The Use of EEG and ERPs in the Study of Aging and Mild Cognitive Impairment (MCI)

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Thesis submitted to the University of Ottawa
in partial fulfillment of the requirements for the
Doctorate in Philosophy in Experimental Psychology

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Acknowledgments

I would like to start by thanking my thesis supervisor, Dr. Vanessa Taler, who took a chance on me as her graduate student. I am very grateful for all her patience, help, and guidance in mentoring me not only as a person, but also as a student. Her expertise vastly improved my communication, writing, and research skills. These skills were necessary for me to complete my graduate journey and have prepared me for my future career.

I would like to further thank Dr. Ken Campbell whose unparalleled expertise and knowledge in auditory research has allowed me to go farther than I thought possible which has brought me to the end of my Ph.D. He has spent countless hours helping me to understand EEG/ERP research and answering all of my questions. The time he has devoted to me and to all others who cross his path cannot be quantified. I simply cannot thank him enough. Since he loves mangoes – I will start there.

I would also like to thank Dr. Charles Collin for getting me interested in programming and helping me to conceive and design my initial projects. The impact of both cannot be understated. I have developed skill sets from both these experiences and rely on them heavily as I go forward. I thoroughly enjoyed our conversations, and his movie recommendations were on point. My feelings when I finished writing my thesis - *I've been ionized, but I'm okay now* (Buckaroo Banzai).

A big thank you to Dr. Patrick Davidson, for his positive attitude and support throughout my Ph.D. Your door was always open, and you were always willing to help and assist whenever I needed it. You always had me thinking outside of my current purview of research ideas and thoughts. Thank you for helping me to expand my thought process and consider the alternative.

There are far too many people to thank and acknowledge in the completion of this thesis. People like Dr. Rory Coughlan who inspired me to go into Academia, Dr. Dwayne Schindler who helped me to understand linear mixed modelling. I have learned a lot from them all and will forever be indebted to them for their efforts in training and supporting me. I would like to thank Cassandra, my family, and friends who have always been there. This journey was made all the more special and rememberable with all of you.

Abstract

With increased age, some individuals experience cognitive declines that are more severe than what is observed in healthy cognitive aging. This decline may be related to mild cognitive impairment (MCI) and Alzheimer's disease (AD). Much of the current research on dementia attempts to detect subtle cognitive and memory declines before behavioral and cognitive symptoms are more apparent. Intense research interest has focused on MCI, a condition that includes impairment in some areas of cognitive functioning but is not severe enough to warrant the diagnosis of dementia. MCI may represent a transitional stage between healthy aging and AD and is considered a risk factor for AD development. The purpose of the present thesis was to examine if EEG and ERPs can be used as reliable predictors of cognitive changes in aging and MCI.

Study 1 was designed to examine if there is evidence of changes in the EEG between cognitively healthy older adults and people with MCI. The purpose of this study was to examine differences in EEG activity between healthy older adults and people with MCI during early and late portions of a longer-than-normal resting-state recording. Resting state recordings typically last 1-3 minutes. It would be advantageous to run a longer testing session because this would provide more data, but such a procedure might be problematic because it might result in increased drowsiness in the latter half of testing. If this drowsiness affected those with MCI more than healthy adults, this might produce artifactual differences between groups. If increased drowsiness occurs as the duration of the recording becomes longer, an increase of low-frequency EEG activity should be observed, particularly in the delta band. Resting state EEG was recorded in 20 healthy older adults and 20 people with MCI who rested with their eyes closed. The EEG recording was divided into two three-minute halves. People with MCI exhibited a significant increase in theta power density over posterior regions of the scalp compared to healthy older

adults. Power density for all frequency bands did not change over the two halves of the recording. That is, there was little evidence of drowsiness in the second half of the recording. Taken together, these findings indicate that longer resting-state EEG recording can be reliably employed without increased risk of drowsiness.

Study 2 examined whether there is evidence of a dysfunction in the salience network in older adults. Previous research suggests that older adults may be less able to compute the level of salience of unattended stimulus inputs. The transient detector system is a specialized network of brain areas for detecting sudden changes in the intensity of an auditory stimulus. The output of this system, as reflected by the auditory ERP components N1 and P2, provides a measure of the level of salience of the stimulus. Twenty younger adults and healthy older adults participated in this study. A single auditory stimulus was presented rapidly, every 1.5 s, or very slowly, every 12 s, in different conditions. When the stimuli were presented rapidly, group differences were not observed for the amplitudes of N1 and P2, peaking at 100 and 180 ms, respectively. When stimuli were presented very slowly, their amplitudes were greatly enhanced for younger adults but did not increase for older adults. The failure to observe a large increase in the amplitude of N1 and P2 in older adults for very slowly presented stimuli provides strong evidence of a dysfunction of the salience network in this group.

There is evidence that both the functioning of salience network and the frontoparietal network deteriorate in cognitively healthy older adults. These networks might further deteriorate in people with MCI. In study 2, when stimuli were presented slowly, the P2 was delayed and peaked at a time that is more consistent with a P3a. The P3a is elicited by a potentially highly salient, but unattended stimulus input that interrupts the functioning of the frontoparietal network, resulting in a switch of processing priorities away from current task demands and

toward the processing of the stimulus input. In study 3, auditory stimuli were again presented either rapidly or very slowly to 20 healthy older adults and 20 people with MCI. The amplitude of N1 did not differ between the two groups in either the fast or slow conditions. Thus, there is little evidence that people with MCI have a deficit in computing the salience of unattended auditory stimuli. When stimuli were presented slowly, the P2/P3a was significantly smaller in people with MCI compared to healthy older adults. The attenuated P2/P3a in people with MCI may reflect a reduced frontoparietal ability to determine processing priorities. In people with MCI, priority of processing may not be switched from the ongoing cognitive task to the potentially much more relevant auditory input.

In the results of studies 2 and 3, there was ambiguity regarding whether the positivity observed in the slow condition reflected P2 or P3a activity. A more definite P3a had been elicited in oddball paradigms. In the oddball paradigm, the participant is presented with a sequence of frequently presented homogenous standard stimuli. At rare and unpredictable times, a deviant is presented, the deviant representing a change in a feature of the standard. Deviants that represent a large change from the standard may elicit a P3a. Two experiments were run in which at least one of the deviants had previously been shown to elicit a large P3a in younger adults. Study 4 consisted of two experiments. In Experiment 1, the deviants represented either decreases or increases in the intensity of the standard. The deviant that represented an increase in intensity has been found to elicit a large P3a in previous studies. In Experiment 2, six different deviants were presented. The deviants included a white noise burst and environmental sounds, both of which have elicited a large P3a in previous studies. Across both experiments, the MMN/DRN and P3a did not differ between healthy older adults and people with MCI. Previous studies have indicated that the P3a is reduced in amplitude in healthy older adults compared to

younger adults. The results of study 4 indicate that the P3a was not further reduced in people with MCI. This is in contrast to study 3 in which the P2/P3a was reduced in people with MCI.

This could be because of the use of the oddball paradigm in study 4. Detection of the deviant would be carried out, at least in part, by the change detection system while in study 3, the presentation of a single stimulus would have been detected only by the transient detection system. Operations of the frontoparietal network controlling processing priorities can be interrupted by sufficient output from either the transient or change detector systems. This results in a switch of processing from an ongoing task to the processing of the potentially more relevant stimulus input. When this interrupt is sent from the change detection system, the operations of the frontoparietal network do not appear to deteriorate in people with MCI compared to what is observed in cognitively healthy older adults.

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General Introduction

A rise in life expectancy has led not only to an increase in the aging population but also to a growing number of older adults with cognitive decline, including mild cognitive impairment (MCI). Cognitive decline is a central component of aging. MCI may represent a transitional stage between healthy aging and Alzheimer's Disease (AD) (Gauthier et al., 2006). It is a condition in which individuals demonstrate more cognitive impairment than what is expected in healthy aging with no impact on social or occupational function (Petersen et al., 1999). This thesis will examine electrophysiological measures in healthy older adults and people with MCI. Initial studies were also run with younger and healthy older adults. While some of the experimental manipulations have been tested in younger adults, there is a paucity of data about these effects in healthy older adults. Three of the studies in this thesis record event-related potentials (ERPs) to monitor the extent of processing of unattended, but potentially highly relevant auditory stimuli. These ERPs reflect different cognitive processes including feature extraction, the computation of salience level, and the establishment of processing priorities.

Aging and cognitive changes

Understanding and mitigating cognitive changes with age has become an area of intense research interest. A variety of neuropsychological and cognitive tasks have been used to examine deterioration in different cognitive functions (Arnáiz & Almkvist, 2003; Saunders & Summers, 2010; Zhang et al., 2007). Some cognitive domains, such as language comprehension, and vocabulary, remain intact with aging (Park et al., 2002; Salthouse, 2010). On the other hand, several cognitive functions are known to decline with aging (Salthouse, 2009; Solbakk et al., 2008; Zanto & Gazzaley, 2019)**.** For example, decreases in processing speed (Salthouse, 2009) and declines in working memory (Daffner et al., 2011), episodic memory (Singh-Manoux et al., 2012), and attention occur with increased age.

Attention may play a particularly important role in aging because it is essential to many cognitive functions (Craik & Salthouse, 2011). The inhibition theory of aging (Hasher & Zacks, 1988) maintains that older adults are less able to inhibit the processing of irrelevant input than younger adults (Chao & Knight, 1997; de Fockert & Bunce, 2009; Parmentier & Andrés, 2009). Distraction may result in a shift of attention away from the demands of a current, higher priority task (Gazzaley et al., 2008; Hasher & Zacks, 1988; Lee et al., 2020; Schmitz et al., 2014) and to processing of the irrelevant distractor. Performance on a number of cognitive tasks will therefore deteriorate upon presentation of the distractor. A recent meta-analysis of distraction studies has, however, questioned whether older adults do exhibit performance deficits following the presentation of distracting stimuli (Rey-Mermet & Gade, 2018).

The sustaining of attention to the task at hand is thought to be a major function of a frontoparietal network that determines cognitive processing priorities (Petersen & Posner, 2012). Because of the limited capacity of the processing system, decisions need to be made about which tasks will receive priority for processing. The frontoparietal network must, however, be flexible in making such decisions. On one hand, attention to a current cognitive task having high priority should not be interrupted by irrelevant stimulus input. On the other hand, attention must not be so focused on the current cognitive task that the individual will not be able to detect an unattended but potentially highly relevant stimulus input that may be critical for survival (Schmitz et al., 2014). A separate salience network is thought to provide initial input to the frontoparietal network to determine which current process requires priority (Goulden et al., 2014). This salience network operates at an early level of processing to determine the salience of unattended incoming stimuli. Salience is often quantified according to bottom-up, stimulus-driven features (see Krüger et al., 2016 for a review). For example, specialized neuronal

populations may increase their firing rate to a particular feature of a stimulus, high intensity. A larger number of neurons within the population may also respond. A rarely occurring stimulus also results in an increase in output from the neuronal population. The context in which a stimulus occurs also defines its salience. Thus, an intense stimulus occurring among other higher intensity stimuli is not salient. On the other hand, a less intense stimulus occurring among the higher intensity stimuli is more salient.

There is evidence that the salience network may be dysfunctional in older adults (Lee et al., 2020). As a consequence, older adults may be unable to accurately compute saliency levels of unattended stimulus input. Therefore, an irrelevant input having low salience may interrupt the frontoparietal network while a more relevant input having high salience may not.

Theories of cognition and aging

Several theories have been postulated to explain cognitive declines observed in older adults. Not all are relevant to the specific context of this thesis, the extent to which unattended stimuli result in attention capture. For this reason, only a brief historical review will be made. There is overlap among the different theories and as a result, determining which one best explains cognitive decline is difficult.

The processing speed theory proposes that declines in processing speed with increased age are the fundamental mechanism that accounts for cognitive decline in older adults (Salthouse, 1996). Cognitive performance declines because of two possible mechanisms, the limited time mechanism or the simultaneity mechanism. On one hand, cognitive performance may decrease because slower processing does not allow later processing to be successfully executed on time (limited time mechanism). On the other hand, cognitive performance may also

decrease because the products of early processing are no longer available when later processes are completed (simultaneity mechanism).

Another theory emphasizes the role of so-called cognitive resources. This theory suggests that with increased age, fewer attentional resources are available for task completion (Craik & Byrd, 1982). When tasks are simple and not demanding of cognitive resources, performance may not differ between younger and cognitively healthy older adults. However, when tasks are more complex, and require more cognitive resources, the performance of older adults may decline compared to that of younger adults. The additional cognitive resources required for the successful completion of the cognitive tasks may not be available in older adults.

Various inter-related theories have been developed to explain the comorbidity of cognitive and sensory impairment in older adults. These hypotheses include the common-cause hypothesis, the cognitive load on perception hypothesis, the sensory deprivation hypothesis, and the information degradation hypothesis (see Ebaid et al., 2017; Schneider & Pichora-Fuller, 2000 for review). The common cause hypothesis suggests that age-related declines in perception and cognitive abilities can be attributed to an underlying factor. This factor accounts for the variance between age, cognition, and perception. The cognitive load on perception hypothesis indicates that decline in cognitive abilities will negatively impact poor performance on perceptual tasks. For instance, decline in sustained attention may adversely affect the ability to perceive auditory or visual stimuli. The sensory deprivation hypothesis highlights that reduced sensory functioning is a precursor for cognitive decline. The sensory deprivation hypothesis points to age-related sensory decline as a catalyst for declines in cognitive performance. The information degradation hypothesis suggests that reduced perceptual input impacts cognitive task performance. These

hypotheses are not mutually exclusive, but all suggest that with increased age there is an association between declines in sensory functioning and cognition.

Park and Reuter-Lorenz (2009) have attempted to explain how compensatory mechanisms can allow older adults to successfully maintain performance on a variety of tasks. Their scaffolding theory of aging and cognition (STAC) indicates that behavioral, structural, and functional declines can be understood within the framework of compensatory scaffolding. Accordingly, the brain attempts to mitigate these declines by building compensatory "scaffolding" in response to neural insults (e.g., decreases in cortical thickness and white matter integrity). This scaffolding may include the recruitment of additional existing circuity to compensate for declining regions that have become inefficient with increased age. Some fMRI studies supporting this view have shown increased activation of prefrontal brain regions in older compared to younger adults (Davis et al., 2008; Gutchess et al., 2005). This age-related over-activation has been observed in many cognitive tasks, including memory and executive functioning (Spreng et al., 2010).

Mild Cognitive Impairment (MCI)

Some individuals experience significant declines in cognition that are greater than expected for their age and education level, but that do not interfere with everyday function. People with this type of decline are diagnosed as having mild cognitive impairment (MCI). As such, their decline is not severe enough for the diagnosis of dementia (Petersen et al., 1999). MCI has been estimated to be observed in approximately 12% to 18% of people over 60 years of age (see Petersen, 2016 for review). Typically, those with a diagnosis of MCI progress to AD at an increased rate compared to healthy older adults (Petersen et al., 2013, 1999). AD-related neuropathological changes can occur during a long preclinical period before cognitive symptoms are clinically detectable (Reisberg, et al., 2010). The transitional stage of MCI (between healthy

aging and AD) may provide insight into the neuropathology of AD. Much research has thus focused on studying people with MCI to identify who go on to develop AD (Sperling et al., 2011).

Identifying who will progress from MCI to AD has been difficult in clinical practice because of the heterogeneous nature of MCI. While MCI may be a precursor to AD, not all people with MCI develop AD, and some people with MCI may revert to normal cognition. This reversion rate is lower than those who remain in the MCI stage or progress to dementia (see Roberts & Knopman, 2013 for review). Approximately 20% of people with MCI will revert to normal cognition at a follow-up evaluation (see Roberts & Knopman, 2013 for review). Some of the factors that may increase the probability of reverting to normal cognition include: younger age, male sex, and the subtype single domain non-amnestic MCI. MCI may also be caused by reversible conditions such as alcohol abuse or medical conditions. Thus, if these conditions are managed, a person with MCI may revert to normal cognition.

Several clinical subtypes of MCI have been observed (Petersen, 2016). Some people with MCI exhibit memory impairment (amnestic MCI, or aMCI) while others exhibit declines in cognitive domains other than memory (non-amnestic MCI, or naMCI). People with both aMCI and naMCI can be further classified into single-domain vs multiple-domain MCI. Single domain aMCI is diagnosed when an individual experiences decline in only memory, whereas multiple domain aMCI is diagnosed when an individual experiences memory decline and also decline in at least one other cognitive domain. Single domain naMCI is diagnosed when the person experiences decline in one cognitive domain other than memory. Multiple domain naMCI is diagnosed when the person experiences decline in at least two cognitive domains, but not in

memory. These different subtypes suggest that MCI could result from various etiologies other than just AD.

Someone with aMCI is more likely to be in the prodromal stage of AD compared to the other subtypes, as people with aMCI typically progress to clinically probable AD at a rate of about 10 to 15% per year (Grundman et al., 2004). People with aMCI who are also positive for amyloid or tau (or a combination of the two) are more likely to progress to AD, and may be in the earliest symptomatic stages of AD (see Petersen, 2016 for review). Individuals with naMCI may be more likely to convert to dementia other than AD, such as vascular dementia or dementia with Lewy bodies (Tabert et al., 2006; see Petersen, 2016 for a review).

Rate of conversion to AD and AD-related pathology also differ between community vs clinical-based studies of people with MCI. In a community sample, people with MCI showed higher stable disease rates and reversion rates while also showing lower dementia and Alzheimer's disease rates than clinic-based samples (Hu et al., 2017). Additionally, community-based MCI samples have shown less severe AD pathology, more cerebral infarcts and more mixed-pathologies compared to clinic-based samples (Schneider et al., 2009).

Many MRI studies have reported declines in the thickness of grey matter in people with MCI compared to healthy older adults (Driscoll et al., 2009; Madden et al., 2012; Salami et al., 2012; Wang et al., 2009). Studies have also observed an association between structural changes and cognitive functioning in people with MCI. For example, deteriorations in the prefrontal cortex have been associated with declines in executive functioning and attention in people with MCI (Chao et al., 2009; Reinvang et al., 2012).

As mentioned, neuropsychological measures are a frequently used method for detecting cognitive decline. However, AD brain pathology may occur years before the neuropsychological

measures can reliably identify cognitive and behavioral impairment. Structural and functional magnetic resonance imaging (MRI & fMRI) techniques may also allow for the early detection of cognitive decline. They are, however, very costly and are not readily available in everyday medical practice. The use of neuroimaging methods as a biomarker for the early detection of dementia offers promise.

Electroencephalography (EEG) is an inexpensive, time-efficient, and non-invasive alternative to behavioral and imaging measures. It also has the advantage that it can be recorded in people with varying cognitive abilities regardless of native language (Rosazza & Minati, 2011). EEG methods might thus be well-suited for screening for early neurophysiological changes that may predict later cognitive decline in healthy older adults and people with MCI. The first study in this thesis examines resting-state EEG in cognitively healthy older adults and people with MCI.

Electroencephalography (EEG)

Human brain activity was first successfully recorded by a Swiss psychiatrist, Hans Berger (1929). The recording of electrical brain activity was called the electroencephalogram (EEG). It probably reflects the summation of activity of an enormously large population of cortical neurons. Berger also described different types of EEG activity, including alpha waves, consisting of a highly rhythmic 8-10 Hz frequency activity. It was not until the 1930s with the innovative multi-channel recording techniques employed by Adrian and Matthews (1934) that the alpha rhythm was confirmed. EEG activity was later sub-divided based on its frequency and amplitude using Greek letters into delta (0.5 – 4 Hz), alpha (8 – 12 Hz), and beta (12 – 30 Hz) activity representing slower to higher frequencies. A frequency band between delta and alpha was also included and labelled as theta activity (4 – 8 Hz) and was thought to originate in the thalamus

(Loomis et al., 1938). These authors were also the first to observe the slowing of the EEG frequencies and an increase in amplitude during the sleep onset period and the loss of consciousness. The different frequency bands reflect different levels of arousal. Slow-wave delta frequencies are often associated with drowsiness and the loss of consciousness, for example, during deep sleep. By contrast, beta frequencies are associated with alertness and cognitive activity. Alpha activity is frequently associated with relaxed wakefulness. When subjects are asked to relax and close their eyes, the rhythmic, synchronized alpha activity is especially apparent over posterior and occipital areas of the scalp. When the eyes are opened and the cortex is bombarded with visual imagery, alpha waves are said to be blocked and replaced by higher frequency desynchronized beta activity (Adrian & Matthews, 1934).

In human participants, the EEG is generally recorded from electrodes placed on the scalp. A standard EEG placement system, the International 10-20 system was developed in the 1950s (Jasper, 1958). This was later revised to a 10-10 system by the American Electroencephalographic Society (1994) to permit the inclusion of additional electrode placements. All electrical signals are recorded from two points. In a so-called monopolar recording, each of the EEG channels records the difference in the electrical activity between the scalp electrode and a common “reference” electrode. Ideally, the reference electrode should be inactive. In reality, no electrode site is truly inactive. Common references include the mastoid, the earlobes, and the tip of the nose, but all will record at least minimal brain electrical activity. Mastoid and earlobe references pick up some activity from both the auditory and visual regions. When interest is in auditory processing, the tip of the nose is often used as a reference. An average reference (the average of electrical activity from all electrode sites) has been recommended by some researchers. The advantage of its use is that the averaged reference

approximates a true zero voltage. A marked disadvantage of its use is that a very large number of electrodes need to be placed on regions including the upper, inferior, and lateral surface of the scalp but also the face and neck areas (Picton, 1995).

Older EEG systems employed passive electrodes. These consist of a metal disk, the electrode, attached to a junction box by a 1-2 meter cable and then relayed to the amplifier. The long cable also acts as an antenna picking up other electromagnetic signals or "artifact" within the testing room. This artifactual noise will summate with the true brain signal. An electrical signal is picked up from the point of least resistance. Thus, the impedance of the scalp needs to be reduced to a minimum (typically less than 5 kOhm) to increase the likelihood the signal originates at the scalp site and is not introduced in the long cable as an artifact. Low impedance at the scalp is accomplished by abrading and scratching the scalp, often with a blunted needle, in order to break through the tough keratinized epidermis and thus provide better contact between the electrode and the scalp. When many electrodes need to be placed, this procedure becomes very time-consuming and mildly uncomfortable for the participant. Newer systems often employ active electrodes. Rather than relaying the EEG signal to a distant amplifier via a long cable, the amplifier is built into the electrode enclosure. The advantage of this system is that impedance on the scalp can be relatively high (20-50 kOhms) overcoming the need for the abrasion of the skin.

Quantifying the EEG

It was not until the advent of modern, powerful computers that EEG signal quantification became possible. EEG is a complex signal containing many different frequencies. A Fourier Transform is often used to compute a spectrogram to decompose the EEG into its different sine and cosine wave frequency components. EEG recording is divided into a series of short, often 2 s, segments (or epochs), and a Fast Fourier Transform (FFT) is computed on each of the

segments. The EEG is comprised of signal and noise. This signal is assumed to be constant in each segment. Noise, by definition, is random. It is sometimes negative-going and sometimes positive-going. If noise is summed across an infinite number of segments, the average of this activity should be zero. The FFTs in the single segments are therefore averaged in order to reduce residual noise, allowing the signal to emerge.

Resting-state EEG in Aging and MCI

Resting-state EEG is often recorded in some clinical settings. Resting-state EEG has the advantage that no task demands are required from the participant. The participant is simply asked to relax, often with eyes closed during the brief recording period, usually lasting only a few minutes. Resting-state EEG also has the advantage that it can be recorded in people with varying cognitive abilities regardless of native language (Rosazza & Minati, 2011).

Increased age is associated with a generalized slowing of EEG activity (see Rossini et al., 2007 for review). Alpha activity has consistently been reported to decrease with increased age (Babiloni et al., 2006; Breslau et al., 1989; Fan et al., 2014; Polich, 1997; Sleimen-Malkoun et al., 2015; Vysata et al., 2014). Although research on alpha has been consistent, there is less consensus about how delta and theta activity change with increased age. While some studies have observed increases in delta and theta activity, others have shown decreases (Babiloni et al., 2006; Cummins & Finnigan, 2007; Finnigan & Robertson, 2011; Vlahou et al., 2014).

Studies have reported differences in resting-state EEG activity between healthy older adults and people with MCI. Research shows that people with MCI have lower alpha power than healthy older adults. A recent systematic review found that in four studies, alpha power was smaller in people with MCI compared to healthy older adults (Lejko et al., 2020). Theta power has been observed to be larger in people with MCI and AD compared to healthy older adults

(e.g., Babiloni et al., 2009; Grunwald et al., 2001). While some studies have found that people with MCI show higher beta power than healthy older adults (Fauzan et al., 2015; Huang et al., 2000), others have found smaller beta power in MCI compared to healthy older adults (Michels et al. 2017; Musaeus et al., 2018).

The duration of most resting-state EEG recordings in people with MCI has tended to be very short. This is disadvantageous because the extent to which noise is reduced in the EEG measurements is highly dependent on the number of segments that are available for averaging and this in turn is dependent on the length of the testing session. That is, when the total EEG recording is brief, only a limited number of segments will be available for analysis. A particular problem with recording EEG in older adults and people with MCI is the frequent occurrence of non-cerebral artifacts caused by body and eye movements and blinking. Segments containing artifacts are rejected from the averaging procedure, often leaving relatively few segments available for averaging. As a result, some studies rely on the analysis of less than 1 min of artifact-free data (Dierks et al., 1993; Dierks et al., 2000; van der Hiele et al., 2007). However, short EEG sessions continue to be used with older populations because of fears that participants will become drowsy or otherwise lose focus over longer testing periods.

This issue is not limited to electrophysiological measures, of course. Indeed, a serious issue with most neuropsychological and cognitive tasks is that they require attention to be maintained for a relatively long period of time. The need to sustain active attention is critical to many higher aspects of cognition. Success on some cognitive tasks will inevitably be affected if the participant is unable or unwilling to maintain attention (Buschman & Miller, 2010; Oberauer, 2019; Sturm et al., 1999). Several authors have noted that attentional control and the maintenance of attention to the task at hand may be problematic for older adults and people with

MCI (Bier et al., 2017; Braver et al., 2001; Salthouse, Atkinson, & Berish, 2003; Verhaeghen, 2011).

A second issue with behavioural tasks is that they provide only an indirect measure of cognitive processing. What researchers actually measure during cognitive tasks is performance. Performance is measured in terms of accuracy of decision-making and, at times, the speed of responding (reaction time, RT) to a stimulus. Performance on the task is then used to infer the extent of processing that led to a decision. Cognitive researchers using strictly behavioural measures cannot directly observe the processes that occurred that led to the response. Rather, they must infer these processes based on the performance measures. Many laboratories now employ event-related potential (ERPs) methods to monitor real-time processing prior to, at the time of, and following a behavioural response. ERPs are the minute changes in the ongoing electrical activity of the brain (the "EEG") that are elicited by external stimuli or internal psychological events. The ERPs and the EEG have both been used as predictors of changes that occur with aging and in people with MCI.

Event-Related Potentials (ERPs)

EEG activity can be used as a measure of the general state of arousal and alertness. It is not, however, a direct measure of cognitive processing, although it may be correlated with it. By contrast, the stimuli used in various cognitive tasks will elicit very small amplitude ERPs, embedded in the much larger amplitude ongoing EEG. These ERPs consist of a series of negative- and positive-going "components", thought to reflect different aspects of information processing.

ERP components are often classified as being either exogenous or endogenous (Donchin, Ritter, & McCallum, 1978; Sutton et al., 1965). Exogenous (exo=outside) components are

affected by the physical parameters of the stimulus (outside the body). The exogenous components are not affected by psychological or cognitive events. Thus, an increase in the intensity of an auditory stimulus might affect an exogenous component. On the other hand, a manipulation of a psychological parameter, such as the level of attention that the participant directs to the physical stimulus, will have little effect on the exogenous component. Such components would thus be described as occurring pre-attentively, prior to the effects of attention. They might also be described as occurring pre-consciously, prior to the participant being conscious (or aware) that a stimulus has been presented. Endogenous (endo = inside) components are minimally affected by the physic al parameters of the stimulus. They are affected by psychological factors (inside the body) such as the level of attention directed to the stimulus channel, memory comparison, and decision-making.

The detection of a rare target stimulus occurring among a train of frequently-occurring standard stimuli has been associated with the classic endogenous component, the P300, first reported by Sutton et al. (1965). If the participant fails to detect the target, or if they ignore the stimulus, a P300 is not elicited, even though the rarely-occurring physical stimulus has been presented. The exogenous ERP components that were elicited by the target would still be elicited even if the participant failed to detect it. If the features of the standard and target are reversed, the standard now becoming the rarely occurring target, its detection now elicits the P300. Thus, even though the physical features of the rare stimulus are very different, it still elicits the P300. In general, exogenous ERPs that mainly reflect sensory processing occur early in processing while endogenous ERPs that mainly reflect psychological events occur later. Some researchers thus classify ERPs according to their time (or latency) of occurrence as early (“fast”), middle, or late (“slow”) components.

Signal averaging

An external stimulus will elicit a series of ERP components (the signal) that are embedded within the ongoing, spontaneous EEG (the noise). The ongoing EEG reflects general, overall brain activity associated with perhaps other ongoing processing activities. The amplitude of the ERP components is almost always much smaller than that of the ongoing background EEG. With advances in early computing systems, a signal averaging method to reduce the amplitude of the background noise was described by Dawson (1954). The signal averaging procedure requires that the same stimulus involving the same sensory and/or cognitive processing be repeatedly presented. The continuous EEG is divided (or cut) into different segments (or epochs) for each stimulus presentation. The EEG segment usually begins prior to stimulus onset and often continues for several hundred ms after, depending on processing complexity. Importantly, it is assumed that the amplitude of the signal (the ERP component) is invariant. Its amplitude is the same and its peak latency does not vary with repetition of the stimulus. On the other hand, at any one time, the amplitude of the background EEG noise is, of course, random. The various segments are then averaged. The average of the signal is constant (thus, the average of +5, +5, +5….+5 is +5). With a sufficiently large number of stimulus repetitions, the average of a random event, that is at times, negative-going and at times, positive-going should tend to 0, allowing the constant ERP component to emerge.

The amplitude of the random noise decreases as a function of the square root of the number of trials (Picton et al., 1995). Thus, after 4 stimulus presentations, the amplitude of the background EEG is reduced by 2 (i.e., it is now ½ of its single-trial amplitude). The signal-to-noise ratio (S/N) increases as the number of stimulus repetitions increases. The amplitude of the signal will probably still be much smaller than that of the attenuated noise after 4 trials. If the

researcher wishes to again halve the amplitude of the noise (thus doubling the S/N ratio), the number of trials must increase 4 times (i.e., 16 trials). If after 16 trials, the S/N is not sufficient to allow the signal to emerge and the researchers want to double it (make the signal twice as large as the noise), 64 trial presentations will now be needed, not 32. A major problem with the use of ERP methodology is that the time required to collect a sufficient number of trials can be very long.

Despite the enormous power of signal averaging methods to allow ERP signals to emerge, there is a major limitation. When the amplitude of the ERP component is very small, the number of stimulus repetitions may need to be exceedingly high. This can be very time consuming. When attention to a task needs to be sustained for a long period of time, this may be particularly problematic. As noted earlier, healthy older adults and people with dementia may not be able to tolerate long-duration testing sessions. Thus, in a study that may last as long as two hours, the changes that are observed over time might not reflect differences in actual cognitive processes associated with the task, but rather processes associated with diminished attention. Some ERPs are, however, elicited independent of attention and regardless of what the participant is asked to do. Such ERPs are said to be elicited passively. Neither the direction nor the strength of attention will benefit from processing. One of the major issues with neuropsychological testing is that attention will act as a confound. The performance will decline if attention cannot be sustained for a long period of time. The sustaining of attention is a particular problem for healthy older adults and in people with MCI (Giambra, 1997; Saunders & Summers, 2011). In the various studies described in this thesis, participants will be asked to ignore the stimuli that elicit the different ERP components while they attend to a different task (watching a video).

Thus, whether the participant can sustain attention to the visual task or not is incidental. Variance in attention will have little effect on the ERPs being recorded.

Classification and labelling of components

Different methods for labelling ERP components have been developed. There is still no single standard method. One method labels the ERP component according to its polarity and latency. For example, the N100 is a negative deflection occurring approximately 100 ms post-stimulus presentation. This system can cause confusion when an ERP component's peak latency changes as a result of experimental manipulations. The classic P300 can occur as late as perhaps 500 ms when the rare target is difficult to detect. Should it now be labelled P500, even though it reflects the same cognitive process as the P300? To avoid this confusion, another naming convention ensued. The P300 is also labelled as the P3. This indicates that the component is positive-going and is a third major positive peak that occurs following stimulus onset. However, other issues arise with this naming convention. Other negative- and positive components may subsequently be discovered to occur prior to the occurrence of the component of interest. For example, the P3 was initially described as a positivity occurring after the P2. It was elicited when the participant actively detected a rarely occurring stimulus. This P3 did not occur when the participant ignored the stimuli. However, a positivity between the P2 and P3 was apparent when the rare stimulus was ignored. This positivity was therefore labelled as a P3a, the later positivity associated with the active detection of the rare stimulus, now being labelled as the P3b. Labelling components based on their functional significance has also been employed. In this thesis, a mismatch negativity (MMN) will be described. This component is a negative component that reflects the detection of a mismatch between the features of a current auditory stimulus and that which had been presented previously (Näätänen, 1990).

Näätänen's model of the auditory experience

The first study in this thesis examines the resting-state EEG. The remaining studies examine attention capture in healthy older adults and in people with MCI. In these experiments, the participant is engaged in a visual task (watching a video) and asked to ignore an auditory sequence. Some of the unattended, rarely occurring auditory stimuli are so potentially highly relevant that they interrupt the frontoparietal network controlling processing priorities. As a result, the processing of ongoing cognitive activity is halted and priority is switched to the processing of the unattended auditory input.

A Finnish cognitive neuroscientist, Risto Näätänen, has developed an elaborate model of the auditory experience (Näätänen, 1990; Näätänen et al., 2019). In this model, Näätänen describes three routes by which an observer can become conscious of auditory input. The first route involves active, top-down selective attention. The observer chooses to direct attention selectively to certain stimulus inputs that are deemed to be relevant, in order to become conscious of their content. At the same time, the observer chooses to ignore other irrelevant stimulus inputs. Processing of this irrelevant input must be inhibited or gated prior to its "reaching" consciousness. If this processing is successful, the observer will not be conscious of these unattended inputs. It is possible, however, that the observer will become conscious of certain highly relevant stimulus input that occurs within an unattended channel. This involuntary intrusion into consciousness involves bottom-up processing and has been described as attention capture or passive attention (James, 1890). In the Näätänen model, eventual consciousness of a highly relevant but to-be-ignored auditory input is possible following sufficient activation of two different systems, the transient and the change detection systems.

The transient detection system

The transient detection system detects brief (or transient) changes in an auditory stimulus, such as its onset or offset. Thus, the onset signals an abrupt change from the absence of an auditory stimulus to its occurrence. The offset signals the change from the occurrence of a stimulus to its abrupt absence. The output of this system is affected by two principal manipulations. The output will be higher when the initial energy (or intensity) of the stimulus is higher. The output also varies with the rate of stimulus presentation. The output is higher when stimuli are presented slowly compared to when they are presented rapidly. This output defines the level of salience of the stimulus input. An intense stimulus that occurs relatively often, or a weaker stimulus that occurs very rarely, would therefore both be particularly salient. The offset of an intense, long-duration continuous sound, such as the offset of a fire alarm, will also be very salient.

Determining the extent of processing of to-be-ignored stimulus input is methodologically difficult. The participant cannot be asked to behaviourally respond to a stimulus occurring in the unattended channel. To do so would result in contamination – attention is directed to the channel. The Näätänen model provides a means to quantify the extent of processing, the use of ERPs. The output of the transient detector system is reflected by the amplitude of an obligatory negative component, the N1, occurring around 100 ms post-stimulus (see Näätänen & Picton, 1987 for a review). It is followed by a later obligatory positivity, the P2, occurring around 180 to 200 ms. N1 and P2 are often considered together because manipulations that affect N1 also often affect P2. N1 is maximum in amplitude over fronto-central areas. It inverts in amplitude at the mastoids when a nose reference is used. The N1 consists of sub-components. What was initially labelled as N1 is also labelled as an N1b, maximum, as mentioned, over fronto-central sites. If N1 is also

recorded at temporal sites over the auditory cortex, a negativity occurring before the N1b is observed and this is followed by a later negativity. These temporal negativities are labelled as N1a and N1c**.** A positivity, Ta, is often observed to occur between the N1a and N1c (Connolly, 1993; Matsuda, Igarashi, & Itoh, 2019; Näätänen & Picton, 1987).

Because N1 reflects the output from the transient detector system, its amplitude is affected by the two major experimental manipulations. As the intensity of the auditory stimulus increases, the amplitude of N1 becomes larger. It has also long been shown that the amplitude of N1 progressively increases as stimuli are presented more slowly (Davis et al., 1966; Ritter et al., 1968; Nelson & Lassman, 1968; Fitzgerald & Picton, 1981; Steiner et al., 2014). P2 amplitude is also affected by both the intensity of the auditory stimulus and its rate of presentation (Alcaini et al., 1994; Budd et al., 1998; Muller-Gass et al., 2008). The amplitude of N1 can therefore be employed as a measure of the extent of salience of the encoded stimulus.

The operations of the transient detection system are claimed to function pre-attentively and automatically, prior to the effects of attention (Näätänen, 1990). Attention has often been shown to have little effect on the N1. The N1 will be elicited to *any* perceptible auditory stimulus, even if the participant is not attending. In some studies, having very specific stimulus presentation conditions, N1 has been shown to become larger when attention is directed to the auditory channel (Picton & Hillyard, 1974). This finding is the so-called "N1 effect". Näätänen (1982) insists that the effect of attention is not on the N1 per se. Rather,). In selective attention paradigms, the participant is asked to attend to stimuli occurring in one channel but ignore stimuli occurring in another channel (perhaps, attend to stimuli in the right ear and ignore the stimuli in the left ear). The PN is larger when an auditory stimulus occurs in an attended channel compared to when it occurs in an unattended channel. When the stimuli in attended and

unattended channels are physically very different, discriminating between the two channels is relatively easy. As a result, the PN occurs early, at about the same time as the N1. The N1 and PN therefore overlap and summate.

What is thus observed in the recording is that a negativity occurring at about 100 ms is larger when the stimulus was attended compared to when it was ignored. This 100 ms negativity is not however an N1 per se. Rather it is a composite N1+PN. When the stimuli in the attended and unattended channels are physically quite similar, discriminating between the two channels is more difficult. The PN then occurs later and the ERP waveform displays two negative peaks, the N1 at 100 ms and the later negativity, the PN. Even if it is admitted that the effect of attention is exclusive to N1, this effect can only be observed under very specific, optimal conditions, when stimuli are presented very rapidly (faster than every 1 s) and at relatively moderate intensities (Hansen & Hillyard, 1988; Schwent, Hillyard, & Galambos, 1976; Woldorff, 1995). Care should, however, be taken to assure that the participant is not drowsy. Although N1 does not appear to be affected by attention, its amplitude gradually decreases during the loss of consciousness. N1 is absent during definitive unconscious states such as natural sleep and coma (Campbell & Colrain, 2002; Connolly et al., 2019; Fischer et al., 1999). In studies within this thesis, alert wakefulness will be assured by having participants engage in a task, watching a silent video requiring the reading of sub-titles.

In the Näätänen (1990) model, sufficiently high activation of the transient detector system will result in an interrupt signal being sent to the frontoparietal network controlling processing priorities. If the size of the interrupt signal is sufficiently large, attention may be switched from ongoing cognitive activities and priority will be given to the processing of the intruding/salient stimulus event. A later positivity, the P3a, peaking between 200 and 300 ms, is

thought to reflect processes associated with the switching of attention (Escera et al., 1998; Masson & Bidet-Caulet, 2019). Some researchers have suggested that the P3a better reflects a precursor process that may result in the switch that eventually leads to conscious awareness of the unattended input (for reviews, see Parmentier, 2014; Wetzel, Schröger, & Widmann, 2013).

The P3a is often elicited in oddball paradigms by a deviant representing a large change from a frequently occurring standard stimulus. There is evidence that a P3a can also be elicited by a single, rarely presented stimulus. When the rate of stimulus presentation is very slow (e.g., > than every 10 s), N1 and P2 become very large and their peak latencies are delayed by about 20–30 ms (Alcaini et al., 1994; Budd et al., 1998; Muller-Gass et al., 2008). Berti et al. (2013) questioned whether this P2 might be better described as a P3a. The Berti study required subjects to decide whether a visually presented number was odd or even. On 13% of trials, the visual stimulus was preceded by an irrelevant auditory stimulus. Performance on the visual task deteriorated in these trials, compared to trials in which no auditory stimulus preceded the visual stimulus. This finding suggested that attention had been switched from the processing of the visual task to the processing of the auditory stimulus, resulting in a deterioration in performance on the visual task. The single auditory stimulus elicited an N1 followed by a large positivity at about 200 ms. This could be a P2. On the other hand, the P2 can occur at about the same latency as the P3a. The scalp distribution of P2 and P3a are also similar, being maximum over central regions of the scalp. In the Berti study, the positivity at 200 ms was associated with the switching of attention, a process related to the P3a rather than the P2.

The change detector system

A second system, the change detector system, detects changes to any feature of a frequently occurring, homogenous stimuli, such as its pitch, duration, or location. The transient

detector system is specialized for the detection of a specific change, an increase in intensity. Because the change detector system detects a change to any feature, it will also detect changes to the intensity of the frequently occurring stimulus. The change detector system is often studied using an oddball paradigm, consisting of a frequently occurring standard and a rarely occurring deviant stimulus. The deviant is created by changing at least one feature of the standard. In the Näätänen model, the features of the encoded standard are said to be stored in a brief-lasting sensory memory. The features of the incoming stimuli are then compared to the features of those stored in sensory memory. If the features of the incoming stimuli do match those held in sensory memory, then the memory is strengthened. However, if they fail to match, change is detected[1]. The operations of the change detection system are also thought to occur automatically independent of attention. The output of the change detector system varies directly with the extent of change. A large physical difference between the standard and deviant will result in high output. The output of this system can be monitored by a fronto-central maximum negativity, the mismatch negativity (MMN), peaking from 100 to 200 ms following stimulus onset (Näätänen et al., 2019). Both the standard and deviant elicit the obligatory N1-P2. The deviant also elicits the MMN. The MMN is best-observed in a difference wave computed by subtracting the standard ERP from the deviant ERP. The subtraction process will remove processing that is common to both the standard and deviant (for example, the N1 and P2) leaving processing that is unique to the deviant (for example, the MMN).

[1] A more recent model maintains that the MMN is elicited by a mismatch between the current auditory input and the predictions formed on the basis of the pattern or rules that define the recent auditory sequence. It is this predictive pattern that is stored in memory. A violation of the pattern is automatically detected, and the MMN is elicited (Näätänen, Kujala, & Winkler, 2011; Näätänen et al., 2019; Winkler, 2007; Winkler, Denham, & Nelken, 2009). The repeating, homogenous standard stimulus in the oddball sequence is thus a special case of acoustic regularity. A rule is formed that a standard follows a standard. The occurrence of a deviant violates this rule.

In the oddball paradigm, both the standard and deviant stimulus will also elicit the N1. As mentioned, a deviant representing an increase in intensity from the standard does signal a change from the acoustic past, and it will elicit a large MMN. However, because its intensity is higher, the deviant will also elicit a larger N1 than the standard. In this instance, the MMN will occur at about 100 ms, because the extent of deviance is large. The N1 to the deviant will also occur at about 100 ms. The N1 and MMN also share a common fronto-central scalp distribution. In the deviant-standard difference wave, the N1 will not be removed because it is larger for the deviant than the standard. The difference wave will therefore consist of two negativities, the N1 and the MMN. Because of the temporal and spatial overlap, the two negativities elicited by the deviant will summate. This composite N1+MMN negativity occurring to the deviant is often called a deviant-related negativity (DRN) to distinguish it from a true MMN.

The output of the change detector system, as measured by the MMN/DRN, varies directly with the extent of change. The amplitude of the MMN/DRN provides a measure of the extent of salience of the deviant stimulus. If this output is sufficiently high, a P3a will be elicited. Again, the interruption of the frontoparietal system may result in a switch of attention from ongoing cognitive tasks. This results in the priority of processing being now given to the unattended auditory input.

While almost any perceptible deviant will elicit a MMN, only a small number of these will also reliably elicit a P3a. There has been much discussion of the types of deviants that will do so. In the classic Näätänen model, any deviant stimulus can elicit a P3a providing it represents a large degree of change. Some researchers question this. Some suggest that only a change reflecting an increase will elicit a P3a. Thus, only through sufficient activation of the transient detector system will a P3a be elicited. Rinne et al. (2006) employed an oddball paradigm in

which the deviant was created by decreasing or increasing the intensity of the standard. Because both the decrement and increment deviants represent a change from the standard, they both will be detected by the change detector system. The intensity of the increment deviant is higher for the deviant than the standard. As such, the output from the transient detector system will also increase when the increment is presented. On the other hand, the intensity of the decrement is lower than that of the standard. The presentation of the decrement should therefore result in an output in the transient detector system that is lower than that for the standard. In the Rinne et al. study, both the decrement and increment elicited a MMN. However, a P3a was only elicited by the increment deviant. The decrement did not elicit a P3a, presumably because the output from the transient detector system was insufficient.

Muller-Gass et al. (2007) also employed decrements and increments as deviants. Their decrement, however, reflected a greater degree of change than that used by Rinne et al. (2006). The increment again elicited a large P3a. The decrement elicited a smaller P3a. Thus, a very large output from the change detection system may result in the P3a being elicited, but its amplitude will be small. Shestopalova et al. (2018) have also observed a large P3a following the presentation of an increment. So powerful is this effect that an increment will even elicit a P3a during an unconscious state, natural sleep, while a decrement will not (Macdonald, Jamshidi, & Campbell, 2008).

Highly novel deviant sounds such as a white noise burst, or an environmental sound have also been shown to elicit a large P3a. Tavakoli and Campbell (2016) employed a multi-deviant paradigm including changes to the frequency, duration, and intensity of the standard. They also included white noise and environmental sound deviants. Only the latter elicited a large P3a. The spectrum of these deviants varies over the duration of the stimulus and at times, their intensity

increases. Tavakoli and Campbell (2016) suggested that the elicitation of the P3a by these deviants was probably because they were associated with a large output from the transient detector system. In brief, it would appear that attention capture largely occurs as a result of sufficient activation of the transient detector system.

Aging and auditory ERPs

N1-P2

Few studies have examined how the N1-P2 changes with aging. In these studies, stimuli have usually been presented relatively rapidly, every 1–3 s. Most of these studies have failed to find N1 or P2 differences between younger and older adults, although a few have reported larger responses for younger adults while a few others have reported larger responses for older adults (Bertoli, Smurzynski, & Probst, 2005; Čeponiene et al., 2008; Harkrider, Plyler, & Hedrick, 2005; McCullagh & Shinn, 2013; Pfefferbaum et al., 1980; Stothart & Kazanina, 2016). Marked differences in the features of the stimulus (e.g., intensity, frequency, duration), whether its frequency spectrum is simple (e.g., pure tones) or complex (e.g., speech), and the presence or absence of background acoustic noise could account for some of these differences. It should also be noted that when differences have been observed, they tend to be small, although they may be statistically significant.

As mentioned previously, the amplitude of N1-P2 increases dramatically when stimuli are presented very slowly. Their peak latency is also delayed. Only a single study has examined the effects of the rate of stimulus presentation in healthy older adults. Berti et al. (2017) presented stimuli relatively rapidly (either every 0.5, 1, or 3 s) or very slowly (every 10 s). Participants were presented with an oddball paradigm in which a frequently occurring standard tone was presented on 90% of trials, and a rare novel environmental sound was presented on

10% of trials. Participants were asked to "passively listen" to the auditory stimuli while reading a book. The amplitudes of N1 and P2 to the standard stimulus did not differ between younger and older adults for the faster rates of presentation. On the other hand, when stimuli were presented very slowly, the amplitudes of the standard N1 and P2 were much larger for younger adults compared to older adults. This study suggests that large age differences in N1 and P2 will only be observed when the output of the transient detector system is particularly high for young adults (e.g., when stimuli are presented very slowly). These results suggest that the computation of the saliency of a very rarely presented auditory stimulus within the transient detector system may be dysfunctional in older adults. In younger adults, dramatically different saliency levels are computed for rapidly and very slowly presented unattended auditory stimuli. In older adults, the saliency levels are, however, computed to be quite similar for the same rapidly and very slowly presented stimuli. A problem with the Berti et al. study is the use of an oddball paradigm. Processing of the standard might have been influenced by the presence of the deviant. In the present thesis, an experiment was designed in which a single stimulus was presented either very slowly or very rapidly. The use of a single stimulus method would result in output from a single system, the transient detector system, and thus remove any possible contaminating influence from the change detector system.

MMN/DRN and P3a

Findings regarding how the amplitude of the MMN/DRN changes with aging are mixed. Initial studies observed that frequency deviants elicited MMN amplitudes that did not differ in younger and older adults (Gaeta, Friedman, & Cheng, 2001; Verleger et al., 1991). Tsolaki et al. (2015) employed a larger frequency deviant and did observe a smaller MMN in older adults compared to younger adults. The MMN was also found to be smaller in older adults following a

duration deviant, or a delay in the deviant's onset time (Kiang et al., 2009; Nowak et al., 2016). Morrison et al. (2019) observed a decreased DRN in older compared to younger adults when an increase in intensity (i.e., an increment) was used as a deviant. However, other studies have reported no differences in the amplitude of the MMN between younger and older adults when it was elicited by either a duration (Correa-Jaraba et al., 2016; Ruzzoli et al., 2012) or a decrement (Morrison et al., 2019; Tsolaki et al., 2015).

Results regarding how the P3a differs between older and younger adults has been consistent. It has often been studied using oddball paradigms. When an environmental sound has been used as a deviant, it elicits a large P3a that is much attenuated in older compared to younger adults (Berti et al., 2017; Correa-Jaraba et al., 2016; Tusch et al., 2017). Morrison et al. (2020) employed a multi-deviant paradigm that included six deviants. Two of these deviants, an environmental sound and a white noise, burst elicited a large P3a in younger adults that was much attenuated in older adults. In the Morrison et al. (2019) study, the increment deviant elicited a large P3a in younger adults, which was much attenuated in older adults. This finding suggests that in older adults, the frontoparietal network is less able to switch processing priorities from an ongoing cognitive task to the processing of the intrusive, but unattended auditory stimulus.

MCI and auditory ERPs

N1-P2

A limited number of studies have examined the N1 and P2 in people with MCI (for a review, see Morrison et al., 2018). Most studies have not found differences in the amplitude of N1 and P2 between healthy older adults and people with MCI when stimuli are presented relatively rapidly (Bidelman et al., 2017; Buján et al., 2019; Golob et al., 2002; Lai et al., 2010;

Lister et al., 2016). Some studies have reported a somewhat larger N1 or a smaller P2 in people with MCI, at least in certain conditions (Buján et al., 2019; Golob et al., 2007; Irimajiri, Golob, & Starr, 2005; Lister et al., 2016). It should be noted that Irimajiri et al. (2005) observed differences only when the auditory stimuli were presented at a slower (every 1.5 s), but not when they were presented rapidly (every 0.5 s). The N1 and P2 differences between healthy older adults and those with MCI may thus be dependent on stimulus parameters (e.g., rate of stimulus presentation). Nevertheless, experimental parameters again tend to vary widely across studies, making generalization difficult.

MMN/DRN and P3a

Similar to the N1-P2, only a limited number of studies have examined the MMN/DRN in people with MCI. The MMN/DRN results are also inconsistent. Again, stimulus parameters vary widely. Mowszowski et al. (2012) noted that the MMN elicited by an increase in the duration of the standard was smaller in amplitude at temporal sites in people with MCI compared to age-matched healthy older adults. On the other hand, Ruzzoli et al. (2016) reported a preserved MMN at temporal sites in people with MCI but a smaller MMN at frontal sites following the presentation of shorter duration deviants. Ji et al. (2015) presented deviants that were increased in intensity. The amplitude of the MMN did not, however, significantly differ between people with MCI and healthy older adults. Lindin et al. (2013) employed highly novel environmental sounds as deviants. In this study, the MMN was smaller in people with MCI but only for those between 50 and 64 years of age and not for those older than 65 years of age.

The P3a has not often been studied in people with MCI. Cecchi et al. (2015) employed an active oddball sequence consisting of a frequently occurring standard, a rare pure tone target requiring a manual response, and a rare white noise burst to which the response was to be

withheld. The white noise burst elicited a P3a in healthy older adults; its amplitude was smaller in people with mild AD. The P3a is typically studied when participants are asked to ignore the auditory channel (i.e., the unattended auditory deviants thus capture attention). The use of an active task by Cecchi et al. is therefore problematic. The participants needed to attend to the auditory sequence and to actively classify the noise burst as being a non-target, in order to determine they were not to respond. As such, the occurrence of a P3a would not have been associated with switching of attention from other processing priorities. Correa-Jaraba et al. (2018) examined the influence of auditory deviants on a visual working memory task. An irrelevant auditory stimulus preceded the visual stimulus. On rare trials, a novel environmental sound deviant was presented. A P3a was elicited by the environmental sound, and it was larger in some people with MCI relative to healthy older adults. The extent to which the rare novel stimulus was irrelevant to the task can be questioned. For example, Parmentier (2014) and Masson and Bidet-Caulet (2019) indicate that in auditory-visual paradigms, participants can use the auditory stimulus as a warning signal and, as such, alert them to the subsequent visual stimulus. It is thus possible that people with different subtypes of MCI use compensatory strategies differently, actively attending to the auditory stimuli in an attempt to alert them to the subsequent visual stimulus.

The present thesis

Cognitive and neuropsychological studies have described declines in various cognitive abilities in older adults and in people with MCI. A problem with almost all cognitive tasks is that they require attention to be maintained for a relatively long period of time. The sustaining of attention may be difficult for cognitively healthy older adults but may be especially problematic for people with MCI. The present thesis consists of four studies. Importantly in each study, an

attempt is made to avoid the confound of an inability to sustain attention by recording EEG and ERPs passively, without the need for active attention.

The first study in this thesis compares the resting-state EEG of cognitively healthy older adults and people with MCI. The recording of the resting-state EEG is typically carried out while the participant is at rest and not actively attending to any task. Previous research indicates that lower frequencies such as theta activity may be more apparent in the resting-state EEG of people with MCI than in cognitively healthy older adults. The reliability of these findings can however, be questioned because the duration of the recordings has often been very short, often lasting from 1-3 minutes and perhaps as long as 5 minutes. Longer recording times would provide more reliable data. Authors have, however, cautioned that longer recording sessions may be affected by increasing drowsiness. There is little evidence, however, to support this hypothesis. The frequency spectrum of the EEG is often analyzed using FFT methods. The FFT is computed on very short duration segments of the EEG, typically lasting 2 s. The duration of the segment will affect frequency resolution by a factor of $1/T$, where T is the duration of the segment in seconds. A 2-second segment will thus have a low-frequency resolution of 0.5 Hz. A 0.5 Hz frequency is critical for the identification of drowsiness. The use of longer 8 s segmentation will provide a low frequency resolution of 1/8 Hz (0.125 Hz). The purpose of the initial study will therefore be to compare the effects of different recording durations and analysis techniques on drowsiness in healthy older adults and in people with MCI.

The following three studies employ ERP methods to measure the *passive* processing of unattended, but potentially highly relevant, auditory input in younger and older adults, and in people with MCI. Cognitive deficits in older adults and in people with MCI is often assessed using a battery of neuropsychological and cognitive tasks. Performance on almost all of these

tasks will inevitably be affected by the participant's ability and willingness to maintain attention (Sturm et al., 1999; Buschman and Miller, 2010; Oberauer, 2019). Attentional control and the maintenance of attention may be a challenge for older adults, and particularly for people with MCI (Saunders and Summers, 2010). A good deal of early processing of sensory input is said to be automatic; that is, it is completed whether or not the participant attends to the sensory channel. In the three ERP studies within this thesis, participants will be asked to ignore the auditory stimuli. Thus, whatever differences are observed between older adults and people with MCI cannot be attributed to the fact one group was less able to sustain attention than another. The participants will, nevertheless, be required to be awake and alert. This will be assured by having participants engage in a visual task (i.e., watching a sub-titled silent video).

The purpose of these studies is to examine differences in the processing of unattended stimulus input between younger and older adults and subsequently between cognitively healthy older adults and people with MCI. While the stimuli are to-be-ignored, they are potentially highly relevant and may be critical for survival. Such stimuli have often been reported to result in attention capture in younger adults, resulting in a switching of processing priorities. The studies are pertinent to an inhibition theory of aging (Hasher and Zacks, 1988) which proposes that older adults are less able than younger adults to inhibit the processing of irrelevant stimulus input. Performance on a current task-at-hand will therefore deteriorate more in older adults than younger adults upon presentation of the irrelevant stimulus. This deterioration is because processing of the irrelevant stimulus input is less likely to be inhibited in the older adults than younger adults. As a result, fewer resources for the processing of the task-at-hand will be available, resulting in poorer performance. What is novel about this thesis is that the unattended stimulus input may be potentially highly relevant. As such, processing should not be inhibited.

The second study of this thesis presents a single homogenous auditory stimulus that is to be ignored. The onset of the single stimulus will thus be detected exclusively by the transient detector system, claimed by some authors to be much more involved in attention capture than the change detection system. Most previous studies of the processing of unattended auditory stimuli in older adults and in people have examined processing within the change detection system. Very few have examined processing within the transient detector system. In this study, the rate of presentation of the single stimulus will be manipulated. A very rarely occurring stimulus is highly salient. The output of the transient detector system is very large when stimuli are presented very slowly. In older texts, this was described as the dripping faucet effect. A dripping faucet will intrude into consciousness because the drip occurs infrequently, even though the drip may not be particularly loud. The effects of very slowly presented stimuli have been examined in younger adults but remain relatively unexplored in older adults. The second study, therefore, compares the processing of rapidly and very slowly presented stimuli in younger and cognitively healthy older adults.

Study 3 is a follow-up to the second. The results of the second study indicated that large N1 and P2/P3a differences were apparent between younger and older adults, but only when stimuli were presented very slowly. This suggests that in healthy older adults, there may be deficits in the operations of the salience network and frontoparietal network in determining the priority of processing. Chand et al. (2017) found that these deficits may be more apparent in people with MCI than healthy older adults. The third experiment, therefore, examines the effects of the rate of stimulus presentation in people with MCI compared to cognitively healthy older adults.

The P3a has been most often elicited in oddball paradigms. The fourth study, therefore, employs an oddball paradigm to examine the effects of different types of deviants on attention capture in people with MCI. Two experiments were run. Deviant stimuli known to elicit a large P3a were presented. In the first experiment, the deviants included a decrement and an increment. The increment has previously been demonstrated to elicit a large P3a. In the second experiment, six different deviants were presented among the standards. Two of these deviants, a white noise burst, and an environmental sound have also previously been demonstrated to elicit a large P3a.

Study 1

Study 1 was published in *Clinical EEG and Neuroscience,* and is formatted in accordance with the requirements of this journal.

Kamal, F., Campbell, K., & Taler, V. (2020). Effects of the Duration of a Resting-State EEG Recording in Healthy Aging and Mild Cognitive Impairment. *Clinical EEG and Neuroscience*, https://doi.org/10.1177%2F1550059420983624.

A limited number of studies have recorded the resting-state EEG in people with MCI. Most studies use very short recording times, lasting only a few minutes. Short recording times are, however, problematic. The EEG signal consists of signal (true EEG) and noise. The influence of noise will be higher in short than in long recordings. The use of long duration recording times is also problematic. Researchers warn of the risk of drowsiness in longer-duration recordings. The drowsiness hypothesis has not been empirically tested. The EEG can be quantified by computing the power within different frequencies using a fast Fourier transform (FFT). The EEG recording is often divided into a series of 2 s segments and an FFT is computed on each segment. The FFTs across the different segments are then averaged. Noise will be reduced more when the EEG recording is longer. The initial study therefore examines the effects of the length of the EEG resting-state recording on drowsiness in healthy older adults and in people with MCI.

Abstract

Introduction. The recording of resting-state EEG may provide a means to predict early cognitive decline associated with mild cognitive impairment (MCI). Previous studies have typically used very short recording times to avoid a confound with drowsiness that may occur in longer recordings. The effects of a longer recording have not however been systematically examined.

Methods. Eyes-closed resting-state EEG activity was recorded in 40 older adult participants (20 healthy older adults and 20 people with MCI). The recording period was a relatively long 6 minutes, divided into two equal 3-minute halves to determine if drowsiness will be more apparent as the recording progresses. The participants also completed standardized neuropsychological tasks that assessed global cognition (Montreal Cognitive Assessment) and memory (California Verbal Learning Test, Second Edition). A spectral analysis was performed on both short (2 seconds) and long (8 seconds) segments in both 3-minute halves.

Results. No differences in power density for any of the EEG frequency bands were found between the 2 halves of the study for either group. There was little evidence of increased drowsiness in the second half of the study even when frequency resolution was increased with the 8-second segmentation. Theta power density was overall larger for people with MCI compared to healthy older adults. A negative correlation was also observed between theta power and global cognition in healthy older adults.

Conclusions. The present results indicate that longer resting-state EEG recording can be reliably employed without increased risk of drowsiness.

Introduction

A rise in life expectancy has led not only to an increase in the aging population but also to a growing number of older adults with cognitive decline, including mild cognitive impairment (MCI) and Alzheimer's disease (AD). Much of the current research on dementia, including AD, attempts to detect cognitive and memory decline, before behavioral and cognitive symptoms are apparent.[1] Intense research interest has focused on MCI, in which cognitive impairment is observed, but is not severe enough to warrant the diagnosis of dementia.[2] MCI may represent a transitional stage between healthy aging and AD,[3] and is considered a risk factor for the development of AD.[4] Finding a cost-effective, widely available, and reliable method that can detect early, subtle differences between healthy older adults and people with cognitive impairment is urgently needed.

Neuropsychological measures are the most commonly used method for detecting cognitive decline. However, AD brain pathology may occur years before the neuropsychological measures can reliably identify cognitive and behavioral impairment.[1] Structural and functional magnetic resonance imaging (MRI and fMRI) techniques may allow for the early detection of cognitive decline. They are, however, very costly and are not readily available in everyday medical practice. The use of neuroimaging methods as a biomarker for the early detection of dementia offers promise.

Resting-State EEG

Electroencephalography (EEG) is an inexpensive, time-efficient, and noninvasive alternative to behavioral measures.[5] It also has the advantage that it can be recorded in people with varying cognitive abilities regardless of native language.[6] EEG methods might thus be readily used to detect early neurophysiological changes that may predict later cognitive decline in older adults.[7]

Initial studies have indeed reported differences in EEG oscillations between healthy older adults and people with MCI.[8-11]

EEG activity is often recorded during a so-called resting-state while the individual is awake and resting. The EEG consists of a series of frequency bands commonly labelled as delta, theta, alpha, beta, and gamma, representing lower to higher frequency activity. In the resting-state EEG, higher theta and lower alpha activity have been associated with both healthy aging and AD.[12-14] Some studies have found that people with MCI show higher beta power than healthy older adults[15,16] although others have failed to observe this beta power difference.[17]

An association between resting-state EEG and performance on different cognitive tasks has also been observed.[18-21] Higher alpha and theta power during rest have been shown to be associated with decreased scores on cognitive measures, including the Mini-Mental State Examination (MMSE) and memory performance.[20-23] However, conflicting results have also been reported. For example, some researchers have found that posterior alpha power is positively associated with measures of global cognition.[24,25]

Duration of Recording

A possible reason for these conflicting findings is that the methods employed to record EEG vary across studies. In particular, the duration of the recording in different studies varies between 1 and 5 minutes.[22,26-29] An EEG recording consists of both signal and noise. The EEG recording is divided into a series of short, often 2-second, segments (or epochs) and a fast Fourier transform (FFT) is computed on each of the segments. These FFTs are then averaged in order to reduce residual noise, allowing the signal to emerge. The extent to which noise is reduced is highly dependent on the number of segments that are available for averaging. When the total EEG recording is brief, only a limited number of segments will be available for the FFT

analysis. A particular problem with recording EEG in older adults and in clinical populations is the frequent occurrence of noncerebral artifact. Segments containing artifact are rejected from the averaging procedure, often leaving relatively few segments available for averaging. As a result, some studies are left with less than 1 minute of artifact-free data for their analyses.[22,30,31]

Random variability from residual noise in a few segments then becomes problematic. An advantage of longer recording times is that more segments will be available in the averaging process, reducing the effects of variability in the data.[24] Despite this benefit, the use of longer recording times is often discouraged because of the risk of increased drowsiness.[22,24] This perceived risk has, however, not been verified in people with MCI or cognitively healthy older adults. Additionally, the usual subdivision of the EEG recording into 2-second segments may limit the extent to which drowsiness and a resulting increase in low-frequency delta activity can be quantified. The duration of the segment will affect frequency resolution by a factor of $1/T$, where T is the duration of the segment in seconds. A 2-second segment will thus have a low-frequency resolution of 0.5 Hz. A longer duration segment will provide a better low-frequency resolution but will come at a cost—fewer segments will be available for averaging.

The Present Study

The purpose of the present study was to examine differences in EEG activity in healthy older adults and people with MCI during early and late portions of a longer resting-state recording. If increased drowsiness occurs as the duration of the recording becomes longer, an increase of low-frequency EEG activity should be observed, particularly in the delta band. Previous studies have demonstrated that with shorter duration recordings, people with MCI display higher theta spectral power than healthy older adults. In addition, studies have noted that both theta and alpha power may be correlated with global cognition (e.g., MMSE) and memory (California Verbal

Learning Test, Second Edition [CVLT-II]). We examine whether these correlations are replicated when the EEG is recorded over a longer period of time.

Methods

Participants

Forty-four participants volunteered for this study: 22 healthy older adults (OA) (11 women; mean age 71.81 ± 4.33 years) and 22 OA diagnosed with MCI (9 women; mean age 75.61 ± 6.71). OA were recruited through word-of-mouth and announcements posted at community centers. Participants with MCI were recruited from a memory clinic where they had received a diagnosis of MCI. These participants were diagnosed with MCI by a physician with expertise in neurodegenerative conditions, based on clinical history and a neurological exam. Participants were not included if their cognitive decline was thought to be related to other comorbidities, and they underwent a computed tomography scan and blood work to rule out reversible causes of cognitive impairment. All participants completed an over-the-phone health questionnaire to ensure that they were free from any history of head injuries and neurological and psychiatric conditions. This study was approved by the University of Ottawa and Bruyère Research Institute ethics boards. Participants provided informed written consent prior to starting the study and an honorarium was given as compensation for participation.

Procedure

Participants initially completed neuropsychological tasks (Montreal Cognitive Assessment [MoCA] and CVLT-II). This was then followed by a resting-state EEG recording during which participants were instructed to sit in a relaxed position with their eyes closed.

Neuropsychological Testing

The MoCA was used to screen for cognitive decline and assess global cognition.[32] Most studies examining the relationship between resting-state EEG and cognition have used the MMSE as a measure of global cognitive decline. However, the MMSE is not designed to detect MCI, and specificity and sensitivity are low for MCI.[20] The MoCA, in contrast, is designed to detect MCI.[32] CVLT-II[33] was used to assess memory function. The CVLT reliably differentiates memory performance in healthy older adults compared to people with MCI.[34] In the CVLT-II task, individuals are asked to remember a list of 16 words that are presented to them in 5 trials. They are asked to recall the words after each of the 5 trials, then again following a brief distractor task 5-minute delay (short-term recall) and finally following a 20-minute delay (long-term recall). For the current study, the number of items recalled following the 5-minute delay (CVLT-II short delay: cued recall and free recall) was summed and included as a measure of short-term memory (STM). The total number of list items recalled after the 20-minute delay (CVLT-II long delay: cued recall and free recall) was summed and used as a measure of long-term memory (LTM).

EEG Data Recording and Analysis

EEG was recorded from 31 active silver–silver chloride electrodes, attached to an electrode cap (Brain Products GmbH), placed according to the international 10-20 system. In addition, an electrode was placed on the infraorbital ridge of the left eye to record vertical eye movements. A reference electrode was placed on the nose for all electrode placements. Although active electrodes were used, interelectrode impedance was kept below 20 kΩ to minimize noise artifact. Participants were asked to keep their eyes closed and to refrain from movement. This

was carefully monitored by a research assistant in the same room as the participant. The EEG was continuously recorded for 7 minutes. The EEG was sampled at a rate of 500 Hz.

Each of the datasets was visually examined for excessive noise. If more than 25% of the recording was determined to be noisy, the entire dataset was rejected. Data from 4 participants (2 from each group) were excluded on this basis. Independent component analysis was subsequently used to identify and correct eye movement and blink artifact occurring independent of EEG activity. This correction procedure requires the computation of both vertical and horizontal eye movements. A vertical EOG was computed by subtracting FP1 and infra-orbital ridge activity. Horizontal eye movements are often computed by subtracting activity at nearby lateral frontal electrodes sites; activity is opposite in polarity at left and right sites.[35,36] Horizontal eye movements were thus computed by subtracting F7 and F8 activity. Eye movement artifacts were then partialled out of the EEG. A 50-Hz low-pass filter and a 0.07-Hz high-pass filter were then applied to the corrected EEG data.

The first 6 minutes of recording was divided into two equal 3-minute halves. Each 3-minute interval was subdivided into much shorter segments. In one analysis, the segment had a duration of 2.048 seconds and in another, the duration was 8.192 seconds. There was no overlap between segments. The longer 8-second duration has better low-frequency resolution than the 2-second segment, but fewer segments will be available for averaging. Thus, for each 3-minute interval, 22 segments were available for the 8-second segments while 90 segments were available for the 2-second segments. Therefore, data were analyzed from 20 healthy older adults (OA) (10 women) and 20 older adults diagnosed with MCI (9 women).

The individual segments from each of the remaining participants were subsequently examined for artifact. Any segment containing EEG activity exceeding ±100 μV was considered

to contain artifact and was rejected from the averaging procedure. Such rejection was rare because very noisy data sets had already been identified visually and rejected from further analysis. In addition, the data previously had been corrected for eye movement and blink artifact. The number of segments available for analysis did not significantly differ between group within each half of testing. Power density ($\mu V^2/Hz$), a method commonly used for EEG quantification in studies of early cognitive impairment and AD,[12,14,15,20,37] was computed at each electrode site on each of the remaining artifact-free segments. The frequency resolution was 0.5 Hz for the 2-second segment but 0.0125 Hz for the 8-second segment. To reduce edge effects (or leakage), each segment was weighted using a 10% duration Hann nonrectangular window periodic function. The FFTs in each of the segments within the 3-minute period were then averaged to attenuate random noise variability. For each segment, power density was calculated for the following bands: delta (0.1-3 Hz), theta (4-8 Hz), alpha (8-12 Hz), and beta (12-28 Hz) bands.

Statistical Analysis

Neuropsychological measures of global cognition (MoCA) and memory (CVLT-II) were initially analyzed between groups (OA and MCI) using independent-sample *t* tests. The statistical analyses of the EEG data were carried out at anterior (F3, Fz, and F4) and posterior (P3, Pz, and P4) regions of interest (ROIs), following previous aging studies.[27,38] Resting-state EEG spectral power density was statistically analyzed separately for each frequency band (alpha, beta, delta, and theta) using a mixed-factor analysis of variance. The between-subject factor was Group (OA and MCI) and the within-subject factors were Time (first and second half of recording), and Site (anterior and posterior).

The statistical analyses were carried out using R software (version 3.0.2).[39] When the assumption of sphericity was violated, the Greenhouse-Geisser correction was applied.[40]

Leastsquare means (LS means), with Bonferroni-based adjustments, as implemented in the doBy package in R, was used for post hoc pairwise comparison for main effects and when interactions were significant.

Spearman's rho was used to determine the association between EEG spectral power density and STM and LTM function as measured by the CVLT-II.

Results

Cognitive Measures

Cognitive performances between groups are summarized in Table 1. Older adults performed significantly better on the MoCA ($t(28.15) = 5.65$, $P < .001$, $\eta^2_p = 0.53$), CVLT-II short delay ($t(36.73) = 8.75$, $P < .001$, $\eta 2_p = 0.68$), and long delay ($t(35.66) = 9.09$, $P < .001$, $\eta^2_p = 0.70$) compared to people with MCI. As expected, the overall correlations between the MoCA and CVLT-II short delay and long delay were relatively high, 0.62 and 0.65, respectively ($P < .001$ in both cases).

Table 1. Mean (SD in Parentheses) Neuropsychological Test Scores Between Groups.

Neuropsychological tests	OA	MCI
Global		
MoCA	27.25 (1.58)	22.47 (3.40)*
Memory		
CVLT		
STM	22.24 (5.39)	5.81 (6.55)**
LTM	22.95 (5.23)	5.90 (6.70)**

Abbreviations: OA, older adults; MCI, mild cognitive impairment; MoCA, Montreal Cognitive Assessment; CVLT, California Verbal Learning Test; STM, short-term memory; LTM, long-term memory.
*OA > MCI, $p < .01$
*OA>MCI, $p<.001$

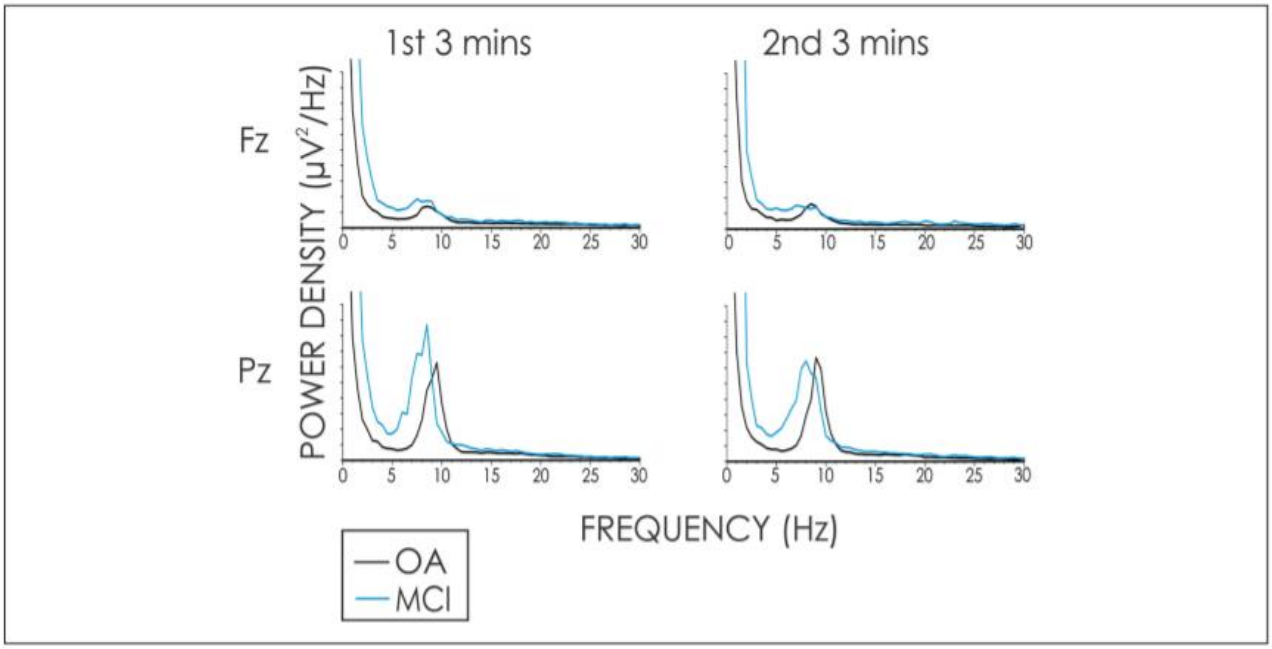

Figure 1. Power density spectra for Fz and Pz electrode sites during the first and second halves of the resting state recording (8-second segmentation). People with mild cognitive impairment (MCI) had greater theta activity at Pz than older adults (OA).

EEG Measures

Long Segmentation. The results of the spectral analysis using 8-second segments are illustrated in Figure 1. There were no main effects of time (first and second half of recording) nor interactions involving time for any of the frequency bands at any ROI ($F < 1$ in all comparisons). Thus, the power density for delta, theta, alpha, and beta activity in the initial 3-minute recording did not significantly differ from that in the second 3-minute recording.

Although people with MCI had somewhat higher delta power than healthy older adults at posterior sites, this difference was not significant (interaction between Group and Site, $F(1, 39) = 2.02$, $P = .16$, $\eta^2_p = 0.05$). On the other hand, people with MCI did exhibit significantly higher theta power density than healthy older adults at posterior regions (interaction between Group and Site, $F(1, 39) = 5.14$, $P = .03$, $\eta^2_p = 0.15$). The group theta difference at anterior sites was not

significant. The interaction between Group and Site was also not significant for either alpha or beta power density ($F < 1$ in both cases).

Short Segmentation. The initial FFT analyses were carried out using 8-second duration segments. The analyses were also carried out using 2-second duration segments, allowing considerably more segments to be available for averaging. In general, the results (illustrated in Figure 2) were very similar to those obtained with the 8-second segment analyses. Group differences in delta power were not apparent ($F < 1$). On the other hand, theta power density at posterior sites was again significantly higher for the MCI than for the healthy older adult group (interaction between Site and Group, $F(1, 39) = 5.23$, $P = .03$, $\eta^2_p = 0.12$). Again, it did not significantly differ between groups at anterior sites. The interactions between Group and Site were not significant for either alpha or beta power density ($F < 1$ in both cases).

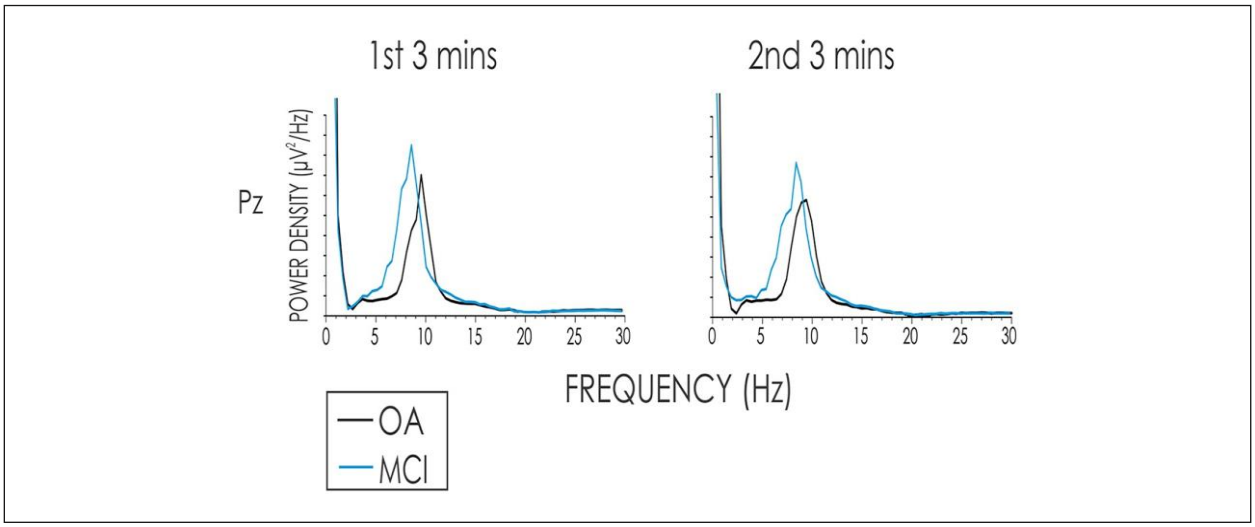

Figure 2. Power density spectra for the Pz electrode site during the first and second halves of the resting state recording (2-second segmentation). People with mild cognitive impairment (MCI) again had greater theta activity at Pz than older adults (OA).

Table 2. Correlations Between Neuropsychological Test Scores and EEG.

	Theta		Alpha		Beta	
Group	Anterior	Posterior	Anterior	Posterior	Anterior	Posterior
Older adults						
Global cognition						
MoCA	−0.48*	−0.44	−0.41	−0.24	−0.26	−0.34
Memory						
CVLT: STM	−0.31	−0.32	−0.07	−0.03	0.14	0.09
CVLT: LTM	−0.26	−0.23	−0.01	0.16	0.07	0.07
Mild cognitive impairment						
Global cognition						
MoCA	−0.20	−0.24	0.02	0.18	−0.23	−0.31
Memory						
CVLT: STM	−0.11	−0.17	−0.31	−0.37	−0.19	−0.55*
CVLT: LTM	−0.21	−0.12	−0.50*	−0.30	−0.45*	−0.67**

Abbreviations: MoCA, Montreal Cognitive Assessment; CVLT, California Verbal Learning Test; STM, short-term memory; LTM, long-term memory.
*$P < .05$.
**$P < .001$.

Correlations with Neuropsychological Measures

In OA, previous research has reported higher alpha power to be negatively associated with memory performance, and higher theta power to be negatively associated with measures of global cognitive decline. The beta band has also been associated with memory.

Correlational analyses are summarized in Table 2. A significant negative correlation was found between resting theta power density and MoCA scores at the anterior site in healthy OA. In people with MCI, beta power density at the posterior site was negatively correlated with CVLT-II scores (STM and LTM). There was also a significant negative correlation between CVLT-II (LTM) and beta power density at anterior sites. Resting alpha power density at anterior regions was negatively correlated with CVLT-II (LTM). Scattergrams of the significant correlations are included as Supplementary Material (available online).

Discussion

The present study examined changes in EEG during a relatively long recording period, comparing early and later portions of the recording. Most studies record EEG for only short

periods of time, lasting from a few seconds to minutes.[22,26-31] The duration of these recordings is somewhat arbitrary and has not been standardized. Longer recordings will, of course, be more reliable than shorter recordings and will reduce the likelihood of noise influencing the results.[24,41] However, increased drowsiness may be a concern with longer recordings,[22,24] especially in people with MCI. This hypothesis was tested in the present study.

A resting-state EEG lasting 6 minutes was employed to determine evidence of drowsiness in the later portion of the recording. Most studies utilize a 2-second segmentation for the spectral analyses. The identification of drowsiness is dependent on the quantification of low-frequency delta activity, and its identification will be compromised by shorter duration segmentation. The results from the present study indicated that delta power density did not significantly differ between early and later portions of the 6-minute recording, whether long 8-second or short 2-second segmentation was used. Theta, alpha, and beta power density did not differ between the first and second halves of the recording for either group regardless of the length of segmentation. There was thus little evidence of increased drowsiness in a longer 6-minute recording, even in people with MCI. Of course, it is possible that drowsiness may become apparent when the recording period lasts longer than 6 minutes.

Previous studies using short duration recording times, have reported an increase in theta activity for people with MCI and AD compared with controls and, in some studies, a decrease in alpha activity.[14,42] In the present study, power density in the theta band was also found to be significantly larger for people with MCI compared with healthy OA, in both halves of the recording. The increase in theta power density found in people with MCI was observed over the posterior scalp regions, also replicating previous studies. Power density in the alpha band did not differ between the 2 groups. Thus, theta activity appears to be a robust, reliable predictor of

MCI, independent of the duration of both the recording time and segmentation used for the FFT analysis. Increases in theta activity have also been reported to be associated with cognitive deterioration in Parkinson's disease.[43,44]

Differences in theta power density were largest over posterior scalp regions. This scalp distribution may be a result of the source activity in the hippocampal region.[45,46] There is evidence that the increased resting theta activity in people with MCI reflects a shift in the dominant EEG frequency from the alpha to the theta band.[21] Also, experimental studies during active tasks in both humans and animals have indicated that increases in theta occur with increases in working memory demands and cognitive engagement (reviewed by Brzezicka et al[47]). Interpreting the higher resting state theta activity in people with MCI as being reflective of greater cognitive engagement does, however, seem to be counterintuitive. Resting-state conditions have also often been employed in fMRI studies. A recent review indicates that different resting state networks may be affected in MCI but unfortunately the pattern of connectivity is complex and inconsistent across studies.[48] The interpretation of functional changes in any resting-state condition is fraught with difficulty because the researcher does not have control over spontaneous thoughts and cognitive processing.[49-51] Certainly, a resting state condition does not imply the absence of mental activity or concurrent information processing. The mental state of the participant is essentially personal, private, and subjective.

EEG data and neuropsychological measures of global cognition and memory data were also significantly correlated in healthy older adults and people with MCI. The results were similar to those observed in previous studies. In healthy older adults, theta power density was negatively correlated with global cognitive functioning.[13,22,23] Van der Hiele et al[22] also noted that while resting-state theta power was correlated with global cognitive functioning, it was not

correlated with any specific cognitive measure. Our results support this finding; theta was not correlated with the CVLT-II measures of memory in either group. Significant negative correlations were also found between alpha power density and the CVLT-II for people with MCI. Previous research has also noted that lower memory performance is associated with increased alpha.[7,22] Beta activity has been less studied compared to other frequency bands. In the present study, power density in the beta band was very low and did not differ between healthy older adults and MCI. The finding that increased beta was associated with lower performance in the CVLT-II for people with MCI should thus be interpreted with caution. Fleck et al[38] have, however, also found lower beta power to be associated with higher scores on the CVLT-II. Still, they observed this correlation in healthy older adults, while in the present study the correlation within this group was not significant.

No differences in delta power density were apparent when a short 2-second segmentation was used. However, when a longer 8-second segmentation was used to improve low-frequency resolution, at posterior sites, people with MCI were observed to have higher delta power density than healthy older adults, suggestive of drowsiness. Although the group differences in delta activity were not significant, caution should still be exercised, particularly when the data are divided into short 2-second segments. While shorter segments will permit more segments to be available for averaging, thus allowing for better reduction of random noise, drowsiness may not be adequately identified. Drowsiness may be better identified with the use of longer segments but doing so risks the inclusion of more residual noise because of the smaller number of segments available for averaging. Also, it is important to note that this increase in drowsiness did not occur only in the later portion of the study. Rather it was observed throughout the entire length of the recording. Critically, the present study has also provided strong evidence indicating

that extent of theta and alpha power density is not influenced by the duration of the resting-state recording. Similarly, whether the recording is subdivided into shorter or longer segments will have little influence on theta and alpha power density.

Resting-state EEG offers promise of a biomarker of early cognitive impairment. It has the advantage of being low cost and readily available and is routinely carried out in clinical settings. The present study did not classify different subtypes of MCI such as amnestic, non-amnestic, or single versus multiple domain. Future work should attempt to replicate the current findings, classifying different subtypes of MCI.

Conclusion

The present study examined the effects of longer duration resting-state EEG recordings in healthy older adults and people with MCI. The EEG recording was subdivided into a series of 8-second segments to allow for optimal low-frequency resolution and the identification of possible drowsiness associated with increases in delta activity. An FFT analysis on these segments did not identify any significant changes in the power density of the frequency bands between the early and the later portions of the recording. Higher theta power density was observed for the people with MCI in both halves of the study. There was evidence of a slight but not significant overall increase in delta power density for people with MCI, providing some evidence of drowsiness in this group. Nevertheless, delta power density did not further increase in the second half of the study for people with MCI. When the number of segments was increased by a factor of 4, by using short 2-second segmentation, differences in delta power density were not apparent, although group differences in theta power density were again observed. In summary, a resting-state EEG condition can be reliably recorded for up to 6 minutes without increased risk of drowsiness in people with MCI.

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Study 2

Study 2 was published in the journal, *Neurobiology of Aging,* and is formatted in accordance with the requirements of this journal.

Kamal, F., Morrison, C., Campbell, K., & Taler, V. (2021). Event-related potential evidence that very slowly presented auditory stimuli are passively processed differently in younger and older adults. *Neurobiology of Aging, 103*, 12-21. https://doi.org/10.1016/j.neurobiolaging.2021.02.014

In Study 1, a significant increase in theta power was observed in people with MCI relative to healthy older adults. The interpretation of changes in any resting-state condition is difficult. It is possible, for example, that the healthy older adults were actively engaged in mental thought while people with MCI were mentally at rest. Unfortunately, the researcher does not have control over spontaneous thoughts and cognitive processing, or what the participants "is doing".

In studies 2, 3, and 4, the mental state of the participants was controlled by having them engage in a visual task. ERPs were recorded to auditory stimuli that are irrelevant to this task and are thus to-be-ignored. Importantly, the ERP components of interest are obligatory responses of the nervous system. Processing thus occurs passively, independently of attention, current task demands, and what the participant is doing. The three studies examined the operations of a salience network and a frontoparietal network by examining how a potentially highly relevant, but unattended, auditory stimulus can result in a switching of processing priorities. The first two studies examine processing exclusively within the transient detector system.

In study 2, a very simple design was used. Some authors suggest that healthy older adults have difficulty in computing the salience of unattended input. A single to-be-ignored auditory stimulus was presented either relatively rapidly or very slowly. The auditory stimulus elicits an

obligatory N1-P2. Their amplitude provides measures of the salience level of the unattended input. When the stimuli are presented relatively rapidly, previous studies have provided mixed results about how N1 and P2 changes with aging. In younger adults, when stimuli are presented very slowly, both N1 and P2 become much larger. This finding suggests that the salience level of the rarely presented stimulus is computed to be very high. The effects of very slowly presented stimuli have not been extensively studied in older adults. If healthy older adults have difficulty in computing the salience of input, then the large increase in N1 and P2 observed in younger adults when stimuli are presented very slowly, may not be observed in this group.

It should be noted that 4/20 of the younger adult participants in study 2 overlapped with the sample in the Morrison et al., (2019, 2020) studies. With respect to the older adults, 14/20 participants in the present study overlapped with Morrison et al., (2019) and 16/20 overlapped with Morrison et al., (2020).

Abstract

The occurrence of a very infrequent and unattended auditory stimulus is highly salient and may result in an interruption of the frontoparietal network controlling processing priorities. Research has suggested that older adults may be unable to compute the level of salience of unattended stimulus inputs. A multi- channel EEG was recorded in 20 younger adults and 20 older adults. In different conditions, a single 80 dB SPL auditory stimulus was presented relatively rapidly, every 1.5 s or very slowly, every 12.0 s. Participants ignored the auditory stimuli while watching a silent video. When the stimuli were presented rapidly, group differences were not observed for the amplitudes of N1 and P2. When stimuli were presented very slowly, their amplitudes were much enhanced for younger adults, but did not increase for older adults. The failure to observe a large increase in the amplitude of N1 and P2 in older adults for very slowly presented auditory stimuli provides strong evidence of a dysfunction of the salience network in this group.

1. Introduction

Research has suggested that older adults are easily distracted by irrelevant stimulus input, resulting in a shift of attention away from the demands of a current, higher priority task (Gazzaley et al., 2008; Hasher and Zacks, 1988; Lee et al., 2020; Schmitz et al., 2014). The sustaining of attention to the task at hand is thought to be a major role of a frontoparietal network that determines processing priorities (Petersen and Posner, 2012). A separate salience network is, however, thought to provide initial input to the frontoparietal network to determine which current processing requires priority (Goulden, et al., 2014). This salience network operates at an early level of processing to distinguish the salience of unattended incoming stimuli. There is evidence that the salience network may be dysfunctional in older adults (Lee et al., 2020; Lopez-Larson et al., 2012). As a consequence, if older adults are unable to accurately compute saliency levels of unattended stimulus input, then an irrelevant input having low salience may interrupt the frontoparietal network while a much more potentially relevant input having high salience may not.

The classic Näätänen model of auditory perception (Näätänen, 1990) explains how an individual can become conscious of input even though they are not attending to the auditory channel. This awareness is possible through sufficient activation of two different systems. The first system, the transient detection system, detects brief transient changes in an auditory stimulus, such as its onset or offset. The output of this system varies directly with the rate of stimulus presentation and the energy (intensity) of the stimulus, thus defining its salience. A second system, the change detector system, detects changes in other acoustic features such as the pitch, duration, location, and intensity of the stimulus.

Acoustic change is often studied using the so-called oddball paradigm. The participant is presented with a sequence of frequently occurring homogenous standard stimuli, and at rare (or odd) times, a feature of the standard is changed to form a deviant. In this task, the features of all incoming stimuli are com- pared against the features of the previously presented standard stimulus stored in sensory memory. When a deviant is presented, its features fail to match those stored in sensory memory and acoustic change is detected. The output of the change detection system varies directly with the extent of change, thus defining its salience.

Determining the extent of processing of unattended input in the absence of a behavioral response is methodologically difficult. Unique to the Näätänen model is the use of event-related potentials (ERPs) to quantify the extent of processing of the auditory stimulus. ERPs are the minute changes in the ongoing electrical activity of the brain (the electroencephalography, EEG) that are elicited by external stimuli or internal psychological events. ERPs consist of a series of negative- and positive-going components, thought to reflect different aspects of information processing.

The output of the transient detector system is reflected by the amplitude of a fronto-central maximum N1 occurring at about 100 ms (see Näätänen and Picton, 1987 for an elegant review). The N1 amplitude will be larger when the intensity of the auditory stimulus is very high. It has also long been known that the amplitude of N1 progressively increases as stimuli are presented more slowly (Davis et al., 1966; Ritter et al., 1968). The subsequent P2, occurring at about 200 ms, is often studied in parallel with the N1 because experimental manipulations that affect N1 often affect P2. When an oddball sequence is employed, the onset of both the standard and deviant will activate the transient detector system and thus elicit an obligatory N1-P2. The deviant also signals a change from the acoustic past. This detection of change will elicit another

negativity, the mismatch negativity (MMN), peaking from 100 to 200 ms, signaling that change has been detected. The output of the change detector system is reflected by the MMN, its amplitude varying directly with the extent of change, thus defining the salience of deviant stimulus input.

An output signal from both the transient and change detection systems is forwarded to the frontal executive controlling processing priorities, and the direction and extent of allocation of attention. If the signal is particularly salient, attention may be switched from the demands of the current cognitive task to the potentially more relevant auditory input. The switching of attention is thought to be reflected by another ERP component, the P3a, a frontocentral component peaking from 200 to 300 ms after stimulus onset (Escera et al., 1998). Others have claimed that the P3a appears to better reflect a process that may eventually lead to the switching of attention and subsequent awareness of the stimulus input (Parmentier, 2014; Wetzel et al., 2013).

The oddball paradigm has often been employed in the study of aging to determine the influence of deviant stimuli on distraction because of the interruption of the frontoparietal network. Only a limited number of deviants will reliably elicit a P3a in younger adults. Rinne et al. (2006) suggested that deviants that elicit a P3a and interrupt the frontoparietal network, do so because they cause high output from the transient detector system. The change detection system plays a minor role, if any, in the interruption of the frontocentral network. Thus, a deviant created by decreasing the intensity (a decrement deviant) of the standard will be detected only by the change detector system and will elicit a small or absent P3a because of its low level of salience. On the other hand, a deviant created by increasing the intensity of the standard (an increment deviant) will be detected by the change and the transient detector system. A large P3a

will then be elicited because the level of salience of the combined outputs will be high (Muller-Gass et al., 2006; Rinne et al., 2006; Shestopalova et al., 2018). Both the increment and decrement deviants signal change from the standard and as such, are detected by the change detector system. However, the increment also signals an increase in intensity relative to the standard and thus results in a large output from the transient detector system.

The large P3a that is elicited in younger adults following presentation of an increment has been reported to be much reduced in older adults (Morrison et al., 2019). A large P3a is also elicited in younger adults, following presentation of novel, environmental sound deviants. These deviant sounds will result in large output from the change detector system. These sounds are acoustically complex, with periodic increases in intensity, and as such, transient changes will also result in a large output from the transient detector system. This environmental sound P3a is also much attenuated in older adults compared to younger adults (Berti et al., 2017; Correa-Jaraba et al., 2016; Morrison et al., 2020; Tusch et al., 2017).

The implication from these oddball studies is that it is mainly the output from the transient detector system that determines the salience of the signal forwarded to the frontal executive controlling processing priorities. Unfortunately, in oddball studies, the output signal is a summation of outputs from both the change and the transient systems. To overcome this confound, a single, repetitive, unchanging stimulus needs to be presented. Because the stimulus never changes, the saliency level of the resulting output can only be attributed to processing within the transient detector system.

The single auditory stimulus will thus elicit the obligatory N1- P2 sequence but will not elicit an MMN. The N1-P2 complex has been the subject of a large number of studies. An earlier P1, peaking at about 50 ms, will also be elicited but it has been studied far less often. There is,

however, evidence that its amplitude increases in older compared to younger adults (Amenedo and Diaz, 1999; Golob et al., 2007; Stothart and Kazanina, 2016).

Importantly, in the Näätänen model, the operations of the transient detection system are claimed to function pre-attentively and automatically, whether the individual is attending the auditory channel or not. Attention has often been shown to have little effect on the N1. In some instances, the N1 may become larger when attention is directed to the auditory channel (Picton & Hill- yard, 1974). The effect of attention on N1 can, however, only be observed under very specific, optimal conditions, when stimuli are presented very rapidly (faster than every 1 s) and at relatively moderate intensities (Hansen & Hillyard, 1988; Schwent et al., 1976; Woldorff, 1995). While most studies have been carried out in younger adults, Ostroff et al. (2003) reported that in older adults, the amplitude of N1 did not change when participants ignored an auditory sequence compared to when they attended to it. Because attention appears to have little effect on N1, participants are often asked to ignore the auditory stimulus sequence and attend to a visual task, such as reading a book.

The N1 response to auditory stimuli that are presented rapidly changes when the stimuli are presented very slowly (> 10 s). In young adults, the amplitude of the N1 becomes very large (Alcaini et al., 1994 ; Budd et al., 1998 ; Muller-Gass et al., 2008 ; Pereira et al., 2014) and its peak latency is delayed, occurring at about 120 ms. The scalp distribution of N1 also changes from its typical fronto-central maximum to a more prominent central scalp distribution (Gascoyne et al., 2016; Godey et al., 2001; Picton et al., 1999; Yvert et al., 2005). The amplitude of the later P2 also becomes very large when auditory stimuli are presented very slowly.

Several studies have examined how the N1 and P2 change with aging. In most of the studies, stimuli have been presented relatively rapidly, from every 0.5 to every 3 s. The results of

these studies are mixed. While many have failed to find N1 or P2 differences between younger and older adults, others have reported larger amplitudes for younger adults, while others have reported larger amplitudes for older adults (Bertoli et al., 2005; Ceponiene˘ et al., 2008; Harkrider et al., 2005; McCullagh & Shinn, 2013; Pfefferbaum et al., 1980; Tremblay et al., 2003; Cranford and Martin, 1991; Fisher et al., 20 0 0; Hymel et al., 1998; McCullagh & Shinn, 2013; Stothart and Kazanina, 2016). Marked differences in the features of the stimulus (e.g., intensity, frequency, duration), whether it is simple (e.g., pure tones) or complex (e.g., speech), and the presence or absence of background noise could account for some of these differences. It should be noted, however, that when differences have been observed, they tend to be small, although they may be statistically significant.

A recent study by Berti et al. (2017) presented stimuli relatively rapidly (either every 0.5, 1, or 3 s) or very slowly (every 10 s). Participants were presented with an oddball paradigm in which a frequently occurring standard tone was presented on 90% of trials, and a rare novel environmental sound was presented on 10% of trials. Participants were asked to *passively listen* to the auditory stimuli while reading a book. The amplitudes of N1 and P2 to the standard stimulus did not differ between younger and older adults for the faster rates of presentation. On the other hand, when stimuli were presented very slowly, the amplitudes of the standard N1 and P2 were much larger for younger adults compared to older adults. This study suggests that large age differences in N1 and P2 will only be observed when the output of the transient detector system is particularly high for young adults (i.e., when stimuli are presented very slowly). These results suggest that processing within the transient detector system may be dysfunctional in older adults. In younger adults, dramatically different saliency levels are computed for rapidly and

very slowly presented unattended auditory stimuli. In older adults, the saliency levels are, however, computed to be similar for the same rapidly and very slowly presented stimuli.

There are, however, limitations to the Berti et al. (2017) study. The age range of both their younger (19-38 years) and older (55-72 years) participants was quite wide. The use of an oddball paradigm may also be problematic. A P3a was elicited by the novel stimulus and was larger for younger than older adults. The authors noted that the presentation of the novel stimulus might have caused an involuntary orientation of attention to the auditory channel. This switching of attention to the auditory channel might have influenced the N1 to the standard stimulus, particularly in the younger adults. The influence on N1 is however questionable; in the Näätänen model, N1 is an obligatory response occurring independent of the direction of attention. Also, the instructions to passively listen to the auditory stimuli may have been interpreted differently by the two groups. It is possible that the younger adults were able to divide their attention between the reading task and also periodically sample (or attend to) the auditory channel. The amplitude of the positivity that was reported as a P3a was unusually large and its latency unusually late (more than 300 ms in younger adults and almost 400 ms in older adults). This latency is consistent with another late positivity, the P3b (or P300) associated with active attention being directed to the auditory channel and overt detection of the rarely occurring novel stimulus. The authors presented a fixed 200 trials within each condition. As a result, the duration of the various conditions differed dramatically from, for example, around 3 minutes in the 1 s condition to more than 30 minutes in the 10 s condition. It is thus possible that factors such as fatigue or habituation might account for the attenuated older adult N1-P2 when stimuli were presented very slowly compared to younger adults.

There is evidence that it is output from the transient detector system that is most effective in interrupting the frontoparietal network controlling processing priorities. In the usual oddball studies, deviant stimuli that activate the transient detector system will also activate the change detector system. To avoid this confound, the present study used a simple, single stimulus paradigm. A single, unchanging stimulus was repeatedly presented either rapidly, every 1.5 s, or slowly, every 12 s. Participants were asked to ignore the auditory sequence while engaged in a visual task, the auditory ERPs thus being elicited passively. The total duration of each condition was the same in an attempt to overcome possible fatigue effects. Fewer stimuli were therefore presented when stimuli were presented very slowly. Each condition was presented twice. The effects of fatigue and habituation could thus be examined by comparing the first and second halves of the study. In addition, changes within each quarter of a condition were also compared to examine shorter term fatigue and habituation.

Previous studies have indicated that in younger adults, the amplitudes of N1 and P2 are much larger when auditory stimuli are presented very slowly compared to when they are presented more rapidly. Events that occur only occasionally are computed to be highly salient. If older adults fail to adequately compute the salience of different, unattended auditory inputs at this early stage of processing, then the output of the transient detector system, as reflected by the amplitudes of N1 and P2, should be similar regardless of whether stimuli are presented rapidly or very slowly. On the other hand, if older adults are able to compute the salience of the auditory inputs, then the amplitudes of N1 and P2 should show a large increase in amplitude when stimuli are presented very slowly compared to when they are presented relatively rapidly.

2. Methods

2.1. Participants

Forty-three participants were recruited into the study. Three participants were excluded from analysis because of noisy EEG data (see Section 2.3). A total of 40 participants' data were therefore analyzed: 20 younger (13 females; mean age = 20.5 years; range = 18-22 years) and 20 healthy older adults (12 females; mean age = 72.2 years; range = 67-77 years). Participants had no prior history of neurological or psychiatric conditions, no major head injuries, and all were right-handed. None were taking medications that influenced the central nervous system. All participants reported normal hearing. In addition, older adults completed pure tone audiometry in the same testing room where the auditory ERPs were recorded. The intensity of a brief 55 ms 500, 1000, or 2000 Hz pure tones was randomly increased or decreased. Participants were asked to press a mouse button when a tone was heard. Hearing thresholds were below 40 dB SPL (about 20 dB HL) in both ears.

All participants completed the Montreal Cognitive Assessment (MoCA) to screen for cognitive decline (Nasreddine et al., 2005). All older adult participants scored above 25 on the MoCA (M = 27.25, SD = 1.37).

This study was approved by the University of Ottawa and Bruyère Research Institute ethics boards. Participants provided in- formed written consent prior to starting the study and an honorarium was given as compensation for participation.

2.2. Stimuli and procedure

Participants were seated in a sound-attenuated room. A single auditory stimulus was presented binaurally through Sony MDR-V6 headphones. The stimulus was an 80 dB SPL 10 0 0 Hz pure tone with a total duration of 55 ms (5 ms rise/fall time). Participants were instructed to

watch a sub-titled silent video and thus were asked to ignore the presentation of the irrelevant auditory stimuli. The rate of stimulus presentation was manipulated in different conditions. In the fast condition, a stimulus was presented every 1.5 s. In the slow condition, a stimulus was presented every 12 s. The order of conditions was randomized across participants. A total of 400 stimuli were presented in the fast condition and 50 stimuli were presented in the slow condition. Each condition thus lasted 10 minutes. The two conditions were repeated a second time in reverse order. A brief rest period was given between each of the conditions. The data were subsequently collapsed within each condition to assure enough stimuli were presented for an optimal N1 and P2 signal-to-noise ratio following averaging procedures. Although the duration of each condition was the same, the total number of stimuli presented in the fast and slow conditions (800 and 100, respectively) differed. The residual noise remaining will therefore be larger in the slow condition. However, previous research has demonstrated that both N1 and P2 are much larger when stimuli are presented very slowly. Therefore, the over-all signal-to-noise ratio should have been very similar in both conditions.

Participants were debriefed following testing. They were informally asked about whether they were aware that auditory stimuli had been presented.

2.3. EEG recording and analysis

The EEG was recorded from 29 active silver-silver chloride electrodes, attached to an electrode cap (Brain Products, GmßH, Munich, Germany) placed according to the international 10-10 system. Electrodes were placed over midline and lateral frontal, central, parietal, temporal, and occipital regions. Additional electrodes were placed on the left and right mastoids (FT9 and FT10). An EOG electrode was placed on the infraorbital ridge of the left eye to record vertical eye movements and blinks. An electrode placed on the nose served as a reference for all

channels. The EEG was sampled at rate of 500 Hz. Inter-electrode impedance was kept below 20 kΩ. Impedance was particularly low (below 10 kΩ) at F3, Fz, and F4 and C3, Cz, and C4, which constituted the regions of interest (ROI) in this study. The data were subsequently reconstructed using Brain Products' Analyzer 2 software. The EEG was then visually inspected for channels containing high levels of noise. These channels were replaced by interpolating the data of the surrounding electrode sites (Perrin et al., 1989). The data of three participants were removed from further analysis because more than 4 channels with excess noise were rejected. Interpolation was not applied to any of the ROI sites. A 20 Hz low-pass digital filter (24 dB/octave roll-off) was then applied to the data.

A vertical EOG was computed by subtracting the inferior orbital and the FP1 channels. Horizontal eye movements were computed by subtracting the FT9 and FT10 channels. Independent Component Analysis (Makeig et al., 1996) was subsequently used to identify vertical/horizontal eye movements and blink artifacts that were statistically independent of the EEG activity. This algorithm was trained to recognize each subject's eye movement and blink signature, and this factor was then partialled out of the EEG traces. The EEG was subsequently reconstructed into single 700 ms segments starting 100 ms before stimulus onset. The average of all activity in the pre-stimulus period served as a zero-voltage baseline. Drifts in post-stimulus voltage from this zero-baseline were then corrected for each segment. The baseline period was subtracted from all data points in the post-stimulus period. Segments containing EEG activity exceeding ±100 μV were rejected from the averaging. Relatively few segments were rejected. The mean number of segments available for averaging was slightly higher for the younger than older participants, 792 vs 784 in the fast condition, and 98 vs 95 in the slow condition.

2.4. ERP quantification and analysis

The onset of the auditory stimulus elicited an N1 and P2 in both the fast and slow conditions. The amplitudes of the N1 and P2 were measured relative to the zero-voltage pre-stimulus baseline. They were quantified as the mean of all data points within ±25 ms of their peak amplitude (identified in the grand average of the group). In the fast condition, the peak of N1 occurred at 95 ms for both groups and was thus quantified from 70 to 120 ms.

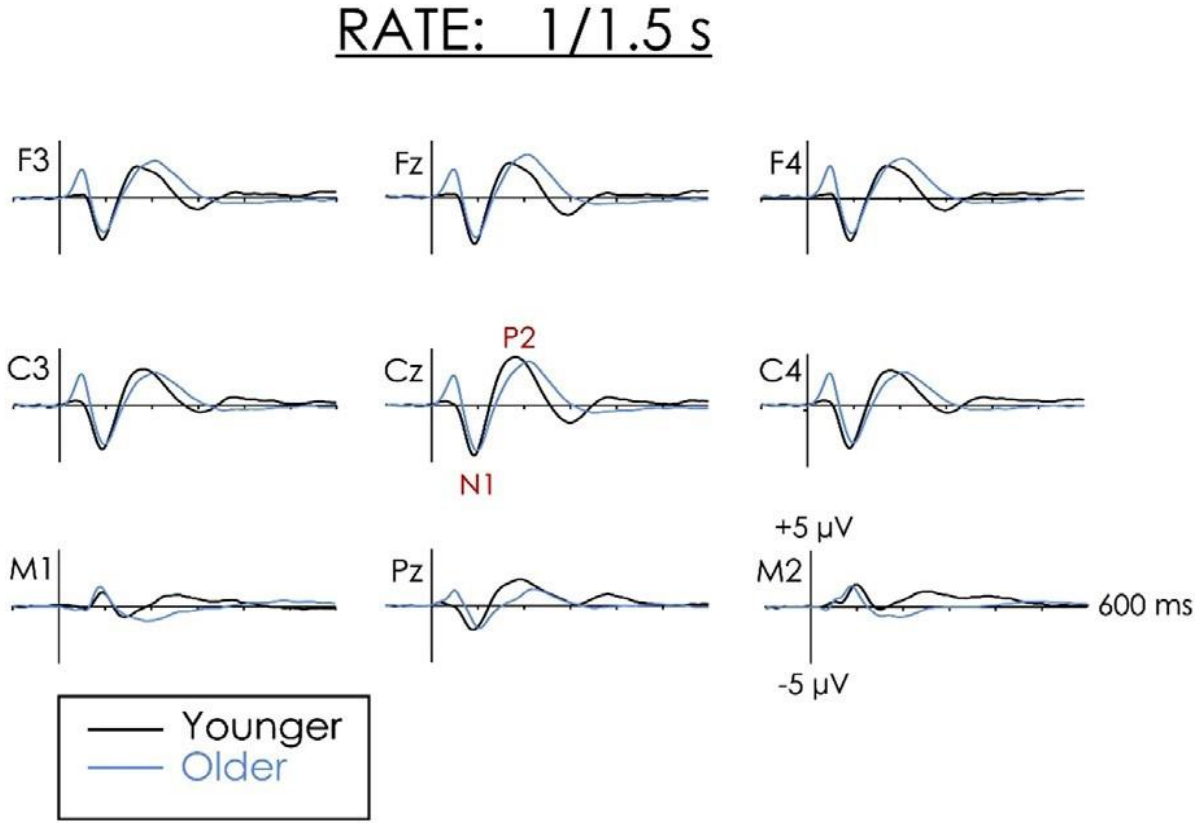

Fig. 1. Younger and older adult ERPs in the fast rate of presentation condition. The amplitude of P1 was larger in older adults than younger adults. Neither the amplitude of N1 or P2 differed between the two groups.

N1 peaked about 20 ms later (at 115 ms) in the slow condition and was quantified from 90 to 140 ms in both young and old adults. The subsequent positivity, P2, peaked at different times for the younger and older adults and between fast and slow conditions. In the fast condition, it peaked at 175 ms for the younger adults and was thus quantified from 150 and 200 ms; for older adults, the

P2 peaked at 205 ms and was quantified from 180-230 ms. In the slow condition, P2 peaked later for both groups, occurring at approximately 205-215 ms for the younger adults (quantified from 190 to 240 at frontal sites and 170 to 220 ms at central sites). For older adults, the P2 occurred around 230 ms at all regions and was quantified from 205 to 255 ms.

While the focus of this study was on the N1 and P2, an earlier P1 occurring at about 50 ms was apparent in the ERPs of the older group. It was quantified using a narrower time interval as the mean of all data points between 40 and 60 ms. A distinctive P1 peak was difficult to observe in the younger adults. It was there- fore quantified using the older adult time interval.

N1 and P2 were quantified at ROIs, where they are largest. The ROIs thus included frontal (F3, Fz, F4) and central (C3, Cz, C4) electrode sites. Two separate 2-way ANOVAs were run at the frontal and central ROI for all ERP components, with a single between-subjects factor, Group (Younger, Older), and a single within-subjects factor, Rate of Presentation (Fast, Slow).

3. Results

Figs. 1 and 2 illustrate younger and older participants' multi- channel ERPs in the fast and slow conditions, respectively. As may be observed, a positive peak, P1, occurred at about 50 ms was maximum over the centro-frontal regions. It was followed by a negative peak, N1, occurring at about 100 ms was largest over fronto-central areas of the scalp. A later positivity, P2, occurring at about 200 ms was maximum over centro-frontal regions.

3.1. P1

P1 was quantified at the central ROI where its amplitude was largest. A main Group effect, ($F(1,38) = 28.35$, $p < 0$ .001, $\eta^2_p = 0.43$) was apparent, with older adults exhibiting larger P1 overall amplitudes than younger adults. Neither the main Rate of Presentation effect nor the Group x Rate of Presentation interaction was significant ($F < 1$ in both cases).

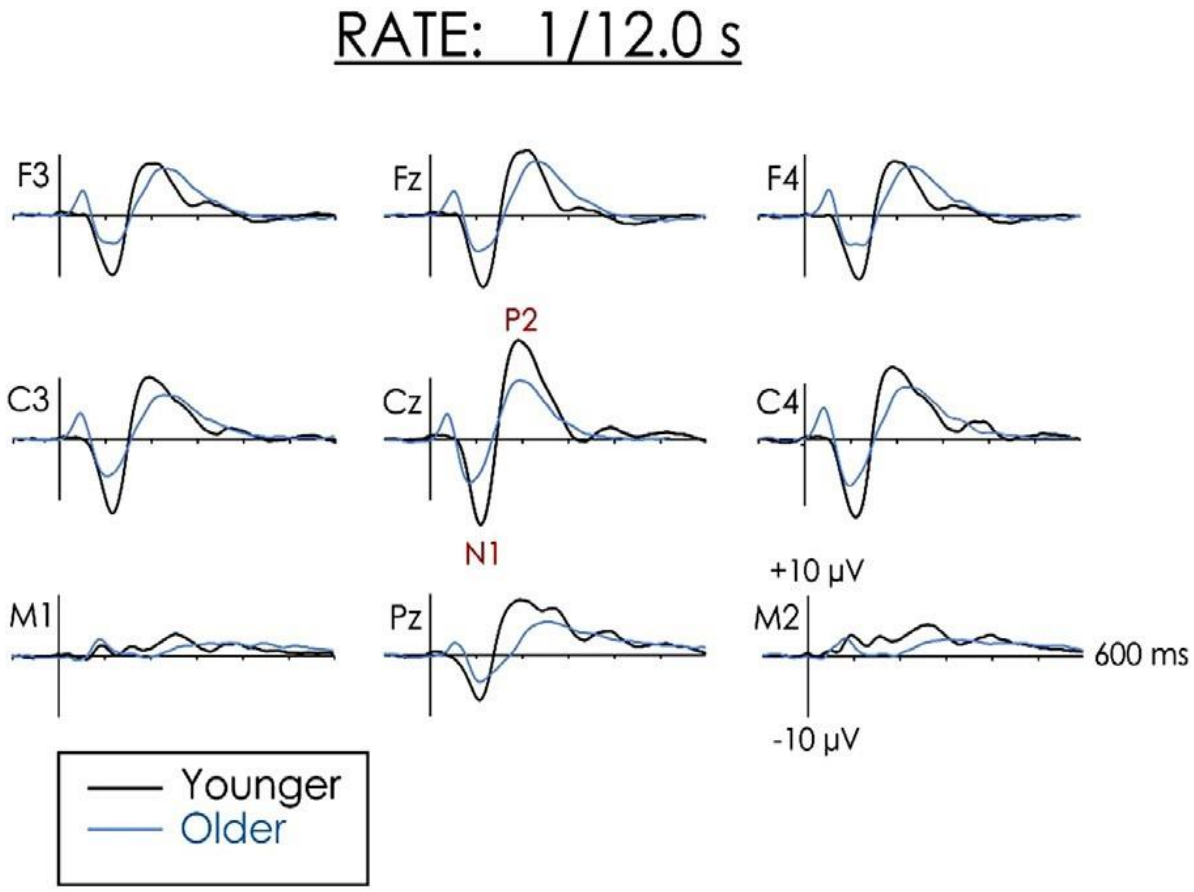

Fig. 2. Younger and older adult ERPs in the slow rate of presentation condition. Note that the waveforms are traced at half amplitude compared to Fig. 1. The amplitude of P1 was again larger in older adults than younger adults. The amplitudes of both N1 and P2 were, however, much larger for younger adults than older adults at the central ROI. The amplitude of N1 was also larger for younger adults than older adults at the frontal ROI.

3.2. N1

At the frontal ROI (F3, Fz, and F4), a main effect of Rate of Presentation was observed for the amplitude of N1, (F (1,38) = 54.61, $p < 0.001$, $\eta^2_p = 0.59$). N1 was much larger in the slow than the fast condition. Importantly, a significant Group x Rate of Presentation interaction was apparent, (F (1,38) = 15.44, $p < 0.001$, $\eta^2_p = 0.29$). Follow-up testing using a Fisher post hoc procedure was used to reveal the sources of this interaction. For the fast rate of presentation, the amplitude of the N1 did not differ between younger and older adults ($p = 0.41$). On the other

hand, for the slow rate of presentation, the amplitude of N1 was much larger for younger adults than for older adults ($p < 0.01$). The effects of the rate of stimulus presentation were also striking within each group. For younger adults, the amplitude of N1 was much larger in the slow than in the fast rate of presentation condition ($p < 0.001$). For older adults, the amplitude of N1 was slightly but significantly larger in the slow than in the fast rate of presentation condition ($p = 0.02$).

The central region (C3, Cz, and C4) analysis revealed similar effects. Thus, a main effect of Rate of Presentation, was again observed, (F (1,38) = 71.96, $p < 0.001$, $\eta^2_p = 0.65$). A Group x Rate of Presentation interaction was also observed, (F (1,38) = 14.48, $p = 0.001$, $\eta^2_p = 0.28$). In the fast condition, N1 amplitude did not differ between younger and older adults ($p = 0.53$). On the other hand, in the slow condition, N1 was again much larger for younger than older adults, ($p < 0.01$). For younger adults, the amplitude of N1 was again much larger in the slow than in the fast rate of presentation condition ($p < 0.001$). For older adults, the amplitude of N1 was somewhat larger in the slow than in the fast rate of presentation condition ($p < 0.01$).

Fig. 3 A presents the grand averaged ERPs including individual variance around the average. A pirate plot (similar to the more commonly used violin plots, but with more graphical options) presenting both descriptive and inferential statistics (Phillips, 2017) of the N1 data is traced in Fig. 3 C. The mean of N1 is represented by a solid horizontal line. The light rectangular box represents the 95% confidence intervals (CIs) around the mean. As may be observed, there was considerable overlap in the CIs between the younger and older groups in the fast condition. On the other hand, the amplitude of the N1 was much larger for the younger than the older group in the slow condition and there was no overlap of the CIs. The width of the smooth density curve (shaded area) represents the number of individuals having a similar

amplitude. The plot also presents the distribution of N1 for individual participants within each group (the small dots, jittered to avoid overlap). While the amplitude of N1 was significantly larger in the slow condition for the younger group, there was overlap among some individual younger and older participants.

3.3. P2

The frontal ROI analysis revealed that only the main effect of the rate of presentation affected the P2. A larger P2 was elicited when the stimuli were presented slowly compared to when they were shown rapidly (main effect of Rate of Presentation, F (1,38) = 52.59, p < 0.001, η^2_p = 0.58). Neither the main Group effect nor the Group x Rate of Presentation interaction was significant *(*F < 1 in both cases).

Rate of Presentation also significantly influenced P2 at the central ROI. P2 amplitude was much larger in the slow than the fast presentation condition (main effect of Rate of Presentation, F (1,38) = 68.98, p < 0.001, η^2_p = 0.65). A significant Group x Rate of Presentation interaction was also observed, (F (1,38) = 5.68, p = 0.02, η^2_p = 0.13). For the fast condition, P2 amplitude did not significantly differ between younger and older adults (p = 0.65). On the other hand, for the slow condition, younger adults displayed a significantly larger P2 than older adults, (p = 0.02). For younger adults, the amplitude of P2 was much larger in the slow than in the fast rate of presentation condition (p < 0.001). For older adults, P2 amplitude was somewhat, but significantly, larger in the slow than in the fast rate of presentation condition (p < 0.01).

A pirate plot of P2 distribution at the central ROI is traced in Fig. 3 D. The amplitude of the P2 was larger for the younger than the older group but only in the slow condition and there was no overlap of the CIs. Again, while the amplitude of P2 was significantly larger in

the slow condition for the younger group, there was overlap among some individual younger and older participants.

3.4. N1-P2

At the central ROI, the baseline-to-peak measures of both N1 and P2 were significantly larger for the younger than the older group when the stimuli were presented very slowly. N1-P2 was also measured peak-to-peak at the central ROI. The pirate plot of both the baseline-to-peak of N1 (Fig. 3 C) and baseline-to-peak of P2 (Fig. 3 D) illustrate a tendency for extremely high outlier young adults to *pull up* the overall mean amplitude. Fig. 3 D presents the pirate plot of the N1-P2 data measured peak-to-peak. The young adult amplitude distribution for the peak-to-peak no longer displayed such extreme scores. A Group x Rate of Presentation interaction was again still observed, (F (1,38) = 13.83, p = 0.001, η^2_p = 0.27). In the fast condition, the peak-to-peak amplitude did not differ between younger and older adults (p = 0.49). In the slow condition, the amplitude was much larger in the younger than older adults (p = 0.001). Fig. 3 B presents the pirate plot of the N1-P2 peak-to-peak distribution, including the mean and the CIs around the mean for the two groups.

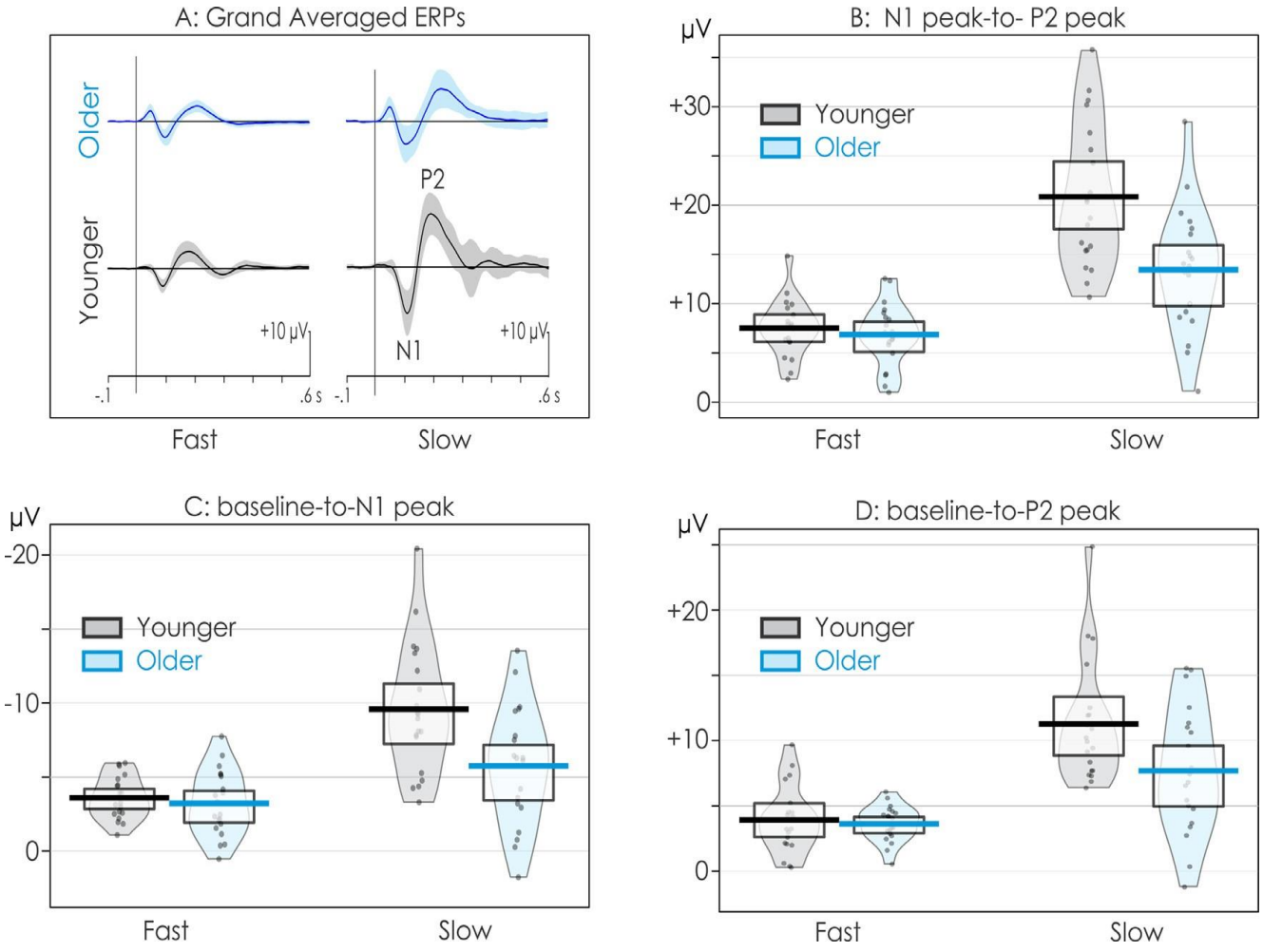

Fig. 3. Pirate plots of baseline-N1, baseline-P2, and N1-P2 peak-peak providing both descriptive and inferential statistics. Data are collapsed across all central electrode (C3, Cz, C4) sites. The grand average and SD (shaded area) are illustrated in part A. The mean (thick, solid horizontal line), 95% confidence intervals (light horizontal box), smooth frequency distribution (shaded area), and individual data points (jittered) are presented in parts B, C, and D. The N1, P2, and N1-P2 were larger for the younger than the older adults when stimuli were presented slowly. While the CIs do not overlap, there is overlap among individuals within each group.

3.5. Changes across quarters

A much-reduced N1 and P2 amplitude was observed for older adults when stimuli were presented slowly. This reduction might be a result of the averaging process. It is possible that the N1 and P2 were initially quite large for older adults but then became progressively smaller as a result of fatigue or habituation. On the other hand, it is possible that these ERPs were invariant

over time with the younger adults. Thus, on average, N1 and P2 were reduced in older compared to younger adults. To examine this possibility, the slow rate data were reanalyzed. The response to the first presentation of the stimulus was excluded because it represented the initiation of a new condition. The remaining data were divided into four equal quarters. Thus trials 2-13, 14-25, 26-37, and 38-49 were averaged separately. The amplitudes of N1 and P2 were analyzed using a 2-way ANOVA with a single between factor, Group (younger and older), and a single within factor, Quarter (1^{st}, 2^{nd}, 3^{rd}, 4^{th}). The ANOVAs were again run at both frontal and central ROIs.

The results are illustrated in Fig. 4. At the frontal ROI, the effect of Group was again significant, (F (1,38) = 10.06, $p < 0.01$, $\eta^2_p = 0.21$). Younger adults displayed a much larger N1 amplitude than older adults. A significant Group x Quarter interaction was also observed, (F (3,114) = 5.69, $^p = 0.002$, $\eta^2_p = 0.13$). The follow-up to the interaction revealed however that N1 amplitude for older adults did not differ among the quarters ($p < 0.05$). N1 amplitude did however differ among the four quarters for younger adults. It was largest in the first quarter and then declined slightly in amplitude in the remaining three quarters ($p < 0.02$).

Similar results were obtained at the central ROI. Thus, a significant interaction between Group x Quarter was again apparent, (F (3,114) = 5.20, $p < 0.01$, $\eta^2_p = 0.12$). For older adults, N1 did not differ among the four quarters, but for younger adults N1 was larger in the first quarter than the subsequent quarters ($p < 0.01$). N1 amplitude was significantly larger in each quarter for younger adults ($p < 0.03$).

The P2 results obtained at the frontal ROI also revealed a significant interaction, (F (3, 114) = 3.11, $p = 0.04$, $\eta^2_p = .076$). In this case, for younger adults, P2 amplitude was smaller in the first quarter than in the other three quarters ($p < 0.01$). There were no P2 amplitude differences

across the four quarters for older adults. At the central ROI, the Group x Quarter interaction was not significant ($p = 0.06$).

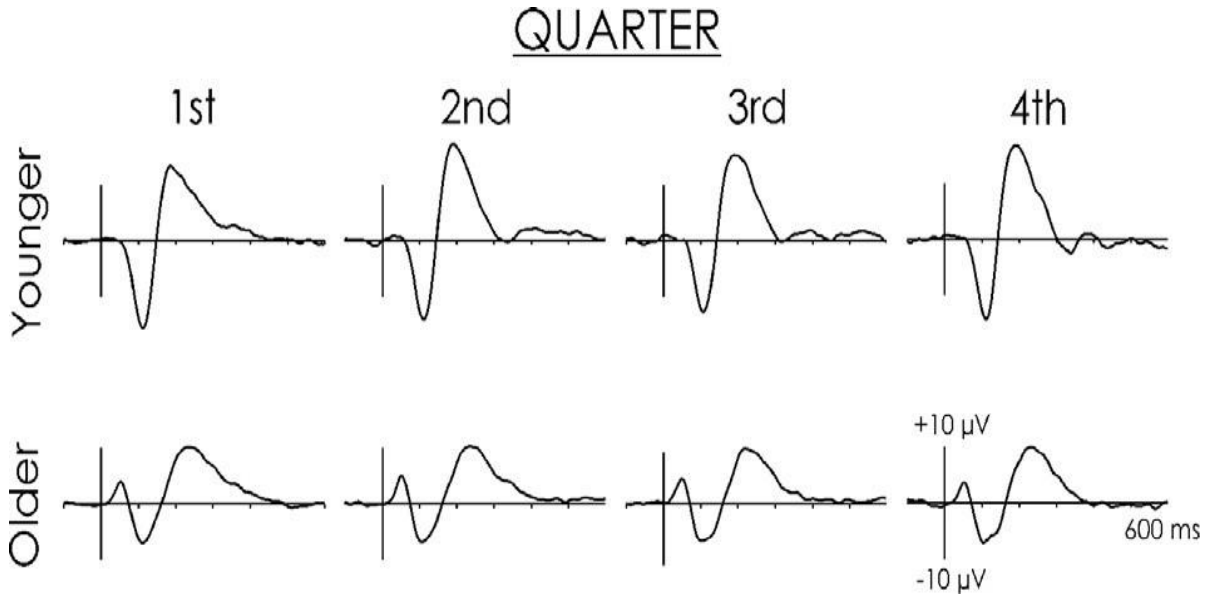

Fig. 4. Younger and older adult ERPs across the four quarters of the slow rate of presentation. Data are from the Cz electrode site. Note that the N1-P2 does not change across the four quarter for older adults. N1 is somewhat larger and P2 somewhat smaller in the first quarter than in the other three quarters for younger adults.

4. Discussion

The present study recorded ERPs during the presentation of a simple, single stimulus passive auditory paradigm. The to-be- ignored auditory stimulus was presented either rapidly, every 1.5 s, or slowly, every 12 s. Although the auditory stimuli were irrelevant and to-be-ignored, the obligatory N1 and P2 deflections were robustly elicited in both younger and older groups, regardless of the rate of presentation. Large ERP differences between the groups were apparent, but only when the stimuli were presented very slowly.

When stimuli were presented every 1.5 s, the morphology of the ERPs was similar for both younger and older adults. Neither the amplitude of the N1 nor the P2 differed between the

two groups. This finding replicates many other studies that have used similar presentation rates. Some studies have reported that N1 or P2 might be somewhat smaller or larger in older adults, but marked differences in stimulus parameters make discrepancies across studies difficult to interpret. Generally, when simple pure tones are presented in a quiet background, similar to the design employed in this study, differences between younger and older participants are not apparent (Tremblay et al., 2003). Even when N1 differences have been reported, the differences are relatively small. When auditory stimuli are presented relatively rapidly, N1 is maximum over front-central areas of the scalp and inverts in amplitude at sites inferior to the temporal cortex. The scalp distribution of this N1 has been explained by sources in and around the auditory cortex in the temporal lobe (Picton et al., 1999; Godey et al., 2001; Yvert et al., 2005; Gascoyne et al., 2016). The present findings suggest that the processing of auditory stimuli within regions of the auditory cortex did not differ between the younger and older groups. The results are also consistent with fMRI studies. Profant et al. (2015) noted that activity in the auditory cortex may be similar or perhaps somewhat higher in older compared to younger adults when simple, non-complex auditory stimuli are presented.

When the single stimulus was presented very slowly (every 12 s), in younger adults, the amplitude of N1 increased dramatically while its peak latency was delayed, occurring at about 120 ms. Importantly, the N1 and the later P2 were much reduced in older than younger adults. As is evident in the pirate plots (Fig. 3), for both younger and older participants, the variance around the means was larger when the stimuli were presented slowly. This variability was also observed by Berti et al (2017) for their slowest rate of stimulus presentation. The N1 amplitude in older adults was only slightly larger in the 12 s than the 1.5 s condition. These findings provide strong support for the notion that at an early level of processing, older adults may not

adequately compute the level of salience of an unattended incoming auditory stimulus (Lee et al., 2020). In the Näätänen (1990) model, sufficiently high activation of the transient detector system can result in the interruption of the frontoparietal network. It is thus somewhat surprising that a P3a was not also observed for the young adults in the present study, when an auditory stimulus was presented very rarely. In this regard, Morrison et al. (2019) noted that a high-intensity auditory stimulus that should have resulted in a large output from the transient detector system did elicit a large P3a in younger adults that was much attenuated in older adults. In the present study a large positivity, labelled as a P2, was elicited in younger adults and it was also much attenuated in older adults. Its latency was however delayed by about 40 ms. This latency is unusually late for a P2 but is consistent with the early occurrence of a P3a. Thus, it is possible that this positivity is a composite P2 + P3a. The P2 may have overlapped and summated both temporally (occurring at about the same time) and spatially (sharing a similar scalp distribution) with the P3a. Berti (2013) has also suggested that a longer latency P2 may also overlap and summate with the P3a. The large difference between the younger and older adult P3a is consistent with previous oddball studies when they use deviants that can be detected by the transient detector system.

The present results do not appear to support the often-observed increased distractibility in older adults (Gazzaley et al., 2008; Healey et al., 2008; Parmentier and Andrés, 2010; Schmitz et al., 2014). The small N1 and P2/P3a amplitude in older adults for both the rapid and very slow rates of presentation suggests that the strength of the interrupt signal that is sent to the frontoparietal network is too weak to cause a switch of attention away from the task at hand. The present findings and those from other P3a studies would suggest that older adults should be rarely distracted by unattended stimulus input. It is possible, however, that the threshold for

interruption may be set quite low in older adults. As such, the frontoparietal network controlling the direction and extent of attention would then be interrupted indiscriminately and frequently, regardless of the saliency level of the unattended input (Uddin, 2015). If this were the case, almost any unattended auditory input should elicit a P3a in the older group. In actual fact, a P3a is rarely elicited, even by stimuli that are biologically very relevant, such as the rare occurrence of a high intensity stimulus. This interpretation assumes that the P3a provides a precise measure of distraction. Parmentier (2014) reviews examples of studies demonstrating a dissociation between P3a and behavioral measures of distraction. Thus, it is possible for an unattended stimulus to result in a deterioration in performance on a primary task, yet not elicit a P3a.

Näätänen (1992) suggests that the N1 elicited by rapidly presented stimuli reflects a general pre-conscious, detection of the auditory environment that may subsequently lead to a general type of consciousness. Campbell et al. (1992) use the cybernetic term *fuzzy consciousness* to describe awareness that a stimulus has been presented, but without knowledge of its specific features. There is evidence that the sources for the N1 elicited by very slowly presented auditory stimuli are different from those elicited by more rapidly presented stimuli. In addition to the temporal source identified for rapidly presented stimuli, the sources of the slowly presented N1 are widespread but do include the frontal lobes (Alcaini et al., 1994; Giard et al., 1994; McEvoy et al., 1997; Sams et al., 1993). The additional widespread activation of different cortical regions that is apparent in younger adults might be less apparent in older adults. Näätänen suggests this delayed N1 may reflect a process involved in the subsequent integration and synthesis of auditory features to form a meaningful percept. Activation of several different brain regions, but especially the frontal lobe, is consistent with a widespread

salience network. The proposed integrative-synthesis of auditory features may also be necessary for computation of the saliency level of an unattended input.

There are alternate explanations for the findings. The much-diminished N1-P2 in older adults with the slow rate of stimulus presentation might also have been a result of undetected sensorineural hearing loss. If this were the case, it would have been expected that the earlier P1 would also have been attenuated in the older adults. It was, in fact, larger in the older adults in both the slow and fast conditions compared to young adults. The N1-P2 was also not attenuated in older adults in the fast condition, contrary to what would have been predicted with sensorineural hearing loss. Moreover, the intensity of the auditory stimulus (80 dB SPL) was relatively high. At higher intensities, a sound is perceived to be equally loud for both a person with elevated hearing thresholds and a person with normal hearing (Moore, 1995).

The auditory stimuli were presented using a fixed, rather than a jittered, SOA. This might have permitted participants to actively predict and anticipate the onset of the stimulus. In the present study, attention was directed to the visual modality while participants were asked to ignore the auditory sequence. It is possible that the younger adults could have divided their attention between watching the video and attending to the auditory sequence to anticipate the onset of each stimulus, particularly when stimuli were presented slowly.

Historically, very early studies of ERPs observed that when the participant actively attempted to anticipate the onset of a stimulus, a long-lasting, negative-going contingent negative variation (CNV) potential slowly developed in the time prior to its onset (Tecce, 1972; Walter et al., 1964). This negative slow wave shift should have been apparent during the pre-stimulus baseline period had participants actively attempted to anticipate the onset of the stimulus. As is apparent in the grand averaged waveforms, the pre-stimulus baseline period

was essentially flat for both younger and older participants. Moreover, active detection of the occurrence of a rarely occurring stimulus is associated with a later positivity occurring around 300 ms, the P3b. The P3b was absent in both groups. Thus, there appears to be little support for the notion that the younger group divided their attention between the visual and auditory modalities.

Even assuming that they did divide attention between the two modalities, directing attention to the auditory channel should have had little effect on the N1-P2. Ostroff et al. (2003), for example, have noted that younger and older N1-P2 group differences were not affected by whether participants actively attended to an auditory sequence or ignored it by watching a video. More recently, an fMRI imaging study (Rienäcker et al., 2020) observed few differences in the pattern of activation in younger and older adults when participants were asked to attend to a visual task while ignoring stimuli presented in the auditory modality.

This interpretation does not assume that participants were able to completely ignore the auditory stimuli. When queried, all participants did report a passive awareness of the to-be-ignored auditory stimuli. Such passive awareness is consistent with the Näätänen's claim that the presence of an N1 reflects a general (or fuzzy) consciousness of the auditory stream.

There has been much debate about the cause of the large re- duction in N1 as stimuli are presented with increasing rapidity. A common explanation is that this reduction in N1 is a result of the refractoriness of the neuronal population involved in its generation (Budd et al., 1998; Ritter et al., 1968; Rosburg & Mager, 2021). The refractory period may be directly influenced by the brief duration of auditory echoic memory (Picton et al., 1978). The amplitude of N1 will therefore be small if a stimulus occurs prior to the fading of the representation of the previous stimulus in echoic memory.

Other authors appear to favor an alternative habituation ex- planation (Ruusuvirta, 2020; but see Rosburg & Mager, 2021). N1 amplitude is large in the initial trials but then decays upon repetition of the stimulus. The reduction in the N1 and P2 in older adults with the slow rate of presentation might thus have been a result of a rapid habituation of the response, or a fatigue effect over the duration of the study. That is, the initial responses of the older adults may have been as large as those of younger adults, but subsequently, N1 amplitude would have decayed while the amplitude for younger adults remained stable. However, there is little evidence to support the notion that responses decayed over time for older adults. Averages computed over both halves of the study did not differ. Moreover, within the slow condition, averages computed in each of the four quarters of the study revealed that the ERPs were very stable in each quarter for both younger and older adults.

The results of the present study may also have many potential clinical implications. Results were measured both baseline-to- peak and peak-to-peak. Baseline-to-peak measurement will be affected by slow baseline drift. Thus, in an individual participant, a negative-going baseline drift might cause the N1 to be exceedingly large and the P2 exceedingly small. An N1-P2 peak-to-peak measure will not be affected by these baseline shifts. The peak-to-peak measure did serve to reduce the number of outliers. The N1-P2 peak-to-peak difference between younger and older adults was also much larger than the respective baseline-to-peak differences. The peak-to-peak N1-P2 measure also has the advantage that fewer stimuli repetitions will be needed because its amplitude (about 20 μV in younger adults) will be larger than either N1 or P2 alone (about 10 μV for each). These findings indicate that overall testing time can therefore be reduced.

Nevertheless, from a theoretical perspective, interpreting the sensory and cognitive processes reflected by a composite N1-P2 measure will be more difficult. The peak-to-peak measure assumes that N1 and P2 are affected by similar experimental manipulations, reflecting similar processes. In brief, N1 and P2 co-vary and are not independent ERP components. While many experimental manipulations, including the effects of stimulus intensity and its rate of presentation, do indeed affect N1 and P2 in a similar manner, not all experimental manipulations do so. For example, during unconscious states, such as natural sleep, the amplitude of N1 may be much reduced but the amplitude of P2 may be much enhanced compared to the waking state (see Colrain and Campbell, 2007; Crowley and Colrain, 2004 for early reviews). The functional dis- tinction between the N1 and P2 components may be somewhat incidental from a clinical and applied diagnostic-biomarker perspective. What is critical from a biomarker perspective is whether a measure can accurately classify individuals.

5. Conclusion

A simple paradigm, consisting of a single moderate intensity auditory stimulus occurring either relatively rapidly (ever 1.5 s) or very slowly (every 12 s), was passively presented to younger and older participants. The amplitudes of N1 and P2 did not significantly differ between the two groups when stimuli were presented rapidly. On the other hand, the amplitudes of N1 and P2 were much larger for the younger than the older group when stimuli were presented slowly.

Stimuli that occur very rarely are highly salient. These results suggest that older participants are less able to compute saliency levels of unattended stimulus input than younger participants. There was some overlap in the N1 and P2 data between individual younger and older participants. Additional research is required to determine optimal stimulus parameters. The

effects of even slower rates of stimulus presentation and perhaps different intensity levels warrant further investigation. Still, a marked advantage of the use of this very simple paradigm is that the ERP responses occur independent of attention, task demands, and what the participant *is doing*. Testing could be completed during a brief 15-minute testing period. Because the paradigm is so simple, it can be implemented on almost any low-cost commercial ERP system, requiring only a few electrode placements.

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Study 3

Study 3 was published in *Frontiers in Aging Neuroscience* and is formatted in accordance with the requirements of that journal.

Kamal, F., Morrison, C., Campbell, K., & Taler, V. (2021). Event-Related Potential Measures of the Passive Processing of Rapidly and Slowly Presented Auditory Stimuli in MCI. *Frontiers in Aging Neuroscience 13*, 161. https://doi.org/10.3389/fnagi.2021.659618

This study was a follow-up to study 2. In study 2 when stimuli were presented slowly, N1 and P2 were smaller in older adults compared to younger adults. It is possible the P2 that was elicited by the very slowly presented stimuli may be overlapped by the P3a, reflective of the interruption of the frontoparietal network.

Study 3 employs the same simple paradigm used in study 2, in which a single auditory stimulus was presented either rapidly or slowly. The same sample of 20 older adults from Study 2 were compared to 20 people with MCI. Some authors suggest that deficits observed in the salience and frontoparietal network systems in healthy older adults may further decline in people with MCI. If this is the case, it might be expected that when stimuli are presented very rarely, the N1 and P2/P3a would be smaller in people with MCI than in the healthy older adults.

Abstract

Much research effort is currently devoted to the development of a simple, low-cost method to determine early signs of Alzheimer's disease (AD) pathology. The present study employs a simple paradigm in which event-related potentials (ERPs) were recorded to a single auditory stimulus that was presented rapidly or very slowly while the participant was engaged in a visual task. A multi-channel EEG was recorded in 20 healthy older adults and 20 people with mild cognitive impairment (MCI). In two different conditions, a single 80 dB sound pressure level (SPL) auditory stimulus was presented every 1.5 s (fast condition) or every 12.0 s (slow condition). Participants were instructed to watch a silent video and ignore the auditory stimuli. Auditory processing thus occurred passively. When the auditory stimuli were presented rapidly (every 1.5 s), N1 and P2 amplitudes did not differ between the two groups. When the stimuli were presented very slowly, the amplitude of N1 and P2 increased in both groups and their latencies were prolonged. The amplitude of N1 did not significantly differ between the two groups. However, the subsequent positivity was reduced in people with MCI compared to healthy older adults. This late positivity in the slow condition may reflect a delayed P2 or a summation of a composite P2 + P3a. In people with MCI, the priority of processing may not be switched from the visual task to the potentially much more relevant auditory input. ERPs offer promise as a means to identify the pathology underlying cognitive impairment associated with MCI.

INTRODUCTION

Mild cognitive impairment (MCI) is a condition in which individuals demonstrate cognitive impairment with no impairments in social or occupational function. MCI may represent a transitional stage between healthy aging and Alzheimer's disease (AD) with 20–40% of people with MCI progressing to dementia (Roberts and Knopman, 2013). The early identification of MCI and prediction of decline associated with progression to AD has been the subject of intense research (Sperling et al., 2011). Much of this research is devoted to the development of a simple, low-cost, and readily available biomarker to determine the early signs of neuropathology underlying AD.

Neuropsychological tests are often used to diagnose AD. Performance on almost all neuropsychological and cognitive tasks will inevitably be affected by the participant's ability and willingness to maintain attention (Sturm et al., 1999; Buschman and Miller, 2010; Oberauer, 2019). Attentional control and the maintenance of attention may be a challenge for older adults, and particularly for people with MCI (Saunders and Summers, 2010). A good deal of early processing of sensory input is said to be automatic; that is, it is completed whether or not the participant attends to the sensory channel. Determining the extent of processing of unattended input is methodologically difficult. The processing of unattended input can be measured by event-related potentials (ERPs), the changes in the electrical activity of the brain elicited by an external stimulus or internal psychological event. ERPs consist of a series of negative- and positive-going components, thought to reflect different aspects of information processing. Some of these ERP components are elicited independently of attention.

All auditory stimuli elicit an obligatory negative component, the N1, occurring around 100 ms post-stimulus, followed by a later positivity, the P2, occurring around 180 ms. In the

classic Näätänen (1990) model of auditory processing, a transient detector system detects abrupt onsets and offsets of auditory stimuli. The output of this system, reflected by the amplitude of N1, varies directly with the rate of stimulus presentation and the energy (intensity) of the stimulus, thus defining its salience. N1 and the P2 will therefore be larger for higher intensity auditory stimuli and stimuli presented slowly. Critically, it has long been known that attention to the auditory channel has relatively little effect on N1 and P2 (Picton and Hillyard, 1974), especially when stimuli are presented slower than every 1 s (Schwent et al., 1976; Hansen and Hillyard, 1988; Woldorff, 1995).

In the Näätänen (1990) model, sufficiently high activation of the transient detector system will result in an interrupt signal being sent to the frontoparietal network controlling processing priorities (Goulden et al., 2014). Attention may then be switched from the ongoing cognitive activities to the processing of the highly salient stimulus event. A later positivity, the P3a, peaking between 200 and 300 ms, is thought to reflect processes associated with the switching of attention (Escera et al., 1998; Masson and Bidet-Caulet, 2019).

The P3a is often elicited in oddball paradigms by a deviant representing a large change from the frequently occurring standard stimulus. There is evidence that a P3a can also be elicited by a single, rarely presented stimulus. When the rate of stimulus presentation is very slow (> than every 10 s), N1 and P2 become very large and their peak latencies are delayed by about 20–30 ms (Alcaini et al., 1994; Budd et al., 1998; Muller-Gass et al., 2008; Pereira et al., 2014). Berti (2013) questioned whether this P2 might be better described as a P3a. The Berti study required subjects to decide on a visual stimulus. On 13% of trials, the visual stimulus was preceded by an irrelevant auditory stimulus. Performance on the visual task subsequently deteriorated, compared to trials in which no auditory stimulus preceded the visual stimulus. This

suggested that attention had been switched from the processing of the visual task to the processing of the auditory stimulus. Such processing is associated with the P3a rather than the P2. In the present study, we describe the positivity following the very slow presentation of the stimulus as a composite P2/P3a. Rinne et al. (2006) and Muller-Gass et al. (2007) employed oddball paradigms in which the rare deviant was created by either decreasing or increasing the intensity of the standard. Only the intensity increase elicited a large P3a, presumably because it resulted in large output from the transient detector system. In this regard, Cecchi et al. (2015) employed an oddball paradigm with a white noise burst deviant. The intensity of white noise at times increases and as such will be detected by the transient detector system. A P3a was elicited by the noise burst in healthy older adults but was reduced in amplitude in people with MCI.

There is disagreement about how the N1 and P2 change with aging. In most studies, stimuli are presented relatively rapidly, every 1–3 s. Many of these studies have failed to find N1 or P2 differences between younger and older adults, while some have reported larger responses for younger adults and others have reported larger responses for older adults (Pfefferbaum et al., 1980; Cranford and Martin, 1991; Bertoli et al., 2005; Harkrider et al., 2005; Čeponiene et al., 2008; McCullagh and Shinn, 2013; Stothart and Kazanina, 2016; Kamal et al., 2021). Stimulus features and experimental parameters differ widely across studies, making comparison difficult. In general, even when differences between younger and older participants are observed, they tend to be small. More consistent results have been observed when stimuli are presented very slowly. Berti et al. (2017) and Kamal et al. (2021) varied the rate of stimulus presentation of the to-be-ignored auditory stimuli. When the auditory stimuli were presented very slowly (every 10 and 12 s respectively), the amplitude of both N1 and P2/P3a was much reduced in the older compared to younger adults.

A limited number of studies have examined the N1 and P2 in people with MCI (for a review see Morrison et al., 2018). When the stimuli are presented relatively rapidly, most studies have not found N1 and P2 differences between healthy older adults and people with MCI (Golob et al., 2002; Lai et al., 2010; Lister et al., 2016; Bidelman et al., 2017; Buján et al., 2019). Some studies have reported a somewhat larger N1 or a reduced P2 in people with MCI, at least in certain conditions (Irimajiri et al., 2005; Golob et al., 2007; Lister et al., 2016; Buján et al., 2019). While some of these differences have been attributed to the severity of MCI, experimental parameters again tend to vary widely across studies.

The effects of very slowly presented stimuli have yet to be examined in people with MCI. The large age-related changes in N1 and P2/P3a elicited by auditory stimuli presented very slowly offer much promise for early identification of MCI. The paradigm used by Kamal et al. (2021) has many advantages. Testing can be completed within 15 minutes. Moreover, the participant does not need to attend to the auditory stimuli; the ERPs are elicited passively, independent of attention. In the present study, participants were asked to ignore the auditory stimuli while engaged in a visual task. We compared the passive processing of the auditory stimuli in people with MCI and cognitively healthy older adults. The auditory stimuli were presented rapidly and very slowly in separate conditions. Berti et al. (2017) and Kamal et al. (2021) observed large N1 and P2/P3a differences between younger and older adults only when stimuli were presented very slowly. It was therefore expected that with the additional decline observed in people with MCI compared to healthy older adults, ERP amplitude differences would also only be observed in the slow condition.

MATERIALS AND METHODS

Participants

Forty-one participants took part in this study. One participant was excluded from the analysis because of noisy EEG data (see "EEG Data Recording" section). A total of 40 participants' data were therefore analyzed: 20 cognitively healthy older adults (12 females; age range = 67–81 years; M = 72.4 years) and 20 people with MCI (10 females; age range = 68–84 years; M = 74.2 years). Older adults were recruited through word-of-mouth and announcements displayed at community centers. Participants with MCI were recruited from the Bruyère Memory Program. They were diagnosed with MCI based on the clinical history and a neurological exam by a physician with expertise in neurodegenerative conditions. They underwent a CT scan and blood work to rule out reversible causes of cognitive impairment. Participants were not included if their cognitive decline was thought to be related to other comorbidities.

The Montreal Cognitive Assessment (MoCA) was used to screen for cognitive decline (Nasreddine et al., 2005). The cutoff for the MoCA in cognitively healthy older adults was 24. Healthy older adults scored significantly higher ($p < 0.001$) on the MoCA (M = 27.05, SD = 1.46) than people with MCI (M = 22.79, SD = 3.24). Participants also completed a one-hour neuropsychological battery to assess general cognitive functioning (see Supplementary Table 1). The healthy older adults also participated in the Kamal et al. (2021) study. All participants reported no history of neurological or psychiatric conditions. All participants reported normal hearing but also completed pure tone audiometric testing for 500, 1,000, and 2,000 Hz frequencies.

This study was approved by the University of Ottawa and Bruyère Research Institute ethics boards. Participants provided informed written consent before starting the study and an honorarium was given as compensation.

Stimuli and Procedure

Participants were seated in a sound-attenuated testing room. A single 80 dB SPL (sound pressure level) 1,000 Hz pure tone auditory stimulus, having a total duration of 55 ms (5 ms rise/fall time) was presented binaurally through Sony MDR-V6 headphones. The stimuli were presented every 1.5 s in a fast condition and every 12.0 s in a slow condition. A total of 400 and 50 stimuli were presented in the fast and slow conditions, respectively. Each condition lasted 10 min. The order of the two conditions was randomized across participants. The auditory conditions were presented a second time in reverse order. A total of 100 and 800 stimuli were therefore presented in the slow and fast conditions, respectively. The repetition of stimulus presentations served to reduce the amplitude of the random background noise in the EEG.

Participants were instructed to watch a silent, subtitled video and to ignore the presentation of the irrelevant auditory stimuli. Processing of the auditory stimuli thus occurred passively.

EEG Data Recording

Continuous EEG activity was recorded from 31 active silver-silver chloride electrodes, attached to an electrode cap placed according to the international 10-10 system. An EOG electrode was placed on the infraorbital ridge of the left eye to monitor vertical eye movements and blinks. An electrode placed on the tip of the nose served as a reference for all channels. An advantage of active electrodes is that impedance can be relatively high (Kappenman and Luck, 2010). Inter-electrode impedance was kept below 20 kΩ. The impedance at F3, Fz, F4, and C3, Cz, C4, which comprised regions of interest (ROIs), was below 10 kΩ. The EEG and EOG signals were sampled at a rate of 500 Hz.

The EEG was then visually examined to remove channels containing high levels of noise. These channels were substituted by interpolating the data of the surrounding electrode sites (Perrin et al., 1989). Interpolation was not applied to any of the ROI sites. The data of one participant were removed from further analysis because more than four channels with excessive noise were rejected. A 0.5 Hz high-pass and a 20 Hz low-pass digital filter (24 dB/octave roll-off) were then applied to the data.

Eye movement and blink artifacts occurring independently of EEG activity were identified and corrected using Independent Component Analysis (ICA; Makeig et al., 1996). To do so required computation of vertical and horizontal EOG activity. A vertical EOG was computed by subtracting FP1 from the inferior orbital activity. Horizontal eye movements were computed by subtracting the FT9 and FT10 activity. The EEG was subsequently reconstructed into single 700 ms epochs starting 100 ms before stimulus onset. The average of all activity in the pre-stimulus period served as a zero-voltage baseline. Drifts in post-stimulus voltage from this baseline were then corrected for each epoch. Epochs containing EEG activity exceeding ±100 μV were subsequently rejected from the averaging. In the fast condition, fewer than 1% of trials were rejected for healthy older adults, while fewer than 3% were rejected for people with MCI (p = 0.20). In the slow condition, fewer than 2% of trials were rejected for either group.

ERP Quantification

The amplitude of N1 and P2/P3a was quantified as the mean of all data points within ± 25 ms of their peak amplitude identified in the grand average of each group. In both groups, N1 peaked at 95 ms in the fast condition and 115 ms in the slow condition. The subsequent P2/P3a positivity peaked at 205 ms in the fast condition and 230 ms in the slow condition.

N1 and P2/P3a were quantified at frontal (F3, Fz, F4) and central (C3, Cz, C4) ROIs, where they are largest. Separate 2-way ANOVAs were initially run at these ROIs for both the N1 and P2/P3a with a single between-subjects factor, Group (Older, MCI), and a single within-subjects factor, Rate of Presentation (Fast, Slow). The results were quite similar at both electrode sites. For this reason, the data were collapsed across ROIs. A 3-way ANOVA was then run with the between-subjects factor, Group (Older, MCI), and two within-subjects factors, Rate (Fast, Slow) and ROI (Frontal, Central). Previous research has shown large ERP differences between younger and older participants but only when stimuli were presented very slowly. We, therefore, expected to observe differences between MCI and healthy older adults only in this condition. For this reason, planned comparisons were run on interactions involving Group and Rate of Presentation.

RESULTS

Figures 1, 2 illustrate the multi-channel ERPs for both groups in the fast and slow conditions, respectively. As may be observed, a robust negative peak, N1, occurring at about 100 ms was elicited in both conditions followed by a later positivity, P2/P3a, occurring at about 200 in the fast condition and 230 ms in the slow condition.

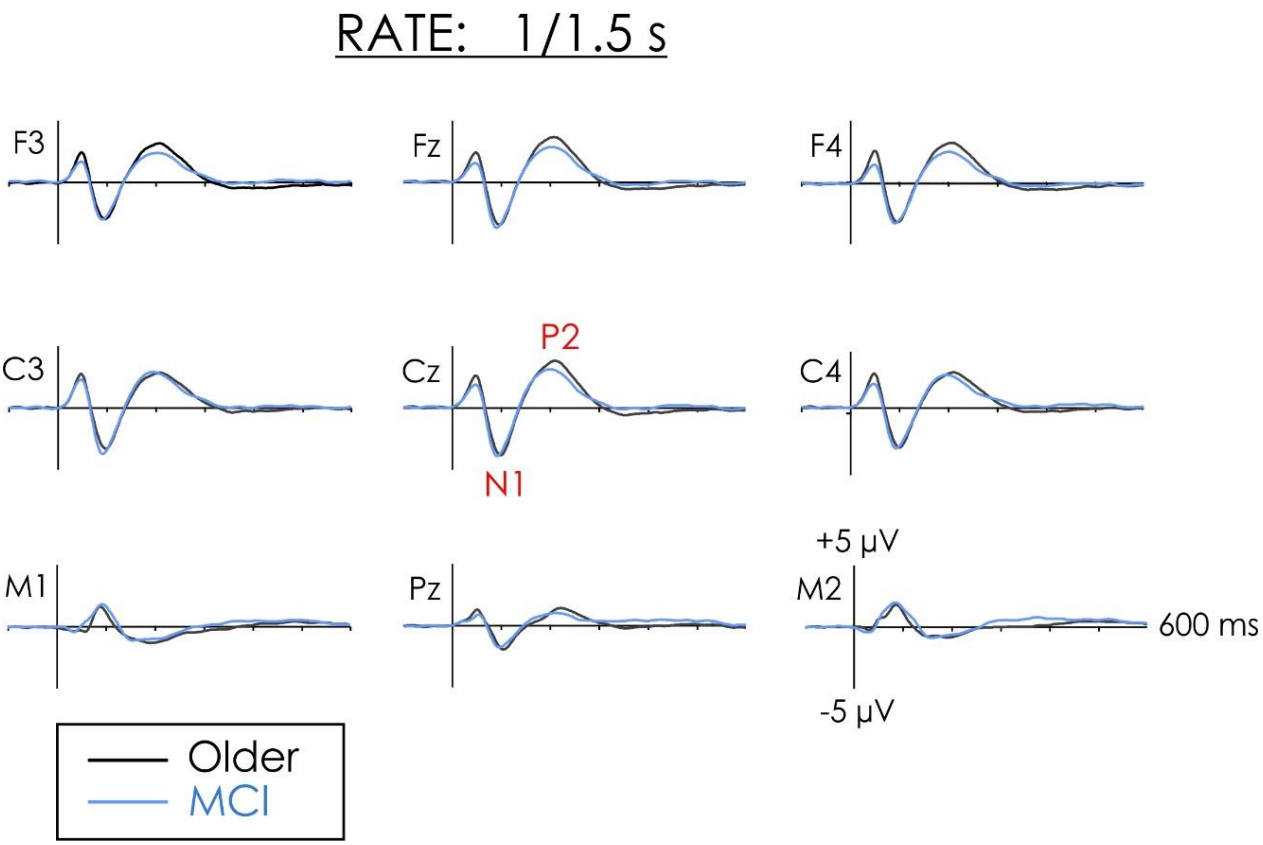

FIGURE 1 | Grand averaged event-related potentials (ERPs) from healthy older adults and people with mild cognitive impairment (MCI) in the fast rate of presentation condition. N1 and P2 amplitude did not differ between the two groups.

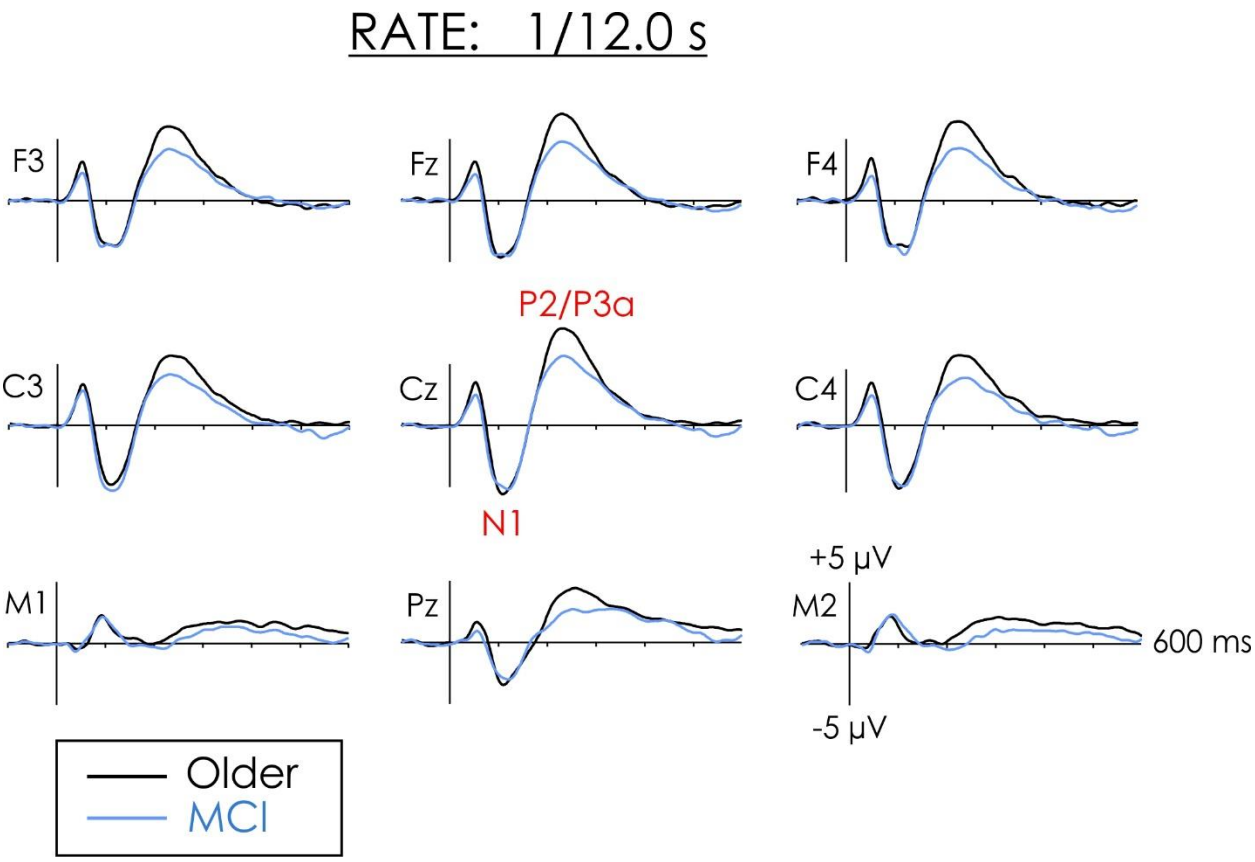

FIGURE 2 | Grand averaged ERPs from healthy older adults and people with MCI in the slow rate of presentation condition. The amplitude of N1 did not differ between the groups. The amplitude of P2 was larger for healthy older adults than people with MCI at both the frontal and central regions of interest (ROIs).

N1

A major effect of Rate of Presentation was observed for the amplitude of N1, $F(1,38) = 29.05$, $p < 0.001$, $\eta^2_p = 0.43$. N1 was larger in the slow than in the fast condition. Overall Group differences were not significant ($F < 1$) and interactions involving Group were not significant ($F < 1$). Thus, regardless of the rate of presentation, the amplitude of N1 did not significantly differ between groups at either frontal or central ROIs.

Figure 3A presents the grand averaged ERPs at Cz including SDs around the average. A pirate plot illustrating both descriptive and inferential statistics (Phillips, 2017) of the N1 data is presented in Figure 3B. As may be observed, the confidence intervals (CIs) for N1 were very

similar for both groups. There was considerable overlap between healthy older adults and people with MCI in both the fast and slow conditions.

P2/P3a

An overall significant main effect of the Rate of the presentation was also observed for P2/P3a. P2/P3a was larger in the slow than the fast condition, $F(1,38) = 28.30$, $p < 0.001$, $\eta^2_p = 0.43$. The Group × Rate interaction was not significant $F(1,38) = 2.53$, $p = 0.12$, $\eta^2_p = 0.06$. The trend of the interactions was, however, in keeping with a priori predictions. Follow-up Fisher's Least Square Significance procedures revealed the source of the interactions. Group differences were not significant in the fast condition ($p < 0.20$). However, in the slow condition, P2 was significantly larger for healthy older adults than for people with MCI ($p < 0.03$). The Group × Condition × ROI interaction was not significant, $F < 1$.

A pirate plot of the P2/P3a at the central ROI is presented in Figure 3C. The mean amplitude of the P2/P3a was larger for the older than the MCI group, but only in the slow condition. There was, however, considerable overlap in individual participants' amplitudes within the two groups.

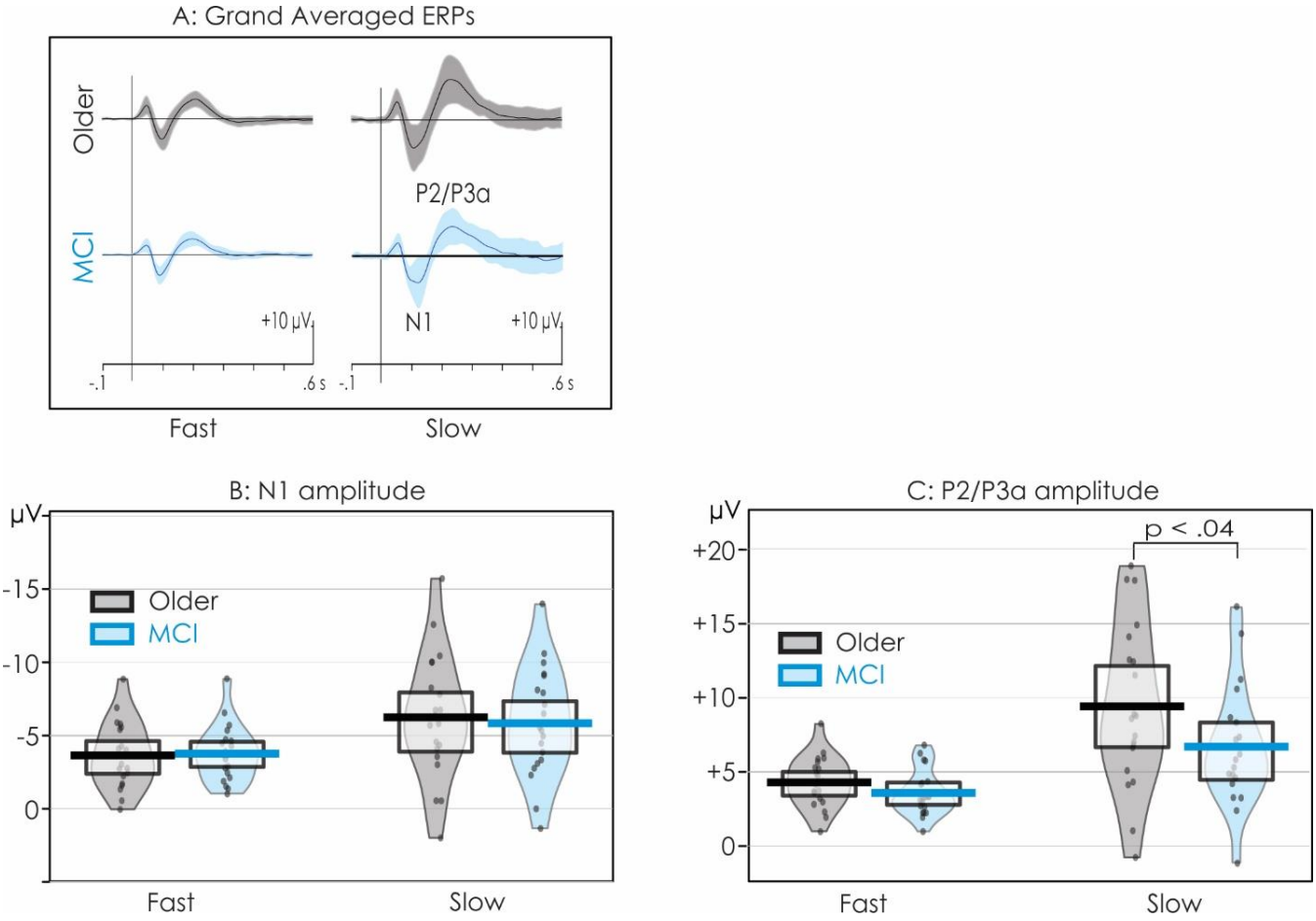

FIGURE 3 | Pirateplots of N1 and P2 data providing both descriptive and inferential statistics. Data are collapsed across all central electrode (C3, Cz, C4) sites. The grand averages and SDs (shaded) are illustrated in panel (A). The mean amplitudes of N1 and P2 (thick, solid horizontal line), 95% confidence intervals (CIs; light horizontal box), smooth frequency distribution (shaded area), and individual data points (jittered) are presented in panels (B,C) respectively. The mean amplitude of N1 did not differ between the groups in the fast condition. On the other hand, P2 was larger for the healthy older adults when stimuli were presented slowly.

Changes Across Quarters

A reduced P2/P3a was observed in people with MCI in slow condition (see Figure 4). Possibly, their ERPs varied over time, while being more consistent for healthy older adults. The data were separated into four equal quarters to explore changes over time. The first trial was excluded from this analysis because it marked the initiation of a new condition. Thus, for the slow condition trials 2–13, 14–25, 26–37, and 38–49 were averaged separately. The main effect of the Quarter

was not significant ($F < 1$). Importantly, the Group x Quarter interaction was also not significant ($F < 1$).

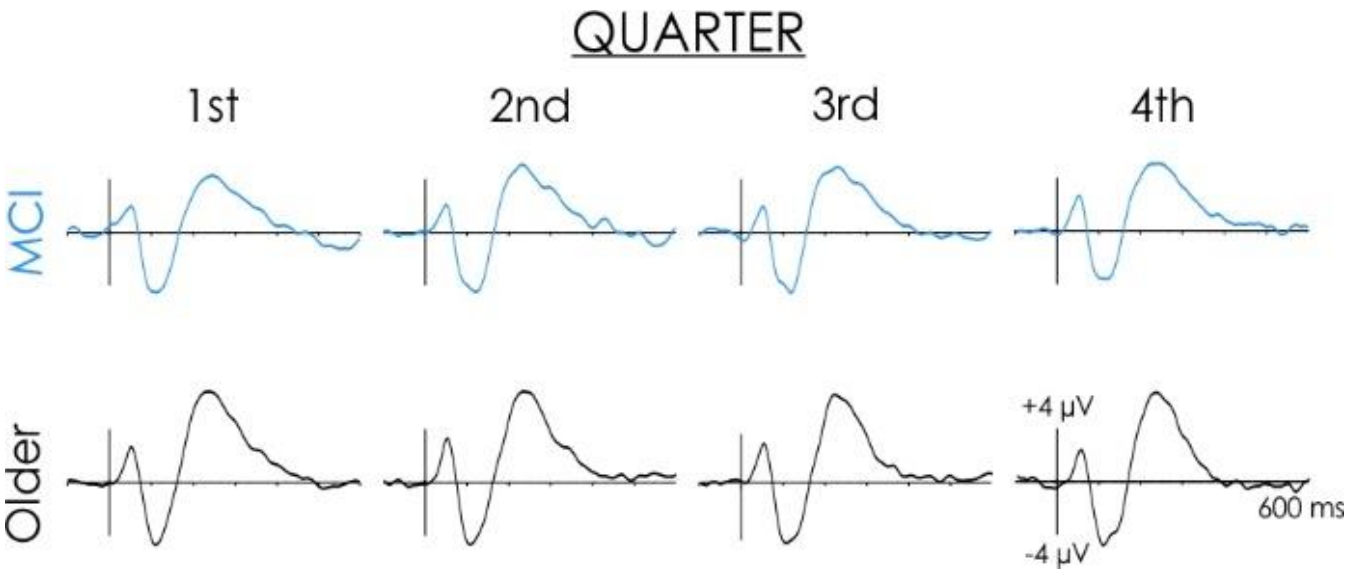

FIGURE 4 | Healthy older adult and MCI grand averaged ERP waveforms across the four quarters of the slow rate of presentation condition. Data presented are from the Cz electrode site. Note the N1 and P2 did not change across the four quarters for either healthy older adults or people with MCI.

Correlations

Correlations were also computed between the P2/P3a amplitude and the MoCA scores within the MCI group. In the fast condition, no significant correlations were found $r = 0.24$, $p = 0.22$ at Fz, and $r = 0.32$, $p = 0.22$ at Cz. In the slow condition, the correlations were also not significant, $r = 0.32$, $p = 0.19$ at Fz, and $r = 0.40$, $p = 0.09$ at Cz.

Scalp Distribution

N1 and P2/P3a were both large over fronto-central areas of the scalp. Interactions involving Site and Group and Site and Rate were not significant for either N1 or P2/P3a ($F < 1$ in all comparisons). Spline-interpolated scalp distribution maps of N1 are illustrated in the Supplementary Figure 1.

DISCUSSION

The auditory stimulus in both the fast and slow conditions elicited a robust N1 and P2/P3a. In both healthy older adults and people with MCI, the amplitude of N1 and P2/P3a increased and their latencies were prolonged when the stimuli were presented very slowly. This finding replicates several other studies in younger adults (Alcaini et al., 1994; Budd et al., 1998; Muller-Gass et al., 2008; Pereira et al., 2014). There is evidence that the sources of the auditory N1 differ depending on the rate of stimulus presentation. When stimuli are presented relatively rapidly, the sources have been identified to be in and around the auditory cortex. When stimuli are presented very slowly, the large increase in the amplitude of the N1 and P2/P3a, and their prolonged latencies has been explained by activation of additional widespread sources, particularly in the frontal lobes (Sams et al., 1993; Alcaini et al., 1994; Giard et al., 1994; McEvoy et al., 1997). Many imaging studies have noted a deterioration and loss of function in the frontal regions with age and in early dementia (Driscoll et al., 2009; Machulda et al., 2009; Madden et al., 2012; Salami et al., 2012).

It was expected that differences between healthy older adults and people with MCI would be largest when stimuli were presented very slowly, and smallest when stimuli were presented rapidly. The finding that the N1 and P2 amplitudes did not differ between the two groups in the fast condition is consistent with other studies (Golob et al., 2002; Lai et al., 2010; Lister et al., 2016; Bidelman et al., 2017; Buján et al., 2019). However, contrary to expectations, the amplitude of N1 was not significantly reduced in people with MCI when stimuli were presented slowly. The amplitude of N1 can be used to define the salience of stimulus input. N1 amplitude is larger when transient energy (intensity) is higher or when the time between the onset of stimuli is very long (i.e., when stimuli are presented slowly). In the present study, there is thus little

evidence that at the early level of processing, people with MCI have a deficit in computing the salience of unattended auditory stimuli compared to healthy older adults.

In the present study, when stimuli were presented very slowly, planned comparisons indicated that the P2/P3a was significantly larger in older adults than in people with MCI. Its peak latency, around 230 ms, is more consistent with that of a P3a than a P2. Distinguishing between the P2 and P3a processes can be difficult because they may overlap and summate both temporally (occurring at about the same time) and spatially (sharing a similar scalp distribution).

When stimuli were presented slowly, it could be argued that the reduced P2/P3a in people with MCI is a result of a variable response within this condition. The reduction in this positivity in people with MCI in the slow condition might have been a result of rapid habituation, or a fatigue effect throughout the study. Ruusuvirta (2021) notes that the ERP response will be large in the initial trials but will decay upon repetition of the stimulus. Thus, in people with MCI, it is possible that the P2/P3a response was large in the initial trials but subsequently became much smaller. By contrast, in healthy older adults, the P2/P3a response may not have varied within the condition. However, there was little evidence to support this notion. When the averages were computed across each quarter of the study, ERP response showed little variance over time for either group.

The reduced P2/P3a in MCI, also observed by Cecchi et al. (2015), supports the view that the operations of the frontoparietal network may be dysfunctional in MCI. At first glance, the reduced P2/P3a does seem to contradict the theory that people with MCI are less able to inhibit the processing of irrelevant, unattended stimulus input (Belleville et al., 2008; Johns et al., 2012; Rabi et al., 2020; but see Rey-Mermet and Gade, 2018). In the present study, although the auditory stimuli were not attended to, their very rare occurrence should have been deemed to be

a potentially highly relevant event. The amplitude of N1 did not significantly differ between people with MCI and healthy older adults. This finding suggests that people with MCI can establish the relevance/salience of the incoming stimulus event. To determine the actual relevance of such input would require a switch of processing priorities and the continuation, rather than the inhibition, of further processing. The dysfunction in people with MCI, therefore, appears to occur later as a result of a reduction in the ability to determine processing priorities.

In people with MCI, the correlational analyses indicated a small positive relationship between the amplitude of P2/P3a and MoCA scores. Nevertheless, the correlations did not attain statistical significance, perhaps because of the limited range of MoCA scores. It is also possible that the specific cognitive functions reflected by the P2/P3a are different from the more global cognitive functions measured by the MoCA.

CONCLUSION

Several studies have proposed the use of electrophysiological measures as a biomarker of MCI (Gu and Zhang, 2017; Morrison et al., 2018; Paitel et al., 2020). The very simple paradigm used in the present study has the advantage that it could be readily implemented on almost any low-cost commercial system. Testing can be completed in a short 15-min period. It has the marked advantage that the ERP responses elicited by the slowly-presented auditory stimuli occur relatively independent of attention, task demands, and what the participant is doing. From a clinical and applied perspective, whether the positivity occurring around 230 ms reflects P2 or P3a activity may be somewhat incidental. What is critical for its use as a biomarker is how accurately ERPs can classify people with MCI and cognitively healthy older adults. Despite overlap among individual participants, the P2/P3a group differences in the slow condition were significant. ERPs thus offers promise as a means to identify the pathology underlying cognitive

impairment associated with MCI. Future research should examine the effects of even slower rates of stimulus presentation and different intensity levels. The use of an oddball paradigm which includes white noise and novel environmental sound deviants, known to elicit a large P3a, might also be employed. A longitudinal design should also be employed to examine differences between MCI participants who convert to dementia and those who remain stable. These studies could reveal the electrophysiological changes associated with conversion to dementia at an individual level.

Supplementary Table 1: Healthy older adult and MCI means (SD) for demographic neuropsychological measures.

	Healthy Older Adult	MCI	*p*
Age	72.41(3.85)	74.21(4.69)	.12
Education	16.00(2.85)	16.61(3.57)	.56
MoCA	27.05(1.46)	22.79(3.24)	**<.001**
Digit Span Forward	10.85(2.39)	10.16(2.17)	.18
Digit Span Backward	7.80(2.42)	7.47(2.14)	.33
Letter # Sequencing	10.45(2.21)	8.95(2.01)	**.017**
WCST	3.75(1.33)	2.50(1.33)	**<.001**
Stroop1-3	56.75(22.84)	60.39(12.40)	.28
Stroop2-3	29.85(13.25)	30.28(10.03)	.46
Digit Symbol-Written	44.95(5.47)	34.37(11.58)	**<.001**
Digit Symbol-Oral	52.40(9.32)	40.32(11.77)	**<.001**
FAS Fluency	42.00(9.70)	34.94(7.70)	**.008**
Animals	20.45(5.36)	13.67(4.80)	**<.001**

Notes: Independent sample one-tailed t-test were computed on the neuropsychological scores because it was expected that MCI would score lower than healthy older adults. WCST= Wisconsin Card Sorting Test (categories completed). Stroop1-3= a subtraction of Stroop 3 which requires participants to name the ink color of color words printed in a different color (e.g., the word "RED" printed in green ink) from Stroop1 which requires participants to read name of colors. Stroop 2-3 = a subtraction of Stroop 3 from Stroop 2 which requires participants to name the color of "X's". Digit Symbol-Written = match the digit to corresponding symbol by writing the answer. Digit Symbol-Oral= match the digit to corresponding symbol by reading the answer aloud. FAS Fluency = is a sum score of three individual fluency tasks in which participants are asked to list as many words as they can that begin with three letters (F, A, and S) in 1 minute. Animal fluency = participants are asked to list as many animals as they can in 1 minute.

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Study 4

Study 4 has been submitted to the journal, *Neuroimage,* and is formatted in accordance with the requirements of this journal.

Kamal, F., Morrison, C., Campbell, K., & Taler, V. (2021). The influence of different types of auditory change on processes associated with the switching of attention in older adults and people with MCI. Submitted to *Neuroimage*.

Study 4 was carried out as a follow-up to Study 3. In Study 3, when the stimuli were presented very slowly, the amplitude of N1 and P2 increased in both groups and their latencies were prolonged. The amplitude of N1 did not significantly differ between the two groups. However, the subsequent positivity was reduced in people with MCI compared to healthy older adults. There is some evidence that this P2 may also be overlapped both spatially and temporally with a later positivity, the P3a. The lower P2/P3a in people with MCI suggests that the frontoparietal network may fail to give sufficient priority to the processing of potentially highly relevant stimulus input. A limitation to this interpretation is that it is based on the assumption that the late positivity observed in the single stimulus paradigm does indeed reflect P3a activity. A true P3a has often been recorded in oddball paradigms consisting of a frequently presented standard and a rarely presented deviant. Not all deviants will elicit a P3a. In Study 4, the P3a in healthy older adults will be compared to that of people with MCI in two different experiments (36/40 participants in this study overlapped with the participants in Study 3). In Experiment 1, the deviants represented either decreases or increases in the intensity of the standard. The increase in intensity has elicited a large P3a in other studies. In Experiment 2, six different deviants were presented, including white noise and environmental sounds, known to elicit a large P3a in previous studies.

Abstract

The involuntary detection of acoustic change following presentation of rarely presented deviant auditory stimulus will elicit an event-related potential (ERP), the deviant-related negativity (DRN). If the deviant stimulus is potentially highly relevant, a later P3a may also be elicited. This is thought to reflect processes associated with the switching of attention away from current processing demands. Previous studies have indicated that cognitively healthy older adults are less able to switch processing priorities upon presentation of these stimuli. The present study examined if people with mild cognitive impairment (MCI) are less able to switch processing priorities than healthy older adults. Two experiments were run. In each, 20 healthy older adults and 20 people with MCI were presented with to-be-ignored auditory stimuli while engaged in a visual task. The auditory stimuli consisted of frequently-presented standards and different types of deviants. In Experiment 1, the deviants represented either decreases or increases in the intensity of the standard. In Experiment 2, six different deviants were presented. In both experiments, a DRN was elicited by all deviants. Its amplitude did not, however, significantly differ between the two groups. Only the increment, white noise, and environmental sound deviants elicited a P3a. This P3a also did not significantly differ between the two groups. These results indicate that there is no evidence that the ability to switch processing priorities differs between people with MCI and cognitively healthy older adults.

Keywords: attention capture, MCI, Auditory ERPs, MMN, DRN, P3a

1. Introduction

An increase in the aging population has led to a rise in the number of older adults with cognitive decline, including mild cognitive impairment (MCI) and Alzheimer's disease (AD). MCI may represent a transitional stage between healthy aging and AD (Gauthier et al., 2006). It is a condition in which individuals demonstrate some cognitive impairment with no impact on social or occupational living (Petersen et al., 1999). Much effort has been devoted to the early detection of this cognitive decline before it interferes with daily functioning (Sperling et al., 2011).

Several studies have reported that when older adults are engaged in a cognitive task, they may be susceptible to distraction from irrelevant, to-be-ignored stimulus input (Gazzaley et al., 2008; Lee et al., 2020; Hasher and Zacks, 1988; Schmitz et al., 2014). The series of processes leading to distraction has been labeled "attention capture" or passive (involuntary) attention (James, 1890). A frontoparietal network is critical for the sustaining of appropriate attentional focus and task execution (Petersen and Posner, 2012). The vulnerability to distraction from stimulus input occurring outside of the current focus-of-interest may be increased in people with MCI compared to healthy older adults (Aurtenetxe et al., 2016; Ruzzoli et al., 2016). A reduced ability to sustain attention to the task-at-hand in people with MCI (compared to healthy older adults) might be attributed to a disruption in the frontoparietal network. This network is involved with establishing and maintaining processing priorities (Petersen and Posner, 2012). The frontoparietal network must, however, be flexible. On the one hand, attention to a current cognitive task having high priority should not be interrupted by irrelevant, unattended stimulus input. On the other hand, attention must not be so focused on the current cognitive task that the individual will not be able to detect an unattended but potentially highly relevant stimulus input that may be critical for survival (Schmitz et al., 2014).

A separate salience network computes the salience of unattended stimulus inputs, forwarding this information to the frontoparietal network (Goulden et al., 2014). The frontoparietal network must then determine whether attention should be maintained on the processing of current cognitive demands or switched to the unattended stimulus input, if its potential salience is especially high. Relatively few studies have examined the salience network in people with MCI. Chand et al. (2017) employed fMRI methods during resting state to examine the dynamic shifting of activity between the default resting and the frontoparietal networks. This activity is modulated by the salience network. The extent of this modulation was impaired in people with MCI compared to cognitively healthy older adults.

The classic Näätänen (1990) model of auditory processing discusses two different modes by which an individual can become aware of highly salient but unattended input. The two modes include a transient detector and a change detector system which are involved in the detection of different salient features of an auditory input. The output from each system provides a means to measure the salience of the auditory stimulus.

Measuring the extent of processing of unattended stimulus input is difficult in the absence of a behavioral response. Some researchers attempt to overcome this problem by requiring a response to at least some input occurring in the unattended channel. However, the requirement to respond will inadvertently direct attention to the unattended channel, contaminating the results. Näätänen (1990) proposes the use of event-related potentials (ERPs) to quantify the extent of processing of the unattended auditory stimulus.

The transient detector system detects the brief transient onsets and offsets of an auditory stimulus. Its output is directly proportional to the energy (intensity) of the stimulus and the time between stimulus presentations, establishing the extent of salience. The output of the transient

detector system is reflected by a negative ERP component, N1, occurring about 100 ms after stimulus onset, followed by a later positivity, P2, occurring at about 180 ms. N1 and P2 are particularly large following the presentation of a loud or a very slowly presented auditory stimulus. The transient detector system forwards an interrupt signal, proportional to the salience of the stimulus input, to the frontoparietal network controlling processing priorities. If the size of the interrupt signal is sufficiently large, attention may be switched from ongoing cognitive activities and priority will be given to the processing of the intruding stimulus event. A centro-frontal maximum positivity, the P3a, peaking from 200-300 ms, has been associated with this switching of attention (Escera, 2007; Escera et al., 1998). However, some researchers have suggested that the P3a better reflects a precursor process that may result in the switch that eventually leads to conscious awareness of the unattended input (for reviews, see Parmentier, 2014; Wetzel et al., 2013).

Berti et al. (2017) and Kamal et al. (2021a) presented to-be-ignored auditory stimuli either rapidly (every 1 to 3 s) or very slowly (every 10 and 12 s respectively). A stimulus that occurs very rarely is highly salient. In both studies, when stimuli were presented rapidly, the amplitude of N1 and P2 did not differ between younger and older adults. When the stimuli were presented very slowly and occurred rarely, the amplitude of N1 was smaller in older adults compared to younger adults. These findings suggest that the salience of the slowly-presented auditory stimulus was computed to be much lower in the older than the younger adults.

Kamal et al. (2021a) also reported that the subsequent positivity, labeled as a P2, was lower in the older than the younger adults. In the Näätänen (1990) model, a P3a would be expected following the presentation of the highly salient, rarely-occurring stimulus. The peak of the positivity labeled as P2 was delayed by 25 ms in the slow condition, a latency that is more

consistent with that of a P3a. Berti (2013) also suggested that the P2 and P3a components may overlap temporally and spatially and therefore may summate.

Kamal et al. (2021b) also compared healthy older adults and people with MCI using both a fast and very slow rate of stimulus presentation. N1 amplitude was larger in both groups when stimuli were presented very slowly than when they were presented more quickly rapidly and did not differ between groups. This finding suggests that people with MCI were as able to establish the salience of the unattended stimulus as cognitively healthy older adults. Importantly, in the slow rate of stimulus presentation, P2/P3a amplitude was lower in people with MCI compared to healthy older adults. The lower P2/P3a in people with MCI suggests that the frontoparietal network may fail to give sufficient priority to the processing of potentially highly relevant stimulus input.

A limitation to this interpretation is that it is based on the assumption that the late positivity observed in the Kamal et al. (2021a, b) single stimulus paradigm does indeed reflect P3a activity. The P3a has been studied most often in the so-called oddball paradigm, which is designed to examine the effects of acoustic stimulus change. In the oddball paradigm, a sequence of frequently occurring homogenous standard stimuli is presented, and at rare (or odd) times, a feature of the standard is changed to form a deviant. However, the change detector system detects changes in any feature of an auditory stimulus, not only intensity. The output of the change detector system is reflected by a fronto-central maximum negativity, the mismatch negativity (MMN) peaking at about 100-150 ms. The amplitude of the MMN varies directly with the extent of change, providing a measure of the extent of salience. If the extent of change is large enough, a P3a may again be elicited; operations in the frontoparietal network may be

interrupted, and attention may be switched from ongoing cognitive activities and to the processing of the intruding stimulus event.

Importantly, Näätänen indicates the operations of both the transient and change detector system occur independent of attention and concurrent task demands. Thus, the N1 and MMN are often recorded while the participant's attention is diverted to a visual task. The amplitude of the auditory MMN is very similar when the visual task is very difficult, presumably requiring a great deal of attention, and when it is very easy, presumably requiring much less attention (Muller-Gass et al., 2007).

A limited number of studies have examined the MMN and P3a in people with MCI. The MMN results have not always been consistent, perhaps because recording parameters vary widely. Mowszowski et al. (2012) noted that the MMN elicited by a deviant representing an increase in duration from the standard was smaller in amplitude at temporal sites in people with MCI compared to age-matched healthy older adults. On the other hand, Ruzzoli et al. (2016) reported a preserved MMN at temporal sites in people with MCI but a smaller MMN at frontal sites following presentation of shorter duration deviants compared to healthy older adults. Ji et al. (2015) presented deviants that varied in frequency and intensity. The amplitude of the MMN did not, however, significantly differ between people with MCI and healthy older adults. Lindín et al. (2013) employed highly novel environmental sounds as deviants. In this study, the MMN was smaller in people with MCI aged between 50 and 64 years, but not for those older than 65 years of age.

While almost any perceptible deviant will elicit an MMN, only a subset of these deviants, those having very high salience, will elicit a P3a. A stimulus change that is known to elicit a particularly large P3a is an abrupt increase in intensity (Shestopalova et al., 2018). Indeed, Rinne

et al. (2006) claimed that only deviants that are created by increasing the intensity of the standard will elicit a P3a. Other studies have, however, indicated that deviants representing a change in any other feature, such as the frequency or duration of the standard, will elicit a small or absent P3a. For example, Muller-Gass et al. (2007) observed a large P3a following a deviant representing an increase in intensity (an "increment") from the standard but only a small P3a following a large decrease (a "decrement") in intensity. This effect is so powerful that an increment will even elicit a P3a during sleep, while a decrement will not (Macdonald et al., 2008). Deviants that represent an increase in intensity may be effective at eliciting a very large P3a because they are detected by both the change detector system (the increment signals change) and the transient detector system (the increment represents an increase in intensity).

A deviant representing an increase in intensity will also elicit a large MMN because it signals a change from the acoustic past. However, because its intensity is higher, the deviant will also elicit a larger N1 than the standard. The N1 and the MMN occur at about the same time and share a common fronto-central maximum scalp distribution. Because of the temporal and spatial overlap, the two negativities elicited by the deviant will summate. This increase in negativity relative to the standard is often called a deviant-related negativity (DRN). In the present study, the composite N1+MMN negativity that occurs following the deviant will be described as a DRN.

Morrison et al. (2019) employed an increment-decrement oddball paradigm to compare the DRN and P3a elicited in younger and older adults. In both younger and older adults, only a small P3a was elicited by the decrement. P3a amplitude did not significantly differ between the groups. However, the presentation of the increment elicited a very large P3a in the younger adults, and a much smaller P3a in older adults. The DRN was also smaller in the older compared

to the younger adults in the increment condition. These findings suggest that older adults may not be able to establish the salience of stimulus input. As such, potentially highly salient information that will elicit a large P3a in younger adults may not do so in older adults.

The P3a has been little-studied in people with MCI. Cecchi et al. (2015) employed an active oddball task consisting of a standard, a rare pure tone target requiring a manual response, and a rare white noise burst to which the response was to be withheld. The authors indicated that the white noise burst elicited a P3a that was smaller in people with mild AD compared to healthy older adults. The use of an active task is, however, problematic because the participants needed to attend to the auditory sequence and to actively classify the noise burst to know whether they should respond. As such, the occurrence of the noise burst would not have been associated with a switching of attention from other processing priorities.

Correa-Jaraba et al. (2018) reported that the P3a may be larger in some people with MCI than in healthy older adults. Participants in their study completed a visual working memory task in which an irrelevant auditory stimulus preceded the visual stimulus. When a rare novel environmental sound deviant was presented, a P3a was elicited, which was larger in some people with MCI than healthy older adults. Again, the extent to which the rare novel stimulus was irrelevant to the task can be questioned. For example, Parmentier (2014) and Masson and Bidet-Caulet (2019) indicate that participants can use the auditory stimulus as a warning signal to alert them to the subsequent visual stimulus, facilitating performance. It is thus possible that people with MCI actively attended to the auditory stimuli in an attempt to alert them to the subsequent visual stimulus.

In both the Cecchi et al. (2015) and Correa-Jaraba et al. (2018) studies, the auditory deviants eliciting the P3a were not irrelevant to processing of the active task. The present study

consisted of two experiments. The second experiment was a follow-up to the first. Importantly, in both experiments, participants attended to a visual task (watching a video) and were asked to ignore the auditory sequence. The unattended auditory stimuli were irrelevant to the visual task and are thus processed passively.

In the first experiment, a decrement-increment oddball paradigm was used. Previous studies have indicated that only the increment deviant will elicit a larger P3a, although both the decrement and increment deviants elicit an MMN/DRN. Kamal et al. (2021b) used a single stimulus paradigm and found that a late positivity, which may have been a late P2 or an early P3a, was smaller in people with MCI compared to healthy older adults. The P3a is most often observed in oddball paradigms. It might therefore be expected that a P3a, elicited by an increment deviant occurring within an oddball sequence, will also be smaller in people with MCI compared to healthy older adults.

Experiment 1

2. Methods

2.1 Participants

A power analysis was initially carried out to determine an appropriate sample size. The Kamal et al. (2021) study reported that the mean amplitude of the P2/P3a Cz was reduced by 2.71 μV (*SD* = 1.47 μV) in people with MCI compared to healthy older adults. This difference corresponded to a moderate to large effect size (Cohen's *d* = 0.6). In the present study, with a predicted effect size of 0.6, a sample of 14 participants per group was determined to be adequate. A total of 42 participants were recruited for this experiment. Two participants were excluded from analysis because of noisy EEG data (see Section 2.3). Therefore, this study included 20 healthy older adults (12 females; age range = 67-81 years; *M* = 72.4 years) and 20 older adults with MCI (10 females; age range = 68-84 years; *M* = 74.6 years). All participants were right-handed, with no

history of neurological or psychiatric conditions, and had not suffered any major head injuries. All participants underwent a brief hearing test to verify normal hearing. All participants reported normal hearing. Objective hearing thresholds were verified to below 40 dB SPL using audiometric procedures for the 55 ms duration stimuli used in this study. Thresholds were tested for 500, 1000, and 2000 Hz frequencies. Healthy older adults were recruited through word-of-mouth and announcements shown at community centers. Thirty-six of the forty participants (18 in each group) that took part in experiment 1 also participated in two other studies (Kamal et al., 2021a,b). Participants with MCI were recruited from the Bruyère memory program. They were diagnosed with MCI based on clinical history and a neurological exam by a physician with expertise in neurodegenerative conditions. They underwent a CT scan and blood work to rule out reversible causes of cognitive impairment. Participants were not included if their cognitive decline was thought to be related to other comorbidities. Participants also completed the Montreal Cognitive Assessment (MoCA) to screen for cognitive decline (Nasreddine et al., 2005). The cutoff for the MoCA in the healthy older adults was 24 (Pugh et al., 2018). Healthy older adults scored significantly higher ($p<.001$) on the MoCA ($M = 27.05$, $SD = 1.46$) than people with MCI ($M = 22.30$, $SD = 3.16$). Participants also completed a one-hour neuropsychological battery to assess general cognitive functioning. Table 1 presents demographic information and the results of the neuropsychological assessment in Experiment 1.

This study was approved by the University of Ottawa and Bruyère Research Institute ethics boards. Participants provided informed written consent before starting the study and an honorarium was given as compensation for participation.

Table 1. Demographic and neuropsychological information for participants in Experiment 1. Values are means (SD in parentheses).

	Experiment 1		
	Older Adults	MCI	*p*
Age	72.4 (3.8)	74.62 (7.0)	.17
Education	16.0 (2.8)	16.19 (4.4)	.86
MoCA	27.0 (1.5)	22.30 (3.2)	**<.001**
Digit Span Forward	10.8 (2.4)	11.05 (2.3)	.39
Digit Span Backward	7.8 (2.4)	7.33 (2.4)	.26
Letter # Sequencing	10.4 (2.2)	8.48 (2.5)	**.006**
WCST	3.7 (1.3)	2.35 (1.2)	**<.001**
Stroop1-3	56.7 (22.8)	62.65 (13.1)	.16
Stroop2-3	29.8 (13.5)	31.05 (9.8)	.37
Digit Symbol-Written	44.9 (5.5)	35.09 (12.3)	**<.001**
Digit Symbol-Oral	52.4 (9.3)	37.40 (13.4)	**<.001**
FAS Fluency	42.0 (9.7)	33.28 (9.1)	**.002**
Animal Fluency	20.4 (5.4)	16.30 (8.1)	**<.03**

Notes: Independent sample one-tailed t-tests were computed on the neuropsychological test results because it was expected that MCI scores would be lower than healthy older adults. WCST= Wisconsin Card Sorting Test (categories completed). Stroop1-3= a subtraction of Stroop 1, which requires participants to read aloud the name of colors) from Stroop 3 (which requires participants to name the ink color of color words printed in a different color (e.g., the word "RED" printed in green ink). Stroop 2-3 = a subtraction of the scores for naming the color of "X's" - Stroop3. Digit Symbol-Written = match the digit to the corresponding symbol by writing the answer, Digit Symbol-Oral= match the digit to the corresponding symbol by reading the answer aloud. FAS Fluency = sum score of the F, A, and S fluency, which are three individual tests in which participants are asked to name as many words as possible (within 60 s) that start with the letters F, A, and S. Animal fluency: participants are asked to name as many animals as possible (within in 60 s).

2.2 Procedure

Participants were seated in a sound-attenuated testing room. They were asked to watch a silent, subtitled video and to ignore concurrently presented auditory stimuli. The auditory stimuli were thus irrelevant, and their processing was carried out passively.

An auditory oddball sequence was presented binaurally through Sony MDR-V6 headphones. The sequence consisted of a frequently presented standard and rarely-presented

deviants. The standard was an 80 dB SPL 1000 Hz pure tone with a total duration of 55 ms (5 ms rise/fall time). The standard occurred on 85% of trials. Two types of deviants were also presented, each occurring on 7.5% of trials. The "increment" and "decrement" deviants had intensities of 90 dB SPL and 60 dB SPL, respectively. The 10 dB increment and the 20 dB decrement represent approximately equivalent physical changes in acoustic energy. The order of presentation of the standards and deviants was pseudo-randomized. The auditory sequence started with a minimum of 4 consecutive standards, and deviants were separated by at least 3 standards. The first sequence consisted of only standards to establish a memory trace for the standard stimulus. The stimulus-onset-asynchrony (SOA) varied from 354 to 454 ms. The sequence lasted approximately 9 minutes and was presented a second time to ensure enough trials were presented to obtain an optimal ERP signal-to-noise ratio. A brief rest period was provided between blocks.

2.3 EEG recording and pre-processing

Electroencephalography (EEG) was recorded from 30 active silver-silver chloride electrodes attached to an electrode cap (Brain Products, GmbH, Munich, Germany) placed according to the international 10-20 system. Another electrode was placed on the infraorbital ridge of the left eye to record vertical eye movements and blinks. An electrode was also placed on the tip of the nose to serve as the reference for all channels. The EEG was sampled at a rate of 500 Hz. Electrode impedance was below 20 kΩ. Impedance was below 10 kΩ at F3, Fz, F4, C3, Cz, and C4, regions of interest (ROIs), where the ERPs were measured.

The EEG data were subsequently analyzed using Brain Products Analyser2 software. The data were digitally filtered using a high pass filter set at 0.5 Hz and a low-pass filter set at 20 Hz (24 dB/octave roll-off). The waveforms were then visually inspected for channels containing

high levels of noise. Channels with high levels of noise were replaced by interpolating the data of the surrounding electrode sites (Perrin et al., 1989). The frontal and central regions had lower electrode impedance and as a result, tended to have lower levels of noise. Thus, interpolation for these channels was not required.

Eye movements and blink artifacts occurring independent of EEG activity were identified and corrected using Independent Component Analysis (ICA) (Makeig et al., 1996). To do so required a computation of vertical and horizontal EOG activity. Vertical EOG movements were computed by subtracting activity at the FP1 and the inferior orbital sites. Horizontal eye movements were computed by subtracting FT9 activity from that of FT10.

The EEG was reconstructed into single 700 ms epochs starting 100 ms before stimulus onset. The average of all activity in the pre-stimulus period served as a zero-voltage baseline. Drifts in post-stimulus voltage from this baseline were then corrected for each epoch. Epochs containing EEG activity exceeding $\pm$100 μV were rejected from averaging. Two healthy older adults were removed from further analysis because more than 25% of their trials contained artifact. The rejection rate was very low for the remaining participants. On average, 1% (range 0-5%) of all epochs were rejected for the healthy older adults while 2% (range 0-10%) were rejected for people with MCI. The rejection rate was very similar for standards and the two deviants.

2.4 ERP analysis

The standard and the deviant stimuli elicited obligatory N1 and P2 ERP deflections. The deviants elicited a series of additional deflections, including the MMN/DRN and an optional P3a. The additional deviant deflections are best observed in a difference wave computed by subtracting point-by-point the average response of the standard from that of the deviant. The subtraction

process removes responses that are common to both the standard and the deviant, leaving only processing that is unique to the deviant. This procedure is illustrated in Figure 1, which displays the "raw" standard and deviant waves and the deviant-standard difference wave. ERP components were quantified using the mean of all data points within ±25 ms of the peak identified in the grand averaged difference wave (time windows used are presented in Table 2). The components were measured relative to the zero-voltage pre-stimulus baseline. This procedure is also illustrated in Figure 1. N1 and P2 were identified in the grand average of the standard stimulus. N1 peaked at about 100 ms and P2 around 190 ms, and we measured the mean amplitudes of N1 and P2 from 75-125 ms and 165-215 ms post-stimulus respectively. The DRN to the increment was measured from 95 to 145 ms. The MMN to the decrement peaked later and was measured from 150 to 200 ms. P3a to the increment was measured from 220-270 ms. A P3a, peaking at about 335 ms, was elicited by the decrement in the older adult group. This P3a was not apparent in people with MCI. It was therefore quantified within the same 310-360 ms used for the healthy older adults.

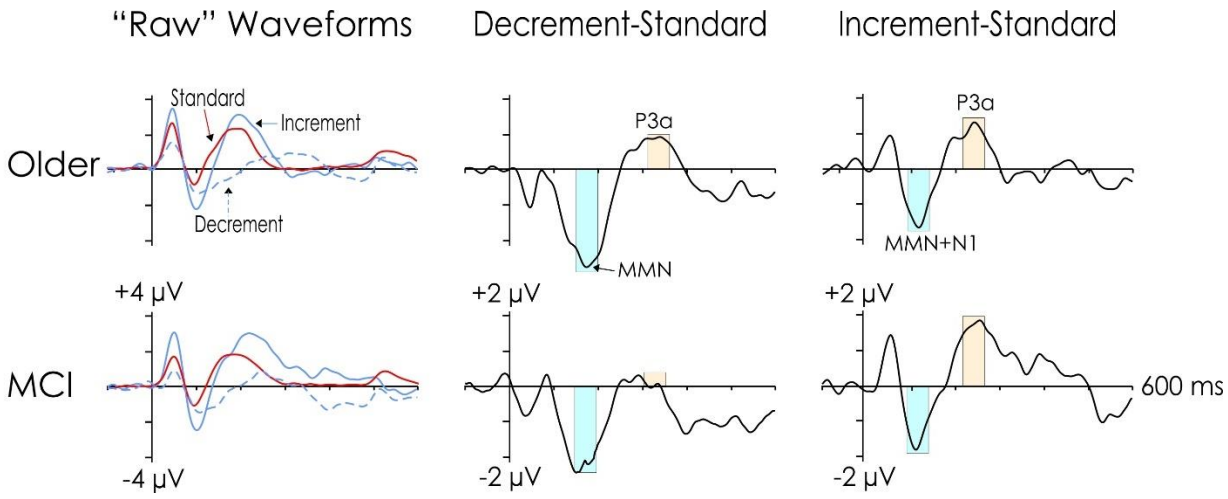

Fig. 1. Raw standard, decrement, and increment ERPs (left column) in healthy older adults and people with MCI. Data are from the Cz electrode site. Positivity in this and all other figures is indicated by an upward deflection. The obligatory N1 and P2 occurred around 100 ms and 185 ms, respectively, following presentation of the standard stimulus. The decrement-standard

difference waves are illustrated in the center column and the increment-standard difference waves in the right column. The 50 ms time intervals in which the MMN/DRN and P3a were measured are shaded in blue and beige respectively.

Table 2. 50-ms time windows analyzed for the amplitude for the DRN and P3a in all participants in Experiment One

Experiment/ Deviant	**Experiment 1**	
	MMN/DRN	**P3a**
Decrement	150-200 ms	310-360 ms
Increment	95-145 ms	220-270 ms

In order to determine whether the deviants elicited a DRN or P3a, confidence intervals (CI) were computed for each, and we tested whether they differed significantly from the pre-stimulus zero-voltage baseline. This procedure is equivalent to computing a t-test between the standard and deviant waveforms (Winer et al., 1971). Confidence interval testing was conducted at Fz for the MMN/DRN and Cz for the P3a, where they tend to be largest. Both deviants elicited a significant MMN/DRN for both groups. In contrast, a significant P3a was elicited by both deviants for healthy older adults and only by the increment deviant for people with MCI. Therefore, both deviants were included in the ANOVA for the DRN, but only the increment deviant was included for the P3a. Electrode sites were grouped into frontal (F3, Fz, F4) and central (C3, Cz, C4) ROIs and separate ANOVAs were run at each ROI. A 2-way ANOVA was run for the DRN. The ANOVA consisted of a single between-subjects factor, Group (older, MCI), and a single within-subject factor, Deviant (decrement, increment).

Because only the increment elicited a significant P3a, a one-way ANOVA was run to compare group differences. In the case of the MMN/DRN, for both ROIs, neither the Group main effect nor the Group x Deviant interaction were significant. Similarly, for the P3a, group differences were not significant for either ROI. MMN/DRN and P3a amplitudes were reduced in

amplitude at the lateral relative to central sites. The reduced amplitudes at these lateral sites might have lowered the overall group differences. The ANOVAs in the case of the MMN/DRN and t-tests in the case of the P3a were therefore run only at the midline Fz and Cz sites, where responses were largest. All data were analyzed with the Statistical Package for the Social Sciences (v.22) (SPSS).

4. Results:

4.1 Standard N1-P2

A deviant-standard difference wave was used to compute the MMN/DRN and P3a. Its use is based on the assumption that group differences in these components were a result of differential processing of the deviant. It is possible however that processing of the standard varied between the groups. To confirm that the processing of the standard did not differ between groups, a separate independent group t-test was run on the N1 and P2 standard data. These results are illustrated in Figure 1. Neither the amplitude of N1 nor P2 significantly differed between the healthy older adults and people with MCI, $t < 1$ in both cases and at both Fz and Cz sites.

Figures 2 and 3 illustrate the deviant-standard difference waves for the decrement and increment, respectively. A negativity occurring at about 100 to 150 ms was elicited by both the decrement and increment deviants. As is apparent in the figures, its scalp distribution, maximum in amplitude over fronto-central regions and inverting in polarity at the mastoids, is consistent with an MMN/DRN. This negativity was followed by a later positivity, the P3a occurring from about 250 to 325 ms for the increment and decrement deviants, respectively. The P3a was maximum over fronto-central areas of the scalp.

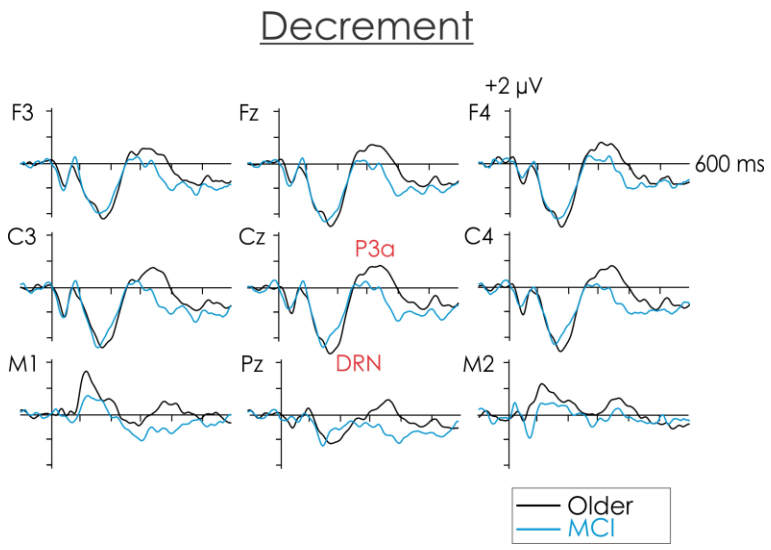

Fig. 2. Decrement-standard difference wave across several electrode sites. A fronto-central maximum mismatch negativity that inverted in amplitude at the mastoids is apparent around 100–150 ms. Its amplitude did not differ between healthy older adults and people with MCI. This was followed by a small P3a occurring around 250–325 ms.

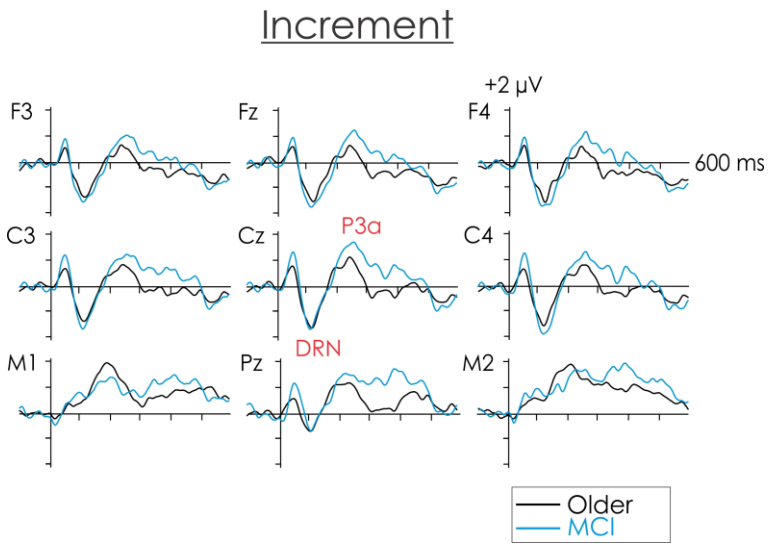

Fig. 3. Increment-standard difference wave across multiple electrode sites. A large composite N1+MMN (deviant-related negativity) was elicited by the increment. Its amplitude did not differ between healthy older adults and people with MCI. This was followed by a large P3a. Its amplitude did not differ between healthy older adults and people with MCI.

4.2 MMN/DRN

Figure 4A presents the pirateplot of the MMN/DRN results. The pirateplot provides both descriptive and inferential statistics including the mean and 95% confidence intervals.

The results of the ANOVA procedure indicated that the main effect of Group was not significant for the MMN/DRN, at both the Fz and Cz sites, $F<1$ in both cases. The Group x Deviant interaction was also not significant at Fz ($F(1,38)=1.14$, $p=.29$, $n_p^2=0.03$) and Cz sites ($F(1,38)=1.74$, $p=.20$, $n_p^2=0.04$). That is, neither the amplitude of the MMN following the decrement nor the amplitude of the DRN following the increment significantly differed between healthy older adults and people with MCI at either Fz or Cz sites.

4.3 P3a

Figure 4B presents pirateplot of the P3a results. At both Fz and Cz, the amplitude of the P3a to the increment deviant was not significantly different between healthy older adults and people with MCI, $t<1$ in both case

The failure to find significant P3a differences between the two groups cannot be used as evidence that the null hypothesis was true. A Bayes factor can be computed to evaluate the strength of evidence supporting either the alternate hypothesis (i.e., support favoring a group difference in the amplitude of the P3a) or the null hypothesis (no group difference in the P3a). The Bayes factor test computes the ratio (expressed as BF_{10}) of the strength of evidence supporting the alternate hypothesis (1) compared to the null hypothesis (0). The BF_{10} for the P3a was found to be 0.38 at both Fz and Cz. Wetzels and Wagenmakers (2012) suggest that a ratio this small ratio provides moderate to anecdotal evidence in support of the null hypothesis.

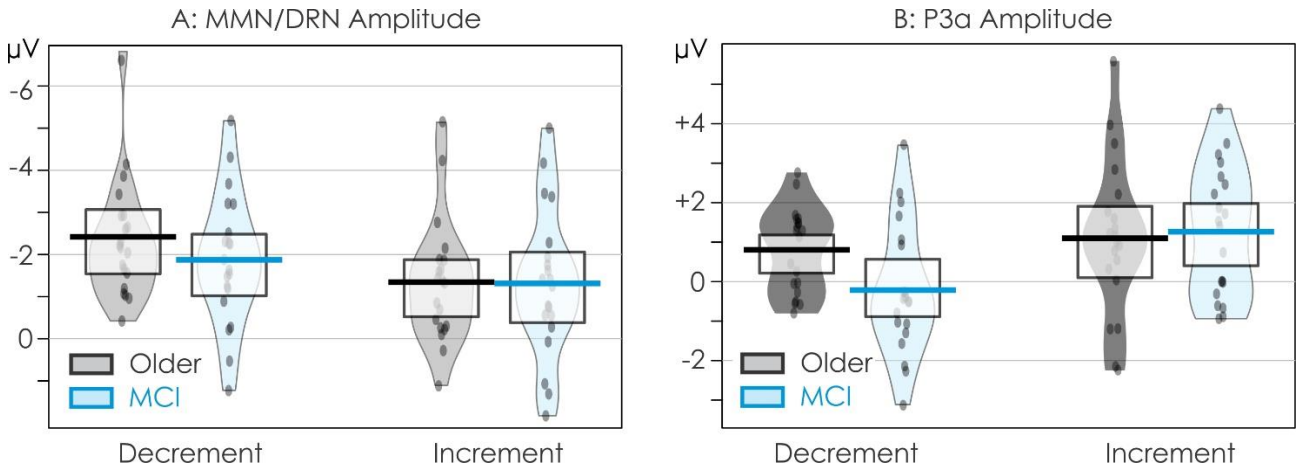

Fig. 4. Pirateplots of MMN/DRN and P3a data providing both descriptive and inferential statistics. Data are shown at Cz sites. The mean amplitudes of MMN/DRN and P3a (thick, solid horizontal line), 95% upper and lower confidence intervals (light box), smooth frequency distribution (shaded area), and individual data points (jittered) are presented in parts A and B, respectively.

5. Discussion

The results of Experiment 1 indicate that the overall amplitude of the MMN/DRN did not significantly differ between healthy older adults and people with MCI following presentation of deviants representing either a decrease or an increase in the intensity of the standard. Similarly, the amplitude of the P3a following presentation of the increment did not significantly differ between the two groups. A failure to observe significant differences between groups does not however necessarily imply that the null hypothesis should be accepted. A Bayes factor procedure was used to determine whether the present P3a results provided more support for the null hypothesis (no group differences) or the alternative hypothesis (group differences). These results supported the null hypothesis. Ji et al. (2015) and Papadaniil et al. (2016) also failed to observe MMN differences between healthy older adults and people with MCI when using frequency deviants. Other studies have, however, reported that the MMN/DRN is smaller in MCI for duration deviants (Mowszowski et al, 2012; Ruzzoli et al., 2016) relative to healthy older adults.

Experiment 1 failed to find signfiicant group differences in the amplitude of the P3a to the increment deviants.

A smaller P3a in people with early AD has, however, been reported following the presentation of white noise (Cecchi et al., 2015). Correa-Jaraba et al. (2018) reported a larger P3a to environmental sound deviants in some people with MCI compared to healthy older adults. However, in both P3a studies, participants may have actively attended the auditory stimuli. The intensity and the frequency spectrum of both white noise and environmental sound deviants will change from that of the standard. In the present study, while the increment deviant did represent an increase in intensity from the standard, its frequency was the same. A major reason for the discrepancies across studies is the use of very divergent stimulus parameters including the rate of stimulus presentation, the features of both the standard and deviant, and their probability of occurrence. To determine the extent of processing of the several different deviants that have been employed in previous studies requires the presentation of a number of deviants in a single study. A follow-up study to Experiment 1 was therefore run to determine the effects of several different types of deviants.

Unfortunately, the presentation of several different deviants would be very time-consuming because a different oddball sequence would be required for each deviant. This limitation can be overcome through the use of a variation of the oddball paradigm. A time-efficient multi-feature paradigm (Näätänen et al., 2004) has been developed to include different deviants, each representing a change of a different feature (thus, “multi-feature”) of the standard. In the Näätänen et al. (2004) study, six different types of deviants were presented. In this optimized multi-feature paradigm, the standards and deviants alternate. Thus, while the probability of occurrence of a standard or deviant was 0.5, the probability of occurrence of a

specific deviant was only 0.083. Importantly, in the Näätänen et al. (2004) study, the MMN/DRN that was elicited by the different deviants in a single multi-feature sequence was very similar to that elicited by the different deviants when presented in multiple oddball sequences, one for each deviant.

Laptinskaya et al. (2018) employed the Näätänen et al. multi-feature paradigm comparing the MMN elicited by each of the six deviants in cognitively healthy older adults and people with MCI. The amplitude of the MMN did not significantly differ between the groups for any of the deviants. However, they did not examine the P3a, probably because the extent of deviance from the standard for each of the six deviants was relatively small.

Cecchi et al. (2015) and Correa-Jaraba et al. (2018) employed white noise and novel environmental sounds as deviants, both known to be associated with a large P3a. Tavakoli and Campbell (2016) modified the Näätänen et al. (2004) multi-feature paradigm to include deviants known to elicit a large P3a, thus permitting the study of attention capture. Again, six different deviants were presented. Two deviants (white noise and environmental sounds) elicited a large P3a, while the remaining four elicited a small or absent P3a. Tavakoli and Campbell also noted that DRN and P3a results were very similar when a single run of the multi-feature paradigm was compared to multiple runs of the single deviant oddball paradigm. Morrison et al. (2020) employed the multi-feature P3a paradigm to compare attention capture in younger and older adults. As expected, the white noise and environmental noise deviants elicited a large P3a in younger adults. The P3a to both deviants was much reduced in older adults.

The results of the first experiment in this study indicated that the amplitude of P3a to the increment deviant did not significantly differ between the two groups. On the other hand, Cecchi et al. (2015) and Correa-Jaraba et al. (2018) indicate that P3a group differences might be

apparent to white noise or environmental sound deviants. The second experiment thus employed a multi-feature paradigm to compare the processing of six different deviants including increment, white noise, and environmental sound deviants, in cognitively healthy older adults and in people with MCI.

Experiment 2

6. Methods

6.1 Participants

Thirty-two participants from Experiment 1 (16 healthy older adults and 16 MCI) also participated in this experiment. Eight additional participants were recruited to reach a sample size of 20 participants for both groups (the same number as in Experiment 1). A total of 40 participants' data were analyzed: 20 healthy older adults (13 females; age range = 67-82 years; *M* = 72.6 years) and 20 older adults with MCI (10 females; age range = 68-84 years; *M* = 74.6 years). Healthy older adults scored significantly higher ($p<.001$) on the MoCA (*M* = 27.3, *SD* = 1.6) than people with MCI (*M* = 22.5, *SD* = 3.4). Again, thirty-six of the forty participants (18 in each group) that took part in Experiment 2 also participated in two other studies (Kamal et al., 2021a,b). Table 3 presents both demographic information and the results of the neuropsychological testing in Experiments 2.

Table 3. Demographic and neuropsychological information for participants in Experiment 2. Values are means (SD in parentheses).

	Experiment 2		
	Older Adults	MCI	*p*
Age	72.6 (4.0)	74.6 (6.6)	.28
Education	16.1 (2.5)	16.3 (4.9)	.87
MoCA	27.3 (1.6)	22.5 (3.5)	**<.001**
Digit Span Forward	10.1 (2.4)	11.2 (2.5)	.35
Digit Span Backward	7.5 (2.3)	7.5 (2.6)	.46
Letter # Sequencing	10.2 (2.1)	8.6 (2.9)	**.02**
WCST	3.8 (1.4)	2.4 (1.3)	**.001**
Stroop1-3	53.0 (18.7)	62.7 (12.9)	**.03**
Stroop2-3	28.6 (13.2)	31.3 (9.9)	.24
Digit Symbol-Written	45.4 (5.6)	35.4 (11.8)	**.001**
Digit Symbol-Oral	49.3 (13.8)	37.8 (14.2)	**.006**
FAS Fluency	41.1 (9.7)	33.6 (8.4)	**.006**
Animal Fluency	23.0 (9.6)	15.8 (7.4)	**.005**

6.2 Procedure

As in Experiment 1, participants were asked to watch a silent sub-titled video and to ignore the irrelevant, concurrently presented auditory stimuli.

A multi-feature auditory sequence was presented consisting of alternating standard and deviant stimuli (each with a probability of 0.50). The standard stimulus was an 80 dB SPL 1000 Hz pure tone burst with a duration of 200 ms and a rise-and-fall time of 5 ms. Six different deviants were created by changing a feature (or features) of the standard: a 10 dB increase in intensity (increment), a 20 dB decrease in intensity (decrement), a 100 Hz increase in frequency, a 100 ms decrease in duration, a white noise burst (80 dB peak SPL), or a novel environmental sound (with an average intensity of 80 dB SPL). A different environmental sound was presented on each trial. The features of the environmental sounds are described in detail by Fabiani et al. (1996). These include animal sounds (e.g., dog, cat, bird), human-produced sounds (e.g.,

coughing, sneezing), musical instruments (e.g., piano, guitar), sounds within a daily environment (e.g., water flowing, car horns), and mechanically-produced sounds.

The order of occurrence of the six different deviants was pseudo-randomized such that in an array of 12 alternating standards and deviants, each deviant was presented once, and the same deviant was never presented consecutively. Thus, while the probability of occurrence of deviants over the entire sequence was 0.50, the probability of occurrence of a specific deviant was 0.083. The first ten sounds in the sequence consisted of only standards to establish a memory trace for the standard stimulus. Stimuli were presented with a stimulus onset asynchrony (onset-to-onset) of 600 ms. Each sequence lasted about 10 minutes with 472 standards (including the initial 10) and 77 of each type of deviant being presented. The multi-feature sequence was presented twice. A brief rest period was provided between blocks.

The duration of 200 ms was longer than the duration of 55 ms used in Experiment 1. The longer duration was needed for each of the environmental sounds to be perceived as being unique. The SOA (onset-to-onset) also needed to be longer in Experiment 2 because of the longer duration of the stimuli. The time between the offset of one stimulus and the onset of the next was, however, approximately the same in both experiments (on average, 400 ms).

6.3 EEG recording

The EEG recording and pre-processing procedures were the same as those used in Experiment 1. Again, epochs containing EEG activity exceeding $\pm$100 μV were rejected from averaging. No participants were rejected on the basis of excessive artifact. On average, 2% (range 0-6%) of all epochs were rejected for the healthy older adults while 4% (range 0-8%) were rejected for people with MCI. The rejection rate was very similar for standards and the six deviants.

6.4 ERP analysis

The standard and deviants again elicited an obligatory N1 and P2 deflection occurring around 100 and 185 ms, respectively. The DRN and P3a were again measured in a standard-deviant difference wave. Both the DRN and P3a were quantified for each individual participant using the mean amplitude of all data points within ±25 ms of the peak identified in the grand averaged difference wave for each group. The occurrence of both the DRN and P3a differed across the six deviants (novel environmental sounds, white noise, decrement, increment, duration, and frequency deviant). Time windows used for the mean amplitudes of the MMN/DRN and P3a are presented in Table 4.

Table 4. 50-ms time windows analyzed for the amplitude for the DRN and P3a in all participants in Experiment 2

Experiment/ Deviant	**Experiment 2**	
	MMN/DRN	**P3a**
Environmental	115–165 ms	245–295 ms
White noise	115–165 ms	250–300 ms
Decrement	135–185 ms	260–310 ms
Increment	75–125 ms	345–395 ms
Duration	85–135 ms	275–325 ms
Frequency	85–135 ms	275–325 ms

While the MMN/DRN is elicited by any perceptible deviant, only a few of the deviants have been demonstrated to elicit a P3a (Tavakoli et al., 2018). Confidence interval testing was again conducted at Fz for the DRN and at Cz for the P3a, where they are known to be largest. Only those deviants that elicited a significant DRN or P3a were subsequently compared using the ANOVA procedure.

Confidence interval testing for the MMN/DRN revealed that all deviants elicited a negativity that was significantly smaller than the zero-voltage baseline in at least one of the groups. On the other hand, confidence interval testing for the P3a revealed that only the white

noise and novel environmental sounds elicited a significant positivity for both groups. A separate 2-way ANOVA was computed for the MMN/DRN and the P3a, with each having a single between-subjects factor, Group (older, MCI), and a single within-subject factor, Deviant. In the case of the MMN/DRN analysis, all deviants were included in the within-subjects factor. In the case of the P3a, only the white noise and environmental sound deviants' data were analyzed. The ANOVAs were run separately at Fz and Cz.

7. Results

7.1 Standard N1-P2

The standard ERP waveform for healthy older adults and people with MCI is shown in Figure 5. The amplitude of N1 and P2 was small because of the rapid rate of stimulus presentation. The amplitude of N1 did not differ between groups at either Fz ($F(1,38)=3.03$, $p=.09$, $n_p^2=.07$) or Cz sites, ($F(1,38)=2.24$, $p=.11$, $n_p^2=.06$). P2 also did not significantly differ between healthy older adults and people with MCI at Fz or Cz sites, $F<1$ in both cases.

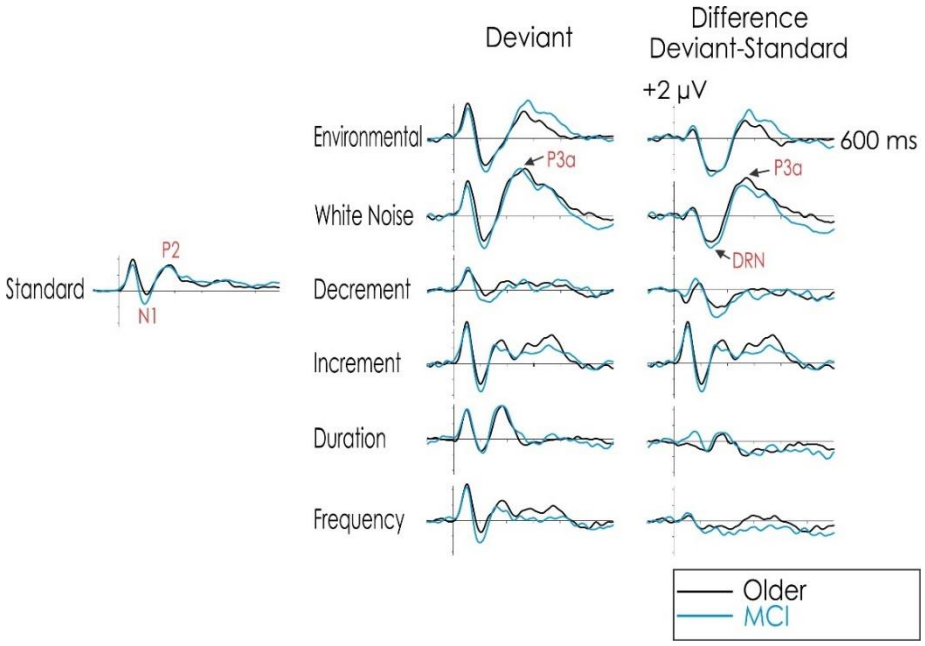

Fig. 5. Raw standard and deviant ERPs (left and middle portions) and deviant–standard different wave (right portion) for healthy older adults and people with MCI, at electrode Cz. A small negative deflection (N1) and later positive deflection (P2) is apparent after the presentation of the standard at about 100 ms. Their amplitude was not significantly different between the two groups. All deviant stimuli elicited a significant DRN. Only the novel environmental sounds and white noise deviants elicited a significant P3a.

7.2 DRN

Figure 6A presents the pirateplot of the MMN/DRN results. As is apparent in portion A of the pirateplot, the lower limit of the 95% CIs indicates that a significant DRN occurring from 100-150 ms was elicited by all deviants. The main effect of Group was not significant at Fz (F<1) or Cz (F<1). Similarly, the Group x Deviant interaction was not significant at Fz (F(5,190)=1.61, p=.16, n_p^2 =.04) or Cz (F<1).

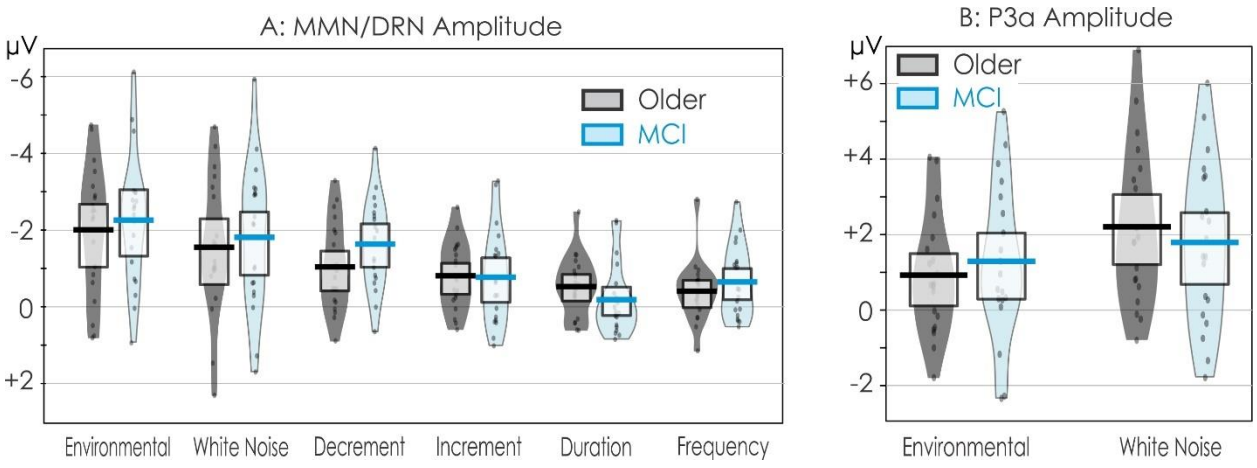

Fig. 6. Pirateplots of MMN/DRN (Part A) and P3a (Part B) data providing both descriptive and inferential statistics. Data are shown at Cz sites. The mean amplitudes of MMN/DRN and P3a (thick, solid horizontal line), 95% upper and lower confidence intervals (light box), smooth frequency distribution (shaded area), and individual data points (jittered) are presented. The mean amplitude of MMN/DRN and P3a did not differ between the groups.

7.3 P3a

Figure 6B presents the group means and CIs for the P3a. Confidence interval testing revealed a significant P3a following presentation of only the white noise and novel environmental sound deviants. The multi-channel grand averaged data for these two deviants are presented in Figures 7 and 8, respectively. The P3a occurred between 250 and 300 ms for both deviants and was maximum over centro-frontal regions in both healthy older adults and people with MCI.

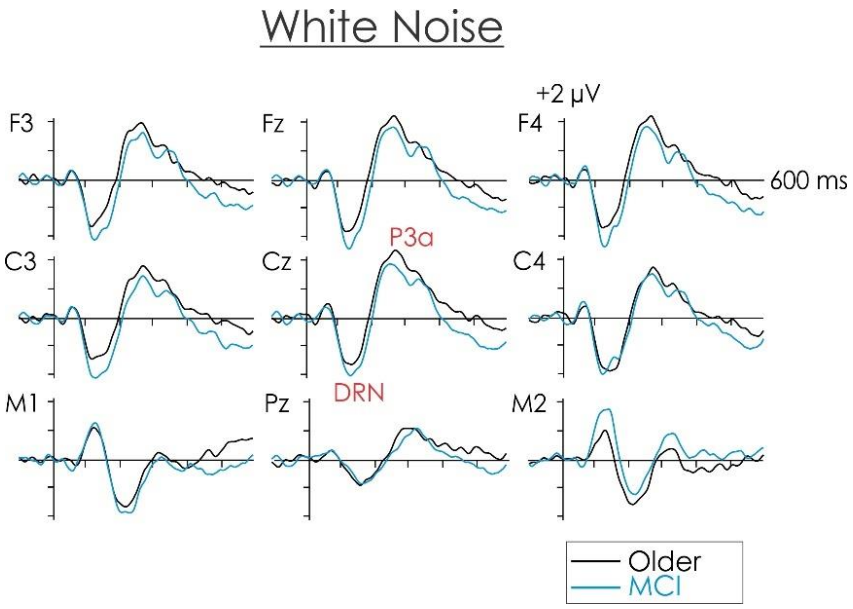

Fig. 7. Environmental sound deviant–standard difference wave across frontal, central, and parietal sites for healthy older adults and people with MCI. A frontocentral maximum DRN is apparent around 115–165 ms. Its amplitude did not differ between healthy older adults and people with MCI. This negativity was followed by a P3a occurring between 245-295 ms. The P3a did not differ between healthy older adults and people with MCI.

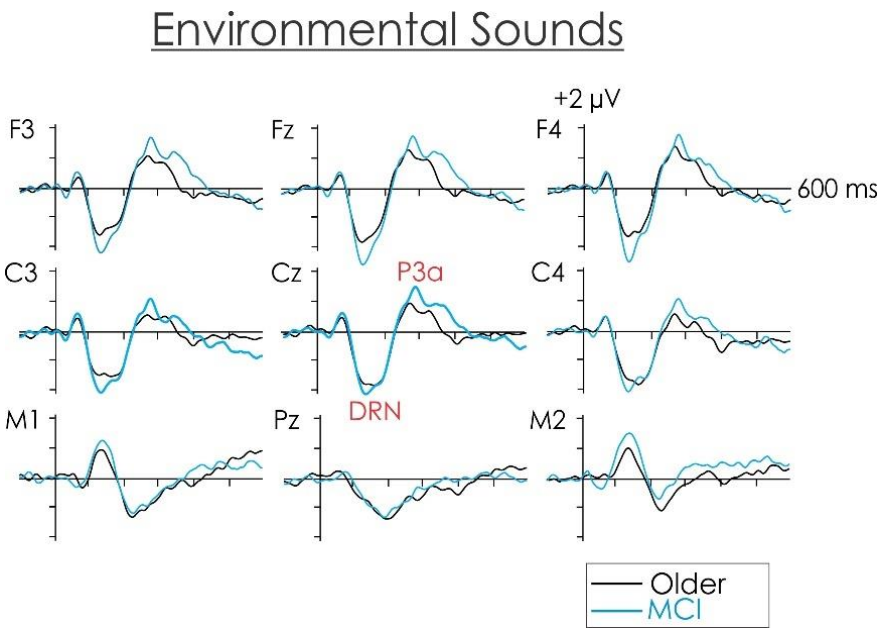

Fig. 8. White noise deviant–standard difference wave across frontal, central, and parietal electrode sites for healthy older adults and people with MCI. A frontocentral maximum DRN is apparent around 115–165 ms. Its amplitude did not differ between healthy older adults and people with MCI. This was followed by a P3a occurring between 250-300 ms. The P3a did not differ between healthy older adults and people with MCI.

The main effect of Group was not significant at Fz or Cz, $F<1$ in both cases. The Group x Deviant interaction was significant, at both the Fz ($F(1,38)=4.53$, $p=.040$ $n_p^2=.11$) and Cz sites ($F(1,38)=4.19$ $p=.048$, $n_p^2=.10$). A follow-up was again run using liberal one-tailed *t*-tests to identify possible group differences. P3a amplitude did not significantly differ between healthy older adults and people with MCI for white noise or environmental sound deviants, $t < 1$ in both cases. This interaction was driven by older adults exhibiting a larger amplitude P3a to the white noise than the environmental sound deviant at both Fz ($p=.01$), and Cz ($p<.001$). A Bayes factor test was run on the white noise and environmental sound P3a data to determine if the findings were more consistent with the alternate hypothesis (group differences) or the null hypothesis (no group differences). For the white noise P3a, BF_{10} was 0.38 and 0.36 at Fz and Cz, respectively. For the environmental sound P3a, BF_{10} was 0.36 and 0.39 at Fz and Cz respectively. In all cases, the evidence for support of the null hypothesis would thus be considered to be moderate or anecdotal (Wetzels and Wagenmakers, 2012).

The largest P3a was observed following presentation of the environmental sound and white noise deviants. Spherical scalp distribution maps were therefore computed for the P3a to these deviants. These are displayed in Figure 9. As may be observed, the P3a displayed a typical centro-frontal maximum amplitude. Its amplitude was much reduced at inferior and posterior sites, where the P3a was recorded as a negativity. This scalp distribution was similar for healthy older adults and people with MCI.

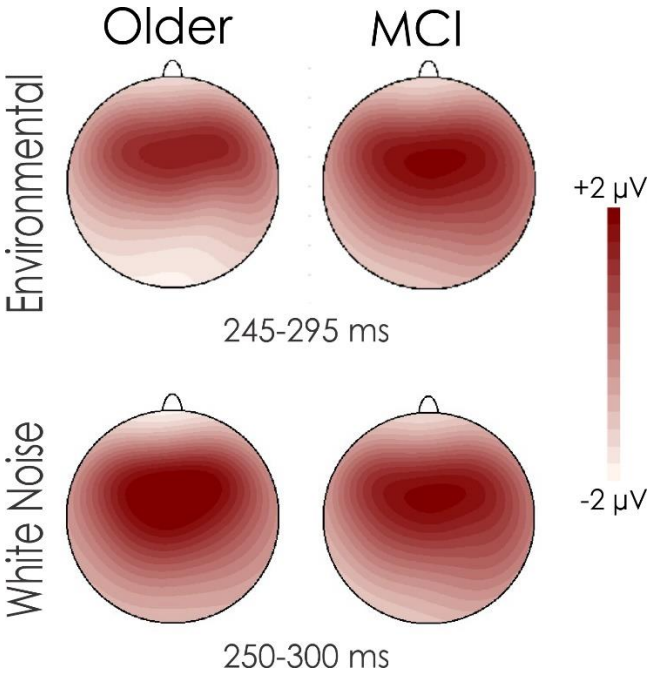

Fig. 9. Spherical scalp distribution maps of the P3a for healthy older adults and people with MCI. The maps were computed following presentation of the environmental sound and white noise deviants. A linear, equidistant perspective of a "flattened". head is illustrated. In this view, the projection was extended down 20° below the Fp1-T7-Oz-T8-Fp2 circumference to show data from the mastoids (orTP9 and TP10) and inferior frontal-temporal (FT9, FT10) sites. The P3a was maximum in amplitude over centro-frontal regions of the scalp and its amplitude was much reduced in amplitude at lateral and posterior sites. At the inferior and posterior sites, the positive-going peak was at times recorded as a negativity. This negativity did not however reflect an inversion in the polarity of the P3a. For this reason, the amplitude calibration color scale is traced from deep to light red reflecting the higher to lower amplitude of the positive-going peak.

8. General Discussion

In both Experiments 1 and 2, the standard N1 and P2 deflections did not significantly differ between the cognitively healthy older adults and people with MCI. Thus, any group differences in the various deviant-standard waveforms could largely be attributable to the difference in processing of the deviants rather than the processing of the standard.

The results of Experiment 1 indicated that following the presentation of both decrement and increment deviants, the amplitude of the MMN/DRN did not significantly differ between cognitively healthy older adults and people with MCI. Similarly, the amplitude of the P3a elicited by the increment did not significantly differ between the two groups. Other studies have

employed different types of deviants and have reported group differences. A follow-up study, Experiment 2, therefore presented several additional deviants including frequency, duration, white noise, and environmental sound deviants. In Experiment 2, the amplitude of the MMN/DRN again did not differ between the two groups for any of the six deviants. These findings replicate those of Laptinskaya et al. (2018) who also used a multi-feature paradigm and did not observe any MMN/DRN differences between cognitively healthy older adults and people with MCI. There thus appears to be little evidence that the detection of stimulus change MMN/DRN differs between healthy older adults and people with MCI.

A significant P3a was elicited by the white noise and environmental sound deviants. The P3a did not significantly differ between the healthy older adults and people with MCI. This finding is also consistent with the results of the first experiment, in which the amplitude of the P3a to the increment deviant did not significantly differ between the two groups. Again, a failure to observe group differences cannot be used as acceptance of the null hypothesis. Bayes factor testing of the P3a amplitude provided evidence that findings were more consistent with the null hypothesis than the alternate hypothesis. These P3a findings are in contrast to those of Kamal et al. (2021b). They noted that when a single stimulus was presented very slowly (every 12 s), a large amplitude positivity was apparent in healthy older adults but was smaller in people with MCI. They questioned, however, whether this late positivity reflected late P2 or early P3a activity. A more definitive P3a was elicited by the white noise and environmental sound deviants in the Cecchi et al. (2015) and Correa-Jaraba et al. (2018) studies, respectively. As mentioned previously, these deviants were not, however, irrelevant to the visual tasks assigned to their participants. The extent to which the P3a in their studies was associated with an actual switching of attention from the visual to the auditory channels can be questioned.

Most studies employ conservative statistical procedures (for example ANOVAs with post hoc procedures) to determine possible significant group differences. Such procedures will, of course, reduce the risk of false positives (type I error) at the cost of increasing the risk of false negatives (type II error). It is possible that the failure to observe group differences for either the amplitude MMN/DRN or the P3a was a result of the use of such conservative statistical procedures. For this reason, very liberal planned one-tailed t-tests were also applied as follow-up procedures to the Group x Deviant interactions. In spite of the use of these very liberal statistical procedures, significant group differences still were not observed. It is also possible that the failure to observe significant group differences was because the sample size was relatively small. A post-hoc power analysis was computed on the P3a amplitude group differences at Cz for the increment deviant in Experiment 1, and the white noise and environment sound deviants in Experiment 2. In order for these small P3a differences to have attained statistical significance in Experiment 1 would have required the inclusion of at least 125 participants in each group. In Experiment 2, over 550 participants in each group would have been required. The value of such an undertaking can be questioned. Such small group differences would have little clinical significance, even if the differences were statistically significant.

A number of studies have now reported that the amplitude of the P3a shows a large decline with aging (Berti et al., 2017; Correa-Jaraba et al., 2016; Tusch et al., 2017). These studies thus suggest that younger adults are much more able to switch attention to rarely occurring but unattended, highly salient auditory inputs than cognitively healthy older adults. In the present study, Bayes factor follow-up testing provides evidence that the amplitude of the P3a does not however differ in people with MCI compared to cognitively healthy older adults. It would appear that both healthy older adults and people with MCI have difficulty in computing

the priority of the intruding stimulus event, perhaps crucial for survival, to be sufficiently high to warrant a switch of attention from ongoing cognitive activity.

Several studies have suggested that ERPs may be a sensitive tool to use in the detection of early cognitive decline in MCI and AD (Morrison et al., 2018; Paitel et al., 2020; Swords et al., 2018). However, only a limited number of studies have examined the MMN/DRN and P3a. The present findings suggests the paradigms employed in this study may not be sensitive to the underlying pathology associated with cognitive decline in MCI.

While the Kamal et al. (2021b) did observe a smaller P2/P3a in people with MCI compared to cognitively healthy older adults, they employed a single stimulus rather than an oddball paradigm. Their single stimulus used in the Kamal et al (2021b) did, however, occur much more rarely (every 12 s) than the increment deviant in Experiment 1 (about every 7.5 s) and the white noise and environmental sound deviants in Experiment 2 (about every 7 s). Future studies might thus present deviant stimuli much more rarely. For example, Cote et al. (2001) noted that an increment deviant could elicit P3a-like positivity during REM sleep, but only when it was very infrequently presented (p =.05), occurring on average every 30 s. Other types of deviants might also be considered. Pakarinen et al. (2014) employed a multi-deviant paradigm including a bi-syllabic standard and 9 different deviants. Deviants that represented a linguistic change did not elicit a P3a, but deviants that represented an emotional change did elicit a large P3a. Sorokin et al. (2010) noted that that human speech sounds occurring among other environmental sounds elicited a large P3a. It is possible that human speech and emotionally-charged stimuli may be computed to be especially salient.

9. Conclusions

The present study examined the extent to which the frontoparietal network was able to switch attention from a complex visual task to the processing of a potentially highly relevant, but rarely occurring, unattended auditory input, signalling change from a frequently occurring standard. Some of these deviants (increment, white noise, and environmental sound deviants) elicited a significant P3a, both in cognitively healthy older adults and in people with MCI. The amplitude of the P3a did not significantly differ between both groups. The amplitude of an earlier MMN/DRN also did not significantly differ between the healthy older adults and people with MCI, regardless of the nature of the deviant stimulus. There was thus little evidence that people with MCI show a decreased ability to compute the salience of unattended auditory deviants, compared to healthy older adults. When deviant salience was established to be particularly high, there was also little evidence that people with MCI compared to healthy older adults have a decreased ability to subsequently switch processing priorities.

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General Discussion

This thesis has examined the use of electrophysiological measures as a biomarker of MCI. A number of previous studies have also proposed the use of a wide range of ERP components in this context (Gu and Zhang, 2017; Morrison et al., 2018; Paitel et al., 2020). Several unique features do, however, distinguish the studies used in this thesis. An especially unique feature is that very simple paradigms were employed, making minimal demands on the participants. In a large majority of previous cognitive studies, the participant was required to actively attend to a cognitive task for relatively long periods of times. A variety of testing procedures including strict behavioural (neuropsychological and cognitive studies), imaging (fMRI and PET studies) and also other ERP methodologies have been used in these studies. Common to each is, however, the need for the participant to be actively engaged in the cognitive task. A rationale for each of the studies in this thesis is that cognitively healthy older adults may not be able to comply with the need for attention to be sustained for long periods of time. This may be especially true for people with MCI. Unique to this thesis is that this requirement has been removed. The ERP components that were studied occur relatively independent of attention, task demands, and what the participant *is doing*. The ERPs were thus elicited passively. Whatever ERP differences that were observed could not be attributed to group differences in the ability to sustain attention to a task. Testing time was also very brief, and was completed within 15 to 20 minutes. Although a 32-channel recording montage was used, this could be reduced to a few channels, perhaps only the Fz, Cz and Pz midline sites. Because the paradigm is so simple, it can be implemented on almost any low-cost commercial ERP system. The thesis also included an examination of the resting-state EEG. The results indicated that a very brief 3-minute recording can provide a highly reliable measure of the resting-state EEG. Most ERP studies include a short “baseline” recording period prior to the presentation of the actual paradigm, to

ensure that the quality of the EEG is high. This brief period could be used as a resting-state EEG session.

The use of a low-cost system that requires only very short testing periods in which the participant does not need to be actively engaged in a task has many obvious advantages. Ultimately however, the determination of its use as a biomarker for MCI depends on how well it can classify cognitively healthy older adults and people with MCI. To what extent was the resting state EEG and the various ERP studies successful at doing so?

Study 1

Study 1 of this thesis examined whether resting-state EEG differs between healthy older adults and people with MCI. This study also examined if longer recording times can be used without the risk of drowsiness in healthy older adults and people with MCI. Participants were asked to keep their eyes closed and to refrain from movement. The EEG was recorded for 7 minutes and inspected for "bad" (noisy) sections. The analyses were performed on 6 minutes of "good" EEG. The EEG was then divided into two 3-minute halves to determine if there was evidence of drowsiness over time. An FFT was computed on either 2 or 8 s segments. There were thus 90 segments available for analysis in the 2 s segmentation and 22 segments in the 8 s segmentation. The longer 8 s segmentation permitted better lower frequency resolution of delta activity, strongly associated with actual drowsiness, but at the cost of fewer segments being available for averaging.

This study was designed to provide answers to the following questions:

1. Was there evidence of changes in the EEG between cognitively healthy older adults and people with MCI? A significant increase in theta power over posterior regions of

the scalp was observed in people with MCI compared to healthy older adults in both 3-minute halves.

2. Does the EEG change as the duration of the resting state EEG becomes longer? There was no significant change in the power density for any of the frequency bands between the first and second 3-minute recordings in either group.
3. Can longer recording times be used without the risk of drowsiness? There was no evidence of an increase in delta power in the second half of the study for either group. There thus seems to be little risk of increased drowsiness in a longer 6-minute recording.

Study 2

Study 2 of the thesis examined the extent of processing of a single unattended auditory stimulus that was presented relatively rapidly or very slowly. The processing of the salience of a single stimulus would be carried out exclusively by the transient detector system. The output from the transient detector system should be very high when the unattended auditory stimulus is presented very rarely. Because the input of this stimulus should be computed to be very high, it may result in the interruption of the frontoparietal network controlling processing priorities. This type of study had yet to be carried out in healthy older adults. An initial study was therefore required comparing the processing of a very slowly presented stimulus in younger and healthy older adults. Research has suggested that older adults may be unable to compute the level of salience of unattended stimulus inputs. The N1 and P2 response to an auditory stimulus provided a measure of the stimulus salience.

A simple paradigm was employed. A single 80 dB SPL auditory stimulus was presented either rapidly, every 1.5 s, or very slowly, every 12 s, in different conditions. Participants ignored the auditory stimuli and watched a silent, subtitled video. Because the effects of the rate

of stimulus presentation have not been extensively examined in healthy older adults, study 2 compared the N1 and P2 responses to these stimuli in younger and older adults. N1 and P2 group differences were only found when stimuli were presented very slowly. These components were much smaller in older adults compared to younger adults.

Questions this study was designed to answer:

1. Was there evidence of a dysfunction of the salience network in older adults? Both the N1 and P2 were much reduced in older adults compared to younger adults, but only when the unattended auditory stimuli were presented very slowly. This suggests that older adults may not adequately compute the level of salience of unattended incoming auditory stimuli.
2. Was there also evidence of a dysfunction of the frontoparietal network in older adults? When stimuli were presented very slowly, the latency of the P2 was delayed. It is possible that this positivity may reflect P3a activity. In the Näätänen model (Näätänen, 1990), a large output from the transient detector system may trigger attention capture and a resulting P3a. This P2/P3a was much reduced in older adults compared to younger adults. The N1 reflecting the level of salience of the stimulus was also smaller in older adults compared to younger adults. This finding suggests that a switch of processing priorities to a potentially highly salient but unattended auditory stimulus may be less likely to occur in older adults compared to younger adults. The failure of the switching of attention appears because the salience of the incoming stimulus is computed to be very low.

Study 3

Study 3 was a follow-up to study 2 and therefore used the same paradigm. There is evidence of additional deterioration in the functioning of the frontoparietal network in people with MCI compared to healthy older adults. This would suggest that a P3a, reflecting processes associated with a switch of attention from current processing priorities might be attenuated in people with MCI. The rate of presentation of to-be-ignored auditory stimuli was again either rapid or slow. When stimuli were presented rapidly, the amplitude of both N1 nor P2 did not differ between healthy older adults and people with MCI. When stimuli were presented slowly, the amplitude of N1 again did not differ between the two groups. However, the amplitude of the P2/P3a was significantly smaller in people with MCI compared to the healthy older adults.

Questions this study was designed to answer:

1. Was there evidence of a dysfunction of the salience network in people with MCI? The results of the present study do not support this hypothesis. The amplitude of N1, a measure of the level of stimulus salience, did not differ between the two groups. People with MCI appear to be as able as healthy older adults to compute the salience of an incoming stimulus.
2. Was there evidence of a dysfunction of the frontoparietal network in people with MCI? When stimuli were presented very slowly, the P2/P3a was significantly smaller in people with MCI compared to healthy older adults. This finding does indeed suggest a dysfunction of the frontoparietal network in this group. This reduced P3a suggests that people with MCI may be less able to determine processing priorities compared to healthy older adults.

Study 4

In Studies 2 and 3, the P2/P3a positivity may have been a summation of the P2 and P3a. Distinguishing between the P2 and P3a processes can be difficult because they may overlap and summate both temporally (occurring at about the same time) and spatially (sharing a similar scalp distribution). A more definite P3a had been elicited in oddball paradigms. Two experiments were run in which at least one of the deviants has been shown to elicit a large P3a in younger adults. In Experiment 1, the deviants represented either decreases or increases in the intensity of the standard. Increases in intensity have been shown to elicit a large P3a. In Experiment 2, six different deviants were presented, including white noise and environmental sound deviants that have elicited a large P3a in previous studies. This study examined if people with MCI are less able to switch processing priorities than healthy older adults.

Across both experiments, a MMN/DRN was elicited by all stimuli, but its amplitude did not significantly differ between the two groups. Only the increment, white noise, and environmental sound deviants elicited a P3a. These deviants should have caused a large output in both the change and transient detector systems This P3a also did not significantly differ between the two groups, even when very liberal statistical procedures were employed. These results suggest that the ability to switch processing priorities does not further deteriorate in people with MCI compared to what is observed in cognitively healthy older adults.

Questions this study was designed to answer:

1. Was there evidence of a dysfunction of the salience network in people with MCI? The MMN/DRN amplitude did not significantly differ between the healthy older adults and people with MCI, regardless of the nature of the deviant stimulus. This finding suggests that there is little evidence that people with MCI show a decreased ability

compared to healthy older adults to compute the salience of unattended auditory deviants.

2. Was there evidence of a dysfunction of the frontoparietal network in people with MCI? The results of the present study do not suggest that the ability to determine processing priorities further deteriorates in people with MCI compared to what is observed in cognitively healthy older adults. The amplitude of the P3a, a measure associated with attention switching, did not differ between the two groups.

Implications and future research

The initial ERP study examined the processing of to-be-ignored auditory stimuli in younger and healthy older adults. The stimuli were presented rapidly or very slowly. When they were presented very slowly, the amplitude of the N1 and subsequent P2 decreased markedly in the older adults compared to younger adults. There is some evidence that the sources of the N1 elicited by very slowly presented involve widespread cortical areas, including the frontal lobes. Näätänen has suggested that the N1 elicited by very slowly presented stimuli may reflect processes involved in the subsequent integration and synthesis of auditory features. The failure of such integration and synthesis of stimulus features in older adults may explain why they are less able to accurately compute the salience level of the stimulus.

Future fMRI studies might compare the activation of different brain regions in older adults when auditory stimuli are presented rapidly and slowly. It is possible that in older adults, it is mainly the temporal cortex that is activated by such slowly presented stimuli while areas critical for the integration and synthesis of the stimulus, such as the frontal lobes, remain largely inactivated.

The results of studies 2 and 3 also point out the need for a more basic exploration of the operations of the transient detector system in older adults and in people with MCI. The present thesis examined only two rates of stimulus presentation. A more comprehensive study of the effects of the rate of stimulus presentation needs to be completed, including presenting stimuli are extremely slow rates (> every 30 sec). It is possible that older adults might judge these extremely rarely occurring stimuli to be highly salient and thus elicit a large P2/P3a. The output of the transient detector system is also affected by the intensity of the stimulus. Future research should examine the effects of the intensity of the auditory stimulus, including very intense stimuli. Very intense auditory stimuli will elicit eye blinking associated with a startle reflex. The eye blink startle reflex is delayed and smaller in cognitively healthy older adults (Le Duc et al., 2018) and may be modulated by activity in the prefrontal cortex (Mather, 2016).

Large differences in the amplitude of the P3a have been reported between younger and older adults. The present series of studies did not observe a significant difference in P3a amplitude between healthy older adults and people with MCI. The P3a in the healthy older adults was, however, quite small even for deviants that elicit a large P3a in younger adults. Whatever processes account for the failure of attention capture in healthy older adults do not further diminish in people with MCI.

Future research should present deviants that represent an even larger change to the standard. In the present thesis, an increment represented a 10 dB increase to the intensity of the standard. This deviant could be increased to represent a 20 or perhaps a 30 dB change. Changing deviant location also elicits a large P3a. The deviant might thus be presented to the opposite ear than the standard. Study 2 indicated that the frequency of occurrence of an auditory stimulus has a major effect on the ERP responses. In this regard, Cote et al. (2001) examined the effect of

varying the probability of occurrence of an increment deviant during REM sleep. A P3a-like positivity was not elicited by an increment occurring on 10% of stimulus presentations. This probability of occurrence was similar to that used in the present thesis. When the increment only occurred on 5% of trials, a P3a-like positivity was elicited during REM sleep. It is possible that only very rarely occurring deviants will elicit a P3a in older adults. As mentioned in the discussion of study 4, some authors have noted that a P3a can be elicited by affective speech deviants. Younger and older adults also appear to process emotional stimuli differently (Nashiro et al., 2012). Future research might examine whether affective speech deviants or emotional stimuli elicit different P3a amplitudes between younger and older adults.

The present thesis employed a visual task (watching a sub-titled video) as a distractor task. Auditory stimuli that were irrelevant to this task were presented concurrently. The nature of the distraction tasks appears to have little effect on younger adults. Recent research indicates this may not be the case in older adults. Mahajan et al. (2020) had younger and older adults perform two visual tasks. One of the visual tasks required working memory while the other did not. Irrelevant auditory stimuli preceded the presentation of the visual stimuli. The deviant stimulus elicited a P3a in the younger group. Its amplitude was not affected by the nature of the visual task. The P3a was however attenuated in the working memory task in older adults. The visual task used in the present study, watching a sub-titled video, has been used in many ERP studies. This task will, of course, require working memory. Future research should further examine the nature of distraction tasks in older adults and people with MCI.

The P3a has been studied using so-called passive and active paradigms. In the present study, the auditory stimuli were to be ignored and were irrelevant to the visual task. Processing of the auditory stimuli was therefore passive. When the deviant stimulus elicits a P3a, this is

interpreted to reflect a switching of attention from the task at hand to the processing of the auditory deviant. A major problem with this interpretation is that there is no independent evidence of this switching of attention. This independent evidence is available in active studies. In these studies, the auditory deviant occurs within an attended channel. A classic paradigm developed by Schröger and Wolff (1998) presents a sequence of auditory stimuli. Half the stimuli have a shorter duration and half have a longer duration. The participant's task is to detect the duration of the stimuli. Occasionally, the frequency of the auditory stimulus changes to form a deviant. The frequency of the auditory stimulus is however irrelevant to the duration detection task. The irrelevant frequency change elicits a P3a. Evidence of the switching of attention to the processing of the auditory deviant however comes from an independent measure, the performance data. Performance on the duration detection task deteriorates, presumably because processing resources were switched to the processing of the deviant stimulus. Parmentier (2014) indicates that the P3a elicited by the deviant stimulus is much larger when the deviant is presented within an actively attended channel than when the deviant occurs in an unattended channel. In the present thesis, the P3a was elicited by auditory deviants that occurred in an unattended channel. Berti et al. (2013) did not find P3a differences between younger and older adults using an active Schroger paradigm. There are, however, many variations to this paradigm.

The P3a active paradigm has not been used in the study of MCI. There are many difficulties in doing so. For example, the ease of the task needs to be equated between the two groups. If the task is too easy, participants may not need to be fully attentive. If the task is too difficult, participants may simply cease attending and "give up". In both cases, a difference in the P3a could be attributed to the extent to which attention was paid to the task rather than a reflection of the differences in the operations of the frontoparietal network. To equate the

difficulty of the task in the two groups would probably require a confound, the physical features of the stimuli would need to vary between the two groups. The difference in the duration of the short and long stimuli would probably need to vary between the two groups. In addition, attention to the task must be highly focused for a relatively long period of time. This attention to the task might be difficult for healthy older adults and more so for people with MCI.

In the present thesis, overall global cognition was relatively homogenous in people with MCI. Correa-Jaraba et al. (2018) have, however, noted that the amplitude of the P3a may vary between multiple-domain and single-domain MCI. Future research might therefore divide people with MCI into different sub-groups (i.e., amnestic vs non-amnestic MCI, and multiple-domain vs single-domain MCI). Importantly, studying subtypes of MCI may help identify early markers of cognitive decline allowing researchers and clinicians to accurately identify those in the early stages of cognitive decline.

Another method that could be implemented to improve the classification of individual participants as being a cognitively healthy older adult or as a person with MCI is the use of machine learning algorithms. In this thesis, ERP components were quantified according to their peak latency and regions of interest, where their amplitude was largest. This method is used in a large majority of ERP studies. It has however been criticized as being somewhat arbitrary. It also does not quantify data at other time points within the 700 ms epoch and at other scalp locations.

A preliminary application of machine learning was made on the resting-state EEG data in which theta activity was significantly larger in people with MCI compared to healthy older adults. The machine learning algorithm applied to the theta band data was only moderately successful at classifying individual people with MCI and healthy older adults (first 3 min = 0.72 vs. second 3 min = 0.67). An average of 70% accuracy for MCI classification is similar to that

observed in other studies attempting similar classification using EEG data (Meghdadi et al., 2021; Farina et al. 2020).

A machine learning algorithm was also applied to the N1 and P2/P3a data from study 2. In this study, both N1 and P2/P3a were much larger in younger than older adults when stimuli were presented slowly. It would therefore be expected that the machine learning algorithm would be more successful at classifying individuals with these data. Applying machine learning was indeed more successful in the classification of individual participants. The extent of success varied depending on which machine learning algorithm was applied but could, however, exceed 0.80.

Of course, this preliminary analysis only applied the machine learning algorithms to existing data as they were quantified in the different studies. As mentioned, such human quantification may be somewhat arbitrary. The algorithms did not consider the data from scalp locations that were not quantified in the original studies or other data points within the ERP waveform. The algorithms also did not consider subtypes of MCI. It would be beneficial to include for example, those who progress to different dementia subtypes, those that remain stable, and those who revert to normal cognition. The proper use of machine learning does encounter a major obstacle in EEG and ERP studies. It requires a very large sample within each of the MCI subtypes. Many participants are required because classification will self-improve as the machine gradually learns as more data becomes available (Figueroa et al. 2012).

Limitations

There are some limitations in the studies that are important to note. The sample size of the groups may be considered relatively small (20 participants per group). However, the sample size was quite large compared to many ERP studies. In the first three studies, the sample size was sufficient to allow for the rejection of the null hypothesis. Significant group differences in

the theta band of the EEG and in the N1 and P2/P3a ERP studies were found. The fourth study consisted of two experiments. In both experiments, the amplitude of the P3a did not differ between healthy older adults and people with MCI. In these experiments, an a priori power analysis was run employing the P2/P3a group effect size from study 3. Group differences were, however, not significantly different. A post-hoc power analysis was also computed on the P3a amplitude group differences at Cz for the increment deviant in Experiment 1 of study 4. This power analysis revealed that for the small P3a group difference to attain statistical significance, 125 participants in each group would have been required. A post-hoc power analysis was also applied to the white noise and environmental sound P3a data in experiment 2. Over 550 participants in each group would have been required for these P3a differences to attain significance. The practical value of such a time-consuming and expensive undertaking can be questioned. Such small group differences would have little clinical significance, even if the differences were statistically significant.

A number of the same individuals participated in each study. The same sample of older adults was used in both Study 2 and Study 3 and 36/40 participants in Study 4 overlapped with Study 3. A different random sample was therefore not used in each study. Recruiting similar participants across studies has the advantage that differences across the studies cannot be attributed to the use of different random samples. On the other hand, it is possible that the differences or failure to find differences may be unique to those individuals that were tested. Moreover, future meta-analyses of these studies will need to consider the fact that the results in these studies do not reflect independent outcomes.

Conclusion

The Introduction to this thesis noted that,

> *A rise in life expectancy has led not only to an increase in the aging population but also to a growing number of older adults with cognitive decline, including mild cognitive impairment (MCI). Cognitive decline is a central component of aging.*

In addition,

> *Finding a cost-effective, widely available, and reliable method that can detect early, subtle differences between healthy older adults and people with cognitive impairment is urgently needed.*

The paradigms used in this thesis are undoubtedly very cost-effective and widely available. But do they provide a reliable method for the detection of early cognitive impairment? The second study indicated that ERP differences between younger adults and cognitively healthy older adults were quite large when a single stimulus was presented very slowly. The processing of this single stimulus appears to be carried out exclusively within the transient detector system. Unfortunately, very few studies of the aging process have focused on this system. Many additional basic studies therefore need to be carried out. For example, does the large N1 and P2/P3a difference develop gradually with aging or is the change much more sudden? Is the reduction in the amplitude of the N1 and P2/P3a even more pronounced in advanced aging or does it plateau at perhaps 60 to 70 years of age? Importantly, the large N1 and P2/P3a differences were found at a group level. At an individual level, there was some overlap. Why do some younger adults have ERP profiles that are similar to those of older adults? Why do some older adults have ERP profiles that are similar to those of younger adults? This problem is by no means unique to ERP methodology. A similar overlap has also been reported in neuropsychological and neuroimaging studies.

When a single auditory stimulus was presented very slowly, the P2/P3a differences were much smaller, but statistically significant, in cognitively healthy older adults compared to people

with MCI (study 3). The single stimulus results in activation of only the transient detector system. Oddball paradigms were run (study 4) that included rare deviant stimuli that have previously been shown to elicit a large P3a in younger adults. The deviants should have caused activation of both the change and transient detector systems. Only a small P3a was elicited in both cognitively healthy older adults and in people with MCI. The P3a group differences were not significant. Thus, while the amplitude of the P3a is very sensitive to the aging process, there is little evidence that it is further reduced in people with MCI. The amplitude of the P3a elicited by sufficient output from the change detector system will probably not provide a "reliable method that can detect early, subtle" evidence of cognitive decline in people with MCI. On the other hand, there is promise that the P3a elicited by sufficient output from the transient detector system will provide a reliable method. It is also possible that future studies that employ a much more extensive quantification of the ERP waveforms might improve classification of individual participants. As mentioned previously, it is also possible that the ERP methods might be more successful at classifying sub-types of MCI.

There is good evidence that the ERP components studied in this thesis implicate processing within the frontal lobe. These ERPs might thus be used to discriminate frontal and non-frontal degeneration. The ERP methods may be of particular use in the study of the progression to AD. Many of the currently-used diagnostic techniques that rely on cognitive assessment do depend on an ability to sustain attention for the duration of testing. The ability to sustain attention declines as the severity of the disorder progresses. As has been emphasized in this thesis, this is not a limitation when ERPs are elicited passively. In addition, as treatments become available for both the prevention of AD and the slowing of progression within AD, the efficiency of these treatments will need to be tested. Assessing cognitive abilities in AD can,

however, be challenging because of the need for the individual to actively attend to the various tasks, and to understand the instructions. This problem is not a limitation of the paradigms used in this thesis because active participation of the individual is not required. Again, because the paradigms are so simple, intra-group variability will probably be much smaller compared to tasks in which the participant must actively remain attentive. As such, these paradigms may also provide a means to reduce the size of the sample needed to be tested and perhaps the duration of the treatment process. A longitudinal design should also be employed to examine differences between MCI participants who convert to dementia and those who remain stable. These studies could reveal the electrophysiological changes associated with conversion to dementia at an individual level.

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