli for the E-Prime experiment.

3.4.1.2 Experimental Paradigm

The experiment was programmed and run using E-Prime Professional software (version 2.0) (Psychology Software Tools, Pennsylvania, USA) on an HP Notebook-15-ac101tu laptop. Within E-Prime, E-Studio and E-Data Aid modules were used to design the sequence of

presentation of the stimulus. Within the E-Studio; an experimental procedure was created. Initially, a text display object with Instructions to the participant was added. Following this; a "+" sign indicating the center of fixation was given. This was mainly done to make the participants more vigilant and prepared for the actual task.

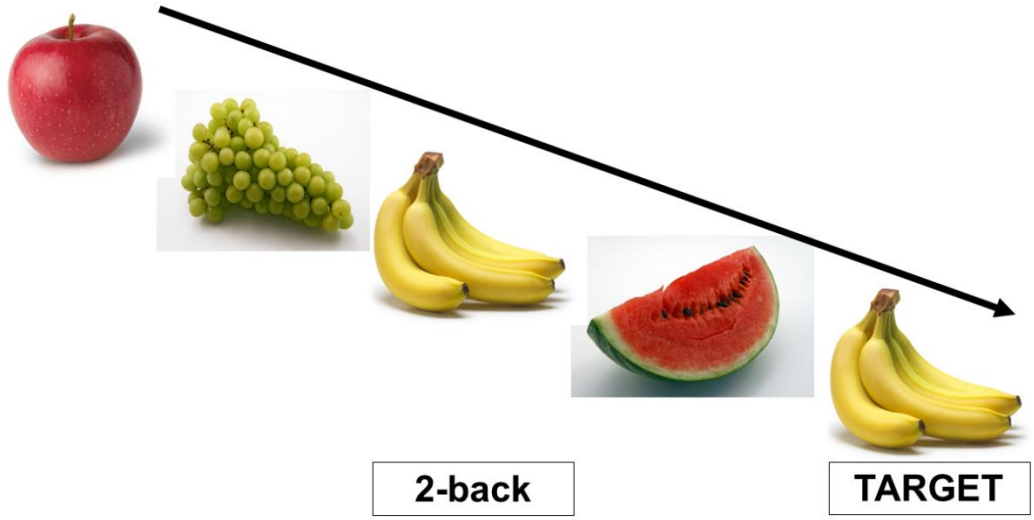
This was followed by the lexical item presentation in a sequential manner. Pictures which were prepared as the stimulus using Microsoft PowerPoint were randomly arranged into the experimental paradigm. Each picture was shown on the screen for a fixed duration of 2000ms. This was followed up by an inter-stimulus interval of fixed duration (1500ms). Following the presentation of the 5^{th} stimulus; a "?" appeared on the screen asking the participants to indicate their response. The response time was also allocated a fixed duration (5000ms). All the stimuli were presented on a white background. The alphabets, digits, and "+" and "?" were in the black color font.

To indicate their response, participants had to press, number keys 'one' or 'two' on a standard US keyboard; with 'one' for a match between test and target stimuli at sequential N^{th}– back and 'two' for a no-match. Responses delayed by more than 5000ms participants were considered as 'no response' and the next trial would begin. The keys were indicated on the keyboard using blue colored tape.

For every n-back five trials were used of which three were test trials and two were caught trials in a random order of presentation to achieve a good construct validity of the Sem-back test. Likewise; 1-back, 2-back, 3-back, and 4-back paradigms were coded and programmed for this study. The experiment was coded in such a way, that the software would automatically record the

participants' accuracy and reaction time for the particular response. An example of the procedure is shown in figure 3.1.

Figure 3.1. An example of 2-back using lexical item fruits



Each of the categories under study viz. was lexical items 'common objects', 'fruits' and 'vehicles', as well as 'alphabets' and 'single digits', were coded into different experiments. This was done to ensure that participants obtained enough rest periods between the categories of stimuli while being tested. Similarly; a trial experiment was also created using a different set of stimuli so as to familiarize the participants with the experimental procedure.

3.4.1.3 Procedure

Participants of the study were seated comfortably in front of the computer screen and were instructed about the n-back task and were given a trial before the actual experiment, using a different set of stimuli. The experiment was programmed and run using E-Prime Professional software (version 2.0) (Psychology Software Tools, Pennsylvania, USA) on an HP Notebook-15-ac101tu laptop. Within E-Prime, E-Studio and E-Data Aid modules were used to design the

sequence of presentation of stimulus with a fixed duration (2000ms), inter-stimulus interval with a fixed duration (1500ms), and participants response time with a fixed duration (5000ms) for both dementia population and neuro-typical individuals. The training and the testing stimuli were presented at the center of fixation to the computer screen following one initial trial. For example, initially, the '+' sign was presented, and the participants had to focus at the center of the screen and followed by lexical item presentation. This was mainly done to make the participants more vigilant and prepare for the actual task. To indicate their response, participants had to press, number keys 'one' or 'two' on a standard US keyboard; with 'one' for a match between test and target stimuli at sequential N^{th}–back (Example of paradigm considered for the present study was: 1-back, 2-back, 3-back, 4-back) and 'two' for a no-match. Responses delayed by more than 5000ms by individuals with dementia were considered as 'no response' and the next trial would begin. For every n-back five trials were used of which three were test trials and two were catch trials in a random order of presentation to achieve a good construct validity of the Sem-back test. After the category of stimuli, participants were given a rest period of about 5 to 10 minutes so that the participants are not fatigued.

3.4.1.4 Scoring

Correct responses for a minimum of three trials within every level of the n-back task determined the level/threshold/accuracy of responses for the participants' sem-back task. For each category of stimuli, the reaction time (RT) (in ms) and accuracy of responses were extracted using the E-Data Aid module within E-Prime 2.0 and were imported into Microsoft Excel 2013 and Statistical Package for Social Sciences (SPSS Version 20) (IBM Corporation, New York, USA) for data analysis.

3.4.2 Experiment 2: Electrophysiological (P300) experimental paradigm

3.4.2.1 Testing Environment

The recording was carried out in a sound-attenuated and electrically shielded room, where the noise levels were within permissible limits (ANSI S3.1-1999). For the same, the recording room of the Department of Speech-Language Sciences was used.

3.4.2.2 Instrumentation

The following instrument was used to record the stimuli and collect data.

1. Net Station 5 Electrical Geodesics Inc. Geodesic EEG Software (version 5.4.2) instrument was used to record Event-Related Potential (ERP) (128 Channels).
2. The recorded stimuli which are scaled and rms normalized was used to obtain the evoked potentials, viz., P300.

3.4.2.3 Stimuli

The E-prime software version 2.0.8.90 (Psychology Software Tools, Inc., PA, USA) on a Hewlett Packard Z240 Tower Workstation (Intel Core i5 at 3.20 GHz and 8.00 GB RAM) running on Windows 7 Pro was used for the preparation as well as the presentation of the stimulus. The EGI equipment supports two machines for carrying out the experiment. The Net Station software records multiple tracks of the stimulus along with the EEG data. Another computer generates and presents the stimuli, and it sends simple triggering or complex stimulus identification information to Net Station software. The speech stimuli used for testing were syllables /ḍa/ and /ga/, where the frequent one was /da/ and the infrequent one (target) was /ga/. The tone stimuli used were 1kHz tone (frequent) and 2kHz tone (infrequent) which were generated using the program *Praat*. These audio stimuli were presented from an audio speaker centered 85 cm above the participant connected to a Creative SB X-Fi audio card. Speech sounds were presented free field at 70 dBSPL,

measured by a Sound Level Meter (SLM). The interstimulus interval was 2000 ms. A total of 250 sweeps was presented. Participants were instructed to listen to the stimuli. The response to the task depended on the capability of the participants. A 700 msec time window was used, and analysis was based on the numerical values of the latencies (ms) and amplitudes (μV). P300 identified as a positive deflection after the N1-P2-N2 complex was considered as response for further analysis.

3.4.2.4 Recording

Planning- The participants had to arrive at the recording room with freshly washed (not wet) hair and had not used any hair products (for example, gels or hair spray) when they had come for recording. Before the participant arrived, the electrolyte solution was prepared, and the necessary items like measuring tape, pipettes, syringes, and three clean towels were kept ready.

Preparing the Electrolyte Formulation- As per the Electrical Geodesics Inc. recommendation, HydroCel Saline (Potassium Chloride electrolyte solution) was used for standard recordings.

1. 10 cc (2 teaspoons) of powdered potassium chloride (KCl) was added into the rinse/electrolyte bucket.
2. 1 litre of warm distilled water was added to it.
3. Following this, 5 cc (1 teaspoon) of Johnson's Baby Shampoo was added.
4. The ingredients were stirred vigorously until the KCl is completely dissolved.
5. The solution was kept idle for 5 minutes.

Head Measurement- The head measurement was found out before applying the Geodesic Sensor Net to the subject's head. The head circumference was measured by running the tape along the side of the head, above the ear, toward the back, and 2.5 cm above the external occipital

protuberance (Inion), around the other side, and above the other ear, and back to the glabella. One end of measurement tape was placed on the glabella, the other end was placed on the Inion, and the midpoint was marked. Similarly, the midpoint between the preauricular joints was also marked. The point at which these two intersect is the vertex point, otherwise called Cz in the international 10-20 system (Klem, 1999; Silverman, 1963). The Net of the appropriate adult size (54-56cm or 56-58cm) was selected based on the measurement obtained.

Marking the Vertex

1. The subject was asked to hold one end of the measuring tape to the nasion.
2. The tape was run over the top of the head until it reached Inion, and the midpoint was located. The midpoint was marked using a marker on the subject's head.
3. The distance between the preauricular points was measured by extending the measuring tape across the top of the head. The midpoint was located, and it was marked on the head. The intersection point of these two lines gave the location of the vertex.

Net Application- The Net was soaked in the electrolyte solution (as it has sponge inserts) and was safely applied on the participant's head in such a way that the Cz electrode came on the vertex marked on the head. The participants were asked to remove earrings, glasses, and hair ties as they would become uncomfortable for them. The high-density hydrocel geodesic sensor nets and associated high-impedance amplifiers have been designed to accept impedance values ranging as high as 100 kΩ, which permits the sensor nets to be applied in under ten minutes and without scalp abrasion, recording paste, or gel.

Soaking the Net in Electrolyte- The Net was not soaked for a longer time, and care was taken for connectors not getting wet.

1. The sensor end of the Net was dipped into the "electrolyte" bucket.

2. The sensors of the Net were dipped in electrolytes for 5 minutes to ensure adequate wetting of the sponges. This was done with help of a stopwatch timer.
3. A towel was given to the participants to catch the electrolyte drips.
4. A towel was draped over the participant's shoulders.
5. The Net was lifted vertically out of the electrolyte bucket and was held in the same position such that the excess electrolyte dripped back into the container.

Then the Net was placed on the participant's head in such a way that the electrode mentioned as Cz was coming on the vertex. It was ensured that all the electrodes were placed correctly on the scalp of the participant. The chin strap was moved underneath the participant's chin and was secured using the cord lock. Participants rested on the reclining chair and they had to remain awake throughout the procedure. It was ensured that the interelectrode impedance was ≤ 50KOhms prior to testing. If the impedance was more, the electrolyte solution was put on the sponge on the electrodes.

During online recording, electrodes FCz and AFz were regarded as reference and ground, respectively. Two additional electrodes, i.e., vertical (VEOG) and horizontal electrooculograms (HEOG) were used to monitor the eye movements. Particularly, VEOG was positioned at the right side of the right eye (Channels 8, 126, 25, 127), and HEOG was positioned below the left eye (Channels 125 and 128). During the whole task, impedances for all electrodes were kept below 50 KΩ.

Net Station acquisition software which is a part of the Net Station 5.4 was used to record P300. P300 was recorded as per the guidelines provided by Duncan et al. (2009). A few of the important guidelines that were considered in the present study were:

1. Use of oddball paradigm (Pokorny et al., 2013) - as it elicits robust P300 and reveals how the brain discriminates stimuli and processes probability.

2. A minimum of 36 or more artifact-free trials with correction for ocular contributions.

3. The elicitor stimulus was delivered binaurally through speakers at 70 dB SPL.

Table 3.4 Summary of the protocol for recording P300

Stimulus Parameters	**Speech stimuli**		**Tone Stimuli**	
Stimuli	Frequent	Infrequent	Frequent	Infrequent
	/ḍa/	/ga/	1 kHz	2 kHz
Frequent to the infrequent ratio	4 to 1 (80:20)		4 to 1 (80:20)	
Ear	Binaural		Binaural	
Transducer	Speaker		Speaker	
Intensity	70 dB SPL		70 dB SPL	
Inter-stimulus-interval	2000 ms		2000 ms	
Total number of sweeps	250		250	
Acquisition Parameters				
Filters	0.1 Hz -30 Hz		0.1 Hz -30 Hz	
Electrode	Cap electrode		Cap electrode	

Response analysis- The obtained raw electroencephalogram (EEG) file from the Net Station Acquisition Program was subjected to pre-processing using the Net Station Tools program and further analysis was carried out using EEGLAB toolbox within the MATLAB software (The Mathworks Inc., MA).

Segmentation- The obtained continuous raw EEG data had to be segmented first. For this purpose, the Net Station Tools program was utilized. Initially, a segmentation tool was created using this program to segment the raw EEG data file. This segmentation tool was named “Speech segmentation” and “Tone Segmentation” respectively. Within the speech segmentation tool, the parameters were set in such a way that, segments containing the stimuli /da/ and segments containing the stimuli /ga/ were segmented. Each segment consisted of 100ms duration before the presentation of the stimulus and 1500ms after the presentation of the stimulus. Thus, each stimulus was segmented into 250 segments (200 segments of frequent stimuli /da/ and 50 segments of

infrequent stimuli /ga/). Similarly, the Tone segmentation tool yielded 200 segments of frequent stimuli 1kHz and 50 segments of infrequent stimuli 2kHz.

File Export- Following segmentation; the files had to be converted to Net Station Simple Binary format (.raw) so as to carry out further analysis using MATLAB. For this purpose, the Net Station Tools program was utilized. A file conversion tool was created in order to convert the segmented files into ".raw" format. This was executed for the speech as well as tone EEG files to obtain converted files in ".raw" format.

Processing in MATLAB- EEGLAB plugin (Swartz Center for Computational Neuroscience, CA) which is an interactive MATLAB toolbox for processing continuous and event-related EEG was used for further analysis. Further analysis in MATLAB was carried out according to Makoto's pre-processing pipeline (https://sccn.ucsd.edu/wiki/Makoto%27s_preprocessing_pipeline). The steps of processing in MATLAB were as follows:

Step 1: MATLAB was opened and the EEGLAB toolbox was loaded into MATLAB.

Step 2: As the data was recorded using 250 Hz sampling frequency downsampling was not applied.

Step 3: Data was subjected to Finite Impulse Response Filtering with a bandpass of 0.1 Hz to 30 Hz.

Step 4: Channel Location for 128 channel Hydrocel Geodesic Sensor Net was imported and applied.

Step 5: Initially, the entire EEG data file was screened via scrolling manually through channel activities for bad channels and visual artifacts. These were removed manually. Following this, clean_rawdata() EEGlab plugin was applied for a controlled, objective rejection criterion.

Step 6: Interpolation of all removed channels was carried out.

Step 7: The data were re-referenced to average reference.

Step 8: Line noise was removed from the data using the CleanLine EEGlab plugin.

Step 9: Independent Component Analysis (ICA) was carried out and 64 components with maximal representation within the channel activities were derived.

Step 10: Independent Components (ICs) with eye-related or muscle-related components were removed and ICs with activities of interest from the brain (confirmed with the presence of dipoles and ERP waves) were selected. In order to maintain a controlled, objective rejection criterion for the removal of ICs, the EEGlab plugin SASICA was utilized. Along with the EEGlab plugin SASICA, an experienced audiologist also verified the ICs manually and retained only those ICs with activities of interest from the brain.

Step 11: Epochs were extracted from the retained ICs with the epoch limit of 0.1 seconds before the stimulus onset and 0.8 seconds after the stimulus onset.

Step 12: Data points were extracted in excel format and ERP images were plotted for each region of the cortex.

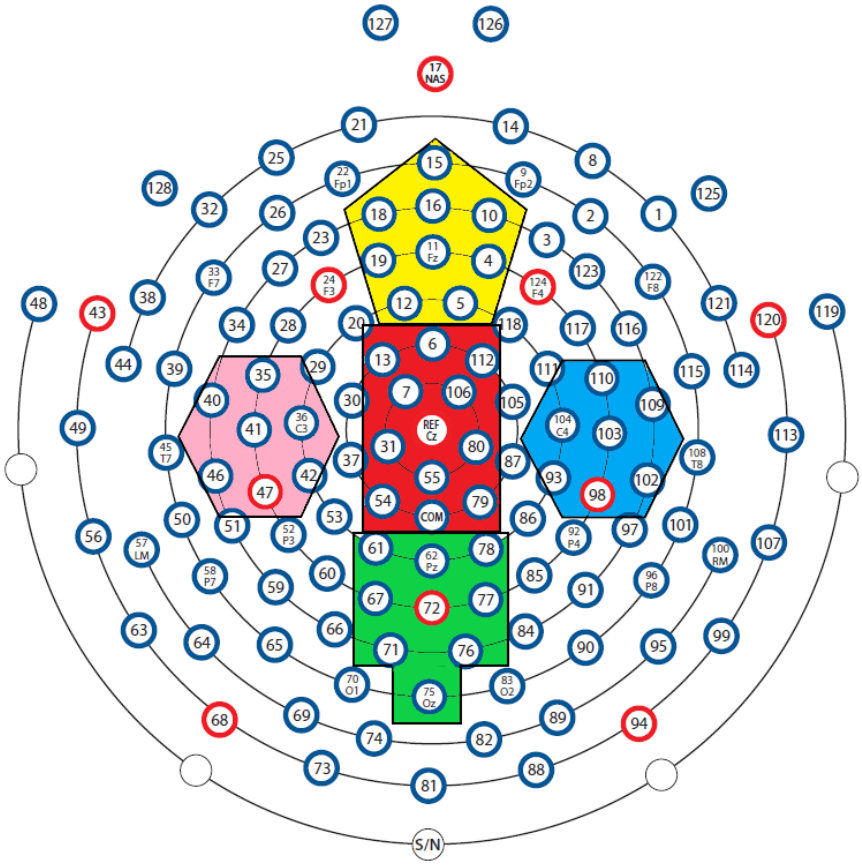
Defining regions of interest- The auditory-evoked potentials of P1-N1-P2 complex and P300 responses were identified in each participant for the oddball paradigms, and it was analyzed to obtain the peak amplitude and latency. The average waves which were recorded for the target, as well as non-target stimuli, were compared.

Apart from these, a topographical analysis at the cortical level was also carried out. For the purpose of topographical analysis, initially, the commonly used procedures of channel reduction from 128 to 110 electrodes reported in the literature were employed (Bian et al., 2014; Calbi et al., 2017). The outermost belt of electrodes of the sensor-net (19 peripheral channels: E43, E48, E49,

E56, E63, E68, E73, E81, E88, E94, E99, E107, E113, E119, E120, E125, E126, E127, E128) was discarded due to their tendency to show residual muscular artifacts. Following this, the electrodes were grouped into frontal, central, left temporal, right temporal, and posterior electrodes according to Bian et al. (2014). However, this did not yield relevant ERP findings as artifacts were higher when a higher number of electrodes were considered for each of the regions mentioned above.

Further, to obtain robust potentials, the number of electrodes for each region was reduced. This led to the identification of five regions of interest. These were, frontal (electrodes surrounding Fz (E11) which included electrodes E4, E5, E10, E12, E15, E16, E18 and E19); central (electrodes surrounding Cz which included electrodes E6, E7, E13, E31, E54, E55, E79, E80, E106 and E112); parietal (electrodes adjacent to Pz (E62) which included electrodes E61, E67, E71, E72, E75, E76, E77, and E78); left (electrodes adjacent to C3(E36) which included electrodes E35, E40, E41, E42, E46 and E47) and right (electrodes adjacent to C4(E104) which included electrodes E93, E98, E102, E103, E109 and E110). These are depicted in figure 3.2.

Figure 3.2. Electrodes distribution of 128-channel Geodesic Sensor Net for this study



Extracting the latency and amplitude of the P1-N1-P2 complex and the P300- The auditory evoked P1-N1-P2 and P300 were marked in the waveforms by an audiologist with experience in the area of event related potentials. This was carried out for both tones evoked ERPs and speech evoked ERPs. The values of amplitude and latencies of each of the events were extracted into a Microsoft Excel sheet for each subject and were later transferred into Statistical Package for Social Sciences (SPSS Version 20) (IBM Corporation, New York, USA) for further data analysis.

CHAPTER IV

RESULTS

The present study aimed to assess the working memory capacity in individuals with dementia (IWD) and neurotypical individuals (NTI) through the use of behavioral and electrophysiological measures. The behavioral measure was a visual n-back task programmed and ran using the E-Prime 2.0 software. The auditory electrophysiological measures were obtained using Electrical Geodesics Inc. (EGI) NetStation 5.4 and were further subjected to post-processing and analysis using EEGLAB plugin on the MATLAB software. Results of behavioral and electrophysiological measures will be discussed under different subsections below.

4.1 Behavioral findings from the n-back task

The n-back task was carried out by the participants across five different categories- Lexical items of fruits, common objects, vehicles, numbers, and alphabets. The experimental paradigm was carried out till the 4-back level, and the output in terms of accuracy and reaction time (RT) (in ms) were recorded. Initially, a qualitative procedure was applied to the analysis of the n-back task. For each accurate response, '1' was coded; and '0' was coded for every inaccurate response. Inaccurate scores were not considered for further analysis. It could be recalled that participants had to respond to five trials at each level of the n-back task, among which three were test trials, and two were catch trials. Accurate responses for a minimum of three trials out of five within each level of the n-back task indicated that the participant could perform the n-back task at that particular level. The threshold level of performance of a participant was defined as the highest n-back level at which the participant could accurately respond to a minimum of three

trials out of five. For further analysis, RT of the best accurate trial i.e., the minimum accurate RT at each level, was utilized. The RT (in ms) at each level of n-back performance and at the determined threshold level of performance were subjected to statistical analysis using the Statistical Package for Social Sciences (SPSS) software (version 26.0).

Initially, the test of normality was done to determine the statistical tests for further analysis. On administration of Shapiro Wilk's test of normality, the majority of the parameters of the n-back task were found to follow a non-normal distribution with $p < 0.05$ (Table 4.1). Hence, non-parametric tests were applied for the statistical analyses of the behavioral data.

Table 4.1. Shapiro Wilk's test of Normality for different n-back levels across categories

Category of stimuli	**n-back level**	**Statistic**	***p*-value**
Fruits	1-back	0.933	0.054*
	2-back	0.977	0.738*
	3-back	0.929	0.041
	4-back	0.929	0.040
Common Objects	1-back	0.926	0.035
	2-back	0.872	0.002
	3-back	0.902	0.008
	4-back	0.824	0.000
Vehicles	1-back	0.948	0.140*
	2-back	0.905	0.009
	3-back	0.936	0.066*
	4-back	0.776	0.000
Numbers	1-back	0.962	0.322*
	2-back	0.925	0.032
	3-back	0.936	0.063*
	4-back	0.937	0.067*
Alphabets	1-back	0.969	0.482*
	2-back	0.848	0.000
	3-back	0.921	0.024
	4-back	0.813	0.000

Note: * Significant at $p>0.05$ level

Further, statistical analysis for the findings of the n-back task in NTI and IWD was carried out to obtain descriptive statistics (mean, median, and standard deviation). This was followed by a between-group comparison on the performance at each level of the n-back task

(Mann Whitney U Test) across different categories of stimuli. Similarly, within-group comparison (Friedman test and Wilcoxon signed-rank test) across different categories of stimuli at each level of n-back was also carried out. Then, a comparison was made across the groups and across different categories of stimuli at their threshold level of performance. The results of these tests are discussed in detail further.

4.2 Descriptive statistics for the n-back task

Mean, me,dian and standard deviation were derived for reaction time (in ms) at each level on the n-back task. These are summarized in Table 4.2. It was observed that the NTI group had a lower RT than the IWD group at all levels of the n-back task across all five categories. A decrease in the number of individuals correctly performing on three out of three trials was observed with increased task complexity (i.e., with an increase in the n-back). Further, IWD did not demonstrate any accurate responses at the 4-back level for all five categories. Hence, descriptive statistics could not be obtained at the 4-back level for the IWD group.

Table 4.2 Results of descriptive statistics of reaction time for the n-back task

Category of stimuli	n-back level	NTI				IWD			
		N	Mean	SD	Median	N	Mean	SD	Median
Fruits	1-back	34	1236	240	1160	16	2408	781	2344
	2-back	34	1693	363	1733	14	2937	972	2899
	3-back	34	2042	410	2053	6	3457	881	3186
	4-back	34	2363	436	2358	-	-	-	-
Common Objects	1-back	34	1395	155	1372	16	2231	1232	1841
	2-back	34	1742	215	1709	13	2024	616	2171
	3-back	34	2049	250	2059	4	3437	267	3420
	4-back	34	2472	341	2378	-	-	-	-
Vehicles	1-back	34	1375	219	1338	16	2181	842	1952
	2-back	34	1660	334	1689	11	2513	942	2153
	3-back	34	2062	255	2014	7	3969	730	4242
	4-back	34	2322	366	2368	-	-	-	-
Numbers	1-back	34	1287	218	1303	16	1826	496	1678
	2-back	34	1748	195	1705	15	2573	852	2431
	3-back	34	2167	287	2076	8	3106	508	3255
	4-back	34	2393	303	2372	-	-	-	-

Alphabets	1-back	31	1233	214	1269	16	1943	975	1636
	2-back	31	1632	278	1715	13	2170	525	2127
	3-back	31	1981	254	1968	5	2718	364	2838
	4-back	31	2398	405	2438	-	-	-	-

4.3 Between-group comparison of the performance on the n-back task

Mann-Whitney U Test was administered to identify the differences across the IWD and NTI groups with respect to their reaction times at each level of n-back of each category of stimuli. It was observed that the groups exhibited significant differences across the majority of the levels of the n-back task for each category of stimuli. Differences were not found across the groups only at 1-back level for the category of common objects (p = .074). The results of the Mann Whitney U test are tabulated in Table 4.3.

Table 4.3 Results of between-group comparison on the performance on n-back task

Category of stimuli	**n-back level**	***/Z/***	***p*-value**
Fruits	1-back	4.888	0.000*
	2-back	4.446	0.000*
	3-back	3.864	0.000*
Common Objects	1-back	1.789	0.074
	2-back	2.331	0.020*
	3-back	3.235	0.001*
Vehicles	1-back	3.848	0.000*
	2-back	3.486	0.000*
	3-back	4.123	0.000*
Numbers	1-back	4.638	0.000*
	2-back	4.425	0.000*
	3-back	3.972	0.000*
Alphabets	1-back	2.963	0.003*
	2-back	4.180	0.000*
	3-back	3.408	0.001*

Note: * Significant at p>0.05 level

4.4 Comparison between the groups at the threshold level of performance

The threshold level of performance for each category across the groups was determined initially using a qualitative analysis. A comparison of the threshold level of performance of the IWD and NTI groups with respect to their median values is depicted in figure 4.1. This threshold

level demonstrated their working memory capacity. RT at the determined threshold level for the groups of participants was also compared using the Mann Whitney U test. These are tabulated in Table 4.4 below.

Table 4.4 Results of comparison between the groups at the threshold level of performance

Category of stimuli	**NTI Threshold level**	**IWD Threshold level**	**/Z/ value**	***p*-value**
Fruits	4-back	2-back	6.860	0.000*
Common Objects	4-back	2-back	6.864	0.000*
Vehicles	4-back	2-back	6.852	0.000*
Numbers	4-back	2-back	6.865	0.000*
Alphabets	4-back	2-back	6.622	0.000*

Note: * Significant at $p>0.05$ level Figure 4.1

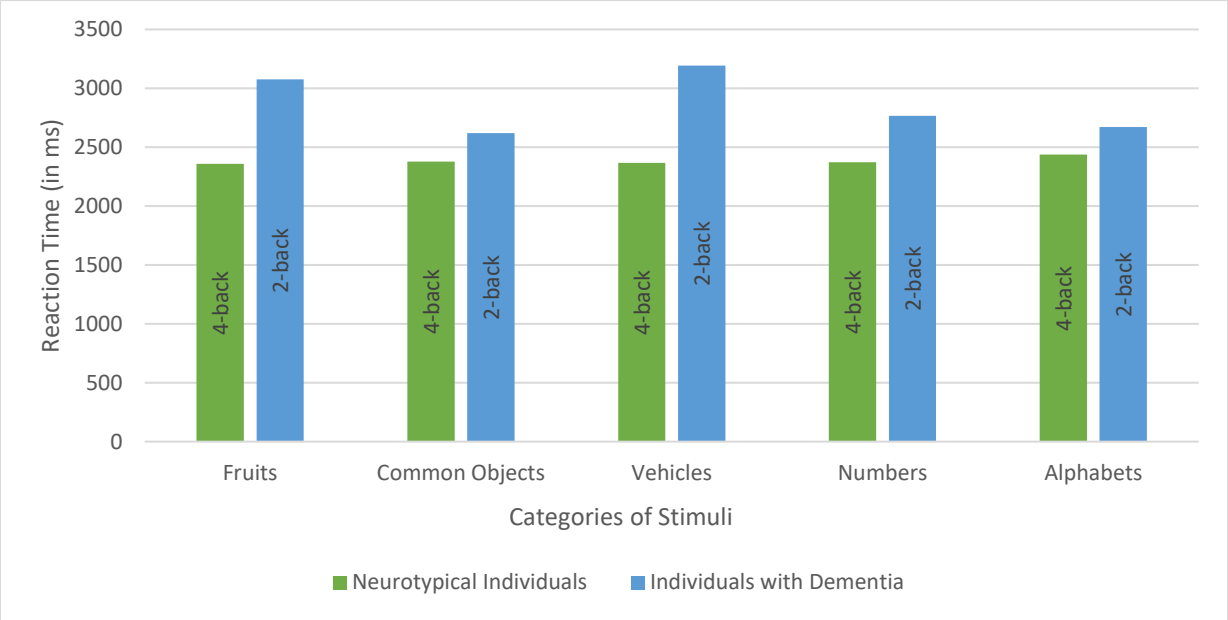


Figure 4.1- Comparison of performance at the threshold level across the groups

4.5 Within-group comparison of the performance on the n-back task in the NTI group

Further, within-group comparisons were carried out using the Friedman test to identify the differences in performance across various levels of n-back within the five different categories

of stimuli. The results of the Friedman test for the NTI group are summarized in table 4.5. It was revealed that significant differences existed among different levels of n-back within the five different categories of stimuli.

Table 4.5 Results of Friedman test to identify within-group differences in NTI

Category of stimuli	**χ^2 value**	***p*-value**
Fruits	80.047	0.000*
Common Objects	92.929	0.000*
Vehicles	78.600	0.000*
Numbers	85.659	0.000*
Alphabets	83.671	0.000*

Note: * Significant at p>0.05 level

Since significant differences were observed in the Friedman test for all the categories of stimuli, post-hoc analysis using the Wilcoxon signed-rank test was carried out for the NTI group. The results of the Wilcoxon signed-rank test are tabulated in table 4.6 for the lexical categories of fruits, common objects, and vehicles, and in table 4.7 for the categories of numbers and alphabets. Significant differences were demonstrated across each level of n-back among all the categories of stimuli by the NTI group.

Table 4.6 Results of the Wilcoxon signed-rank test for the categories of fruits, common objects, and vehicles in NTI

n-back level comparison	**Fruits**		**Common Objects**		**Vehicles**	
	/Z/ value	***p*-value**	**/Z/ value**	***p*-value**	**/Z/ value**	***p*-value**
1-back - 2-back	4.591	0.000*	4.847	0.000*	3.924	0.000*
1-back - 3-back	4.984	0.000*	5.035	0.000*	5.087	0.000*
1-back - 4-back	5.052	0.000*	5.087	0.000*	5.087	0.000*
2-back - 3-back	4.437	0.000*	4.711	0.000*	4.215	0.000*
2-back - 4-back	5.069	0.000*	5.086	0.000*	4.916	0.000*
3-back - 4-back	3.702	0.000*	4.967	0.000*	3.599	0.000*

Note: * Significant at p>0.05 level

Table 4.7 Results of the Wilcoxon signed-rank test for the categories of numbers and alphabets in NTI

n-back level comparison	Numbers		Alphabets	
	/Z/ value	*p*-value	/Z/ value	*p*-value
1-back - 2-back	5.069	0.000*	4.723	0.000*
1-back - 3-back	5.087	0.000*	4.860	0.000*
1-back - 4-back	5.086	0.000*	4.860	0.000*
2-back - 3-back	4.745	0.000*	4.723	0.000*
2-back - 4-back	4.984	0.000*	4.860	0.000*
3-back - 4-back	3.394	0.000*	4.312	0.000*

Note: * Significant at $p>0.05$ level

4.6 Within-group comparison of the performance on the n-back task in the IWD group

Similarly, within-group comparisons were carried out for the IWD group to identify the differences in performance across various levels of n-back within the five different categories of stimuli. Friedman test was carried out in the IWD group for 1-back, 2-back and 3-back levels only as responses were not present at the 4-back level for the IWD group. The results of the Friedman test are summarized in Table 4.8 below. It was revealed that significant differences existed across n-back levels for all the categories of stimuli in the IWD group.

Table 4.8 Results of Friedman test to identify within-group differences in IWD

Category of stimuli	χ^2 value	*p*-value
Fruits	6.33	0.042*
Common Objects	6.00	0.050*
Vehicles	11.143	0.004*
Numbers	13.00	0.002*
Alphabets	8.40	0.015*

Note: * Significant at $p>0.05$ level

Following this, pairwise comparisons using the Wilcoxon signed-rank test was carried out for n-back level within each of the stimulus categories in the IWD group. The results of the Wilcoxon signed-rank test are tabulated in Table 4.9 for the lexical categories of fruits, common objects and vehicles, and in Table 4.10 for the categories of numbers and alphabets. It was

observed that significant differences were observed across the different n-back levels in each category except the category of common objects and 2-back vs 3-back levels in the category of fruits.

Table 4.9 Results of the Wilcoxon signed-rank test for the categories of fruits, common objects and vehicles in IWD

n-back level comparison	Fruits		Common Objects		Vehicles	
	/Z/ value	*p*-value	/Z/ value	*p*-value	/Z/ value	*p*-value
1-back - 2-back	2.041	0.041*	1.293	0.196	2.223	0.026*
1-back - 3-back	2.207	0.027*	1.826	0.068	2.371	0.018*
2-back - 3-back	0.105	0.916	1.826	0.068	2.366	0.018*

Note: * Significant at p>0.05 level

Table 4.10 Results of the Wilcoxon signed-rank test for the categories of numbers and alphabets in IWD

n-back level comparison	Numbers		Alphabets	
	/Z/ value	*p*-value	/Z/ value	*p*-value
1-back - 2-back	3.125	0.002*	2.762	0.006*
1-back - 3-back	2.524	0.012*	2.023	0.043*
2-back - 3-back	2.524	0.012*	2.023	0.043*

Note: * Significant at p>0.05 level

4.7 Within-group comparison across categories on the n-back task in the NTI group

Further, within-group comparisons were carried out using the Friedman test to identify the differences in performance in each level of n-back across the five different categories of stimuli. The results of the Friedman test (Table 4.11) indicated that there were differences across different categories of stimuli at 1-back level (p = 0.001) and at 3-back level (p = 0.022).

Table 4.11 Results of Friedman test to identify within-group differences across categories in NTI

n-back level	χ^2 value	*p*-value
1-back	18.100	0.001*
2-back	1.548	0.818
3-back	11.484	0.022*
4-back	1.858	0.762

Note: * Significant at p>0.05 level

As the Friedman test demonstrated significant differences, post-hoc analysis using Wilcoxon signed-rank test was carried out to identify pairwise differences across categories at 1-

back and 3-back levels in the NTI group. The results of post-hoc analysis using the Wilcoxon signed-rank test are presented in Table 4.12. Differences were observed at 1-back level across categories of fruits and common objects (p = .003), fruits and vehicles (p = .015), common objects and numbers (p = .027), common objects and alphabets (p =.003) and vehicles and alphabets (p = .002). Similarly, differences were also observed at the 3-back level across categories of common objects and numbers (p = .027), and numbers and alphabets (p = .004)

Table 4.12 Results of the Wilcoxon signed-rank test for differences across categories at 1-back and 3-back level in NTI

Category of stimuli	**1-back level**		**3-back level**	
	/Z/ value	***p*-value**	**/Z/ value**	***p*-value**
Fruits - Common Objects	2.932	0.003*	0.060	0.952
Fruits - Vehicles	2.436	0.015*	0.171	0.864
Fruits - Numbers	1.393	0.163	1.188	0.235
Fruits - Alphabets	0.431	0.666	1.019	0.308
Common Objects - Vehicles	0.291	0.771	0.248	0.804
Common Objects - Numbers	2.216	0.027*	2.368	0.018*
Common Objects - Alphabets	2.998	0.003*	1.499	0.134
Vehicles - Numbers	1.829	0.067	1.650	0.099
Vehicles - Alphabets	3.057	0.002*	1.244	0.213
Numbers - Alphabets	0.990	0.322	2.881	0.004*

Note: * Significant at p>0.05 level

4.8 Within-group comparison across categories on the n-back task in the IWD group

Similarly, within-group comparisons had to be carried out using the Friedman test to identify the differences in performance in each level of n-back across the five different categories of stimuli. However, since insufficient valid cases were found to run the Friedman test, pairwise comparisons using the Wilcoxon signed-rank test at each level of n-back were carried out for each pair across various categories of stimuli. The results of the Wilcoxon signed-rank test is summarized in table 4.13. Significant differences were observed across the categories of fruits and numbers at 1-back level (p = .017) and at 2-back level (p = .039), across fruits and common

objects at 2-back level (p = .019) and across fruits and alphabets at 1-back level (p = .023). It should also be noted that a marginal level of significant difference (p = .056) was observed at the 1-back level across the categories of vehicles and numbers. The performance of IWD did not vary significantly across various categories at the 3-back level.

Table 4.13 Results of Wilcoxon signed-rank test for differences across categories in NTI

Category of stimuli	**1-back level**		**2-back level**		**3-back level**	
	/Z/ value	***p*-value**	**/Z/ value**	***p*-value**	**/Z/ value**	***p*-value**
Fruits - Common Objects	1.034	0.301	2.341	0.019*	1.342	0.180
Fruits - Vehicles	1.138	0.255	0.663	0.508	1.095	0.273
Fruits - Numbers	2.379	0.017*	2.063	0.039*	0.447	0.655
Fruits - Alphabets	2.275	0.023*	1.883	0.060	CNT	CNT
Common Objects - Vehicles	0.052	0.959	1.172	0.241	1.069	0.285
Common Objects - Numbers	1.448	0.148	1.153	0.249	1.604	0.109
Common Objects - Alphabets	1.448	0.148	0.078	0.937	1.342	0.180
Vehicles - Numbers	1.913	0.056	0.089	0.929	1.826	0.068
Vehicles - Alphabets	1.189	0.234	0.800	0.424	1.342	0.180
Numbers - Alphabets	0.181	0.856	1.223	0.221	1.214	0.225

Note: * - significant at p<0.05 level
CNT- Could not Test as there were not enough valid cases for comparison

4.9 Within-group comparison across categories at the threshold level of performance

Friedman test was carried out to determine whether there were any statistical differences in performance of the groups across various categories at the threshold level. For this purpose, RT values from the threshold for NTI (4-back) and IWD (2-back) were compared within groups across the five different categories of stimuli. The results of the Friedman Test are tabulated in table 4.14. However, no statistically significant differences were observed within the groups across categories of stimuli at their threshold level of performance.

Table 4.14 Results of Friedman test to identify within-group differences at the threshold level for both the groups

Subject group	**χ^2 value**	***p*-value**
Neurotypical Individuals	1.858	0.762
Individuals with Dementia	4.150	0.386

4.10 Electrophysiological findings

Auditory evoked potentials were obtained from the participants of the study. Auditory electrophysiological responses were obtained from participants of both groups (neurotypical individuals- NTI and individuals with dementia- IWD) for both speech stimuli as well as tone stimuli. The long latency event of P300 was of primary interest in this study. Following the data analysis using the EEGLAB plugin on MATLAB, data points were extracted and waveforms were plotted using the Microsoft Excel program. These are discussed further.

4.10.1 Auditory Evoked Potential Waveforms

The grand averaged waveforms obtained for the auditory evoked potentials for each category of participants (neurotypical individuals- NTI and individuals with dementia- IWD) across tone and speech stimuli are depicted below in Figure 4.2., Figure 4.3., Figure 4.4, and Figure 4.5 respectively.

Figure 4.2- Grand averaged P300 waveform of neuro-typical individuals for tone stimuli

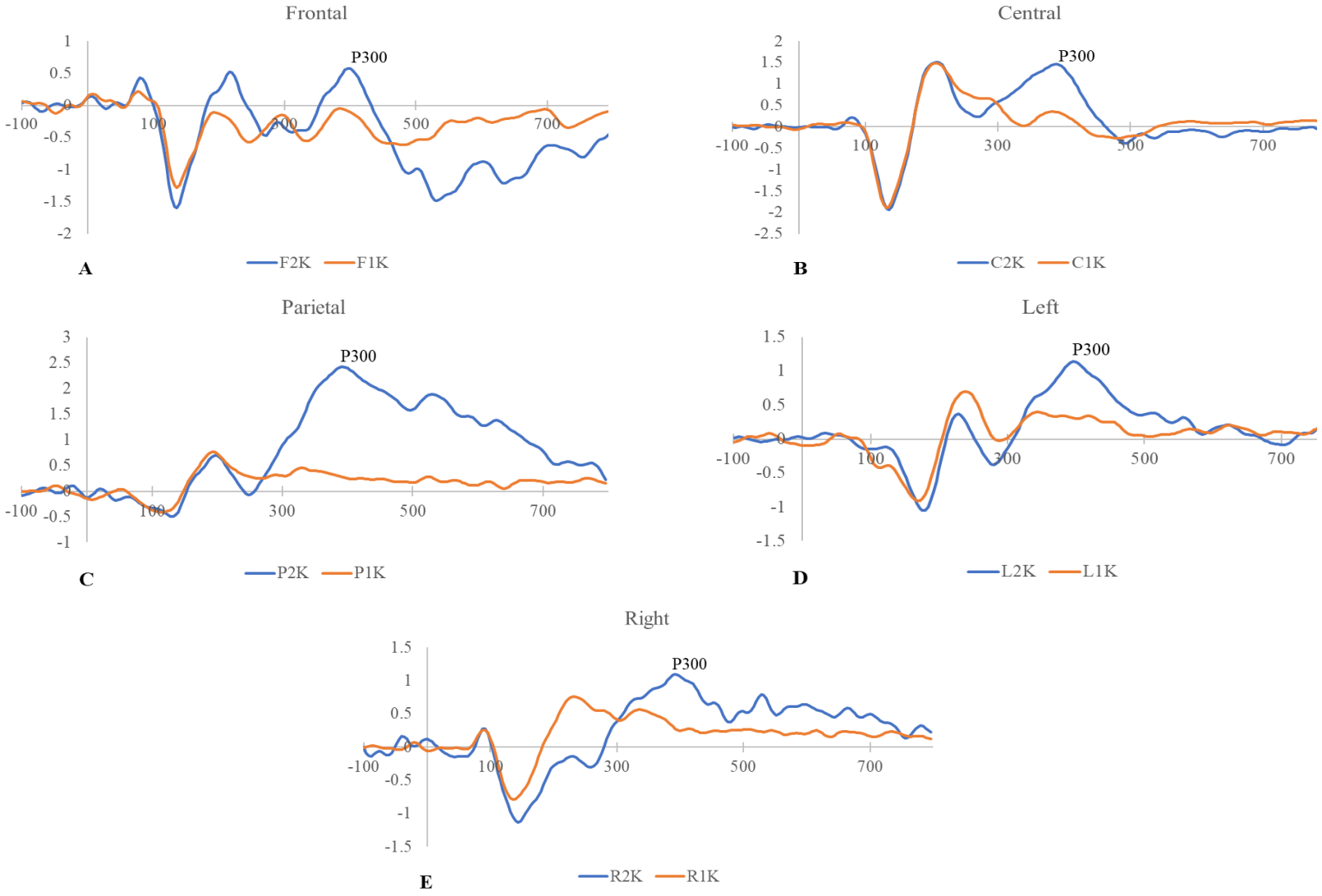


Figure 4.3- Grand averaged P300 waveform of Dementia patients for tone stimuli

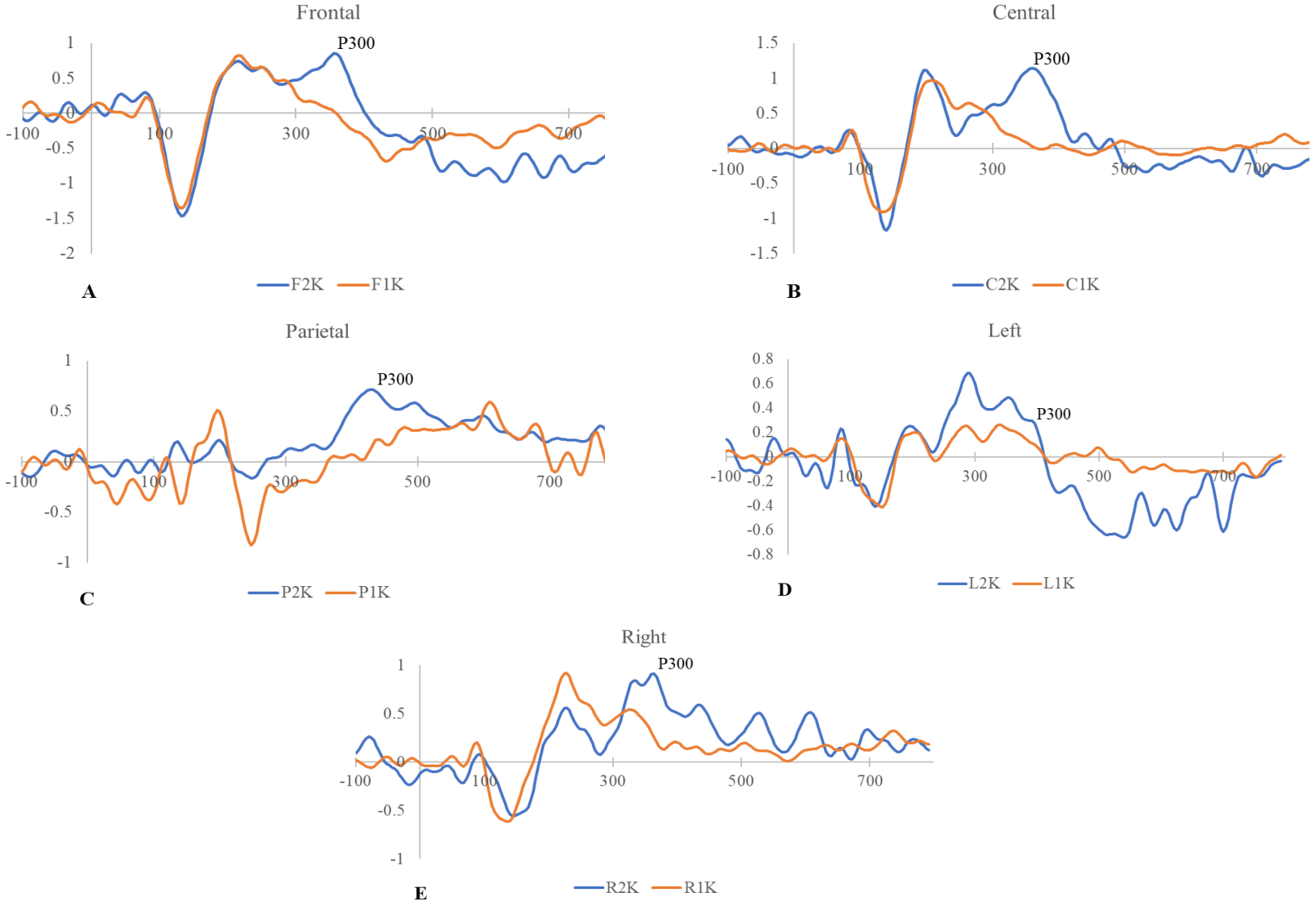


Figure 4.4- Grand averaged P300 waveform of neuro-typical individuals for speech stimuli

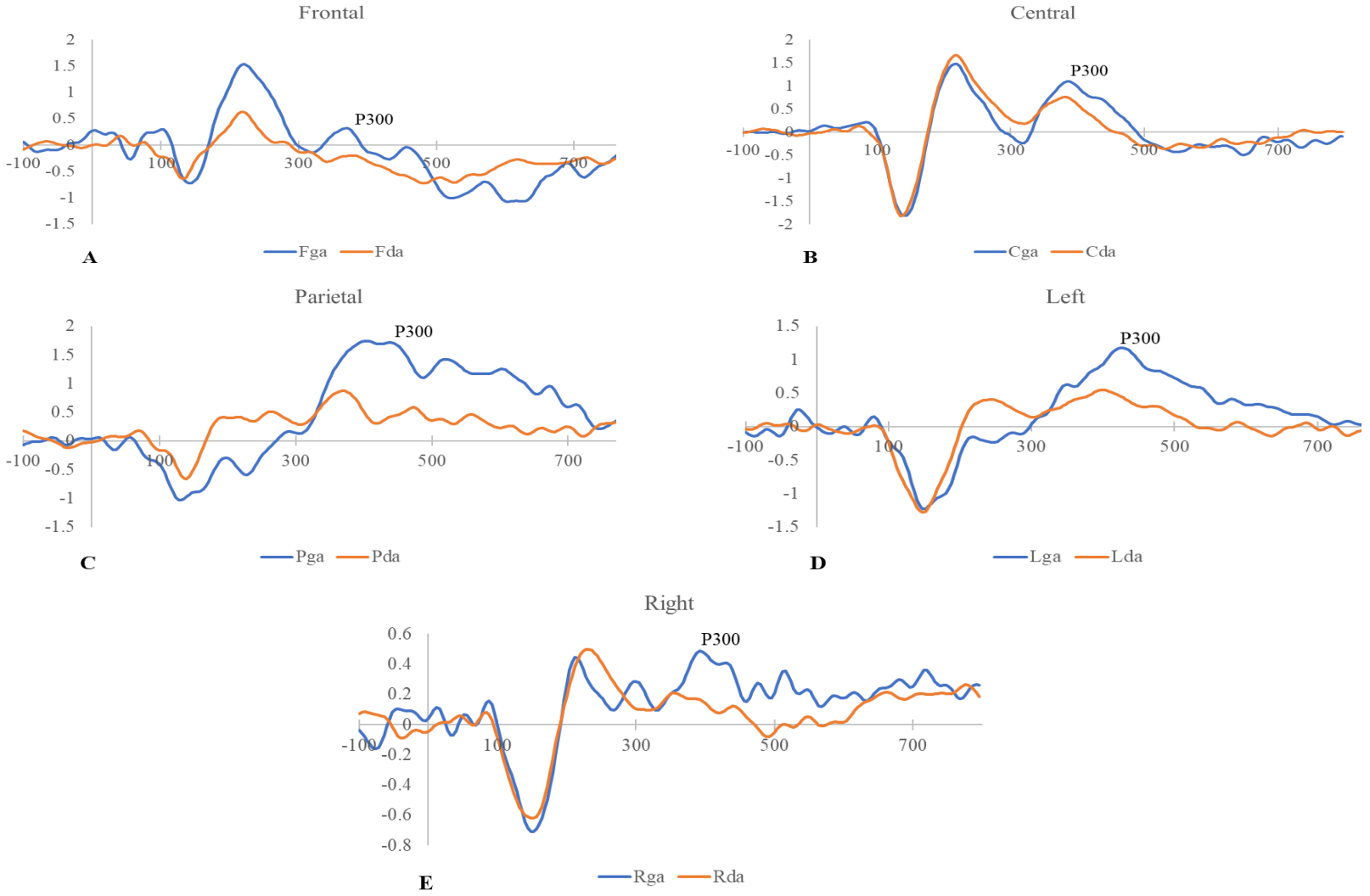
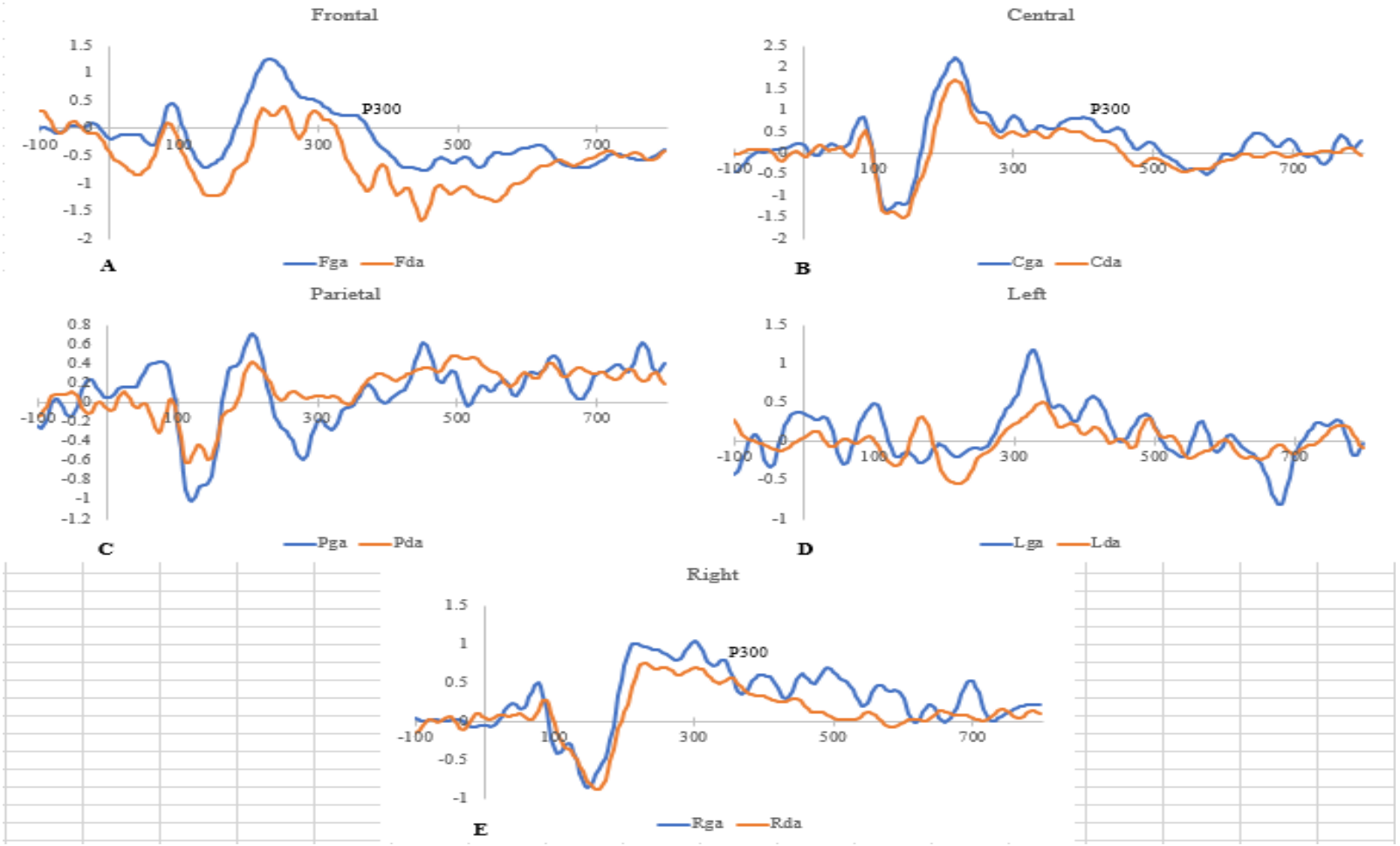


Figure 4.5- Grand averaged P300 waveform of individuals with dementia for speech stimuli



4.11 Descriptive statistics for P300

Mean, median, and standard deviation for the latencies and amplitudes of the P300 event for each stimuli category across different cortical regions (frontal, central, parietal, left, and right) were derived. These are summarized in table 4.15 for the speech stimuli and table 4.16 for the tone stimuli. It could be noted that P300 was not obtained from all the participants in both groups. However, the majority of the participants had P300 at the Parietal region for both speech and tone stimuli. Comparing across the groups, NTI demonstrated shorted latencies of P300 compared to the IWD group. However, the variability in the IWD group was high as suggested by the SD values. It can also be observed that the amplitude for P300 was higher for the NTI group compared to the IWD group.

Table 4.15 Latency and amplitude of P300 for speech stimuli across participant groups

Participant Group	Region	N	Latency			Amplitude		
			Mean	SD	Median	Mean	SD	Median
IWD	Frontal	5	366	71	352	0.54	0.43	0.41
	Central	5	421	49	408	1.29	0.95	1.04
	Parietal	9	471	33	478	0.34	0.25	0.27
	Left	4	362	66	334	1.36	0.77	1.57
	Right	7	360	41	368	1.27	0.92	1.20
NTI	Frontal	17	376	43	372	0.37	0.30	0.43
	Central	24	387	58	402	1.89	1.18	1.47
	Parietal	22	419	26	414	1.89	0.51	1.94
	Left	16	414	35	422	1.46	0.66	1.27
	Right	13	358	39	364	0.30	0.21	0.24

Table 4.16 Latency and amplitude of P300 for tone stimuli across participant groups

Participant Group	Region	N	Latency			Amplitude		
			Mean	SD	Median	Mean	SD	Median
IWD	Frontal	10	363	12	363	0.80	0.42	0.74
	Central	12	369	21	371	1.07	0.37	0.98
	Parietal	9	447	34	450	0.48	0.34	0.36
	Left	5	356	41	356	0.84	0.47	0.72
	Right	11	368	26	368	0.75	0.23	0.74
NTI	Frontal	20	398	24	400	0.75	0.44	0.66
	Central	29	392	22	392	1.43	0.69	1.39

	Parietal	21	388	25	388	1.49	0.27	1.56
	Left	15	409	30	396	0.56	0.35	0.51
	Right	18	407	43	400	1.42	0.94	1.39

In order to carry out comparisons across groups on their performance on P300 latencies and amplitudes and to identify within-group differences across cortical regions statistical analysis using the Statistical Package for Social Sciences (SPSS) software (version 26.0) was performed. Initially, the test of normality was to be carried out to determine the statistical tests for further analysis. However, statistical tests for normality were not administered as several missing values were present across both the groups for P300. Hence, non-normal distribution of the data was assumed and non-parametric tests were applied for the statistical analyses of the entire electrophysiological data.

4.12 Between-group differences on P300 latency and amplitude for speech stimuli

Mann-Whitney U test was carried out to determine the differences across IWD and NTI groups for the infrequent speech stimuli (/ga/). The results of Mann-Whitney U test are tabulated in table 4.17. It was observed that between groups differences existed across both the groups for the speech stimuli only at the parietal region for both P300 latency (/Z/ = 3.355, p = .001) as well as the amplitude (/Z/ = 4.081, p < .001). It could be recalled that NTI group had demonstrated a shorter latency and a higher amplitude for the P300 obtained using /ga/ stimuli.

Table 4.17 Between-group comparison of P300 for speech stimuli across participant groups

Region	**Latency**		**Amplitude**	
	/Z/ value	***p*-value**	**/Z/ value**	***p*-value**
Frontal	0.745	0.456	0.667	0.504
Central	0.867	0.386	1.011	0.312
Parietal	3.355	0.001*	4.081	0.000*
Left	1.614	0.107	0.189	0.850
Right	0.079	0.937	2.419	0.016

* - significant at p<0.05 level

4.13 Between group differences on P300 latency and amplitude for tone stimuli

Similarly, the Mann-Whitney U test was carried out to determine the differences across IWD and NTI groups for the infrequent tone stimuli (2kHz). It was observed that between groups differences existed across latency of both the groups across all regions for the tone stimuli. However, a significant difference in the amplitude of P300 was observed only at the Parietal region (/Z/ = 4.149, $p < .001$) across the two groups. The results of the Mann-Whitney U test have been summarized in table 4.18 below.

Table 4.18 Between-group comparison of P300 for tone stimuli across participant groups

Region	Latency		Amplitude	
	/Z/ value	***p*-value**	**/Z/ value**	***p*-value**
Frontal	3.546	0.000*	0.110	0.912
Central	2.915	0.004*	1.519	0.129
Parietal	3.742	0.000*	4.149	0.000*
Left	2.316	0.021*	1.180	0.238
Right	2.748	0.006*	2.023	0.043

* - significant at $p<0.05$ level

4.14 Within group differences on P300 latency and amplitude in NTI group

In order to determine the differences in the P300 latency and amplitude across cortical regions Friedman test was to be administered. However, because of several missing values and due to differences in P300 at different cortical regions even within participants, paired comparisons were carried out. Hence, Wilcoxon signed-rank test was carried out and pairwise results were obtained. Moreover, for the purpose of analysis, one cortical region was compared with another only if a minimum of 4 participants had demonstrated a valid response. This criterion was kept constant for all investigations of the between-group and within group differences across participants and stimuli categories. The results of Wilcoxon signed-rank test for differences in P300 latency and amplitude for speech stimuli (/ga/) and tone stimuli (2kHz) in the NTI group are tabulated in table 4.19.

Table 4.19 Within group comparison on P300 latency and amplitude in NTI group

Stimuli	**/ga/**				**/2kHz/**			
Regions	**Latency**		**Amplitude**		**Latency**		**Amplitude**	
	/Z/ value	***p*-value**	**/Z/ value**	***p*-value**	**/Z/ value**	***p*-value**	**/Z/ value**	***p*-value**
Frontal-Central	0.14	0.888	3.202	0.001*	1.228	0.219	3.024	0.002*
Frontal-Parietal	1.686	0.092	2.803	0.005*	1.793	0.073	2.901	0.004*
Frontal-Left	1.992	0.046*	2.366	0.018*	0.169	0.866	0.84	0.401
Frontal-Right	0	1.000	0.7	0.484	0.094	0.925	0.91	0.363
Central-Parietal	1.398	0.162	0.08	0.936	0.564	0.573	0.019	0.985
Central-Left	1.619	0.105	1.138	0.255	1.876	0.061	3.124	0.002*
Central-Right	2.001	0.045*	2.934	0.003*	1.942	0.052	0.479	0.632
Parietal-Left	0.314	0.753	1.664	0.096	2.034	0.042*	3.11	0.002*
Parietal-Right	2.499	0.012*	2.803	0.005*	2.203	0.028*	0.362	0.717
Left-Right	2.1	0.036*	2.521	0.012*	0.445	0.657	1.334	0.182

* - significant at $p<0.05$ level

In P300 obtained using infrequent speech stimuli /ga/, latency and amplitude were significantly different across the regions frontal and left (latency (/Z/ = 1.992, p = .046); amplitude (/Z/ = 2.366, p = .018)); central and right (latency (/Z/ = 2.001, p = .045); amplitude (/Z/ = 2.934, p = .003)); parietal and right (latency (/Z/ = 2.499, p = .012); amplitude (/Z/ = 2.803, p = .005)); and across left and right regions (latency (/Z/ = 2.1, p = .036); amplitude (/Z/ = 2.521, p = .012)). However, amplitude of the P300 alone was found to be statistically different across frontal and central (/Z/ = 3.202, p = .001); and frontal and parietal (/Z/ = 2.803, p = .005) regions.

Regarding P300 obtained using infrequent tone stimuli (2kHz), significant differences in both latency (/Z/ = 2.034, p = .042) and amplitude (/Z/ = 3.11, p = .002) were observed only across parietal and left regions. However, parietal and right regions demonstrated significant differences concerning the latency of P300 (/Z/ = 2.203, p = .028). Further, differences in amplitude of P300 was observed across frontal and central (/Z/ = 3.024, p = .002); frontal and parietal (/Z/ = 2.901, p = .004); and central and left (/Z/ = 3.124, p = .002) regions.

4.15 Within group differences on P300 latency and amplitude for speech stimuli in IWD group

In the same way, within group differences in the P300 latency and amplitude were investigated among the IWD group for speech and tone stimuli. The results of Wilcoxon signed-rank test for this purpose are summarized in table 4.20. For P300 elicited using infrequent speech stimuli /ga/, differences across frontal-central, frontal-parietal, frontal-left, frontal-right, central-left, parietal-left, and left-right were not obtained due to lack of enough valid cases (less than four) for comparison. Statistically significant differences were obtained only across the latency of P300 obtained using infrequent speech stimuli /ga/ in the parietal and right regions (/Z/ = 2.201, p = 0.028).

However, P300 obtained using infrequent tone stimuli 2kHz was found to differ across central and parietal regions in terms of both latency (/Z/ = 2.668, p = 0.008) and amplitude (/Z/ = 2.547, p = 0.011). Besides this, differences across regions were observed only for latency of P300 across parietal and frontal regions (/Z/ = 2.521, p = 0.012) and parietal and right (/Z/ = 2.666, p = 0.008) regions.

Table 4.20 Within group comparison on P300 latency and amplitude in IWD group

Stimuli	**/ga/**				**/2kHz/**			
Regions	**Latency**		**Amplitude**		**Latency**		**Amplitude**	
	/Z/ value	***p*-value**	**/Z/ value**	***p*-value**	**/Z/ value**	***p*-value**	**/Z/ value**	***p*-value**
Frontal-Central	CNT	-	CNT	-	0.89	0.373	1.58	0.114
Frontal-Parietal	CNT	-	CNT	-	2.521	0.012*	0.98	0.327
Frontal-Left	CNT	-	CNT	-	0	1	0.135	0.893
Frontal-Right	CNT	-	CNT	-	0.237	0.813	0.178	0.859
Central-Parietal	1.461	0.144	1.461	0.144	2.668	0.008*	2.547	0.011*
Central-Left	CNT	-	CNT	-	0.813	0.416	0.135	0.893
Central-Right	1.461	0.144	0	1	0.28	0.779	1.778	0.075
Parietal-Left	CNT	-	CNT	-	1.826	0.068	0	1
Parietal-Right	2.201	0.028*	1.572	0.116	2.666	0.008*	1.955	0.051
Left-Right	CNT	-	CNT	-	0.73	0.465	0.365	0.715

* - significant at $p<0.05$ level
CNT- Could not Test as there were not enough valid cases for comparison

4.16 Comparison across stimuli used to elicit P300

Following this, a comparison was made across P300 latency and amplitude obtained from NTI and IWD groups using speech and tone stimuli. Mann-Whitney U test was run for this purpose and the effect of stimuli on P300 latency as well as amplitude were compared within the groups. The results of the Mann-Whitney U test are tabulated in table 4.21. It was observed that within the NTI group, statistically significant differences were present across the latency and amplitude of P300 at the frontal (Latency, /Z/ = 1.998, p = .046; Amplitude, /Z/ = 3.019, p = .003), parietal (Latency, /Z/ = 3.481, p < .001; Amplitude, /Z/ = 2.821, p = .005), and right (Latency, /Z/ = 2.945, p = .003; Amplitude, /Z/ = 3.523, p < .001) regions when compared across speech and tone stimuli. Along with these, NTI group also exhibited statistically significant amplitude differences at the left region (/Z/ = 3.637, p = .005) across the speech and tone stimuli. However, within the IWD group, differences between the speech and tone stimuli were observed only at the central region (/Z/ = 2.427, p = .014) for the latency of P300 measure.

Table 4.21 Comparison across stimuli used to elicit P300 within the groups

Region	**Neuro Typical Individuals**				**Individuals with Dementia**			
	Latency		**Amplitude**		**Latency**		**Amplitude**	
	/Z/ value	***p*-value**	**/Z/ value**	***p*-value**	**/Z/ value**	***p*-value**	**/Z/ value**	***p*-value**
Frontal	1.998	0.046*	3.019	0.003*	0.307	0.768	0.980	0.371
Central	0.501	0.616	1.153	0.249	2.427	0.014*	0.264	0.799
Parietal	3.481	0.000*	2.821	0.005*	1.415	0.161	0.915	0.370
Left	0.852	0.394	3.637	0.000*	0.490	0.730	0.980	0.413
Right	2.945	0.003*	3.523	0.000*	0.227	0.860	1.223	0.246

* - significant at $p<0.05$ level

4.17 Correlation between the n-back behavioral task and the P300

The correlation between n-back reaction time at the threshold level and the P300 responses elicited using tone and speech stimuli were examined using the Spearman's rank correlation coefficient (ρ). Findings of correlation analysis are depicted in table 4.22 and 4.23 for NTI group and table 4.24 and 4.25 for the IWD group. Within the NTI group, a fair negative correlation was found to exist between latency of P300 elicited using speech stimuli from the central region and the reaction time at the threshold level of the category of common objects (ρ = -0.428, p = 0.037). Similarly, a moderate negative correlation between latency of P300 elicited using speech stimuli from the left region and the reaction time at the threshold level of the category of numbers (ρ = -0.533, p = 0.034) was also observed within the NTI group.

Concerning the P300 elicited using tone stimuli in the NTI group, latency of P300 from the frontal region showed a moderate negative correlation with the reaction time at threshold level for the category of alphabets (ρ = -0.522 p = 0.032). A fair to moderate correlation was also observed for the latencies of P300 elicited using tone stimuli from the parietal region (ρ = 0.489 p = 0.025) and the right region (ρ = 0.495 p = 0.037) with the reaction time at the threshold level for the category of numbers. The amplitude of P300 elicited using tone stimuli from the central region demonstrated a weak positive correlation with the reaction time at threshold level for the category of alphabets (ρ = 0.379 p = 0.042).

However, within the IWD group, a very strong negative correlation was found to exist between latency of P300 elicited using speech stimuli from the frontal region and the reaction time at the threshold level of the category of common objects (ρ = -0.900, p = 0.037) as well as the latency of P300 elicited using speech stimuli from the central region and the reaction time at the threshold level of the category of vehicles (ρ = -0.900, p = 0.037). Further, a near perfect

negative correlation was also observed between the latency of P300 elicited using speech stimuli from the left region and the reaction time at the threshold level of the category of alphabets (ρ = 1.000, $p < 0.001$). Similarly, a very strong negative correlation was found to exist between amplitude of P300 elicited using speech stimuli from the frontal region and the reaction time at the threshold level of the category of fruits (ρ = -0.900, p = 0.037).

With respect to the P300 elicited using tone stimuli in the IWD group, a strong positive correlation was observed across the latency of P300 from the parietal region and the reaction time at the threshold level of the category of numbers (ρ = 0.767, p = 0.016). Further, the amplitude of P300 elicited using tone from the frontal region showed a moderate to strong negative correlation with the reaction time at the threshold level of the category of common objects numbers (ρ = -0.673, p = 0.033).

Table 4.22 Correlation of n-back reaction time with amplitude and latency of P300 elicited using speech stimuli in NTI group

Parameters	Fruits Reaction Time			Common Objects Reaction Time			Vehicles Reaction Time			Numbers Reaction Time			Alphabets Reaction Time		
	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N
Frontal Latency	-0.277	0.28	17	0.161	0.538	17	-0.419	0.094	17	-0.292	0.255	17	-0.244	0.401	14
Central Latency	0.039	0.857	24	**-0.428**	**0.037***	24	0.309	0.141	24	-0.11	0.608	24	0.137	0.553	21
Parietal Latency	-0.234	0.294	22	-0.29	0.19	22	-0.158	0.483	22	0.041	0.855	22	-0.132	0.579	20
Left Latency	0.206	0.443	16	-0.191	0.478	16	-0.025	0.926	16	**-0.533**	**0.034***	16	0.279	0.334	14
Right Latency	-0.027	0.929	13	-0.159	0.603	13	-0.313	0.297	13	0.000	1.000	13	-0.227	0.502	11
Frontal Amplitude	-0.251	0.331	17	-0.135	0.604	17	0.299	0.243	17	0.323	0.207	17	-0.071	0.81	14
Central Amplitude	-0.002	0.994	24	-0.12	0.576	24	0.023	0.916	24	0.303	0.15	24	0.362	0.107	21
Parietal Amplitude	0.199	0.375	22	-0.14	0.536	22	0.031	0.893	22	-0.084	0.711	22	0.011	0.965	20
Left Amplitude	-0.365	0.165	16	-0.1	0.713	16	-0.059	0.829	16	0.044	0.871	16	-0.125	0.67	14
Right Amplitude	0.396	0.181	13	0.297	0.325	13	0.154	0.616	13	0.181	0.553	13	-0.1	0.77	11

Table 4.23 Correlation of n-back reaction time with amplitude and latency of P300 elicited using tone stimuli in NTI group

Parameters	Fruits Reaction Time			Common Objects Reaction Time			Vehicles Reaction Time			Numbers Reaction Time			Alphabets Reaction Time		
	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N
Frontal Latency	0.054	0.823	20	0.038	0.875	20	-0.38	0.098	20	-0.029	0.905	20	**-0.522**	**0.032***	17
Central Latency	-0.033	0.867	29	-0.176	0.362	29	-0.081	0.675	29	0.154	0.427	29	-0.294	0.144	26
Parietal Latency	0.287	0.207	21	0.22	0.337	21	0.047	0.84	21	**0.489**	**0.025***	21	0.2	0.412	19
Left Latency	-0.263	0.344	15	0.054	0.849	15	-0.313	0.256	15	-0.15	0.593	15	-0.124	0.687	13
Right Latency	-0.063	0.804	18	0.17	0.501	18	-0.05	0.845	18	**0.495**	**0.037***	18	-0.019	0.944	16
Frontal Amplitude	-0.105	0.661	20	-0.275	0.24	20	0.19	0.422	20	-0.241	0.307	20	0.454	0.067	17
Central Amplitude	0.237	0.215	29	-0.211	0.271	29	**0.379**	**0.042***	29	0.043	0.823	29	0.075	0.716	26
Parietal Amplitude	-0.105	0.658	20	-0.01	0.967	20	-0.225	0.34	20	-0.244	0.3	20	0.277	0.266	18
Left Amplitude	-0.113	0.689	15	-0.218	0.435	15	-0.081	0.775	15	-0.016	0.955	15	-0.207	0.498	13
Right Amplitude	-0.018	0.945	18	-0.024	0.925	18	0.203	0.418	18	-0.078	0.757	18	0.115	0.672	16

Table 4.24 Correlation of n-back reaction time with amplitude and latency of P300 elicited using speech stimuli in IWD group

Parameters	Fruits Reaction Time			Common Objects Reaction Time			Vehicles Reaction Time			Numbers Reaction Time			Alphabets Reaction Time		
	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N
Frontal Latency	0.5	0.391	5	**-0.900**	**0.037***	5	0.1	0.873	5	-0.1	0.873	5	-0.1	0.873	5
Central Latency	0	1	5	-0.6	0.285	5	**-0.900**	**0.037***	5	-0.7	0.188	5	-0.5	0.391	5
Parietal Latency	-0.1	0.798	9	0.533	0.139	9	0.533	0.139	9	0.133	0.732	9	0.567	0.112	9
Left Latency	0	1	4	0.4	0.6	4	0.2	0.8	4	-0.2	0.8	4	**-1.000**	**0.000***	4
Right Latency	0.643	0.119	7	0.429	0.337	7	-0.071	0.879	7	0.357	0.432	7	0.036	0.939	7
Frontal Amplitude	**-0.900**	**0.037***	5	0.6	0.285	5	-0.4	0.505	5	0.4	0.505	5	-0.5	0.391	5
Central Amplitude	-0.5	0.391	5	0.3	0.624	5	0.2	0.747	5	0.6	0.285	5	0.5	0.391	5
Parietal Amplitude	0.143	0.736	8	-0.071	0.867	8	-0.024	0.955	8	0.31	0.456	8	-0.048	0.911	8
Left Amplitude	-0.6	0.4	4	-0.2	0.8	4	-0.4	0.6	4	0.4	0.6	4	0.8	0.2	4
Right Amplitude	-0.643	0.119	7	-0.179	0.702	7	0.429	0.337	7	0	1	7	-0.143	0.76	7

Table 4.25 Correlation of n-back reaction time with amplitude and latency of P300 elicited using tone stimuli in IWD group

Parameters	Fruits Reaction Time			Common Objects Reaction Time			Vehicles Reaction Time			Numbers Reaction Time			Alphabets Reaction Time		
	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N	ρ	p - value	N
Frontal Latency	0.371	0.291	10	0.28	0.434	10	0.377	0.283	10	-0.003	0.993	10	0.067	0.854	10
Central Latency	0.259	0.417	12	0.385	0.217	12	0.224	0.484	12	0.231	0.47	12	0.161	0.618	12
Parietal Latency	0.267	0.488	9	0.283	0.46	9	-0.217	0.576	9	**0.767**	**0.016***	9	0.15	0.7	9
Left Latency	-0.1	0.873	5	-0.4	0.505	5	-0.6	0.285	5	0.00	1.000	5	-0.7	0.188	5
Right Latency	-0.351	0.29	11	0.059	0.863	11	-0.41	0.21	11	-0.048	0.889	11	0.118	0.729	11
Frontal Amplitude	-0.406	0.244	10	**-0.673**	**0.033***	10	-0.37	0.293	10	0.122	0.738	10	-0.552	0.098	10
Central Amplitude	0.312	0.324	12	-0.354	0.259	12	-0.242	0.449	12	0.081	0.803	12	-0.319	0.313	12
Parietal Amplitude	-0.4	0.286	9	-0.467	0.205	9	-0.467	0.205	9	-0.033	0.932	9	-0.317	0.406	9
Left Amplitude	0.2	0.747	5	0.3	0.624	5	-0.3	0.624	5	-0.5	0.391	5	-0.1	0.873	5
Right Amplitude	-0.364	0.272	11	-0.209	0.537	11	-0.182	0.593	11	-0.583	0.06	11	0.136	0.689	11

CHAPTER V

DISCUSSION

Alzheimer's disease (AD) is known as a major public health concern in the developing countries due to its increasing prevalence (Vecchio & Määttä, 2011). This study was carried out to explore the performance of individuals with dementia due to Alzheimer's disease (IWD) on the behavioral n-back task and on the electrophysiological measure of P300 (elicited using both speech as well as tone stimuli). The performance of these individuals with dementia was was also compared with that of neurotypical individuals (NTI). Further, correlations of the performance on the behavioral and electrophysiological tasks were also carried out for both the IWD and the NTI groups.

5.1 Behavioral findings from the n-back task

The n-back task is a WM measure that is being used more frequently in research, clinical settings, and training studies (Pelegrina et al., 2015). In order to carry out the n-back task, an individual needs several cognitive processes such as short-term memory, updating of representations, etc (Kensinger et al., 2003).

5.1.1 Performance of the NTI and IWD groups on n-back tasks

Findings from the behavioral n-back task indicated that the performance of the IWD group was inferior to that of the NTI group. It was noted that the NTI group had a lower (better) reaction time (RT) at all levels of the n-back task across all five categories compared to the IWD group. Successful performance on the n-back task requires several cognitive processes for the storage, maintenance, and manipulation of information as well as inhibitory and interference control (Kensinger et al., 2003; Shalchy et al., 2020). These processes could be thought of as being impaired in IWD which resulted in their poorer performance on the n-

back task compared to that of the NTI. Although long-term memory deficits are the hallmark of AD, several investigations have reported that individuals with AD perform poorly in tasks requiring short-term memory of information and also demonstrate higher-level deficits associated to the capability to synchronize multiple tasks or to inhibit irrelevant information (Kensinger et al., 2003). Semantic memory is reported to be impaired in IWD especially those with AD (Calderon et al., 2001). Further, the ability to access semantic information could also be impaired in individuals with dementia which are hypothesized as working memory (WM) deficits (Belleville et al., 1996; Bragin et al., 2015; Crawford & Higham, 2016; Grossman et al., 1996; Morris & Baddeley, 1988; Nagaraj et al., 2021).

Findings from fMRI studies suggest that the performance on the n-back task is regulated by regions at the prefrontal, frontal and parietal areas (Huntley & Howard, 2010; Lamichhane et al., 2020; Owen et al., 2005). Alzheimer's Disease affects the cortical structures with neurofibrillary tangles and brings about a change in the cortical morphology (Kumar et al., 2015). The impact of the AD on various cortical regions responsible for the n-back performance could have led to the poor performance of the IWD on n-back tasks compared to the NTI. The performance on the n-back task is also known to be affected by the subject's fatigue (Pergher et al., 2021). Even though a sufficient rest period was given in between the various n-back tasks in the current study, there are chances that the elderly subjects in the current study would have got fatigued in between the task which could also have impacted the results.

Performance on the n-back task has been reported to be poorer in subjects with schizophrenia (dorsolateral prefrontal cortex dysfunction) (Perlstein et al., 2001), and aphasia (Deepa & Hema, 2019; Korani & Hema, 2019) compared to NTI. Likewise, the current findings suggest that the performance on the n-back task is inferior for IWD compared to the NTI. As the task employed in the present study was a visual n-back task, it could be thought

that the poor performance on the visual n-back task arises from the impaired functioning of the visuospatial sketchpad, the episodic buffer, as well as a central executive of Baddeley's working memory model. Similar findings have also been reported in the literature (Baddeley et al., 1986; Huntley & Howard, 2010).

It was observed that the IWD required longer RTs to indicate their responses for the n-back task than the NTI group. This was true across all the levels of the visual n-back task and for all the different categories of stimuli considered in this study. These prolonged RTs could correspond to the longer processing time to access and retrieve information from the WM. Findings from previous studies (Baddeley et al., 1986; Bragin et al., 2015; Calderon et al., 2001; Stopford et al., 2012) suggest that there is a slowed processing for tasks involving WM in IWD. There is also evidence for generalized cognitive slowing in IWD (Collette, 1999; Myerson et al., 1998; Nebes & Brady, 1992; Parasuraman & Haxby, 1993). The present findings are also no different in reporting the slower RTs of IWD compared to the NTI group. The slower processing in IWD can account for the degraded cognitive performance in them as observed from the n-back task. The Processing-Speed Theory (Salthouse, 1996) states that "cognitive performance is degraded when processing is slow because relevant operations cannot be successfully executed and because the products of early processing may no longer be available when later processing is complete." The WM is considered as "a limited-capacity storage system that is responsible for the maintenance and manipulation of information over short durations of time" (Baddeley, 1986). The n-back task is a cognitively demanding task that requires the individual to maintain and manipulate information at a faster rate (Gevins & Cutillo, 1993). It is known that the n-back performance significantly correlates with the measure of processing speed (Miller et al., 2009). It is possible that the IWD are unable to process the information at a faster rate which leads to a poorer performance on the n-back task compared to the NTI. Taken together, these account

for the significant differences across the groups at each level of n-back for the various categories of stimuli investigated.

5.1.2 Performance of the NTI and IWD groups at a threshold level of n-back tasks

Further, there were significant differences across the IWD and NTI groups on their threshold level of performance. NTI was able to perform till 4-back tasks for all categories of stimuli whereas the IWD were limited in their performance to 2-back level for the various categories. This threshold level of n-back performance indirectly corresponds to the WM capacity. It was also noted that the NTI was superior to IWD at the threshold level of performance. The reduced span of WM performance in IWD has been reported in the literature (Belleville et al., 1996). On the contrary, there are also reports that the WM span and n-back were weakly associated (Kane et al., 2007). However, the current findings suggest that a lower threshold of performance in the n-back task for various categories by the IWD participants is indicative of their WM span. This further upholds the notion that WM is affected in IWD (Belleville et al., 1996; Bragin et al., 2015; Crawford & Higham, 2016; Morris & Baddeley, 1988; Nagaraj et al., 2021; Stopford et al., 2012). Deficits in the WM memory are often attributed to the pathophysiology of AD affecting the cortical regions and these WM deficits often lead to deficits in their communicative abilities (Bayles, 2003).

5.1.3 Impact of task complexity of n-back tasks on the NTI and IWD groups

Another notable observation made from the findings of the present study was that, in the IWD group, there was a decrease in the number of individuals correctly performing three out of five trials with increasing task complexity. Moreover, IWD did not demonstrate any accurate responses at the 4-back level for all five categories. These correspond to the degraded performance with an increase in task complexity (Haynes et al., 2017). It is also

known that IWD finds it difficult to maintain mental sets (Lamar, 2002). The n-back task at the 1-back level corresponds to the easiest level of performance which requires only minimal taxing of the WM system. However, with the increase in the 'n', the task becomes more and more complex and the person has to hold information in the WM system for longer durations along with processing the incoming stimuli (Kirchner, 1958; Pelegrina et al., 2015). This leads to a breakdown of performance at higher n-back levels. Similar findings have been reported in the studies of individuals with dementia (Bragin et al., 2015) as well as individuals with depression (Bragin et al., 2008). Poor performance with increasing levels of task complexity has also been noted in individuals with aphasia for both semantic and syntactic n-back tasks (Deepa & Hema, 2019; Korani & Hema, 2019). The difficulties that IWD face with the speed of information processing and in the allocation of attentional resources to incoming information (Nestor et al., 1991) also play a role in decreased performance at higher levels of task complexity of the n-back.

5.1.4 Impact of various levels of n-back tasks on the NTI and IWD groups

Yet another significant finding from the current study was the significant differences across the various levels of n-back performance in both NTI and the IWD groups. These differences were more evident in the NTI group than the IWD group. Similar findings have been reported in the literature for normal aging, IWD, as well as typically developing children and adolescents (Bopp & Verhaeghen, 2018; Nagaraj et al., 2021; Pelegrina et al., 2015). Differences across the levels of the n-back task can be explained by delineating the specific contributions of familiarity and recognition mechanisms towards the n-back task (Oberauer, 2005; Pelegrina et al., 2015). Responses at the earlier levels of n-back (e.g., 1-back) could be due to familiarity, whereas at the higher levels, recollection of the information becomes mandatory (Oberauer, 2005; Pelegrina et al., 2015). Moreover, the need to regularly

update the information content within the WM for the higher levels of n-back (Pergher et al., 2020) could also lead to differences in performance across the levels of n-back. There are also reports in the literature that differences are observed in alpha band power when individuals attend to a higher n-back level (2-back or higher) compared to a lower n-back level (1-back) for visual n-back tasks (Pesonen et al., 2007). These findings affirm that information maintenance and manipulation load varies with increasing levels of n-back leading to varied performances at different levels of n-back.

5.1.5 Impact of various categories of stimuli on the n-back performance of the NTI and IWD groups

Findings from the current study also report differences in performance across categories of stimuli. These differences were evident at the 1-back and 3-back levels for the NTI group and the 1-back and 3-back levels for the IWD group. At the 1-back level, the NTI group exhibited differences in performance to various categories of stimuli including the lexical items of fruits, common objects, and vehicles and also with that of alphabets and numbers. However, at the 3-back level, differences were observed within the NTI group across the lexical category of common objects and numbers and numbers and alphabets. However, in the IWD group, differences were noted at the 1-back level only among the various lexical categories of fruits and numbers and across fruits and alphabets. Similarly, at the 2-back level, IWD exhibited within-group differences only across the categories of fruits and common objects and fruits and numbers. Differences in stimuli modality may bring about changes in the performance of the n-back task (Bopp & Verhaeghen, 2018). Findings from fMRI studies have revealed that different stimuli categories tend to be processed through specific pathways in the brain (Carreiras et al., 2015). In NTI, some brain regions are more receptive to letters than to numbers or other stimuli and vice versa. The familiarity of the

participants to the participants to alphabets also facilitates its faster processing compared to the other stimuli (Ngiam et al., 2019). Findings from the current study also support the findings of Carreiras et al. (2015) and Ngiam et al. (2019) relating to differences in performance across the lexical categories and alphabets. Recent research findings have also revealed that stimuli used for the n-back task influence the n-back performance in NTI (Jaeggi et al., 2010; Shalchy et al., 2020). As already stated, the n-back task is known to be influenced by familiarity and recollection (Oberauer, 2005; Pelegrina et al., 2015). Familiarity can obscure the relation to recall-based complex items leading to differences in the performance of the n-back task, especially at higher levels and stimuli with varied familiarity. Several models of visuospatial and verbal memory across the adult life span have been suggested (Park et al., 2002). These models report that WM has domain-specific subsystems, which are related yet independent visuospatial and verbal pools. These subsystems could lead to varied processing of information across various categories of stimuli at different n-back levels. However, as the reliability of the n-back task as reported in the literature is poor (Jaeggi et al., 2010), these results need to be replicated in a larger sample before applying to the entire population.

5.2 Findings from the Electrophysiological measures

In the current study, electrophysiological measures of P300 were obtained from the NTI and IWD groups using the EGI Net Station 5.4 and processed using the EEGLAB plugin within MATLAB software. An auditory oddball paradigm was used to obtain the auditory evoked potential responses where frequent and infrequent stimuli were presented in the ratio 80:20. Electrophysiological measures were obtained using the speech and tone stimuli wherein the syllable /da/ and 1kHz tone served as frequent stimuli and the syllable /ga/ and 2kHz tone served as infrequent stimuli.

The P300 is regarded to play a key role in audiology among other auditory evoked Long Latency Potentials. This is because of its capability to reflect potentials generated in the auditory central nervous system related to cognition without employing invasive methods (Côser et al., 2010). P300 provides information about the brain processes that are fundamental to auditory perception and processing (Côser et al., 2010; Polich, 1996, 2007).

5.2.1 Performance of the NTI and IWD groups on an electrophysiological measure of P300

Even though the event-related potential P300 is expected to occur at 300ms post-stimulus onset, literature reports that the P300 peak can be expected to occur between 250 and 500 ms (Linden et al., 1999; Polich & Criado, 2006). Findings from the Indian population (Puttabasappa et al., 2017) have reported prolonged latencies of P300 in typically aging individuals as well. Results of the current study are also in consensus with these findings and have reported the presence of P300 potential within 300ms to 500ms post-stimulus onset.

Performance of the NTI and the IWD groups were different on the electrophysiological measure of P300 as revealed from the findings of this study. P300 responses were better in the NTI group compared to the IWD group for both speech and tone stimuli. Latencies of the P300 at different cortical regions showed varied results when compared across the IWD and NTI groups. The amplitude of P300 at various cortical regions was found to be reduced for the IWD group compared to the NTI group for P300 elicited using both speech and tone stimuli. These findings are similar to those reported in the earlier literature wherein the performance on P300 has been found to be poorer in individuals with dementia compared to those reported in neurotypical individuals (Bennys et al., 2007; Cecchi et al., 2015; Emek et al., 2013; Howe et al., 2014; Juckel et al., 2008; Lee et al., 2013; Medvidovic et al., 2013).

The P300 has been widely reported as parieto-central and temporoparietal positivity that arises when an individual perceives an informative task-relevant stimulus (Pedroso et al., 2012; Sutton et al., 1965). However, literature also reports that P300 could be a result of concurrent activity in different parts of the brain (Halgren, Baudena, Clarke, Heit, Liégeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995; Halgren et al., 1980; Horn et al., 2003; Johnson, 1989; Mccarthy et al., 1997; Menon et al., 1997; Opitz, 1999; Stevens et al., 2000; Verleger et al., 1994). Recent findings also confirm that P300 is elicited from multiple cortical regions (Pedroso et al., 2012). Individuals with dementia due to Alzheimer's disease (AD) manifest variations in the cortical morphology due to the presence of neurofibrillary tangles and also demonstrate cortical atrophy (Kumar et al., 2015). These could in turn impact the functioning of various cortical regions responsible for the production of P300 in response to the auditory stimuli. Brain atrophy measured using MRI in cognitively impaired patients (including those with dementia) has been reported to correlate well with the P300 responses (Braverman et al., 2015). Thus, the general impact of AD on the cortex of the individuals with dementia would have led to their poor responses in the P300 compared to the participants in the NTI group.

Prolonged latency of P300 has been well established in the literature for subjects with AD (Farina et al., 2006; Golob et al., 2007; Jackson & Snyder, 2008; Pokryszko-Dragan et al., 2003). P300 latency reflects the cognitive function and speed of processing as well as the diverse pathogenic changes in the brain (e.g., atrophy and neuronal signaling pathways disconnection) (Szilasiová et al., 2020). Cognitive function as well as the speed of processing are impaired in individuals with AD. These explain the prolonged latency of P300 observed in the participants of the IWD group compared to the NTI group in the current study.

Findings of the current study have also reported a reduction in the amplitude of P300 elicited using both speech stimuli as well as tone stimuli in the IWD group compared to the

NTI group. This is in consensus with the findings reported in the literature that amplitude of P300 is impaired in individuals with dementia (Bennys et al., 2007; Caravaglios et al., 2008; Hedges et al., 2016; Juckel et al., 2008; Medvidovic et al., 2013). However, the reduced amplitude of P300 has also been reported in a variety of conditions with altered cortical morphology, such as traumatic brain injury (Duncan et al., 2003; Nandrajog et al., 2017) and schizophrenia (Jeon & Polich, 2003). Thus, it can be concluded that changes in the cortical morphology resulting due to AD contributes to the reduction in the P300 amplitude as evidenced from the findings of the current study as well. The P300 amplitude decreases with age even in NTI, however, this reduction is further exaggerated by AD (Saito et al., 2001). Further, the reduction in amplitude of P300 for the IWD group can also be explained through the context-updating hypothesis (Donchin, 1981). This hypothesis suggests that the mental model of the subject evaluates and updates itself when a deviant stimulus is introduced into the environment. However, as this mental model is impaired in individuals with AD, it reflects the reduction in the P300 amplitude (van Dinteren et al., 2014).

P300 is known to reflect cognitive processes such as attention, recognizing and classification of stimulus, and also working memory and decision making (Pedroso et al., 2012). P300 amplitudes at the Cz and Pz electrodes are known to correlate well with performance on the neuropsychological tests in AD patients (Lee et al., 2013). Further, P300 has been reported to be influenced by cognitive aging (van Dinteren et al., 2014). IWD involved in the current study demonstrated diminished amplitudes and prolonged latencies of P300 which could reflect the poor cognitive functioning in these individuals. Thus, the findings of the current study further strengthen the available literature that cognitive processes such as attention and working memory are impaired among individuals with dementia.

However, it is noteworthy that, despite having been diagnosed as having AD, and having significant deficits in communication and cognition, the responses to P300 were not fully absent in the IWD group. This would suggest that the brain mechanisms responsible for various cognitive processes continue to remain active in individuals within the IWD group even though their cognitive communicative functions are diminished. Thus, P300 can be suggested as a tool to monitor the deterioration of brain-related functions in individuals with AD. Supporting studies have been reported in the literature wherein P300 has been reported as a tool for monitoring disease progression in individuals with multiple sclerosis (Szilasiová et al., 2020). However, on the contrary, some studies suggest that ERP findings may not be directly correlated with cognitive impairment (Bicalho et al., 2017).

5.2.2 Differences in P300 response elicited from various cortical regions

P300 was evoked from five different cortical regions in the current study. These were frontal, central, parietal, left, and right regions. A comparison was made across the P300 elicited using both speech and tone stimuli within the NTI as well as the IWD group to identify the differences across regions responsible for P300. Statistically significant differences were observed across the P300 evoked from different cortical regions in the NTI group for both speech and tone stimuli. It is generally regarded that the parietal region (specifically the Pz) is a robust generator of the P300 potential (Pedroso et al., 2012; Sutton et al., 1965). Along with the parietal region, the central, as well as the frontal cortical regions, also contribute to the P300 (Halgren, Baudena, Clarke, Heit, Liégeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995; Halgren et al., 1980; Horn et al., 2003; Johnson, 1989; Mccarthy et al., 1997; Menon et al., 1997; Opitz, 1999; Stevens et al., 2000; Uohashi et al., 2006; Verleger et al., 1994). Various contributions from the different cortical regions would have led to the varied responses for P300 in the NTI group. Even though P300 can be elicited from various cortical regions, the amplitudes and latencies across each of

these regions would vary. Findings were no different in the current study as well, as the amplitudes and latencies of P300 elicited using both speech and tone stimuli across each of these regions were found to vary. A higher amplitude of P300 was observed in the frontal as well as central regions for both speech and tone stimuli in the NTI group. With aging, an anterior shift of topography has been reported in the literature (van Dinteren et al., 2018). The findings of the current study uphold the notion that the P300 can be more robustly obtained from the parietal and central regions compared to the other cortical regions (Halgren, Baudena, Clarke, Heit, Liégeois, et al., 1995).

However, differences in P300 across various cortical regions were minimal for the IWD group. Differences were significantly more across the regions for tone elicited P300 than speech elicited P300. Stimuli-related differences will be described in a further section. Differences in P300 across the cortical regions for the IWD suggest a difference in the cortical functioning compared to the NTI group. The P300 amplitude and latency are known to vary across various cortical regions for different stimuli (Huang et al., 2015; van Dinteren et al., 2014, 2018). However, the altered cortical morphology in AD would have equalized the performance of various cortical regions in response to the P300 task due to functional compensations (van Dinteren et al., 2014, 2018). These are further supported by the findings of a meta-analysis (Hedges et al., 2016). It has been reported that effect sizes of the amplitude of P300 between three common sites of P300 acquisition (Fz, Cz, and Pz) were not statistically different from each other (Hedges et al., 2016). Lack of differences across amplitudes of P300 elicited from Fz, Cz and Pz were attributed to the widespread impact of the AD on the different brain regions. Recent literature involving MRI suggests that P300 elicited from frontal, central, and parietal regions positively correlated with gray matter volume in those regions (Pergher et al., 2019). As AD leads to a reduction in the gray matter volume of the brain, one can expect reductions in the function of the cortex as well

corresponding to the reduction in the gray matter volume(Braverman et al., 2015). Yet, there are also reports of varied findings in P300 for various cortical regions. Statistically, significant differences were noted for amplitudes of P300 elicited using tones from the right and left parietal and occipital electrodes than other electrodes in AD subjects (Emek et al., 2013).

5.2.3 Effect of stimuli used to evoke P300

The current study utilized both speech stimuli (/da/ and /ga/) as well as tone stimuli (1kHz and 2kHz) to elicit P300 responses from the NTI as well as the IWD group. Initially, a between-group comparison was carried out to determine the differences in latency and amplitude of P300 elicited from various regions across IWD and NTI groups for both speech and tone stimuli. Between-group differences were observed for P300 elicited using both speech and tone stimuli. It was observed that both latency and amplitude of the P300 evoked from the parietal region using speech stimuli were significantly different across the groups, whereas other cortical regions did not show a difference. Speech elicited P300 was shorter in latency and higher in amplitude in the NTI group compared to the IWD group. The amplitude and latency of P300 elicited from the parietal region (specifically the Pz) is regarded to be more robust than other cortical regions (Pedroso et al., 2012; Sutton et al., 1965). However, a change in the cortical functioning owing to AD would have led to a prolonged P300 latency and a diminished P300 amplitude from the parietal region for speech stimuli.

However, P300 elicited using the tone stimuli was found to be significantly different across all the regions relating to the latency of P300 and also relating to the amplitude of the parietal region. Speech elicited P300 has been reported to be more robust than tone elicited P300 in neurotypical individuals (Lew et al., 1999). Thus, one would expect a lower amplitude and prolonged latency for the P300 elicited using tones compared to speech elicited P300. However, current findings suggest that latencies of P300 were shorter in the

IWD group than in the NTI group at all regions except the parietal region. Further, these differences concerning the latency of P300 elicited using tone stimuli were statistically significant as well. These findings could be attributed to the unfamiliarity with the stimulus (tones) used. In support of these findings, some studies have reported shorter latencies and higher amplitudes with tone stimuli compared to speech stimuli (C. Gonçalves et al., 2011; Ramteke & Meshram, 2020). However, contradictive findings have also been reported in the literature with higher amplitude and shorter latencies for speech evoked P300 than those evoked with tone in individuals with traumatic brain injury (Lew et al., 1999) and in neurotypical individuals(de Freitas Alvarenga et al., 2013; Didoné et al., 2019).

Further, a comparison was also made across the groups for P300 elicited based on stimuli used to elicit P300. Statistically significant differences were evident across speech evoked and tone evoked P300 in the NTI group. However, this difference was limited only to a difference in the latency of P300 elicited from the IWD group. Results of the current study revealed shorter latencies and higher amplitudes for speech evoked P300 compared to tone evoked P300 at the majority of cortical regions. These are similar to the findings reported in the earlier literature (de Freitas Alvarenga et al., 2013; Didoné et al., 2019; Lew et al., 1999). Speech stimuli are preferred over tone stimuli in clinical practice as they also provide information on the function of cortical regions dedicated to speech signal processing (Didoné et al., 2019). Further, there are also reports which suggest that not all normal individuals tend to have a P300 in response to tone stimuli (O'Mahony et al., 1990).

Better latency of P300 was observed for the tone stimuli at the central region compared to the speech stimuli in the IWD group. This could be because of the allocation of attention to the tonal stimuli. Literature also reports differences in P300 due to the stimulus used to elicit P300. Right hemisphere dominance, precisely at the frontal and central electrode sites has been reported for P300 elicited using tones (Polich, 1997).

Further, direct comparisons of the current study with other studies reported in the literature are not possible. This is because of the involvement of a group of electrodes used in the current study than a specific electrode at a particular site.

5.3 Correlation between the behavioral and electrophysiological findings

Results of the current study also revealed certain associations of P300 latency and amplitude with the n-back task threshold. Latencies and amplitude of P300 elicited from various cortical regions showed a fair to moderate correlation with the threshold reaction time of the n-back task in the NTI group. These fair to moderate correlations observed for the latency and amplitude of P300 and the better working memory capacity as evidenced by the n-back performance in the NTI group are similar to those reported in the literature (Ally et al., 2006).

However, the IWD group demonstrated strong to perfect negative correlations across the latencies and amplitudes of P300 elicited from different cortical regions with the threshold reaction time of the n-back task. As the n-back task was not simultaneous with the P300 in the current study, a relation between these two can only be inferred. Yet, the strong negative correlation across these behavioral and electrophysiological measures in the IWD group suggests a possibility of association. With an increase in reaction time in the n-back threshold, a reduction in the amplitude of P300 or prolongation in the latency of P300 can be expected. However, these would need to be verified in a simultaneous task to arrive at firm conclusions. In the literature, The amplitude of P300 has been reported to be proportional to the number of attentional resources allocated to the specific task (Gonsalvez & Polich, 2002; Kramer & Strayer, 1988; Wickens et al., 1983) and has been related with superior memory performance (Fabiani et al., 1990). Since the performance on a working memory task (n-back task) also deteriorated in the individuals with dementia in the current study similar to those

reported in the literature (Mencarelli et al., 2019), a reduction in the amplitude of P300 can be reasoned out from this. Moreover, a reduction in the P300 amplitude is supposed to arise out of diminished activation of the brain (Magnano et al., 2006) or cognitive dysfunction (Polich, 1986). This diminished activation of the brain and cognitive dysfunction could also lead to longer and slower reaction times in the n-back task, thus making these two measures inter-related. Furthermore, a generalized slowing of processing of information is thought to occur in individuals with dementia (Collette, 1999; Myerson et al., 1998; Nebes & Brady, 1992; Parasuraman & Haxby, 1993). This would also be a cause for the increased reaction evidenced from the n-back task as well as the prolonged latencies of P300.

Recently several researchers have started to use the n-back task parallel to ERP measures (Fraga et al., 2017; Scharinger et al., 2017; Shalchy et al., 2020). In one of the earliest attempts to elicit electrophysiological responses through the n-back task (Fraga et al., 2017), it was observed that NTI demonstrated reliably increased beta and alpha responses than MCI and AD subjects. These were observed at various electrode locations within the fronto-central and temporal-parietal areas. Yet another recent study involving P300 elicited using n-back tasks across young and old adults reported that significant amplitude differences in the Fz and Pz location for the 3-Back task (Pergher et al., 2019). However, these methodologies are still under refinement and are yet to yield strong statistically significant results.

CHAPTER VI

SUMMARY AND CONCLUSIONS

Working memory deficits are a recognized feature of Alzheimer's disease (AD). Due to the alarmingly increasing prevalence of AD, there is a need to have a better understanding of the characteristics of dementia resulting from AD. The current study aimed to examine the visual and auditory processes of working memory capacity in individuals with dementia (IWD) and neurotypical individuals (NTI) through the use of behavioral and electrophysiological measures.

The behavioral task employed in the present study was a visual n-back task. This task was programmed and run using the E-Prime 2.0 software. The behavioral n-back task was obtained for five different stimuli categories, viz., common objects, fruits, vehicles, numbers, and alphabets. The n-back task was probed till the 4-back level in the current study. The outcomes of the behavioral task were the reaction time and threshold of performance for each category of stimulus. These were extracted and was subjected to further analysis.

The auditory electrophysiological measures were obtained using Electrical Geodesics Inc. (EGI) NetStation 5.4 and were further subjected to post-processing and analysis using the EEGLAB plugin on the MATLAB software. The primary auditory electrophysiological measure was the P300 elicited using both speech and tone stimuli. An oddball paradigm was employed to elicit P300 from the participants. For this purpose, frequent and infrequent stimuli were presented in a sound field in the ratio of 80:20. Frequent stimuli for speech was the syllable /da/ and for tone, it was 1kHz pure tone. Infrequent stimuli used to elicit P300was the syllable /ga/ for speech and tone, a 2kHz pure tone was utilized. Further, the P1-N1-P2 complex was also obtained and subjected to analysis. The latency and amplitude of these evoked potentials were considered for further analysis.

These behavioral and electrophysiological measures obtained from IWD as well as NTI were compared for between-group as well as within-group differences. Further, correlations across these visual and auditory-based tasks were carried out.

6.1 Behavioral findings from the n-back task

The performance of the IWD group on the n-back task was poorer compared to the NTI group. NTI group demonstrated shorter reaction times and higher thresholds compared to the IWD group for various categories of stimuli. The threshold of performance of the NTI group was observed to be 4-back level for various categories of stimuli whereas the performance of the IWD group was scattered at different levels. The majority of the participants of the IWD group could only reach a threshold of 2-back level for various categories of stimuli. In general, the performance of the IWD group was more variable and scattered compared to the NTI group who were more consistent and stable.

Significant between-group differences were noted at almost all levels of the n-back task for all categories of stimuli employed in the current study. Comparison of reaction time at the threshold level of performance also revealed significant differences across the groups with superior performance by the NTI group. Within-group performance among the NTI group revealed significant differences across each level of n-back task across categories. However, this was not very evident in the IWD group. Further, category-wise differences were explored which revealed differences across stimulus categories at 1-back and 3-back levels for the NTI group. Differences across stimulus categories were observed at 1-back and 2-back levels for the IWD group.

6.2 Electrophysiological findings from the P300

Similar to the n-back task, the performance of the NTI group was superior to the IWD group in the electrophysiological measures as well. Prolonged latencies and diminished amplitudes were observed for the IWD group for both speech and tone stimuli with some

exceptions. Between-group differences revealed that P300 elicited using both speech and tone stimuli from various cortical regions were different in terms of their latency and amplitude, especially at the parietal region. Within-group differences were also observed in the NTI group for P300 elicited using both speech and tone stimuli. In contrast, within-group differences were minimal in the IWD group. Further, the findings of the current study also revealed statistically significant differences across stimuli used to elicit P300 in both groups. It was observed that shorter latencies and higher amplitudes were present for speech evoked P300 compared to tone evoked P300 at a majority of cortical regions.

6.3 Correlation across behavioral and electrophysiological measures

Behavioral and electrophysiological findings of the current study were correlated to observe for any possible associations. These revealed certain associations of P300 latency and amplitude with the n-back task threshold. Latencies and amplitude of P300 elicited from various cortical regions showed a fair to moderate correlation with the threshold reaction time of the n-back task in the NTI group. Whereas, the IWD group demonstrated strong to perfect negative correlations across the latencies and amplitudes of P300 elicited from different cortical regions with the threshold reaction time of the n-back task.

6.4 Implications of the current study

The findings of the behavioral and electrophysiological processes have been discussed in depth relating to existing literature and possible reasons for the results of the current study have been provided. The majority of the deviant results in the IWD group are attributed to the changes in the brain structure and function due to AD. Aging has impacted the performance of NTI as well, however, not as much due to the pathological changes exhibited by the IWD group.

The findings of the current study uphold the value of evoked auditory potentials and the working memory n-back tasks in differentiating between neurotypical individuals and those with AD. These measures can reflect the cognitive changes that are manifested in these individuals with AD. Even these two tasks utilize two different modalities of vision and auditory skills, some correlations are also observed across these, especially in the IWD group. Further studies are warranted to validate the findings of the current study.

6.5 Limitations and Future directions

- The current study was carried out with a limited number of participants owing to the COVID-19 scenario. This limits the generalizability of findings to the entire population of IWD. Hence, future studies can employ a higher sample number.
- The behavioral n-back task was carried out only till the 4-back level. This would not be a reflection of the true working memory threshold of the neurotypical individuals involved in the current study. Future studies can explore even higher levels of n-back task (e.g., till the maximum level which a participant can perform the n-back task, than just limiting to 4-back or 5-back). However, this would require a reprogramming of the paradigm used within the E-Prime software.
- The present study did not investigate the n-back task and P300 simultaneously. The visual n-back and auditory P300 were obtained one after the other in a random order, which would have led to differences in attention for the different tasks. If the visual n-back task is used to elicit P300, it can be correlated with auditory P300 to obtain specific and relevant information.
- The behavioral responses to the auditory P300 were not documented in the current study. Quantification of the behavioral responses to the infrequent stimulus would

provide objective information on the correct implementation of P300 and also ensure the attention allocation from the subject.

- The current study considered only individuals with AD. Future studies can investigate Mild Cognitive Impairment and different severities of dementia and also explore the differences in these tasks across various types of dementia.
- Current study involved participants of both genders. However, they were not separately analyzed based on gender due to the lower sample size. Future studies can explore the effects of gender on these tasks.

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