Age effects on auditory sensory memory:

a cognitive neuroscience perspective

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This thesis is submitted for the degree of Doctor of Philosophy,

University of Newcastle, Australia

Submitted: February 2009

Statements by the candidate

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I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers. I have here included as part of the thesis a statement clearly outlining the extent of collaboration, with whom and under what auspices.

The second study presented in this thesis was completed in collaboration with two researchers, Ms Rosemary Clark and Ms Rebbekah Atkinson. Approximately one third of the participants tested for study 2 were tested by Ms Clark. Ms Clark submitted her honours thesis in psychology based on the data she collected from this subset of participants. Ms Atkinson was also responsible for testing approximately one third of participants for study 2 as a research assistant.

Candidates signature: ……..

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Acknowledgements

First and foremost, I would like to thank my primary supervisor, Professor Pat Michie, for her expert guidance and support. It has been a pleasure to have been supervised by such an inspiring woman. In addition, I would like to thank my co-supervisor, Dr. Juanita Todd, for her thought provoking comments and fresh perspectives. Juanita's passion for her work sparked my initial interest in aging and event-related potential research. Thanks also to Bill Budd for helpful comments on my work.

I am indebted to all the participants who offered their time to take part in this research. For their assistance in recruiting older adults, I would like to thank the Hunter Medical Research Institute and those running the research volunteer register, Debbie Quain and Trisha D'Accione. I wish to acknowledge the support of the School of Psychology and the Faculty of Science and IT for providing research funding throughout my studies. I was also supported by an Australian Postgraduate Award. For the technical support that I received during the course of my doctoral studies, I would like to thank David Paul, Damien Mannion, Gavin Cooper, Bryan Paton, David McKenzie, and Tony Kemp. I would also like to thank Rosemary Clark and Rebbekah Atkinson for their help in testing participants for my second study. The general staff in the school of psychology deserve special mention for their assistance with administrative aspects of my studies: Anne Quayle, Sharon Harris, Lynne Brunt, Jeff Drummond, Sandra Dimmock, and Kyle Holmes.

Thanks to the members of the Functional Neuroimaging Laboratory, especially those who helped me in the early days, Carmen, Rebecca, Amy, Natasha, Matt, and Sharna. To my office mates past and present, thank you for brightening up those long office days. A special thanks goes out to all my family and friends who helped me through the PhD highs and lows.

Dedication

Thank you to my dear husband, Rusty. I have saved my greatest cliché for you: I could not have done this without you (at least not with my sanity quite so intact). You believed in me throughout. You cooked me delicious dinners, listened to the dramas, remained calm, kept me laughing, and generally helped me through. For these reasons and many more, I would like to dedicate this work to you.

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Abstract

It is well established that there are changes in cognition and in peripheral sensory mechanisms that occur with age. However, there is much less known about the cause of either change or indeed the relationship between age-related change in sensory processing and age-associated cognitive decline. Understanding these mechanisms could improve our capacity to devise strategies which could assist older adults in aging successfully. In this thesis, I aim to bridge a gap in our knowledge concerning the relationship between age-related change in sensory processing and age-associated cognitive decline by studying the effect of age on what can be considered an intermediary process, sensory memory (in the auditory modality). I continue this line of research by examining the relationship between auditory sensory memory and other types of memory for auditory information in young and older adults. To address these goals, I adopted a cognitive neuroscience approach, relating electrophysiological data to data derived from behavioural memory assessments.

In the following thesis, I present a literature review, four studies, and a general discussion of results. Several waveforms of the auditory event-related potential (ERP), including N1, P2, repetition positivity (RP), and mismatch negativity (MMN) were studied. More specifically, in study 1, we looked at the effect of age on N1 and P2 amplitude. In study 2, we examined the conditions eliciting two repetition effects, RP and the MMN memory trace effect, in the auditory ERP of young adults. Studies 3 and 4 concerned the effect of age on RP and the relationship between RP and implicit memory for contextual information as well as explicit memory for auditory information.

We concluded that i) age affects auditory sensory memory, ii) the potential relationship between auditory sensory memory and implicit memory for auditory information requires re-investigation, and iii) there is a relationship between auditory

sensory memory and explicit memory for auditory information that is altered with age. That is, we concluded that RP occurring in the N1/P2 and MMN latency period indicates memory trace formation and that age affects RP amplitude (restricted to an anterior RP generator). In addition, we showed that RP may be related to implicit memory (priming) in both young and older adults. Across two studies, we found a positive correlation between the response to repetition in the ERP (due to RP activity) and explicit auditory verbal memory in young adults but a negative correlation in older adults.

Therefore, although age-related change in RP could reflect the capacity of older adults to encode the context of auditory stimulation, this is potentially due to compensatory activity. We argue it is possible that implicit memory changes with age as a result of age-related change in explicit episodic memory. As a result of well established changes that occur in episodic memory with age, older adults may begin to rely on implicit memory as a source of memory more so than young adults. Our data shows that the implicit memory system may, as a result, favour content over contextual information. An important theme outlined in the discussion of results involves the idea that age-related changes in cognition that are commonly interpreted as cognitive deficits may in fact be beneficial in certain circumstances.

We review our results in relation to cognitive theories of aging and find that several theories are applicable to the data, including the frontal hypothesis (incorporating the inhibitory deficit hypothesis), the information degradation hypothesis, and the speed of processing hypothesis. Future research in this area could focus on exploring whether top-down or bottom-up or influences primarily contribute to the age effect on auditory sensory memory and RP, as well as evaluating our hypothesis that the age-related change in RP may be beneficial for explicit item memory but detrimental for implicit contextual memory

in older adults (i.e. compensatory mechanisms). While the studies presented in this thesis have provided the foundations guiding our understanding of these issues, researchers in the field of cognitive neuroscience are well equipped to resolve such questions in the future.

Chapter 1: Introduction

Age effects on auditory sensory memory: a cognitive neuroscience perspective

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A review of aging research and the cognitive neuroscience of aging

Over the past century, with medical advances and the amelioration of social conditions, the average lifespan in Australia has increased by approximately 20 years (Australian Bureau of Statistics, Australian Social Trends, 1995). As a result, the percentage of older adults living in the community is also increasing (Australian Bureau of Statistics census data 2006). Research shows that there are many sensory and cognitive changes that occur as part of the aging process such as hearing (Schneider & Pichora-Fuller, 2000) and memory difficulties (Craik, 2000) which can impinge upon the quality of life of older adults. All of these factors have contributed to the growing interest in researching the aging brain. Improving our understanding of how the brain changes as we age and identifying the mechanisms underlying such change will bring us one step closer to improving the cognitive fitness of older adults and potentially improving quality of life in old age. For example, there is evidence that cognitive training (Nyberg, 2005) and exercise (Colcombe & Kramer, 2003) can benefit cognition in old age. In a similar vein, Prull, Gabrieli, and Bunge (2000) have discussed how targeted biological interventions may ameliorate specific age-related cognitive deficits once the underlying neurological causes of such deficits are understood.

Due to the demographic changes in our societal make-up described above, our perceptions regarding who qualifies as an older adult may have altered over time. It is therefore important to define what I mean by the term ‘older adult’. In the context of the present research, older adults have been defined as adults 50 years of age and over while young adults have been classified as adults between the ages of 18 and 30. It is recognized

that this definition of the older adult (aging) covers a wide age range. However, this type of definition is commonly used (e.g. Gazzaley & D'Esposito, 2005) as it enables us to determine what, if any, age-related changes are present in different cognitive domains. Once the wider picture is established, it will be possible to refine this definition to observe when in the lifetime cognitive changes related to old age commence (e.g. by examining middle-aged adults) and to clarify the extent and progression of age-related change in the latter period of life (e.g. by comparing older adults in successive decades of life).

Although there are many perspectives from which to examine the aging process, from the cellular to the social level, researchers in the emerging field of cognitive neuroscience are attempting to address major challenges surrounding aging research such as how to relate the multitude of cognitive and physiological brain changes that occur with age (e.g. Cabeza, Nyberg, & Park, 2005; Fabiani & Gratton, 2005), to differentiate between healthy and pathological age-related changes (e.g. Cabeza et al., 2005; Grady, 2005), and to identify the factors contributing to the interindividual variance in cognitive change associated with the aging process (e.g. Buckner, 2005). Another challenge facing the field is to differentiate between neurobiological makers that are representative of a corresponding cognitive deficit from those that represent compensatory activity (e.g. Cabeza et al., 2005; Daselaar & Cabeza, 2005; Prull et al., 2000).

In line with one of the stated aims of the cognitive neuroscience of aging, the broad aim of the research presented in this thesis was to use the event-related potential (ERP) to link electrophysiological and cognitive changes associated with aging. Although research into age-related change in peripheral sensory systems clearly shows that deficits occur with age, there is little research into age effects on sensory memory (Craik, 2000). Craik adds that such research would help to gauge the relationship between age-related deficits in

peripheral sensory systems and higher order cognitive systems. Primarily we aim in this thesis to contribute to the understanding of how age affects auditory sensory memory. We explore the electrophysiology of age-related change in this facet of sensory memory processing and then attempt to relate these findings to neuropsychological and behavioural data. In the following, I review topics pertinent to this research including theories regarding the cause of age-related sensory and cognitive changes and a summary of the precise nature of age effects on the auditory system and memory systems including auditory sensory memory. I explain the relevance of an electrophysiological measure, the event-related potential, for research on the effect of age on auditory sensory memory.

Theories regarding the relationship between sensory and cognitive functioning with age

As stated, it is well understood that sensory decline occurs with age. For example, in the auditory modality, lifespan data shows that a decline in hearing sensitivity begins as early as the third decade of life (see review in Willott, 1991). Similarly, in the cognitive domain, lifespan data shows that by the third decade of life, speed of processing and working memory measures begin to decline (see review in Park, Polk, Mikels, Taylor, & Marshuetz, 2001). However, Park et al. (2001) argue that performance on vocabulary tasks remains relatively age-invariant (if anything, vocabulary may show a small increase with age). As not all cognitive functions are deficient in older adults, a comprehensive theory of cognitive aging must explain how it is that some brain functions are relatively spared by age compared to others. The purpose of the present section is to broadly explain the relationship between the age-related change that we see in sensory sensitivity and cognition before exploring specific theories of cognitive aging.

At present there are several theories that relate the sensory and cognitive changes that occur with age. One type of model suggests that there is a common cause for the sensory and cognitive changes observed with old age while another suggests that there are multiple causes impinging on the integrity of sensory and cognitive systems with advanced age. There are models that imply that sensory deficits lead to impaired cognitive functioning and vice versa (see review in Schneider & Pichora-Fuller, 2000). The specific possibilities outlined by Schneider and Pichora-Fuller to account for age-related change in sensory and cognitive functioning include the common cause hypothesis, the sensory deprivation hypothesis, the information degradation hypothesis, and the cognitive load on perception hypothesis. The common-cause hypothesis states that age-related changes in sensory and cognitive domains are the result of one factor such as widespread degeneration of neural integrity within the aging brain. The sensory deprivation and information degradation hypotheses assume that information from sensory processing is either lost or degraded with age resulting in deficient cognitive processing. The cognitive load on perception hypothesis is essentially the inverse hypothesis, stating that cognitive deficits associated with age affect sensory processing in a negative manner.

However, to make a strict delineation between where sensory processing ends and cognitive processing begins is difficult as we know that information processing is both bottom-up (e.g. sensory information) and top-down (e.g. cognitive inferential information) within the brain. Schneider and Pichora-Fuller (2000) argue that to understand age-related changes in sensory or cognitive domains, one must consider sensory and cognitive processes as part of an integrated system. Therefore, if one system were affected in a degenerative manner, it is likely that the other system would also be negatively affected. In fact, a strong link has been shown between peripheral sensory functioning in older adults

and performance on cognitive tasks testing speed, reasoning, memory, knowledge, and fluency (Baltes & Lindenberger, 1997; Lindenberger & Baltes, 1994). Lindenberger and Baltes took these data as evidence for a common cause hypothesis. However, as outlined above, the sensory deprivation, information degradation, or cognitive load on perception hypotheses are not ruled out by these data.

Not only has a strong link between sensory and cognitive functioning been observed, it has also been shown that there is an increase in the strength of the relationship between sensory and cognitive processes with age. Schneider and Pichora-Fuller (2000) describe how correlations between audition and cognitive functioning (as well as between vision and cognitive functioning) are larger in older than young adults. This supports a discontinuity view of aging, which states that there are age-associated factors that affect the relationship between various abilities. One discontinuity view that has been discussed in the aging literature is that concerning 'dedifferentiation' of abilities across the lifespan. Dedifferentiation is a term that has been used differently by cognitive and neuroimaging researchers (e.g. see Anstey, Hofer, & Luszcz, 2003; Park et al., 2001). In the cognitive sense, the term dedifferentiation has been used to describe the increasing strength of relationship between cognitive factors with age. However, there is more recent longitudinal evidence that this type of dedifferentiation, does not occur with age (Anstey et al.). In terms of neuroimaging data (which we will discuss in a later section), dedifferentiation is a term that describes the opposite process to that of differentiation. Differentiation of brain regions is a maturational process that allows the brain to perform specialized operations. Therefore, dedifferentiation refers to the reduction in specialization of brain areas and the possible recruitment of alternate brain regions to perform various tasks. In this sense, it is possible

that dedifferentiation is a common cause hypothesis which accounts for age-related changes in cognition.

Another line of research that provides insight into the relationship between sensory and cognitive processing across the age span is that which attempts to equate the sensory functioning of young adults to that of older adults. This is achieved by degrading the sensory information available to young adults in specific tasks. Murphy, Craik, Li, and Schneider (2000) found that young adults' performance on an auditory memory task was reduced when the auditory signal was presented in the context of background noise. This study indicates that one of the possible reasons why older adults may perform more poorly on some memory tasks relative to young adults is that degraded sensory input in the older adults affects higher order cognitive processes such as memory (i.e. information degradation hypothesis). However, in opposition to this finding, Lindenberger, Scherer, & Baltes (2001) found that degrading auditory and visual stimuli for middle aged adults did not reduce their cognitive performance.

In sum, whether a common cause or multiple causes impact upon sensory and cognitive processing with age, and whether there is a bidirectional influence of sensory and cognitive decline or whether sensory decline primarily affects cognitive decline or vice versa, remains to be seen. However, beyond this debate, cognitive aging researchers have postulated further reasons to explain age-related cognitive decline. In the following I explore specific theories of cognitive aging and review more recent neuroscience research that seeks to complement our understanding of the factors underlying age-related changes in cognition. As the next section will show, current cognitive theories of aging tend to focus on a single factor that could potentially explain age-related changes in cognition (common cause hypothesis).

Cognitive aging theories

One of the earliest theories put forward to explain age-related cognitive decline is the cognitive resources view outlined by Craik and Byrd (1982). Essentially, the cognitive resources view states that older adults lack the attentional or cognitive resources to complete tasks to the same degree of accuracy as young adults. However, a problem with this viewpoint is the fact that the 'cognitive resources' construct is ill-defined (see Hasher & Zacks, 1988). Park (2000) describes cognitive resources as "the quantity of mental processing power or mental energy that a given individual has available to use when performing a cognitive task" (p. 4). While this definition of cognitive resources still defies empirical measurement, it is a definition which embraces several key (empirically measurable) concepts that fall within the rubric of cognitive resources. Those concepts thought to best represent the notion of cognitive resources are: speed of processing, working memory, and inhibitory functioning (Park, 2000). We will briefly describe each of these as common cause hypotheses of cognitive aging.

The processing speed hypothesis, proposed by Salthouse (1996) suggests that cognitive declines observed with age are a result of reduced speed of processing that takes place with age. Two aspects of Salthouse's (1996) hypothesis explain how reduced speed of processing could result in reduced cognitive ability with age. Firstly, Salthouse (1996) proposes a "limited time mechanism" which represents the limited time available for later stage processes to occur when early stage processes are executed more slowly than usual on a time driven task. Secondly, a "simultaneity mechanism" refers to the fact that the result of early stage processing may be lost to later stages when there is a slowing of successive processing steps. Reduced processing speed in old age is thought to affect processes related

to fluid cognition such as memory, reasoning, and spatial abilities (Salthouse, 1996). Two metaphors to explain how the limited time and simultaneity mechanisms could contribute to such age-related cognitive change are presented by Salthouse (1996); the time limited mechanism resembes an assembly line with a fault that reduces the quality of the final outcome and the simultaneity meachanism, a juggling act that requires synchronization of various subroutines in order for the primary task to be performed well. Salthouse (2000) outlines several mechanisms that could contribute to age-related slowing, including: an age-related reduction in number of neurons in the brain, in dendritic branching, myelination, dopamine transmission, or synchronization of neural firing. However, it has been argued that speed of processing does not fully account for age-related change in all aspects of cognition (see Park et al., 1996; Salthouse, 1996). Using structural equation modeling, Park et al. (1996) have shown that speed of processing in combination with working memory contribute to performance on spatial, cued, and free recall tasks in young and older adults.

Working memory is best described as the process which allows an individual to hold information in short-term memory and simultaneously manipulate this information (see Baddeley, 1986; Baddeley & Hitch, 1974). Park (2000) suggests that Craik and Byrd's (1982) description of processing resources is in fact closest to our modern day conception of working memory, although Craik and Byrd used the term attentional resources. There is evidence that working memory declines with age (see section on age-related changes in memory functioning). As working memory is active in more effortful memory tasks such as free recall compared to cued recall, age-related decline in working memory will affect the performance of older adults on more challenging memory tasks (e.g. Park et al., 1996). An element of cognitive processing with a strong association to working memory (Reuter-

Lorenz & Sylvester, 2005), inhibition, forms the basis of another commonly cited cognitive aging theory, the inhibitory deficit hypothesis.

The hypothesis that cognitive deficits in older adults primarily stem from deficient inhibitory mechanisms was originally proposed by Hasher and Zacks (1988). These researchers suggest that older adults have difficulty inhibiting the processing of task-irrelevant information and as a result have reduced capacity to process task relevant information. However, using inhibitory processing or working memory as cognitive resource explanations of cognitive aging begs the question as to what causes the age-related change in working memory or inhibitory processing? As both working memory and inhibitory processing are reliant on the frontal cortex (see reviews in Fletcher & Henson, 2001; Raz, 2000; West, 1996), the frontal hypothesis of aging is a candidate to unite working memory and inhibitory deficit explanations and to add a further causal layer to these explanations of cognitive aging.

The frontal hypothesis (also known as the executive functioning hypothesis) of aging states that the area of the brain most vulnerable to aging is the frontal cortex and that functions mediated by the frontal cortex are consequentially those most affected by age (West, 1996; West, 2000). The frontal hypothesis evolved due to the observation that older adults show cognitive deficits similar to patients with frontal lesions (e.g. impairments on verbal fluency, Stroop, and Wisconsin card sorting tasks; Moscovitch & Wincour, 1992). However, West (1996) notes that the frontal hypothesis is unlikely to explain all of the age-related changes observed in cognition and describes the hypothesis as “useful but incomplete” (p. 289). For example, both Moscovitch and Wincour and West (1996) discuss memory deficits shown by older adults (e.g. in recall tasks) that likely stem from alterations

in the functioning of the medial temporal lobe rather than or in addition to the frontal cortex.

To summarise, this section outlines various theories of cognitive aging, none of which alone can account for all of the changes in cognition associated with age. One point that will become evident in the following section is that neuroimaging evidence can be used to evaluate cognitive aging theories. I will also show that neuroimaging data provides scope for the emergence of new theories of aging.

Neuroimaging evidence: Mechanisms potentially mediating cognitive age-related change

The mechanisms through which the aforementioned cognitive theories may be mediated include structural changes in the brain (e.g. atrophy, cell loss), changes in neurotransmitter levels (e.g. dopamine), or functional changes in the way different brain areas respond to stimuli (e.g. HAROLD model described below). Although the title of this section would suggest that I am attempting to explain cognitive age-related change via functional or structural brain changes that occur with age, there is another viewpoint that I will also expose. That is, that observed age-related neurological changes will likely reflect not only the deleterious effects of aging on the brain but also the emergence of compensatory mechanisms (e.g. Buckner, 2005).

Neuroimaging data relating to functional age-related change in the frontal cortex has been explored in several studies by Cabeza and colleagues. Their findings can be viewed as an extension of the frontal hypothesis of aging. Initially, the right hemiaging model (reviewed by Dolcos, Rice, & Cabeza, 2002) suggested that the right hemisphere of the brain was more sensitive to the effects of age than the left. However, this model has been superseded by the Hemispheric Asymmetry Reduction in Old Age (HAROLD) model

of aging (see review in Daselaar & Cabeza, 2005). The HAROLD model states that whereas young adults generally show lateralized frontal brain activity while performing certain tasks, older adults tend to show bilateral activity (Cabeza, 2002; Dolcos et al.). One explanation of the reduction in lateralization of brain activity in old age is that the aging brain undergoes a process of dedifferentiation (see also the section on 'theories regarding the relationship between sensory and cognitive functioning with age'). That is, just as the process of brain maturation involves emerging differentiation of brain regions for the purpose of performing specialized operations, dedifferentiation refers to the reduction in specialization of brain areas and therefore the recruitment of alternate brain regions to perform various tasks. However, whether dedifferentiation or compensation (e.g. Cabeza, Anderson, Locantore, & McIntosh, 2002) explains the age-related reduction in lateralization of brain activity is still under debate (see discussion in Fabiani & Gratton, 2005).

While the debate over the precise nature of age-related functional changes in the frontal cortex is set to continue, there is another prominent debate present in the neuroimaging/aging literature regarding structural age-related change within the brain. Whereas it was once thought that age-related loss of neurons was a primary contributor to age-related cognitive change, it is now thought that this claim may have been overstated (see review in Raz, 2000). Certainly there is a reduction in brain weight and volume with age, however, rather than representing mass attrition of neurons, this most likely represents the fact that neurons shrink and that the dendritic tree debranches with advanced age (see reviews in Raz, 2000; 2005). In a similar vein, Gazzaley and D'Esposito (2005; 2007) have expressed the view that rather than gross structural age-associated changes affecting cognition, it is the functional connection between brain regions that alters with age.

Gazzaley and D'Esposito defend this view by emphasizing the role of neural networks in cognition (i.e. involving distributed brain regions) rather than the role of distinct isolated brain structures (see also Grady, 2005; 2008). Bäckman and Farde (2005) add to this debate by proposing that connectivity changes could result from an alteration in the signal to noise ratio in the aged brain and this could be mediated by deficient dopaminergic functioning.

Although the notion that aging is related to increased neuronal noise is not a new one, it is only recently that possible mechanisms underlying this phenomenon have been elucidated (Li, 2005). Li outlines how a decline in the functioning of the dopamine system with age could decrease the signal to noise ratio within the brain. This process could occur via a reduction in responsivity of neurons leading to increased neural noise and lack of distinctiveness of neural representations. If less distinctive neural representations are a feature of the aged brain, this could affect various cognitive processes (Li, 2005). Furthermore, Braver et al. (2001) have devised a computational model which implicates deficient dopamine modulation in age-related reductions in tasks dependent on cognitive control such as working memory, attention, and inhibition.

In sum, the neuroimaging evidence reviewed here has revealed three key points. Firstly, evidence showing that aging is associated with reduced lateralization of frontal cortex activity has been found (HAROLD model). This could be seen as an additional element of the frontal hypothesis of aging discussed earlier. However, although the HAROLD model was established on the basis of findings relating to the prefrontal cortex, it is possible that the HAROLD model holds for other brain regions (Dolcos et al., 2002) including the temporal cortex (Cabeza, 2002). This is in line with the second point of this review suggesting that age-related alterations in neural networks rather than specific regional changes could hold the key to unraveling why cognitive decline is experienced

with age. Thirdly, it is possible that deficient neuromodulation (i.e. dopaminergic) disrupts connectivity of neural networks and reduces signal to noise in the aged brain. The degree to which any or all of these neuroimaging findings relate to the processing speed hypothesis of Salthouse (1996) has not been clearly established. Therefore there is still some way to go before we see a full integration of neuroimaging evidence with theories of cognitive aging. Nonetheless, bearing in mind the current theories discussed above, I will now specifically explore two areas in which age-related sensory and cognitive change has been observed. Firstly, I review age-related changes in the auditory modality, followed by age-related changes in different memory systems. These overviews will provide the necessary background to the present studies that are focused on age effects on auditory sensory memory.

Overview of sensory changes which occur with age in the auditory modality

Some elevation of hearing thresholds, especially for high frequency sounds, is common to almost all older adults (Willott, 1991). Presbycusis is the term generally used to describe the increased hearing thresholds that older adults exhibit relative to young adults primarily in response to high frequency stimuli (Hull, 1995). More specifically, Willott defines presbycusis as "the decline in hearing associated with various types of auditory system dysfunction (peripheral and/or central) that accompanies aging and cannot be accounted for by extraordinary ototraumatic, genetic, or pathological conditions" (pp. 2). This definition encompasses not only the increase in hearing thresholds that commonly occurs with age but also more subtle aspects of hearing decline involving various aspects of auditory perception (e.g. speech perception). Interestingly, although presbycusis is a term most commonly associated with old age, its symptoms can onset as early as the third

decade of life (Willott). Willott outlines the six different types of presbycusis that can be defined based upon the pathology thought to underlie observed age-related change in hearing. Five types, sensory, neural, strial, mechanical, and vascular, refer to damage to the organ of corti, spiral ganglion cells, stria vascularis, cochlear mechanics, and the vascular system respectively. The final and most common type, sensorineural presbycusis, refers to a combination of pathologies involving different cochlear tissues.

Despite the fact that many adults experience a reduction in hearing sensitivity with age, Schneider and Pichora-Fuller (2000) acknowledge that hearing aids are of assistance to fewer than 10 percent of older adults. There are at least two factors that could contribute to this outcome. Firstly, hearing aids amplify all auditory signals (including distracting background noise), not just auditory signals of interest (e.g. a person's voice). Secondly, there may be a degree of central auditory system degeneration that is associated with age which compounds the effect of age-associated degeneration in the peripheral auditory system. Evidence for this stems from the fact that older adults with auditory thresholds similar to young adults may still have problems understanding speech (Hull, 1995; Willott, 1991) especially in noisy environments relative to quiet environments (see review in Fozard & Gordon-Salant, 2001; Schneider & Pichora-Fuller).

Besides the general age-related decline in the ability to detect low-intensity stimuli and filter out background noise, areas of auditory functioning in which older adults may experience difficulties include: locating sounds in space, and discriminating small changes in frequency and sound duration (Willott, 1991). Since frequency discrimination, temporal discrimination, sound localization, and speech perception are all auditory functions that are reliant on neural synchrony, Schneider and Pichora-Fuller (2000) have proposed that an age-related reduction in neural synchrony may best explain these auditory deficits

associated with age. We will elaborate on this point by discussing age-related decline in frequency discrimination and temporal discrimination in more detail. The effect of age on these two aspects of hearing is relevant to the studies conducted as part of this thesis.

Frequency discrimination, the ability to distinguish between tones of different pitch, is thought to be compromised with age. For example, König (1957) and Abel, Krever, and Alberti (1990) have shown that frequency difference limens (the smallest difference in pitch required to distinguish sounds) could be two to three times greater for older versus young adults for sounds in the 500 to 1000 Hz range. Whereas the average difference limen for young adults at these frequencies in these studies was approximately 5 Hz, it was approximately 10 Hz for older adults. Age-related hearing loss could certainly contribute to the reduced frequency discrimination ability observed in older adults as frequency discrimination tends to be poorer in older adults with greater hearing loss (Abel et al.). However, it is thought that age-related factors other than hearing loss also contribute to the loss of frequency discrimination ability with age. Support for this stems from the fact that, in older adults, frequency discrimination is poorer for low frequency sounds, whereas elevation of hearing thresholds tends to be worse for high frequencies (He, Dubno, & Mills, 1998). Schneider and Pichora-Fuller (2000) propose that loss of neuronal synchrony could account for the age-related deficit in frequency discrimination because frequency discrimination at low frequencies is thought to rely on phase locking and degree of phase locking decreases as frequency increases.

If neural synchrony is impaired with age then the precision with which processing of the temporal aspects of auditory stimuli takes place could clearly be affected. In fact, temporal processing abilities are impaired with age (Willott, 1991). For example, Abel et al. (1990) have shown that the duration difference limen for older adults is greater than for

young adults with respect to a standard tone of 20 ms presented at 500 Hz or 4000 Hz. While the duration difference limen for young adults was approximately 15 ms, it was approximately twice this for older adults. Similarly, Schneider and Pichora-Fuller (2000) suggest that the threshold at which older adults can detect a silent gap placed within a sound is increased relative to young adults. Age-related decline in central rather than peripheral hearing mechanisms is thought to be primarily responsible for the age-related change in temporal processing (Fozard & Gordon-Salant, 2001). Since intact temporal processing is integral to the comprehension of speech, the loss of temporal processing ability with age could be a factor contributing age-related speech discrimination difficulty. In fact, Wingfield (2000) has suggested that older adults may rely more on top-down contextual information to process speech than young adults as the speech signal reaching the older adult auditory system (bottom-up process) may be degraded relative to young adults.

In order to more comprehensively understand the causes and consequences of age-related change in auditory processing, Schneider and Pichora-Fuller (2000) have called for further research into the relationship between perceptual measures and higher order cognitive processing. In the following section I review age-related changes in memory which represents a higher order cognitive process that, as previously mentioned, could be affected by some of the sensory processing difficulties described here.

Overview of memory systems and age-related changes in memory functioning

The term ‘memory’ in its most general sense refers to the process of encoding, storing, and retrieving information within the brain. However, beyond this definition, there are many specific types of memory that are described in the memory literature. Far from

being exhaustive, our review of the memory literature is selectively focused on presenting an overview of several different types of memory as a platform for discussing age-related effects. As will also be outlined, not all forms of memory are affected by age to the same degree. Finally, we attempt to integrate information concerning the discussed memory processes with information pertaining to the neural substrates underpinning such processes. That is, we will discuss the effect of age on 'memory systems', defined by Prull et al. (2000) as specific memory processes which are regulated by specific neural networks. By examining the effect of age on different memory systems, we draw conclusions as to the potential cause of age-related change in memory and highlight the need for research into sensory memory. A detailed assessment of sensory memory in the auditory modality is presented later.

What has been dubbed the 'modal model' of memory has greatly influenced our conceptualization of the processes involved in remembering information. Three key factors contribute to the modal model including sensory memory, short term-memory, and long-term memory (e.g. Broadbent, 1958; Atkinson & Shiffrin, 1968). According to Atkinson and Shiffrin, sensory memory comprises a very brief (in the order of 100 – 200 ms) storehouse of information coming from the senses and determining perception. Short-term memory was thought to be a secondary storehouse of information that could be held for seconds whereas long-term memory described when a state of permanency was transferred to memories currently represented in the short-term store. While the modal model seemed to suggest that information traveled through the described subdivisions of memory in a sequential fashion, there have been subsequent claims contrary this idea. For example, Cowan (1988) proposed a more unitary system of memory with the assertion that short-term memory representations are currently activated long-term memory representations

(where previously formed long-term representations of currently relevant information exist; Cowan, 1995).

In another revision of the modal model, Baddeley and Hitch (1974) made the distinction between short-term memory and what they termed 'working memory'. The essential difference between short-term memory and working memory is that working memory involves the manipulation of items that are otherwise passively stored in short-term memory. In view of this distinction, there are researchers who posit that short-term memory and working memory exist on a continuum, with working memory being a more demanding (in terms of mental resources) form of short-term memory (Craik, 2000; Reuter-Lorenz & Sylvester, 2005). One of the core aspects of Baddeley's (1986) definition of working memory involves the description of a 'central executive' which controls and co-ordinates sensory memory information. Although Atkinson and Shiffrin had discussed the importance of 'control processes' in effectively running the memory subsystems, in giving name to such processes, Baddeley and Hitch (1974; Baddeley, 1986) emphasized their importance for the working memory concept. More recently, Reuter-Lorenz and Sylvester (2005) argued that there are at least four processes involved in working memory: executive attention (defining our ability to focus on task-relevant information), inhibition (our ability to ignore task-irrelevant information), task management (being able to organize different processes which need to be conducted in order to pursue a goal), and set shifting (which defines our ability to change tasks and goals should circumstances warrant it). This description of working memory reveals that the contemporary version of the modal model contains greater complexity relative to its initial conception.

Our discussion of age-related change in memory will also benefit from a description of the distinction between implicit and explicit forms of memory (e.g. Graf & Schacter,

1985). Explicit memory (also referred to as direct or declarative memory) can essentially be divided into two categories, episodic memory and semantic memory, which describe memory for specific events and factual information (i.e. general knowledge) respectively (e.g. Tulving, 1972). Episodic memory can be tapped using recall and recognition tasks (although see below for another potential influence on these tasks). Source memory (i.e. memory for the precise context in which information was learnt) also represents an explicit episodic memory task. In contrast to explicit memory, implicit memory (also referred to as indirect or non-declarative memory) is defined by cases where there is biased behaviour towards a previously presented item relative to novel items even though there might not be conscious awareness that previously presented items were previously encountered (e.g. this is clearly apparent in patients with amnesia for whom implicit memory may remain relatively intact while the capacity to remember new episodic information is lost). Implicit memory can be explored in conditioning, procedural memory (including skill learning), and priming tasks. Jennings and Jacoby (1993) have outlined that, in certain cases, implicit memory may contribute to performance on explicit memory tasks and vice versa. Thus the distinction between explicit and implicit memory cannot always be made as a function of the particular task used to assess memory functioning.

Does the conceptual distinction between short-term memory and working memory and between explicit and implicit memory provide insight into the effect of age on memory functioning? The literature describing the effect of age on memory is consistent in demonstrating that, relative to young adults, older adults show larger deficits in working memory tasks than short-term memory tasks and in explicit episodic memory tasks compared to implicit memory tasks (see reviews in Bäckman, Small, & Wahlin, 2001; Craik, 2000; Craik & Jennings, 1992; Hoyer & Verhaeghen, 2006; La Voie & Light, 1994;

Park, 2000; Prull et al., 2000). For the remaining component of the modal model of memory discussed earlier, long-term memory, we also see an age-related decline (for a review see Park & Gutchess, 2005). However, it is thought that one form of explicit memory noted previously, semantic memory, may be relatively spared with age (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005; see reviews in Buchler & Reder, 2007; Craik, 2000; Park, 2000). Therefore, it appears that there are age-related declines in almost all of the types of memory discussed thus far, although the degree of the age-related deficit may vary.

Hoyer and Verhaeghan (2006) emphasize the role of cognitive control factors in providing an explanation of the age-related findings in the memory literature. For example, as there are several processes which contribute to working memory, there could be several explanations for why older adults perform more poorly than young adults on working memory tasks. Age-related changes in contextual encoding (e.g. Braver et al., 2001), executive attention, and inhibitory control could all affect the older individual's performance on working memory tasks possibly by increasing susceptibility to interference (Reuter-Lorenz & Sylvester, 2005). These cognitive control factors might not play as much of a role in simpler short-term memory tasks where passive retention rather than active manipulation of information is emphasized.

Furthermore, in explicit episodic tasks, cognitive control factors may play a role in age-related findings as the degree to which 'strategic information' must be used in a particular task could influence the age effect (see Taconnat, Clarys, Vanneste, Bouazzaoui, & Isingrini, 2007). Strategic information refers to contextual information surrounding memory for an item, such as the explicit source from which an item in memory derived. Explicit memory tasks can differ in the degree to which they require strategic information

(Prull et al., 2000). Older adults are likely to have more difficulty than young adults on source memory tasks which require explicit recollection of the context in which information was previously encountered (e.g. Fabiani & Friedman, 1997; see reviews in Craik, 2000; Hoyer & Verhaeghan, 2006; Light, 2000; Spencer & Raz, 1995; c.f. Mitchell, Raye, Johnson, & Greene, 2006). These age-related deficits in explicit episodic memory are in contrast to the relative sparing of semantic memory with age mentioned earlier. However, there are two important differences between episodic and semantic forms of explicit memory that are potentially important as they may in part explain the difference in the respective age-related findings (see also Spaniol, Madden, & Voss, 2006). First of all, episodic memory is usually tested for instances of newly learned information whereas semantic memory is based on learning which has taken place over the course of a lifetime. Secondly, this means that there may be many episodic instances in memory from which to draw the correct answer to a semantic memory question whereas episodic memory tasks rely on memory for one distinct presentation of an item. Therefore, given the definition of strategic information, semantic memory does not require a high level of strategic information relative to episodic memory, and this may contribute to the difference in age-related findings. In a similar way, Buchler and Reder (2007) have proposed that larger age-related decline in episodic than semantic memory may indicate the cumulative effects of life experience on episodic and semantic memory rather than specific degeneration of the episodic relative to the semantic memory system.

The literature concerning the effect of age on implicit memory tasks has not been as clear as that for explicit memory tasks. In effect, there has been disagreement as to whether implicit memory is spared with age or whether there is a small but significant decline in this type of memory. Using a meta-analysis, La Voie and Light (1994) and Light, Prull,

LaVoie, and Healy (2000) have shown that the effect size for age-related change in priming is not as great as for explicit memory measures such as recall and recognition but that there is a significant deficit in relation to priming in older versus young adults. In addition, although older adults are able to learn new skills, the rate of learning may be diminished in relation to young adults (see review in Prull et al., 2000). Older adults also show a deficit in eyeblink classical conditioning where a puff of air delivered to the eye is teamed with an audible tone (see review in Prull et al.). Similar to the age-related deficit in skill acquisition, this age-related deficit manifests as an age-related decline in the rate of acquisition of the conditioned response (eyeblink in response to the tone) and in the maintenance of the conditioned response over time. In sum, although the age-related differences in implicit memory tasks are smaller than for explicit tasks, they do appear to exist (see also Prull, Dawes, Martin, Rosenberg, & Light, 2006; c.f. Fleischman, 2007). Furthermore, since implicit memories can be formed without conscious awareness, it is unlikely that cognitive control measures play a substantive role in the age-related deficit for this type of memory.

Can identification of the brain areas involved in different memory processes (i.e. memory systems) help explain the variation in the extent of the age-related deficit in different memory processes? West (1996) reviews evidence pertaining to the importance of the medial temporal lobes, including the hippocampus, for short-term memory tasks such as recognition and recall. In agreement, neuropsychological data points to the relevance of the temporoparietal cortex for short-term memory tasks such as auditory verbal short-term memory (see review in Buchsbaum & D'Esposito, 2008). On the other hand, although an exact description of the brain structures underlying working memory is yet to be formulated, it is known that multiple brain regions are involved in working memory,

including the prefrontal cortex (Buchsbaum & D'Esposito; Raz, 2000). Rather than defining different memory systems, short-term memory and working memory may utilize similar neural substrates and exist on a continuum (as suggested earlier) to the extent working memory tasks evoke greater reliance on the frontal cortex than short-term memory tasks. Thus, the deficit that older adults exhibit in these memory processes relative to young adults may rely on the degree to which cognitive control components mediated by the frontal lobes are activated, with a larger age-related effect for more complex (e.g. working memory) over simpler (e.g. short-term memory) tasks.

The dissociation between implicit and explicit memory was derived from studies of amnesic patients who showed a pattern of relatively spared implicit and extensively damaged explicit memory (see review in Henson, 2004). In general, explicit memory tasks rely on medial-temporal lobe structures and the frontal lobes (when high strategic memory requirements are present), while implicit memory is more reliant on cortical and subcortical structures associated with stimulus processing (see Moscovitch & Wincour, 1992; Henson, 2004; Prull et al., 2000). On this basis, explicit and implicit memory tasks can be defined as separate memory systems, however, as mentioned, both systems may be active in varying degrees even in tasks primarily designed to tap into either one of these systems. The differentiation of these systems, in terms of the neural substrates mediating each, most likely explains the difference in the magnitude of the age-related deficit for explicit and implicit tasks.

In sum, the greater reliance of working memory over short-term memory and explicit memory over implicit memory on the prefrontal cortex may be one reason why older adults perform more poorly on working memory and explicit memory tasks than short-term memory and implicit tasks relative to young adults. This conclusion favours the

frontal hypothesis of aging (e.g. Moscovitch & Wincour; West, 1996; West, 2000) as an explanation of age-related change in memory, although the fact that we also see age-related change in short-term and implicit memory processes that do not rely heavily upon the prefrontal cortex suggests that other factors could contribute to age-related change in memory. Light (1991) reviewed evidence for three cognitive aging accounts of age-related change in memory, including age-related slowing of information processing, age-related reduction in attentional resources, and an age-related deficit in working memory and concluded that none of these explanations were able to explain all age effects on memory. Therefore, the cause or causes of age-related change in different memory processes remain to be clarified (Light, 2000).

For all of the aforementioned types of memory in which we see an age-related deficit, there is one common factor: their reliance on sensory memory information. In the introduction to this section, we briefly discussed the role of sensory memory in providing information to the other stages of memory and in an earlier section we discussed how peripheral sensory degeneration could impact upon higher cognitive levels. Craik and Jennings (1992) argue that it is not entirely understood whether the age-related change in memory is due to an age-related reduction in the quality of sensory information which is propagated through later processing stages or whether sensory memory remains intact and deficits occur subsequent to sensory processing. The ubiquity of the age-related deficit over the range of memory processes described above suggests the former (however, the preceding review shows that cognitive control mechanisms mediated by the frontal cortex also likely contribute to the age-related memory deficit). In addition, two other factors implicate age-related change in sensory memory as a contributor to age-related change in other forms of memory. Firstly, it seems that for episodic memory, there is greater age-

related decline in the encoding than retrieval stage of memory (see reviews in Park & Gutchess, 2005; Rugg & Morcom, 2005), suggesting that age-related memory deficits occurs in early stimulus processing stages such as the sensory memory stage of processing (although other processes such as strategic proceeses may influence early stimulus processing stages). Secondly, the fact that age-related deficits are observed in implicit memory which does not require conscious processing also suggests that early stage pre-attentive processing such as that carried out by sensory memory may be compromised. In the next section, we follow this theme by discussing sensory memory in the auditory modality in greater detail.

It is at this stage pertinent to address why we chose to examine sensory memory in the auditory modality. Essentially, this path stems from the decision to use a neuroimaging technique (the event-related potential: ERP) to examine sensory memory and aging. This was chosen as it is possible that neuroimaging (e.g. ERP components used in this thesis) rather than behavioural techniques may be more sensitive to detecting age-related change in auditory sensory memory if the change is of relatively small magnitude. For example, Bertoli, Smurzynski, and Probst (2002) found that older adults did not elicit an ERP waveform (mismatch negativity: MMN) to gaps (placed within a sound) that they were able to detect in a behavioural procedure. Significant MMN was observed in older adults at longer gap durations than those detected behaviourally which demonstrates that the older adults were able to elicit MMN. Bertoli et al.'s study shows that the ERP measure may have been more sensitive than the behavioural measure in detecting age-related change in temporal processing. This is due to the fact that compensatory mechanisms may be utilized by older adults in behavioural paradigms (see also Alain, McDonald, Ostroff, & Schneider,

2004). This could also occur in ERP paradigms but evidence of differential (compensatory) processing as a function of age would be expected to be reflected in the ERP.

Another factor influencing our decision to examine sensory memory in the auditory modality stems from a property of mismatch negativity research. The mismatch negativity has been more extensively investigated with respect to audition compared to other sensory domains. As the foundations for this thesis on sensory memory and aging were influenced by the mismatch negativity literature, the auditory modality was chosen to examine the effect of age on sensory memory.

Auditory sensory memory and the role of the auditory cortex

Winkler (2007) recently argued that the term auditory sensory memory is outdated. For reasons of parsimony, we continue to use the term auditory sensory memory. However, we use it with the intent that our current usage of the term encompasses a richer understanding than the sense in which the term has been used in previous decades. We will explain the additional knowledge that has accumulated regarding auditory sensory memory following a review of the way in which the concept was initially formulated.

As mentioned previously, early conceptions of the sensory processing aspect of memory can be found in Broadbent (1958) and Atkinson and Shiffrin (1968). Broadbent proposed that auditory information was held in a store in the order of seconds as this information could be accessed for a brief post-stimulus period. Atkinson and Shiffrin proposed that a sensory register deals with information received via sensory organs within 100 to 200 ms post stimulus delivery. However, Massaro (1975) and Cowan (1984) expanded the concept of auditory sensory memory by proposing an additional phase to that suggested by Atkinson and Shiffrin. Both Massaro and Cowan (1984) described the first

phase of auditory sensory memory, akin to that described by Atkinson and Shiffrin, as a perceptual auditory store and short phase respectively. The secondary phase was termed the synthesized auditory store and long phase respectively. We will refer to the two phases of auditory sensory memory as phase one and phase two.

Cowan (1984) proposed that phase one of auditory sensory memory endures for 200 to 300 ms following sound onset and in this time, features of the sound are analyzed (e.g. frequency, intensity, etc). Within this early processing period, an integrated sensory memory representation of sound features is encoded (Cowan, 1984; Näätänen & Winkler, 1999). Näätänen and Winkler define the sensory memory trace as 'a unitary sensory stimulus representation of the full auditory event' (p. 826). Given that the representation of sound properties that underpins our discrimination ability is encoded during phase one of auditory sensory memory, the precision of the sensory memory trace is determined in this processing phase. In addition, there is correspondence between the auditory sensory memory trace and perception (Näätänen & Winkler).

Cowan (1984) described phase two of auditory sensory memory as a period in which the memory trace of an encoded sound is maintained. In what could be considered somewhat of a return to the original conception of the modal model of memory, Cowan (1988) has suggested that the second phase of sensory memory might have similar underlying properties to other forms of short-term memory (see also, Kaenbach, 2004). While the second phase is thought to last at least several seconds, Cowan (1984) estimated its duration to be between 10 and 20 seconds. It has been suggested that the integrity of the memory trace declines over this period as it is harder to make judgements regarding sound attributes when the interval between successive tones is increased (Sams, Hari, Rif, & Knuutila, 1993). In the experiment by Sams et al. (1993), judgements concerning whether

tones were the same or different did not exceed chance level when the interval between successive sounds was 12 seconds. However, estimating the absolute duration of auditory sensory memory is complex as other experimental variables besides the absolute timing of sound, such as the contextual relevance of sounds, could have an impact on such estimates (e.g. Cowan, Winkler, Teder, & Näätänen, 1993; Jääskeläinen, Hautamäki, Näätänen, & Ilmoniemi, 1999; Sabri & Campbell, 2001; Winkler, Schröger, & Cowan, 2001). For example, Cowan et al. (1993) showed that auditory sensory memory traces do not necessarily decay but can be dormant or active depending on the auditory context. In agreement, Cowan, Saults, and Nugent (2001) have argued that there is not clear evidence to support the notion that decay of sensory representations takes place. The Sams et al. (1993) study provides one example of the fact that there is a limit to which precise auditory stimulus features can be stored and retrieved in particular contexts, however, whether decay, contextual relevance, or interference best describes the loss of this information is still the subject of debate.

While the previous conceptualization of auditory sensory memory traces focused on storage of information relating to the features of sound (e.g. Cowan, 1984), Winkler (2007) has responded to the more recent findings concerning the importance of the auditory context in determining the response to sound and has provided an updated description of auditory memory traces. Winkler states that the context in which sound is heard is also encoded into auditory sensory memory along with features of sound such as pitch, location, duration, and intensity. This assertion implies that auditory sensory memory traces operate at a level of complexity beyond that previously thought. There is evidence that the auditory cortex, where auditory sensory memory traces are thought to be formed (e.g. Weinberger, 2007), can deal with this degree of complexity. Rather than the traditional view of the

auditory cortex as a simple provider of bottom-up sensory information to higher cognitive levels, Jääskeläinen, Ahveninen, Belliveau, Raij, and Sams (2007) propose that the auditory cortex receives and incorporates top-down information with sensory information[1]. The integration of bottom-up and top-down information facilitating auditory perception is in line with previous accounts of auditory scene analysis that emphasized the role of attention in influencing perception (Bregman, 1990). Also supporting this viewpoint is the fact that there are more top-down inputs than bottom-up inputs entering the auditory cortex (Scheich, Brechmann, Brosch, Budinger, & Ohl, 2007). Jääskeläinen et al. (2007) have described the auditory cortex as "an interaction surface between the auditory environment and the goals of the organism" (p. 657) which seems to be a contemporary interpretation of an earlier sentiment expressed by Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler (2001). Näätänen et al. (2001) referred to evidence of 'primitive intelligence' in the auditory cortex. The term primitive intelligence was primarily used by these researchers to describe the fact that the complex operations ascribed to auditory sensory memory can take place without the need for attention to be directed towards the sound source[2].

When attention is not directed towards sounds, there are several steps proposed to take place in order to deal with the unattended information. Schröger (2007) describes auditory sensory memory as an 'umbrella concept' which summarises a collection of at

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[1] As stated by Dennet (2005), "we should be careful not to take the term 'top-down' too literally" (p. 133). When I refer to top-down connections in this thesis, I essentially refer to neural connections that are the opposite of bottom-up connections. This definition encompasses what Dennet refers to as "sideways influences" (p. 133). According to this definition, top-down connections include not just connections that derive from the frontal cortex but also connections between adjacent areas of cortex.

[2] One other complex aspect of auditory sensory memory that is not discussed here as it is beyond the scope of the present thesis is the relation between auditory sensory memory and other sensory stores such as multi-modal sensory stores. (e.g. see Gardiner & Cowan, 2003, for a discussion of modality effects and their relation to storage of information in memory; see also Scheich et al., 2007, for a discussion of multisensory processing).

least four processes. For example, Schröger claims that in the first step of auditory processing, stimuli are analysed as in phase one of auditory sensory memory. Secondly, it is thought that a model of the pattern (if any) of auditory stimulation is formed by storing information from phase one of auditory sensory memory for a brief period (phase two of auditory sensory memory). The second step can be considered as a stage in which the auditory system extracts 'regularities' from the auditory environment. Where obvious patterns in acoustic stimulation exist, these regularities are well defined. However, in the case where the current auditory context is defined by change, the regularity may be defined as 'a changing auditory environment' (in this scenario, repetition of sound, which would usually be thought of as defining regularity, could signal a violation of regularity). In step three, Schröger argues that predictions about future auditory events are generated via the model (although Schröger also argues that step three may be an unnecessary addition to step two). Finally in this proposed outline of auditory sensory memory processing stages, representations of incoming stimuli are compared against the model's predictions. This outline of processing stages which take place in auditory sensory memory is encapsulated in predictive coding models of auditory processing (see Baldeweg, 2007; Friston, 2005; Garrido et al., 2008). These ideas regarding the processing stages of auditory sensory memory and predictive coding models are discussed further below in relation to theoretical explanations of two event-related potential waveforms, the mismatch negativity and repetition positivity.

In sum, auditory sensory memory has previously been conceived of as a process that occurs within the auditory cortex whereby sound features are analysed and briefly stored as an integrated representation (e.g. Cowan, 1984). Rather than focusing on passive storage of integrated representations of sound features in the auditory cortex, it is now

emphasized that aspects relating to the context in which sound is presented are also encoded into auditory sensory memory (e.g. Winkler, 2007). The contemporary viewpoint concerning auditory sensory memory also differs from the previous perspective by highlighting the role of diverse cortical regions (e.g. parietal and frontal as well as temporal regions) in the analysis of auditory information (e.g. Poremba & Mishkin, 2007; Zatorre, 2007).

Unlike other forms of memory reviewed in the previous section, there is limited research on the effect of age on auditory sensory memory (Craik, 2000; Hull, 1995). Previously, we suggested that an age-related deficit in auditory sensory memory could potentially contribute to age-related deficits in other forms of memory. We also noted that other forms of memory which rely on the frontal cortex could be more greatly affected by the aging process than forms of memory less reliant on frontal brain areas. The preceding review of the current state of knowledge regarding auditory sensory memory suggests that there is a greater involvement of brain areas beyond the auditory cortex, including frontal regions, in this form of memory than was previously thought. This leaves open the possibility that age-related decline in auditory sensory memory could to some extent be mediated by an age-related decline in functioning of the frontal cortex (frontal hypothesis). As the effect of age on auditory sensory memory has been primarily researched using electrophysiological methodologies, we will review age-related change in auditory sensory memory in more detail within the following sections.

The auditory event-related potential

The event-related potential (ERP) is an electrophysiological measure derived from the electroencephalogram (EEG). The EEG records voltage changes in brain activity on the

scale of hundreds of microvolts. The ERP comprises portions of the EEG that have been time-locked to a specific event and averaged together. ERPs usually resolve to the scale of tens of microvolts. In relation to this research, the events that ERPs are time-locked to are auditory stimuli. The ERP is thought to represent postsynaptic activity of large populations of neurons in the cortex (Coles & Rugg, 1995). The advantage of using the ERP to explore cognitive processes is that the ERP can be resolved on the scale of milliseconds. This allows for a detailed examination of the point in the processing chain at which two groups may diverge in their response to a stimulus. In this thesis we will examine several components of the auditory ERP that are exogenous (obligatorily elicited in response to auditory stimuli) and endogenous (elicited only in response to particular stimulus contexts) in nature. In the ERP research field, the term 'component' is often used to refer to a deflection in the ERP, that is, a particular ERP waveform. However, in this thesis I will follow Näätänen and Picton (1987), who restricted the term ERP component to ERP activity that is reflective of a single source of neural activity. Since ERP waveforms can be comprised of activity generated from several sources (see review in chapter 2), I will hereon use the term waveform when referring to deflections occurring in the auditory ERP and reserve the term component for use according to Näätänen and Picton's definition.

Exogenous components of the auditory ERP are exemplified by brain activity contributing to the following ERP waveforms: P1, the first major positive deflection in the auditory ERP, N1, the first major negative deflection, and P2, the second positive deflection. P1 occurs at a latency approximately 50 ms post sound onset, N1 at approximately 100 ms, and P2 at approximately 200 ms. The second major negative deflection in the auditory ERP in the situation where stimuli are passively attended, N2, is not widely discussed in the literature. In addition, there are two endogenous ERP

waveforms which occur within the latency range of the aforementioned waveforms, the mismatch negativity (MMN) and repetition positivity (RP). With respect to the studies presented in this thesis, our interest in these endogenous waveforms is due to the fact that their elicitation is dependent on the context in which auditory stimuli are delivered.

In the following, we will provide basic information on each of the aforementioned ERP waveforms and present age-related findings where they exist. While the obligatory components are more indicative of the first stage of auditory sensory memory where analysis of sensory features takes place, MMN and RP are candidates to provide more information on the second stage of auditory sensory memory where integrated representations are stored for longer periods. Finally, we will summarise proposed relationships between the ERP waveforms and auditory sensory memory.

P1 waveform

A period of approximately eight seconds is required to elicit full recovery of neuronal populations underpinning the P1 waveform (Boutros & Belger, 1999; Zouridakis & Boutros, 1992). Ceponienne, Alku, Westerfield, Torki, and Townsend (2005) state that P1 represents a pre-perceptual processing stage. In agreement, Boutros and Belger claim that the P1 is a pre-attentive index of sensory gating. For example, in Boutros and Belger's study, larger P1 amplitude was elicited to the second tone in a non-identical pair compared to the first. This was interpreted as evidence that larger P1 indicates 'gating in' of novel stimuli. Whereas 'gating in' refers to the enhanced processing of novel stimuli relative to a non-novel stimulus, the term 'gating out' describes reduced neural responding to non-novel stimuli compared to novel stimuli. The interpretation of reduced P1 amplitude as evidence of a sensory gating deficit also derives from a large body of schizophrenia research using

paired stimulus paradigms (typically with an intra-pair interval of 500 ms and an inter-pair interval of 10 secs). The second sound in a paired click paradigm generally elicits smaller P1 amplitude than the first in healthy controls but to a lesser extent in patients (see reviews in Knott, Millar, & Fisher, in press; Patterson et al., 2008). Such findings can be interpreted as indicating a deficit in "gating out" of repetitive stimuli (similar to the concept outlined by Boutros and Belger).

Although older adults tend to show larger P1 amplitude relative to young adults (Amenedo & Diaz, 1998b; Fabiani, Low, Wee, Sable, & Gratton, 2006; Pfefferbaum, Ford, Roth, Hopkins, & Koppel, 1979) there is no consensus on the functional consequences of an age-related augmentation in P1 amplitude. Given the literature associating P1 amplitude with sensory gating, it is possible that larger P1 amplitude in older adults indicates a greater degree of gating in (or reduced gating out) of auditory stimuli with age. However, this interpretation is speculative as different paradigms have been used in the sensory gating studies (paired stimulus paradigms) compared to the studies where age-related P1 differences have been cited (oddball paradigms). In auditory oddball paradigms, a repeating 'standard' sound is generally delivered at a constant rate and infrequently replaced by an acoustically different 'deviant' stimulus. Clearly this method of stimulus delivery differs from paired stimulus paradigms in which there is generally a short interval between stimuli comprising the pair and a longer interpair interval. In chapter 2, I discuss the robust effect of delivery rate on ERP waveforms.

In a similar vein to the P1 gating studies, Chao and Knight (1997) have suggested that middle-latency auditory evoked potentials including P1 could be larger in older adults due to an age-related deficit in inhibitory control mediated by the frontal cortex. In support of this conclusion, Knight, Staines, Swick, and Chao (1999) reviewed the role of the frontal

cortex in modulating auditory ERP amplitude as early as the latency period surrounding P1. For example, it has been shown that patients with frontal damage elicit larger Pa amplitude to controls in response to the rapid presentation of click stimuli (Knight, Scabini, & Woods, 1989). Pa is a middle latency ERP waveform that precedes P1, occurring in the 25-35 ms post stimulus onset. The effect of frontal lesions on P1 amplitude were not directly examined in Knight et al.'s (1989) study but the figure presented in the article shows that P1 was larger in the frontal lesion group relative to controls. Knight et al. (1999) also cited evidence (Skinner & Yingling, 1977 and Yingling & Skinner, 1977) that evoked potentials in the cat sensory cortex increased following temporary cooling of the cat prefrontal cortex. However, as with the sensory gating interpretation, it is unclear whether or not the inhibitory control interpretation of P1 amplitude modulation is a sufficient explanation of the age-related enhancement in P1 amplitude that has been observed in oddball paradigms.

Alternatively, since Erwin and Buchwald (1986) suggest a source of P1 activity might be the ascending reticular activating system, Amenedo and Diaz (1998b) argued that P1 could indicate an arousal response. Therefore, it is possible that larger P1 amplitude previously observed in older adults versus young adults indicates heightened arousal in the older adults. This hypothesis does not seem to fit with Woodruff's (1985) assertion that older adults are generally under-aroused compared to young adults. However, Woodruff also acknowledges that the tonic underarousal that older adults may experience could in certain cases (e.g. novel situations) result in phasic hyperarousal.

N1 and P2 waveforms

Since N1 and P2 waveforms of the auditory ERP were once studied as part of a unitary N1/P2 complex, they will be reviewed together. A more comprehensive review of

these waveforms is presented in the introduction to the first study of this thesis, as they are the focus of study 1.

The N1 is an obligatory response elicited by an abrupt change in energy flow entering the auditory system (Näätänen & Picton, 1987). Näätänen and Picton describe the change in auditory stimulation that triggers the N1 as one in which the immediately preceding stable state is altered. Thus both the onset of sound and offset of longer sounds (greater than 500 ms) can trigger the N1. It has been shown that the N1 also reflects ongoing processing which occurs throughout the duration of a sound (Alain, Woods, & Covarrubias, 1997).

There does not appear to be a correlation between N1 amplitude and auditory perception (Näätänen, 1988). Rather, N1 seems to be involved with the detection of auditory stimuli. For example, Onishi and Davis (1966) report that the N1-P2 amplitude is determined within 30 ms of sound onset, even though loudness summates over a period of hundreds of milliseconds. In fact, the perceptual loudness function has a much steeper slope in relation to sensation level than does N1-P2 amplitude (Davis, Mast, Yoshie, & Zerlin, 1966). In a review of the N1, Hyde (1997) concedes that the functional significance of N1-P2 is still not clearly understood. In sum, N1 may reflect detection of sound, and as such may also have an attention-triggering function (Näätänen, 1988). For example, N1 refractory properties have been shown to drive behavioural disruption on a concurrent task (Campbell, Winkler, & Kujala, 2007). Furthermore, N1 activity could relate to feature analysis and trace formation of sound stimulus properties in auditory sensory memory (Näätänen & Picton, 1987). Näätänen and Winkler (1999) extended this idea by suggesting that N1 generation indicates a prerepresentational processing stage. That is, N1 activity

reflects encoding of feature traces of sound properties but not the integration of these traces into a unitary representation or percept.

Scherg and von Cramon (1985) identified two bilateral sources of auditory ERP components within the N1 and P2 latency range (60 - 250 ms). Sources included the superior temporal plane and lateral superior temporal gyrus corresponding to activation of the primary and secondary auditory cortex respectively. Further to this, it has been suggested that there are three 'true' components that comprise the N1 (Näätänen & Picton, 1987). Component one is classified as a component with maximum amplitude over frontocentral regions and peak latency 100 ms following sound-onset. This component is most likely generated in the supratemporal plane of the auditory cortex and is a frequency specific component (Näätänen et al., 1988). Component two is best recorded from midtemporal sites (probably generated in superior temporal gyrus) and peaks positively at 100 ms and then negatively at 150 ms. Recorded from the vertex, component three has a peak latency of approximately 100 ms and is regarded as a non-specific component. This non-specific component is considered an arousal response, facilitating sensory responses to eliciting stimuli (Näätänen & Picton).

The P2 waveform has been less widely studied than the N1 probably due to the fact that the N1 was considered more sensitive to experimental manipulations (Budd, 2000). The P2 is a positive deflection peaking between 150 and 250 ms following sound onset (Crowley & Colrain, 2004). Although once considered simply part of the N1-P2 complex (peak-to-peak measurement), as early as 1976 there was evidence that P2 indexed different processes in the brain from N1 (Roth et al., 1976). Since then, various studies have shown that the P2 waveform can be dissociated from N1 based on developmental and topographical differences as well as differences resulting from experimental manipulation

(for a comprehensive review see Crowley & Colrain, 2004). Similar to N1, the functional significance of P2 is still not well understood. It has been proposed that scalp recorded P2 activity derives from generators in the planum temporale and Area 22 of the auditory association complex (Godey, Schwartz, de Graaf, Chauvel, & Liegeois-Chauvel, 1991). As for N1, there is evidence that there may be a specific and non-specific component of P2 (see Näätänen, 1992).

The literature surrounding the effect of age on N1 and P2 components of the auditory ERP lacks clarity due to the presence of many contradictory findings (see review in the introduction to study 1). Of course one of the primary reasons for contradictory results across studies could be that studies rarely match perfectly with respect to the auditory stimuli and paradigms used to elicit N1 and P2 waveforms. As there is no current consensus on the effect of age on N1 and P2 waveforms of the auditory ERP, the first study of this thesis attempts to reconcile the literature surrounding the effect of age on these two waveforms.

N2 waveform

There is a dearth of information relating to the passively elicited N2 waveform of the auditory ERP. Due to the latency of this waveform, Čeponiene et al. (2005) claim that the N2 might indicate the integration of sound feature analyses into an auditory representation. Alternatively, Bertoli and Probst (2005) discuss the role of N2 in indexing inhibition of processing of redundant stimuli (see also discussion in Chao & Knight, 1997). In Bertoli and Probst's data, older adults showed very little evidence of an N2 waveform relative to young adults. This pattern has been observed elsewhere (Čeponiene, Westerfield, Torki, & Townsend, 2008), including in our own laboratory (Cooper, McGill,

Todd, & Michie, 2006). Bertoli and Probst explained their data by suggesting that older adults show reduced ability to inhibit irrelevant auditory information compared to young adults. Support for the assertion that N2 is influenced by inhibitory control comes from two observations. Firstly, inhibitory control is necessary during sleep and it has been shown that N2 is greatly enhanced during sleep (Picton, Hillyard, Krausz, & Galambos, 1974). Secondly, in the go-no-go task, larger N2 is seen in 'no-go' conditions, where greater inhibitory control must be exhibited, relative to 'go' conditions. Recently, it has been shown that in young adults, larger N2 in an unattended auditory stream correlates with better performance on a target detection task (Čeponiene et al., 2008). Čeponiene et al. (2008) interpreted this in much the same way as Bertoli and Probst, that is, as evidence of inhibition of unattended stimuli. However, it is also possible that the change in N2 amplitude with age could reflect degenerative structural changes that occur within the aging brain (Bertoli & Probst).

Mismatch Negativity

Since MMN was first recorded in 1978 (Näätänen, Gaillard, & Mäntysalo), our understanding of the mechanisms contributing to MMN generation has developed considerably. While previous descriptions of the MMN generation process have focussed on the MMN as a simple change detection mechanism, the modern interpretation of MMN involves an added layer of complexity (see review in Escera, 2007). This is reflected in Sussman's (2007) assertion that "the MMN deviance detection process as a whole is far more complex than is superficially evident from the auditory oddball paradigm, the most commonly used paradigm to elicit MMN" (p.173). Näätänen (2007) sums up the change in thinking that has occurred over the years by stating that "rather than just detecting

deviations in relation to the past, the MMN system seems to detect deviations against the automatically predicted auditory future" (p. 135). In effect, the modern interpretation still encapsulates the initial view of MMN as a change detection mechanism but broadens the scope to highlight the importance of context in MMN generation. Within this review of MMN, we will begin by describing the traditional way in which MMN activity has been recorded and then delve into the complexities of MMN generation as they have emerged in more recent years.

The MMN of the auditory ERP is elicited approximately 100 to 200 ms following a detectable change in a repetitive sequence of aural stimulation (Näätänen, 2000). MMN is genrally elicited in the oddball paragim in response to infrequent 'deviant' tones that differ acoustically from a stream of repeating 'standard' tones (Picton, Alain, Otten, Ritter, & Achim, 2000). MMN can occur in response to simple changes in sound features such as frequency, duration, intensity, or spatial location (for a review see Näätänen, 1992). The MMN is a subtraction waveform which has been traditionally derived by subtracting the average ERP to the standard tone from the average ERP to the deviant tone. MMN primarily results from increased (negative) activity in the deviant ERP relative to the N1 and P2 period in the standard ERP. This activity is largest when recorded from fronto-central electrode sites (Näätänen, 1992). When attention is directed towards sound it is difficult to observe a pure MMN as attention elicits another ERP waveform at a similar latency, the N2b wave (Näätänen, 2000)[3]. Therefore most MMN studies require that

[3] Although MMN can be elicited without the need for participants to attend to the sound source, it is inappropriate to refer to MMN as a pre-attentive auditory ERP component (Sussman, 2007). Sussman argues that this is due to the fact that attention can modify perceptions of sound organization and therefore modify MMN elicitation under certain conditions.

participants ignore auditory stimuli by engaging in a distracting task such as watching a video.

One way of distinguishing the MMN from other ERP components is by measuring activity from electrodes placed over the mastoid bones and observing the reversal in polarity of the waveform relative to fronto-central sites. This occurs because the major source of scalp-recorded MMN activity is located in the supratemporal auditory cortex which lies between fronto-central and mastoid sites (Sams et al., 1985). MMN amplitude measures derived from the mastoids have been argued to primarily reflect activation of the supratemporal generator in the auditory cortex whereas electrodes located fronto-centrally are believed to be additionally sensitive to activation of a proposed frontal generator (Giard, Perrin, Pernier, & Bouchet, 1990; Näätänen & Michie, 1979). Specifically, the dorsolateral prefrontal cortex (Alho, Woods, Algazi, Knight, & Näätänen, 1994) and the right fronto-opercular cortex (Opitz, Rinne, Mecklinger, Cramon, & Schröger, 2002) have been implicated in MMN generation. However, Deouell's (2007) review of MMN generators suggests that further research is required to clarify whether (or under what conditions) there are frontal contributions to MMN. This is due to the fact that generators of MMN are consistently located within the auditory cortex but there have been mixed findings regarding whether there are MMN generators in the frontal cortex.

There are several factors that affect MMN amplitude, including the degree of acoustic difference between standard and deviant stimuli, the proportion of deviant relative to standard tones, and the rate at which sounds are delivered. Due to the manner in which MMN is affected by such manipulations, Näätänen and Alho (1997) concluded that the MMN indexes the precision with which sound properties are encoded into the first phase of auditory sensory memory (i.e. precision of the neural trace). That is, since larger MMN

peak amplitude and earlier peak latency are associated with better behavioural discrimination of stimuli, it is thought that MMN can reflect the precision of the neural representation of auditory stimulus features. For example, an easily discriminable change in auditory stimulation results in larger MMN amplitude than a poorly discriminable one (Schröger, Näätänen, & Paavilainen, 1992). Similarly, larger MMN is associated with more accurate behavioural discrimination of stimuli (Novitski, Tervaniemi, Huotilainen, & Näätänen, 2004). Also, earlier peak MMN amplitude is related to faster behavioural responses to deviant stimuli (Tiitinen, Patrick, Reinikainen, & Näätänen, 1996). In sum, it seems that the larger the physical difference between standard and deviant stimuli, the better the behavioural discrimination and the larger and earlier MMN peak amplitude (although see Horváth et al., 2008 for a case where MMN is not larger when there is a larger difference between standards and deviants). Aside from indexing the precision of the memory trace established within the first phase of auditory sensory memory, the fact that a memory of the standard tone must be established and maintained for MMN to occur implies that a longer form of memory is involved in the MMN generation process. That is, the secondary phase of auditory sensory memory is also implicated in MMN generation. However, there has been some disagreement regarding exactly what the MMN represents when it is recorded in particular circumstances.

In the simplest case of MMN elicitation, that in which deviant tones differ from standards only in a physical feature such as frequency, it has been suggested that the early part of the MMN may in fact reflect increased activity from nonrefractory, frequency-specific, N1 generating neurons (Näätänen, 1988; Otten, Alain, & Picton, 2000). This account has been revived more recently (Jääskeläinen et al., 2004; Jääskeläinen et al., 2007) by researchers claiming that MMN is generated entirely by neuronal populations

underlying N1 generation, at least for the case where standard and deviant tones differ only in frequency (pitch). In simple cases such as this, refractory properties of N1 may well explain the difference between the standard and deviant ERP in the MMN latency range. However, Näätänen (1992) states that this 'new afferent elements' hypothesis cannot sufficiently explain all MMN activity. Accordingly, even in the simplest case of MMN elicitation, Näätänen (1992) suggests that the latter part of the MMN represents activation of sensory memory neurons, that is, MMN also reflects activity resulting from incoming deviant stimuli being compared to a trace of the repeating standard. Furthermore, Näätänen, Jacobsen, and Winkler (2005) outline five reasons why MMN is not purely driven by the refractory properties of N1 neurons: i) MMN is elicited when a standard tone is omitted from a repeating sequence (e.g. Yabe, Tervaniemi, Reinikainen, & Näätänen, 1997) whilst no N1 is generated coincident with the stimulus omission; ii) MMN is generated in response to violations of a tone-pattern (e.g. replacing one standard with another; Alain & Woods, 1999) which should not involve the activation of nonrefractory feature-specific N1 neurons; iii) the latency and duration of MMN and N1 do not directly correspond; iv) the scalp distribution of MMN and N1 differ; and v) experimental manipulations (e.g. pharmacological) can have different effects on N1 and MMN amplitude. In addition, MMN has been observed using protocols that have been specifically designed to avoid the confound relating to refractoriness of N1 generating neurons (e.g. control-deviant procedure of Jacobsen & Shröger, 2001). In sum, the extent to which the new afferent elements and sensory memory accounts explain MMN activity likely depends on the conditions under which MMN is recorded (i.e. whether deviants differ from standards by a single feature or whether deviants violate a more abstract rule that must be held in sensory memory). In agreement with this notion, Nelken and Ulanovsky (2007) point out that both

the new afferent elements and sensory memory accounts could explain activity in the MMN latency range.

Thus far, I have discussed factors contributing to MMN elicitation, I now turn to the proposed function of MMN elicitation in the brain. In doing so, I will introduce two complementary theories thought to explain MMN generation, the model adjustment hypothesis and the predictive coding model.

Winkler, Karmos, and Näätänen (1996) developed the model adjustment hypothesis to explain the biological function of the MMN. According to this hypothesis, the brain creates a model of incoming auditory stimuli in order to predict what sound is likely to be heard next. It is thought that MMN not only signals that a deviation from the model's prediction has occurred, but also that the model is being updated to incorporate characteristics of the deviant event. This position is reflected in the recent assessment by Horváth et al. (2008) that "the primary function of the MMN-generating process lies in maintaining the neural representation of the auditory environment" (p.67). In addition, as MMN can occur when attention is directed away from auditory stimuli, MMN may also represent a trigger to orient attention to novelty in the auditory environment (Näätänen & Michie, 1979). This formulation of the biological function of MMN generation is compatible with a more recent formulation which involves reference to predictive coding models (e.g. Baldeweg, 2007; Friston, 2005; Garrido et al., 2008; Winlker, 2007).

The predictive coding framework states that bottom-up sensory information travels upstream to aid in the formation of predictions about future stimulation and this top-down inferential information travels downstream to suppress predicted activity in lower levels (see also the section on 'auditory sensory memory and the role of the auditory cortex' for supporting evidence of such connections). 'Memory' is thus represented by the connections

between higher and lower sensory levels (Baldeweg, 2007). In the context of the predictive coding model, MMN is thought to represent the error signal which is propagated upstream when predictions do not match current stimulus input. This error signal amounts to the 'violation of regularity' described by Schröger (2007; see section on 'auditory sensory memory and the role of the auditory cortex'). The predictive coding model of MMN generation is compatible with the model adjustment hypothesis as it essentially describes the mechanism by which the model adjustment hypothesis may operate.

There is pharmacological evidence that supports an association between MMN and predicitive coding models. In his recent review, Baldeweg (2007) argues that the N-methyl-D-aspartate (NMDA) receptor system is critical in both MMN generation and the predictive coding model. There are several findings implicating NMDA receptor system in MMN generation. For example, Javitt, Steinschneider, Schroeder, and Arezzo (1996) have shown that an NMDA receptor antagonist, phencyclidine, prevents elicitation of MMN in intracortical recordings of the monkey primary auditory cortex (while obligatory activity in the MMN latency range was preserved). In humans, there is evidence that MMN is reduced following administration of a subanesthetic dose of the NMDA receptor antagonist, ketamine (Umbricht et al., 2000). In addition, the magnetic equivalent of MMN has been shown to decrease following ketamine administration (Kreitschmann-Andermahr et al., 2001) and Pang and Fowler (1999) have reported that MMN decreased in response to nitrous oxide, a substance with NMDA antagonistic properties. This is in contrast to a finding by Orange et al. (2000) who observed no effect of a subanesthetic dose of ketamine on MMN amplitude and to a recent finding of increased MMN amplitude in response to an NMDA receptor antagonist, memantine (Korostenskaja, Nikulin, Kičić, Nikulina, & Kähkönen, 2007). Nonetheless, the bulk of evidence suggests that the NDMA receptor

system is implicated in MMN elicitation. Baldeweg (2007) describes how the feedback aspect of predicitive coding models implicates NMDA receptors in such models (I will discuss the pharmacology underpinning predictive coding models in more detail in the following section on repetition posititivity).

At the cellular level, there is animal research which provides evidence of neural activity potentially related to MMN and predictive coding. Stimulus specific adaptation (SSA) describes the reduction in firing rate recorded in individual neurons in the cat primary auditory cortex when the same sound is presented frequently as opposed to rarely (Ulanovsky, Las, & Nelken, 2003; Ulanovsky, Las, Farkas, & Nelken, 2004). More recently, Nelken and Ulanovsky (2007) refer to SSA as a form of single-neuron habituation. SSA can also be referred to as a form of repetition suppression as repetition suppression essentially describes the reduction in neural responses to repeated stimuli. Ulanovsky et al. (2003) also subtracted neuronal responses (spike counts measured from population peristimulus time histograms derived from recordings in single neurons) to a stimulus when presented as a standard from those responses to the same stimulus when presented as a deviant to obtain a difference signal. Ulanovsky et al. (2003) related the difference signal derived from data recorded at the single neuron level to MMN recorded at the scalp in humans as they share at least three properties, namely, that the magnitude of both the difference signal and MMN, i) increases as the deviant probability decreases, ii) increases as the frequency difference (Hz) between standard and deviant stimuli increases, and iii) decreases as SOA increases (see also Nelken & Ulanovsky). Therefore SSA may be an individual neuron correlate of the process underpinning MMN generation and auditory sensory memory formation (see ‘repetition positivity’ section for further discussion of this topic).

Considering the preceding review, we have outlined that (depending on the method used to elicit MMN) MMN can provide information on several aspects of auditory sensory memory (see reviews in Näätänen, 2007; Schröger, 2007). For example, MMN can provide an index of the precision with which sound is represented in the auditory system (indicative of the integrity of phase one of auditory sensory memory) and the plasticity of the neural response to repeated sounds or sound patterns (indicative of the longer phase of auditory sensory memory). Furthermore, Näätänen (2007) explains how our idea of MMN has evolved from one which focuses strictly on the link between MMN and auditory sensory memory representations to one which encompasses a link between MMN and memory for auditory information in general. Therefore, MMN may well be a suitable candidate with which to study and compare auditory sensory memory and memory for auditory information in various populations such as older versus young adults.

In general, MMN amplitude is smaller in older adults than young adults. However, this pattern has not been observed in all cases. When sounds have been presented at a short SOA (<1.5 s), some researchers have identified reduced MMN amplitude in an elderly group relative to young controls (Alain & Woods, 1999; Cooper, et al., 2006; Czigler, Csibra, & Csontos, 1992; Gaeta, Friedman, Ritter, & Cheng, 1998; Gaeta, Friedman, Ritter, & Cheng, 2001a; Gaeta, Friedman, Ritter, & Cheng, 2001b; Gunter, Jackson, & Mulder, 1996; Karayanidis, Andrews, Ward, & Michie, 1995; Kisley, Davalos, Engleman, Guinther, & Davis, 2005; Schroeder, Ritter, & Vaughan, 1995; Woods, 1992) whilst others have found no difference between groups (Amenedo, & Dìaz, 1998a; Fabiani et al., 2006; Kazmerski, Ritter, & Friedman, 1997; Pekkonen, Jousmäki, Partanen, & Karhu, 1993; Pekkonen et al., 1996). In addition, four studies have reported reduced MMN amplitude in older compared to young adults when a long SOA was used (Cooper et al., 2006; Czigler et

al.; Gaeta et al., 2001b; Pekkonen et al., 1993; Pekkonen et al., 1996). However, in both Pekkonen et al.'s studies, the difference between groups was only noted at the long SOA and not the short, whereas in Cooper et al. (2006), Czigler et al., and Gaeta et al.'s (2001b) studies a significant reduction in the older group's MMN was seen at a short and long SOA. Furthermore, the magnitude of the reduction in Cooper et al. (2006), Czigler et al., and Gaeta et al.'s (2001b) studies was similar at the short and long SOA. From this, we conclude that older adults have difficulty encoding sound properties into auditory sensory memory and that there is no additional deficit with respect to maintaining sound information in auditory sensory memory (see also Fabiani et al., 2006). Moreover, our research (Cooper et al., 2006) also indicated that there were significant group differences in the ERPs to standard tones especially at the long SOA. Considering the fact that the MMN is a subtraction waveform, it is possible that these group differences in components of the standard waveform (specifically related to N1 and P2) impacted upon our MMN results. The possibility that differences in standard components of the ERP between different clinical populations could account for the interpretation of differences in MMN between populations has been presented elsewhere (Elangovan, Cranford, Walker, & Stuart, 2005; Walker et al., 2001). As a result, the aim of the first experiment in this thesis was to examine SOA-dependent changes in the N1 and P2 components in an older adult population relative to healthy young controls.

Therefore, an important factor emerging from the literature on the effect of age on MMN is that as MMN is a subtraction waveform and directly affected by the response to standard and deviant tones, the effect of age on these separate responses may be of importance in understanding the underlying causes contributing to age-related change in MMN amplitude. Sussman (2007) describes the response to standard and deviant stimuli as

two distinct but intertwined processes that contribute to MMN and adds that "while MMN is most commonly thought of in terms of the deviance detection process…it is the standard formation process that crucially affects its elicitation" (p. 164). The following section describes a relatively newly discovered waveform that has been found to index the response to repetition of standard tones over time. This waveform, the repetition positivity, potentially contributes to MMN and is the focus of several experiments in this thesis.

Repetition Positivity

Repetition positivty (RP) was first reported by Baldeweg, Klugman, Gruzelier, and Hirsch (2004) after they used a variant of the oddball paradigm (see Cowan et al., 1993). As mentioned previously, the oddball paradigm generally consists of a repeating standard tone which is occasionally replaced by a deviant tone that differs from the standard in an acoustic feature. In the roving standard paradigm that has been used to elicit RP, the standard tone changes in pitch following the occurrence of a deviant tone. This means that standards are identical within trains but differ in pitch from train to train. Another important factor of the experimental design leading to the discovery of RP was that the number of standards preceding each deviant was manipulated. When Baldeweg et al. (2004) analysed the ERP for standard tones at the end point of different length trains, RP emerged as a positive waveform (at Fz) superimposed upon the P1, N1, and P2 waveforms in the standard tone ERP (i.e. over the post stimulus latency window from 50 – 250 ms approximately). RP was larger in the ERP to standard tones that ended a long train of standards (e.g. 36 repetitions) compared to a short train (e.g. 2 repetitions). RP has since been shown in other studies (Baldeweg, Wong, & Stephan, 2006; Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005). Since an update of the sensory memory trace of

the standard is continually enforced by the nature of the roving standard paradigm and RP amplitude increased over the repetition period, RP was proposed to index the formation (Haenschel et al.) and strengthening (Baldeweg et al., 2004) of auditory sensory memory traces.

Baldeweg et al. (2004) and Haenschel et al. (2005) have linked RP with a mechanism at the neuronal level that plausibly indexes auditory sensory memory, stimulus specific adaptation (SSA). As mentioned in the section on mismatch negativity, SSA describes the reduction in firing rate recorded in individual neurons in the cat primary auditory cortex when the same sound is presented frequently as opposed to rarely (Ulanovsky et al., 2003; Ulanovsky et al., 2004). Ulanovsky et al. (2003) related the difference signal recorded at the neuronal level to MMN recorded at the scalp in humans as they shared several properties (see review in preceding section). In contrast, Baldeweg et al. (2004) and Haenschel et al. have drawn the direct link between RP and SSA because adaptive change in RP is recorded over the repetition period of the standard tone. To our knowledge, some of the properties of the difference signal recorded by Ulanovsky et al. (2003), that appear to also apply to MMN (namely, that the magnitude of both increases as the frequency difference between standard and deviant stimuli increases, and as SOA decreases), have not yet been fully explored in relation to RP. However, as with the difference signal and MMN, RP increases with decreasing probability of a deviant (Baldeweg et al., 2004). In sum, as it is not a trivial matter to relate findings from single cell recordings and gross surface recordings (e.g. Grill-Spector, Henson, & Martin, 2006; Ulanovsky et al., 2003), the direct association between SSA and RP remains speculative. Nonetheless, since neural adaptation contributes to cortical threshold regulation (Ohzawa, Sclar, & Freeman, 1985) and since increased cortical thresholds have been linked with

positive ERP waveforms at the scalp (Elbert & Rochstroh, 1987), it is plausible that SSA contributes to RP[4].

As RP may index synaptic plasticity (physiological change) mediated by stimulus repetition, it is possible to interpret RP within the context of a predictive coding framework (e.g. Baldeweg, 2007; Friston, 2005; Garrido et al., 2008). The predictive coding framework was also described in the section on mismatch negativity. The question remains, is it possible for both RP and MMN to be linked to the predictive coding model and SSA? Whereas RP is thought to be more closely aligned to the process determining suppression of predicted activity, MMN is thought to represent the error signal which is propagated upstream when predictions do not match current stimulus input (Baldewg, 2007). However, SSA and RP could be considered as factors which contribute to MMN. As described in the section on mismatch negativity, the MMN is defined by the response to both standard and deviant waveforms. Since RP occurs in the standard waveform as a function of repetition, it is plausible that SSA is a neural correlate of RP and that RP contributes to MMN.

Pharmacological evidence also highlights the fact that RP contributes to MMN. Baldeweg et al. (2006) have shown that nicotine (a cholinergic agonist that modulates NMDA receptors) administration selectively enhances RP amplitude without affecting the amplitude of deviant waveforms. Similarly Baldeweg, Moelle, Merle, and Borne (in preparation, cited by Baldeweg, 2007) have shown that RP amplitude is reduced in

[4] Elbert and Rockstroh (1987) suggested that cortical thresholds are regulated by the medio-thalamic-frontocortical system and that it is advantageous for organisms to decrease cortical thresholds to anticipated stimuli. This decrease in cortical thresholds is associated with negative amplitude activity at the scalp (Elbert & Rockstroh). I argue that the converse could be true, that is, it may be advantageous to set high cortical thresholds to repetitive irrelevant stimuli (see also discussion of predicitive coding models in this chapter). As stated, high cortical thresholds have been associated with positive amplitude activity at the scalp (Elbert & Rockstroh).

response to an NMDA receptor antagonist, ketamine, while amplitude of deviant waveforms was not affected. Baldeweg (2007) explains that feedback signals in the predictive coding model are thought to utulise NMDA receptors while feedforward signals (such as those expressed in deviant negativity) likely rely on a different system involving AMPA-type glutamate receptors. In addition, the two studies assessing the neurochemical underpinnings of RP also reveal that there may be RP generators operating on different time scales (see review in Baldeweg, 2007). This is due to the fact that the difference in the standard ERP between placebo and drug conditions was most prominent after a larger number of repetitions in the nicotine study (greater than or equal to six; Baldeweg et al., 2006) than the ketamine study (less than or equal to six repetitions; see Baldeweg, 2007). In sum, Baldeweg and colleages' studies on the pharmacological underpinning of RP reveal that modulation of NMDA receptors affects MMN amplitude by altering RP rather than deviant negativity.

It is precisely due to the fact that MMN reflects the response to both standards and deviants that it has been argued that MMN is only an indirect measure of the establishment of auditory sensory memory representations (Haenschel et al., 2005). This leads to the assertion that RP might be a more precise indicator of the establishment and strengthening of auditory sensory memory traces than MMN amplitude and that RP may provide a clearer guide to whether differences in the formation of auditory sensory memory traces exist between different populations.

Although the effect of age on MMN amplitude has been previously studied (a reduction in MMN amplitude with age is generally observed; see preceding review), to our knowledge, the effect of age on RP has not previously been examined except for in this thesis. As Baldeweg et al. (2006) has associated RP in standard waveforms with improved

stimulus encoding and memory trace formation and has related the negativity in deviant waveforms with the deviance detection process, attenuation of MMN amplitude seen in older adult groups relative to young groups could be due to differences in either or both of these mechanisms. The interest in establishing the contribution of the response to standards and deviants in the age-related attenuation of MMN was the motivation for our initial study on the effect of age on RP. Since, as has been previously explained, one of the overarching themes of this thesis was to investigate the relationship between age-related change in lower and higher levels of cognitive processing, we were also interested in whether age-related change in RP would relate to change in memory for auditory verbal information. Is it plausible that this association could exist?

We have already outlined that RP may be related to SSA which is a form of repetition suppression (recall that repetition suppression describes the reduction in neural responses to repeated stimuli). The notion that repetition suppression can be related to enhanced memory is reviewed in Grill-Spector et al. (2006). These authors summarized several models where repetition suppression could lead to faster and/or more accurate behavioural responses to repeated than non-repeated stimuli. In this way repetition suppression is thought to be a neural correlate of priming (Desimone, 1996; cf. Henson & Rugg, 2003) as priming describes the improvement in performance following repeated exposure to an item relative to when the item is novel (Schacter & Buckner, 1998). Similarly, priming effects increase as repetition increases, as does RP (see review in Wiggs & Martin, 1998). Bergerbest, Ghahremani, and Gabrieli (2004) have shown a correlation between repetition suppression (recorded by fMRI) to repeated auditory stimuli and a behavioural repetition effect (priming) in the superior temporal cortex and frontal regions of the brain. Furthermore, the neurochemical underpinning of RP generation might be

similar to that for repetition priming, that is, the cholinergic system (which modulates NMDA receptors) may be involved in both processes (Thiel, Henson, Morris, Friston, & Dolan, 2001). Finally, Gazzaley and D'Esposito (2007) have shown that the degree of suppression of brain activity to irrelevant stimuli (recorded in an fMRI paradigm) correlated with working memory performance in a group of older adults. Therefore, it seems plausible that RP could be related to certain implicit (e.g. priming) and explicit (e.g. working memory) tasks.

In sum, RP may represent a way to observe age-related changes in auditory sensory memory that are also related to age-related change in other forms of auditory memory such as implicit priming tasks and explicit tasks reliant on efficient encoding of the context in which stimulation has occurred such as recall, source memory, or working memory tasks. This prompted us to search for a relationship between RP and memory for auditory verbal information in young and older adults (study 3 and 4 of this thesis) and between RP and implicit memory for the context of auditory stimulation (study 4).

Summary of the relationship between auditory ERP waveforms and auditory sensory memory

In sum we have outlined that P1, N1, P2, and N2 waveforms of the auditory ERP are obligatory exogenous waveforms that are primarily thought to reflect the first phase of auditory sensory memory which deals with the analysis of sound features. The N2 waveform is identified but not discussed thoroughly in this thesis as there is little known about the functional significance of this waveform which appears to be elicited by young but not older adults. We see exploration of the age-related difference in passively elicited N2 of the auditory ERP as an avenue for future research. Since endogenous waveforms

thought to reflect aspects of auditory sensory memory, repetition positivity and mismatch negativity, can overlap the latency period of the obligatory waveforms, further research is required to understand the unique contribution that neuronal populations generating the obligatory waveforms have on auditory sensory memory. For example, while there is some evidence that P1, N1, and P2 amplitude modulation might reflect memory for sound in particular contexts (e.g. for P1: Dyson, Alain, & He, 2005; for N1: Jääskeläinen et al., 2004; 2007; for a review see Schröger, 1997; for P2: Atienza, Cantero, & Dominguez-Marin, 2002; Bosnyak, Eaton, & Roberts, 2004; Reinke, He, Wang, & Alain, 2003; Schweinberger, 2001; Shahin, Bosnyak, Trainor, & Roberts, 2003; Sheehan, McArthur, & Bishop, 2005; Tremblay, Kraus, McGee, Ponton, & Otis, 2001), the extent to which such changes could be explained by an overlapping endogenous waveform such a repetition positivity needs to be explored.

In contrast to the obligatory waveforms, the endogenous waveforms, repetition positivity and mismatch negativity, have been more strongly linked with phase two of auditory sensory memory, where representations of sound are stored for longer than several hundred milliseconds. The strongest case for a link between an auditory ERP waveform and auditory sensory memory has been made for MMN, while this link has been emerging over recent years in the research devoted to repetition positivity. In the preceding review, we have outlined that both MMN and RP reflect aspects of neural plasticity related to modeling of the auditory environment in auditory sensory memory. While MMN is examined in the second and third studies of this thesis, the studies presented in this thesis also focus on the effect of age on N1, P2, and repetition positivity waveforms of the auditory ERP. The MMN literature has guided the interest in these waveforms and it must

be noted that age-related change in such waveforms potentially contributes to age-related change in MMN.

The present studies

As has been mentioned, in this thesis we were interested in examining the effect of age on auditory sensory memory (using the ERP) as well as the relationship that any age-related changes in auditory sensory memory might have with age-related change in other forms of memory. To answer these research questions, in this thesis, we conducted four studies[5] where we examined the effect of age on N1, P2, MMN, and RP waveforms.

More specifically, study 1 explored the effect of age on the recovery cycle of N1 and P2 waveforms of the auditory ERP. As MMN and RP are subtraction waveforms, it is important to understand the effect of age on the obligatory N1 and P2 waveforms that occur within the same latency range as MMN and RP before examining the endogenous waveforms themselves. For example, although MMN has been used to examine auditory sensory memory in a number of clinical groups (Näätänen, 2003), the possibility that MMN differences between clinical and control groups could at least be partially accounted for by differences in the recovery cycles of neuronal populations underpinning the auditory N1 and P2 waveforms has previously been canvassed (Elangovan et al., 2005; Walker et al., 2001). Similarly, in a recent MMN study designed to assess auditory sensory memory functioning in a group of young and a group of older adults, we observed between group differences in N1 and P2 amplitude that may have contributed to the observed difference in MMN amplitude between the age groups (Cooper et al., 2006). This raises the question of

[5] Note that the studies in this thesis have been presented in a format akin to journal articles and this necessitates some repetition of material from my literature review in order to place each study in its specific context. Details of where each study is to be submitted are provided at the beginning of each chapter.

how to interpret MMN differences between groups that also exhibit N1 and P2 amplitude differences. Our review of N1 and P2 waveforms of the auditory ERP suggests that the effect of age on these waveforms is not entirely clear. By studying the recovery cycle of N1 and P2 waveforms in young and older adults in the first study of this thesis, we aimed to clarify whether age-related change in underlying N1 and P2 components occurs. Our introduction to study 1 will outline our hypothesis that the rate at which sounds are delivered could affect whether age-related change in these components is observed.

During the course of this thesis, the first study recording RP was published (Baldeweg et al., 2004). In that and subsequent studies (e.g. Haenschel et al., 2005; Baldeweg et al., 2006), RP was seen to overlap the latency period of N1 and P2 waveforms of the auditory ERP. Integrating this RP literature into our interpretation of results from study 1, we concluded that RP may have influenced previous reports of age-related change in N1 and/or P2 amplitude. Therefore, to answer this hypothesis, we felt that establishing the effect of age on RP was appropriate. In addition, the fact that RP was thought to represent the formation and strengthening of auditory sensory memory traces (e.g. Baldeweg et al., 2004; Haenschel et al., 2005) provided prime motivation for a study of the effect of age on RP. That is, it seemed plausible that such a study could potentially provide more direct evidence concerning effect of age on auditory sensory memory trace formation than MMN studies had. However, for reasons outlined below, study 2 of this thesis was devoted to identifying the precise conditions eliciting RP in a group of young adults rather than examining the effect of age on RP (studies 3 and 4 explored this issue).

The idea that RP is related to the formation and strengthening of auditory sensory memory traces was influenced by the conditions under which RP was firstly observed, that is, the roving standard oddball paradigm. As stated, in the roving standard oddball

paradigm, a memory trace of the standard tone must be re-established for each standard train. Thus the growth of RP over the course of a standard train could represent the establishment of the memory trace. However, to our knowledge, no attempt to observe RP in a constant standard oddball paradigm has been published. Thus, motivation for conducting study 2 in young adults was to compare and contrast the repetition effect on the auditory ERP in constant standard and roving standard conditions. If RP were observed in a constant standard condition, this could alter our understanding of the functional correlate of RP as a probe of auditory sensory memory trace development. In study 2, we also examined the MMN memory trace effect (see Baldeweg et al., 2004), defined as the growth of MMN amplitude as a function of increased repetition of the standard tone. Whether RP or the effect of repetition on the ERP to deviant tones contributed to the MMN memory trace effect was of interest as this would show the extent to which MMN is influenced by RP. Study 3 continued with this theme by focusing on the effect of age on RP and the MMN memory trace effect. As will be seen, the results of study 2 significantly aided our interpretation of the age effects on RP observed in studies 3 and 4.

In study 3, although the primary goal was to establish whether there was an age effect on RP and/or the MMN memory trace effect (to our knowledge, the effect of age on these ERP measures has not been explored by others), our secondary goal was to find out whether there was a link between these ERP measures and performance on a memory test. We examined the relationship of RP and the MMN memory trace effect to performance on an auditory verbal memory test (Rey Auditory Verbal Learning Test: RAVLT). The RAVLT was chosen as it is a measure of memory for repeated auditory information. Although the RAVLT is an explicit recall task, we identified in our reviews of memory systems and of RP that it is possible that implicit information (such as that reflected by RP

recorded in passive conditions) contributes to performance on explicit tasks. We were interested in whether RP was related to performance on the RAVLT due to our interest in whether age-related change in sensory memory could contribute to age-related change in other forms of memory such as auditory verbal memory. However, due to the fact that RP research has only begun to emerge over recent years we were concerned with whether there was a more direct functional correlate of RP. Thus, in study 4, we extended upon study 3 by additionally attempting to relate RP to a behavioural measure indicative of priming.

The primary aim of study 4 was to better understand the functional significance of the age-related change in RP by exploring the possibility of there being a direct behavioural correlate of RP. To do this we designed a condition in which we examined the effect of repetition on behavioural responses to sound (reaction time and percentage correct). Again, although we designed an explicit task to test the effect of repetition on responses, the task was not contingent upon and did not make reference to the number of repetitions presented. We therefore hypothesized that we would observe a behavioural priming effect in response to sound repetition. As this task required participants to attend rather than passively ignore sound stimuli, we also recorded RP in a passive ignore condition akin to our previous studies. In study 4, this allowed us to compare the effect of age on RP in a new sample of adults and to re-examine the relationship between RP and performance on the RAVLT as in study 3. Thus, in study 4, we aimed to strengthen claims made in study 3 and to add weight to the argument that RP is an auditory ERP waveform associated with the establishment of auditory sensory memory traces by linking RP with a behavioural memory-related repetition effect (priming).

In sum, the cognitive aging literature speculates that age deficits may be apparent at the level of auditory sensory memory, while imaging data (MMN literature) suggests that

age does impact upon auditory sensory memory functioning. Here, we attempt to draw upon both perspectives to examine whether auditory sensory memory functioning is altered with advancing age and whether age-related change in auditory sensory memory is related to age-associated change in other forms of memory. We achieved this by firstly examining the effect of age on obligatory N1 and P2 waveforms of the auditory ERP as age-related change in underlying N1 and P2 components may have contributed to the age effect observed in previous MMN studies. For the remaining three studies of this thesis, we shifted our primary focus to an ERP waveform discovered during the course of this thesis, repetition positivity, as it is in the latency range of N1 and P2, may contribute to MMN, and may be a more direct measure of the establishment of auditory sensory memory traces than MMN. As our review of sensory changes which occur with age in the auditory modality showed that older adults tend to exhibit higher hearing thresholds relative to young adults, we have attempted to deal with this issue in the studies comprising this thesis (refer to methods sections). In the following, I present the four studies of this thesis followed by a discussion of their combined impact upon our understanding of the effect of age on auditory sensory memory. I also discuss how our findings integrate into the broader aging literature.

Chapter 2: study 1

Age-related changes in the auditory event-related potential: the effect of stimulus onset asynchrony[6]

[6] This paper is to be submitted to Psychophysiology with authors Cooper, R.J., Budd, T.W., Todd, J., and Michie, P.T.

Age-related changes in the auditory event-related potential: the effect of stimulus onset asynchrony

Within approximately 300 ms following sound onset, the auditory system is able to analyse the acoustic properties present and integrate this information into a unitary percept (Cowan, 1984). N1 and P2 waveforms of the auditory event-related potential (ERP) are elicited during this period and are thus thought to reflect processes involved in the encoding of sound features in the auditory cortex[7]. Given the fundamental auditory processing role associated with these waveforms, the integrity of auditory information could be compromised in populations in whom N1 and/or P2 are altered relative to healthy controls. Although there is research implying that there may be an age-related deficit in central auditory processing (as speech comprehension deficits can occur in the absence of peripheral hearing abnormalities; Hull, 1995; Willott, 1991), a review of the literature concerning the effect of age on N1 and P2 amplitude does not adequately address this assertion. This is due to the fact that there are conflicting findings concerning the effect of age on these waveforms. For example, there are studies showing that older adults produce larger N1 amplitude relative to young adults (Alain & Woods, 1999; Ford, & Pfefferbaum, 1991; Gaeta, Friedman, Ritter, & Hunt, 2002; Kisley, Davalos, Engleman, Guinther, & Davis, 2005), while some studies show that older adults produce smaller N1 amplitude compared to young adults (Cooper, Todd, McGill, & Michie, 2006; Kisley et al.), and others have shown no difference in N1 amplitude between young and older adults (Barrett, Neshige, & Shibasaki, 1987; Bertoli, Smurzynski, & Probst, 2002; Czigler, Csibra, & Csontos, 1992; Gaeta, Friedman, Ritter, & Cheng, 1998; Iragui, Kutas, Mitchiner, &

[7] This has primarily been described for N1 but N1 and P2 have often been referred to as part of a unitary N1/P2 complex (Näätänen & Picton, 1987). The independence of N1 and P2 has been established but less is known about the functional correlate of P2 relative to N1 (see review in Crowley & Colrain, 2004).

Hillyard, 1993; Pfefferbaum, Ford, Roth, Hopkins, & Kopell, 1979; Pfefferbaum, Ford, Roth, & Koppel, 1980; Picton, Stuss, Champagne, & Nelson, 1984; Smith, Michalewski, Brent, & Thompson, 1980). A similarly inconclusive picture emerges from the P2 literature where larger (Amenedo & Dìaz, 1998; Ford & Pfefferbaum, 1991: Pfefferbaum et al., 1980), smaller (Bertoli et al.; Cooper et al., 2006; Czigler et al.; Smith et al.), and similar (Barret et al.; Iragui et al.; Picton et al.) P2 amplitude has been observed in older relative to young adults. While various methodological differences could account for the inconsistencies between studies, one possibility is that age-related amplitude differences in N1 and P2 waveforms vary according to the rate of stimulation used (stimulus onset asynchrony: SOA). This possibility is explored in the present study in order to clarify the effect of age on N1 and P2 waveforms and the encoding of auditory information.

It is well established that the rate at which sounds are delivered affects the amplitude of N1 and P2 waveforms. As the interval between tones increases (from 500 ms up to a limit of approximately 10 s), so too does the amplitude of N1 and P2 at the vertex (Davis, Mast, Yoshie, & Zerlin, 1966; Hari, Kaila, Katila, Tuomisto, & Varpula, 1982, in a combined EEG and MEG study). This finding is thought to indicate the recovery function of complex neural circuits underpinning these waveforms (Budd, Barry, Gordon, Rennie, & Michie, 1998; Ritter, Vaughan, & Costa, 1968). Support for the hypothesis that there is a differential effect of age on N1 and P2 amplitude depending on the stimulation rate has been forthcoming in studies that employed more than one SOA condition (Cooper et al., 2006; Czigler et al., 1992; Kisley et al., 2005; Papanicolaou, Loring, & Eisenberg, 1984; Pekkonen et al., 1996). At slow stimulation rates (SOAs > 3 s), smaller N1 (Cooper et al., 2006; Kisley et al.; Papanicolaou et al.) and P2 (Cooper et al., 2006; Papanicolaou et al.) amplitude has been observed in older versus young adults. However, this does not appear to

be the case at rapid stimulation rates (SOAs < 3 s) where N1 amplitude in older adults is similar to, if not larger than, N1 amplitude in young adults (Cooper et al., 2006; Czigler et al.; Kisley et al.) and P2 amplitude is more similar between young and older adults than at longer SOAs (Cooper et al., 2006; Papanicolaou et al.). There are two factors which may explain such findings. Firstly, more than one underlying component[8] contributes to the N1 (Näätänen & Picton, 1987) and P2 waveforms (see Crowley & Colrain, 2004; Hari et al.; Näätänen, 1992), and secondly, different components dominate at different stimulation rates (e.g. Budd et al.; Hari et al.). Therefore, it is possible that age differentially affects underlying components of the N1 and P2 waveforms. To pursue this line of reasoning, N1 and P2 components are characterised in greater detail in the following review.

The N1 waveform is the most widely studied waveform of the two that are the subject of this investigation. An abrupt change in energy flow entering the auditory system will necessarily elicit the N1 (Näätänen & Picton, 1987). Näätänen and Picton assert that three 'true' components contribute to N1. Component 1 is a frequency specific component peaking frontocentrally at approximately 100 ms post stimulus onset and is most likely generated in the supratemporal plane of the auditory cortex (Näätänen et al., 1988). Näätänen and Picton propose that component 1 could reflect the formation of an auditory sensory memory trace[9] and discuss the possibility that a memory of previous auditory stimulation is maintained in the pattern of refractoriness of auditory cortex neurons generating N1 component 1. Component 2 is best recorded from midtemporal sites

[8] 'Component' in this sense refers to a localised source of neural activity (generator) that contributes to ERP amplitude recorded at the scalp.

[9] Another auditory ERP waveform, repetition positivity (RP), has been credited with a similar functional role as N1 component 1 (Baldeweg, 2007; Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Cooper, Atkinson, Clark, & Michie, to be submitted a; Cooper, Todd, & Michie, to be submitted b,c; Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005).

(probably generated in superior temporal gyrus) and has a positive peak at approximately 100 ms and a negative peak at 150 ms. The positive peak recorded at midtemporal sites is referred to as Ta, while the negative peak is known as either Tb or N1c. The functional role of N1 component 2 is not well established, although according to Näätänen and Picton, N1 component 2 could have a similar functional role as N1 component 1. Component 3, recorded at the vertex (superimposed on component 1), has a peak latency of approximately 100 ms and is regarded as a non-specific component. As there is evidence that the reticular formation is active during elicitation of N1 component 3 (Velasco & Velasco, 1986; Velasco, Velasco, & Olvera, 1985), Näätänen & Picton assert that N1 component 3 likely represents a cortical projection of activity from the reticular formation. Therefore, N1 component 3 is thought to indicate an arousal response which could facilitate sensory and motor responses to stimuli (Näätänen & Picton).

In addition, to the three N1 components described by Näätänen and Picton (1987), there are several researchers who have proposed the existence of a frontal N1 component (Alcaini, Giard, Thevenet, & Pernier, 1994; Giard et al., 1994; Knight, Hillyard, Woods, & Neville, 1980). Knight et al. originally suggested that the N1 response may be under inhibitory control from the frontal cortex as patients with frontal lobe damage tend to produce larger N1 amplitude relative to controls (see also Alain, Woods, & Knight, 1998). An inhibitory influence on N1, possibly mediated by the frontal cortex, has more recently been proposed by Sable, Low, Maclin, Fabiani, and Gratton (2004). However, Knight, Staines, Swick, and Chao (1999) reviewed evidence suggesting that the frontal cortex mediates both excitatory and inhibitory control of N1 amplitude. Knight et al. (1999) determined that the type of influence exhibited by the frontal cortex on N1 amplitude may be task-dependent.

Budd et al. (1998) found that neuronal populations underpinning N1 component 1 took between one and three seconds to recover, whereas component 3 had a longer recovery period of between three and ten seconds. At shorter SOAs (< 3 s), component 1 is the dominant component contributing to N1 activity recorded at the scalp, while at longer SOAs, component 3 is the dominant component (Näätänen, 1988). Alcaini et al. (1994) proposed that a frontal N1 component recovers within eight seconds[10]. In sum, N1 amplitude recorded at the scalp does not represent a unitary response. Rather, N1 recorded at the scalp reflects the superimposed activity of different generators. In the present study, we attempted to differentiate between N1 components (see methods).

As papers focussing on P2 are far less abundant than those examining N1, the functional significance of P2 is not well established (for a review see Crowley & Colrain, 2004). It is possible that a specific and non-specific component contribute to P2 amplitude recorded at the scalp as is the case for N1 (see Crowley & Colrain; Hari et al., 1982; Näätänen, 1992). Studies that have localised a P2 generator to the primary or secondary auditory cortex (Godey, Schwarz, de Graaf, Chauvel, Liegeois-Chauvel, 2001; Hari et al., 1987; Verkindt, Bertrand, Thevenet, & Pernier, 1994) have used rapid stimulation rates (faster that 1 per 1.5 s). However, other research suggests that a non-specific P2 component, which dominates at longer SOAs, could be generated in the reticular formation (Velasco et al. 1985; Velasco & Velasco, 1986). These findings are similar to those for N1 as it seems that a P2 source dominant at shorter SOAs is located in the auditory cortex and

[10] Although Alcaini et al. (1994) proposed a second frontal N1 component, this will not be discussed in the present study as it emerged at stimulation rates greater than 1/16 s. Alcaini et al. suggested the second frontal component could correspond to activity from N1 component 3.

a non-specific P2 source dominant at longer SOAs is generated elsewhere. As for N1, it is possible that the non-specific P2 component is part of an arousal response.

More recent interest in the P2 waveform has involved the idea that P2 could be related to perceptual learning. When participants were given discrimination training on the same auditory stimuli used in ERP recording sessions, larger P2 amplitude (Atienza, Cantero, & Dominguez-Marin, 2002; Bosnyak, Eaton, & Roberts, 2004; Reinke, He, Wang, & Alain, 2003) and larger N1-P2 peak-to-peak amplitude (Tremblay, Kraus, McGee, Ponton, & Otis, 2001) was observed post-training compared to pre-training. Similarly, larger P2 amplitude to musical tones has been observed in trained musicians versus non-musicians (Shahin, Bosnyak, Trainor, & Roberts, 2003). However, studies have shown increased P2 amplitude in both a trained and untrained group compared to baseline (Reinke et al.; Sheehan, McArthur, & Bishop, 2005) and in response to previously primed voice samples compared to unprimed voice samples (Schweinberger, 2001) which suggests that the increase in P2 amplitude is related more to the amount of exposure to stimuli rather than to conscious discrimination training involving the stimuli. For this reason, Sheehan et al. argued that P2 is more likely to index inhibition of attention to repetitive stimuli rather than perceptual learning. However, this does not rule out the possibility that larger P2 is related to enhanced memory for sound[11]. Interestingly, a recent study has shown that age reduced the increase in P2 amplitude that occured across recording sessions in an MEG study of young and older adults (Ross & Tremblay, 2009). Finally, since the studies that

[11] The extent to which these effects can be attributed to P2 rather than a relatively newly discovered waveform that overlaps the P2 latency period, repetition positivity, remains to be seen. The repetition positivity is a positive going waveform (at frontal sites) that increases in amplitude as a function of repetition of auditory stimuli and is associated with the formation and strengthening of auditory sensory memory traces (Baldeweg et al., 2004; Haenschel et al., 2005).

examined P2 amplitude across sessions used stimulation rates faster than 1 per 3 s, these conclusions may only apply when rapid rates of stimulation are used.

As previously outlined, if age-related differences in N1 and P2 amplitude are dependent on the SOA used, then it is possible that there are independent age-effects on the underlying components that contribute to N1 and P2 waveforms. We therefore examined N1 and P2 amplitude as a function of SOA (temporal profile of N1 and P2 amplitude) in young and older adults using a broader range of SOAs than has previously been tested (500 ms, 1 s, 3 s, 6 s, and 9s). Within this framework we explored neuronal mechanisms responsible for age-related change in the temporal profile of N1 and P2.

Method

Participants

Twenty–five young and 25 older participants were recruited for the study. Ethics approval for the study was obtained from the University of Newcastle Human Research Ethics Committee. All participants gave their written informed consent to participate. One young and one older participant were not included in analyses due to excessive movement artifact in their ERP recordings. A further three older participants were not included due to a hardware malfunction. Data from 24 young (mean age: 20.71 years $\pm$ 3.7, age range: 18 – 30 years, 5 males) and 21 older (mean age: 64.76 years $\pm$ 7.4, age range: 53 – 77 years, 6 males) participants remained for inclusion in analyses. A telephone screen was administered to participants prior to recruitment to screen for neurological and psychological disorders, serious head injury, drug abuse, and visual or hearing impairments. Those in the young group were first year psychology undergraduate students

who received course credit for their participation. Older participants were primarily recruited via posters placed in community centres. All older participants were reimbursed for their travel costs. The Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975) was administered to older participants to screen for dementia (cut-off of 23 out of 30 for dementia; Crum, Anthony, Bassett, & Folstein, 1993). The mean score was 29.24 with a range of 28 to 30.

At the start of each appointment, auditory thresholds were tested in the left then right ear at five frequencies (0.5, 1, 2, 4, and 8 kHz) using a hand held audiometer with a resolution of 5 dB. All participants had less than 20 dB difference between thresholds for each ear at each frequency. Mean auditory thresholds in dB HL are presented in Table 1. Below 2 kHz, all participants had auditory thresholds less than 35 dB HL for both ears. Using the mean hearing thresholds from the young adult group as normative data, we subtracted the mean threshold for the young group at each frequency from older participants' thresholds. Following this computation, all older participants showed normal auditory thresholds (below 20 dB HL) for sounds below 2 kHz. Fifteen of the 21 older participants had thresholds greater than 30 dB HL at 4 kHz and/or 8 kHz even following subtraction of the baseline measure. This suggests that approximately two thirds of our older participants were experiencing the early stages of presbycusis, a condition describing elevated auditory thresholds to high frequency sound in old age. In an attempt to ensure equal auditory input for both groups, we chose a relatively low frequency (800 Hz) stimulus for the experiment and raised intensity 55 dB above each individual's threshold to that tone.

Table 1

Auditory threshold data for the young and older group in dB HL (sd in brackets) and the difference between group means. Note the 5 dB resolution of the audiometer.

	0.5 kHz	1 kHz	2 kHz	4 kHz	8 kHz
Young	16.88 (6.61)	16.56 (7.43)	6.25 (9.53)	4.38 (7.54)	6.56 (9.64)
Older	21.79 (8.05)	21.31 (8.37)	17.26 (11.44)	26.43 (13.07)	43.21 (20.00)
Difference	4.91	4.75	11.01	22.05	36.65

Stimuli and procedure

Sounds were generated by Presentation ® software (Version 9.2, www.neuro-bs.com) and delivered over KOSS TD60 headphones. Before testing began, stimuli were calibrated to dB SPL in an anechoic chamber using a Brüel and Kjaer sound level meter.

During the experiment, an 800 Hz tone (50 ms duration, 8 ms rise/fall) was presented binaurally over stereo headphones at 55 dB SPL above individual threshold to the tone. Individual thresholds were estimated using a method of limits procedure where participants indicated via a keypad whenever they heard the 800 Hz tone. Initial intensity of the test tone was 76.5 dB SPL and participants had 1.5 s to respond before a miss was recorded. The initial step size was 10 dB. After the first miss, the step size was reduced to 5 dB and to 1dB after the second miss. The procedure terminated after a hit and miss combination was directly followed by another hit and miss. The left ear was tested first followed by the right ear. During the experiment, the intensity at which the 800 Hz tone was presented (threshold + 55 dB) was similar in the young group (left ear: 81.17 $\pm$ 3.02; right ear: 82.29 $\pm$ 3.27) and older group (left ear: 82.79 $\pm$ 3.44; right ear: 82.79 $\pm$ 4.01). There was no significant difference between the groups for either ear ($p>.1$)

Experimental stimuli were delivered in five different stimulus onset asynchrony (SOA) blocks: 500 ms, 1 s, 3 s, 6 s, and 9 s. The order of presentation of the blocks was counterbalanced across participants. Since fewer trials are necessary to extract a clear signal from long SOA conditions, fewer stimuli were delivered in the longer SOA conditions than the 500 ms SOA condition. The number of stimuli presented in the 500 ms, 1 s, 3 s, 6 s, and 9 s SOA conditions was 600, 200, 160, 140, and 120 respectively. Thus total ERP recording time was approximately 50 minutes. During this period, participants were instructed to concentrate on a silent video with subtitles and ignore the sounds played over headphones.

EEG Recording

The EEG was recorded from 60 scalp channels and from both mastoids using an electrode cap (Electro-Cap International) with sites based on the 10/20 system and with a nose reference. The vertical electro-oculogram (EOG) was recorded by electrodes above and below the left eye and the horizontal EOG by electrodes at the outer canthi of each eye. Continuous EEG were digitised at 250 Hz (gain 75,000; bandpass filter 0.1 – 40 Hz; notch filter 50 Hz) and recorded for off-line analysis. Scan 4.2 software and synamps hardware was used to acquire data while Scan 4.3 was used to analyse results.

Data Analysis

Movement artefacts were manually removed from the data and eyeblink artefact correction was utilised (Semlitsch, Anderer, Schuster, & Presslich, 1986). A 100 ms prestimulus baseline and 448 ms poststimulus period was used to epoch EEG data. Epochs containing artefacts exceeding ± 100 μV were rejected.

N1 amplitude was extracted at midline sites which, according to Näätänen and Picton's (1987) classification system, primarily reflect activity from component 1 and 3 (and a potential frontal component). We also examined the reversal in polarity of N1 at the mastoids (primarily reflective of component 1). Representing activity from component 2, the second positive (Ta) and second negative (Tb) peaks identifiable at midtemporal sites, T7 and T8, were examined. We chose these sites to attain coverage of the underlying components contributing to N1 (although we acknowledge that overlapping activity from independent components may contribute to N1 amplitude at all sites chosen). Similarly, by comparing midline and mastoid sites for P2 we aimed to compare the non-specific and auditory cortex components of P2, respectively.

We extracted N1 peak amplitude using a search window from 70 – 150 ms to encompass N1 data from midline and mastoid sites at all five SOA conditions for both groups. However, due to the small size of Ta and Tb we extracted mean amplitude at T7 and T8 (search windows 110 – 130 ms and 130 – 150 ms respectively). P2 peak amplitude was extracted using a search window from 140 – 300 ms at midline sites. When we extracted P2 over the mastoids, we limited the search window (to 140 - 250 ms) due to the fact that there was late negative activity at the mastoids in young adults at approximately 300 ms that was not related to the reversal of P2. Individual waveforms were reviewed to ensure that individual peaks fell within the chosen windows.

We analysed mean and peak amplitude (plus latency) over the aforementioned search windows using 5(SOA) x 2(group) x 3(electrode: Fz, Cz, Pz) mixed design mANOVA (Pillai's trace). To examine whether interactions with the factor electrode survived rescaling, we recalculated the amplitude at Fz, Cz, and Pz for each SOA condition as a percentage of the mean amplitude at Cz across participants at each respective SOA

condition (e.g. Scherg, Vasjar, & Picton, 1989). For analyses of Ta and Tb, the factor electrode had two levels: T7 and T8. For analyses at the mastoids we replaced the factor electrode with the factor mastoid (left and right mastoid).

Results

To demonstrate the effect of SOA on the ERP for young and older adults we have plotted the five SOA conditions overlaid in Figure 1[12]. Data are shown at Fz, Cz, Pz, T7, T8, and the left and right mastoid. Following is an analysis of SOA effects and group differences over the N1 and P2 periods.

[12] Figure 1 highlights a group difference in the morphology of the ERP at a latency of 200 - 400 ms post stimulus onset. Young adults show evidence of one or two negative waveforms at midline sites during this period, whereas older adults do not. An age-related difference of this nature has been discussed elsewhere (Bertoli & Probst, 2005) and will not be examined further in this paper.

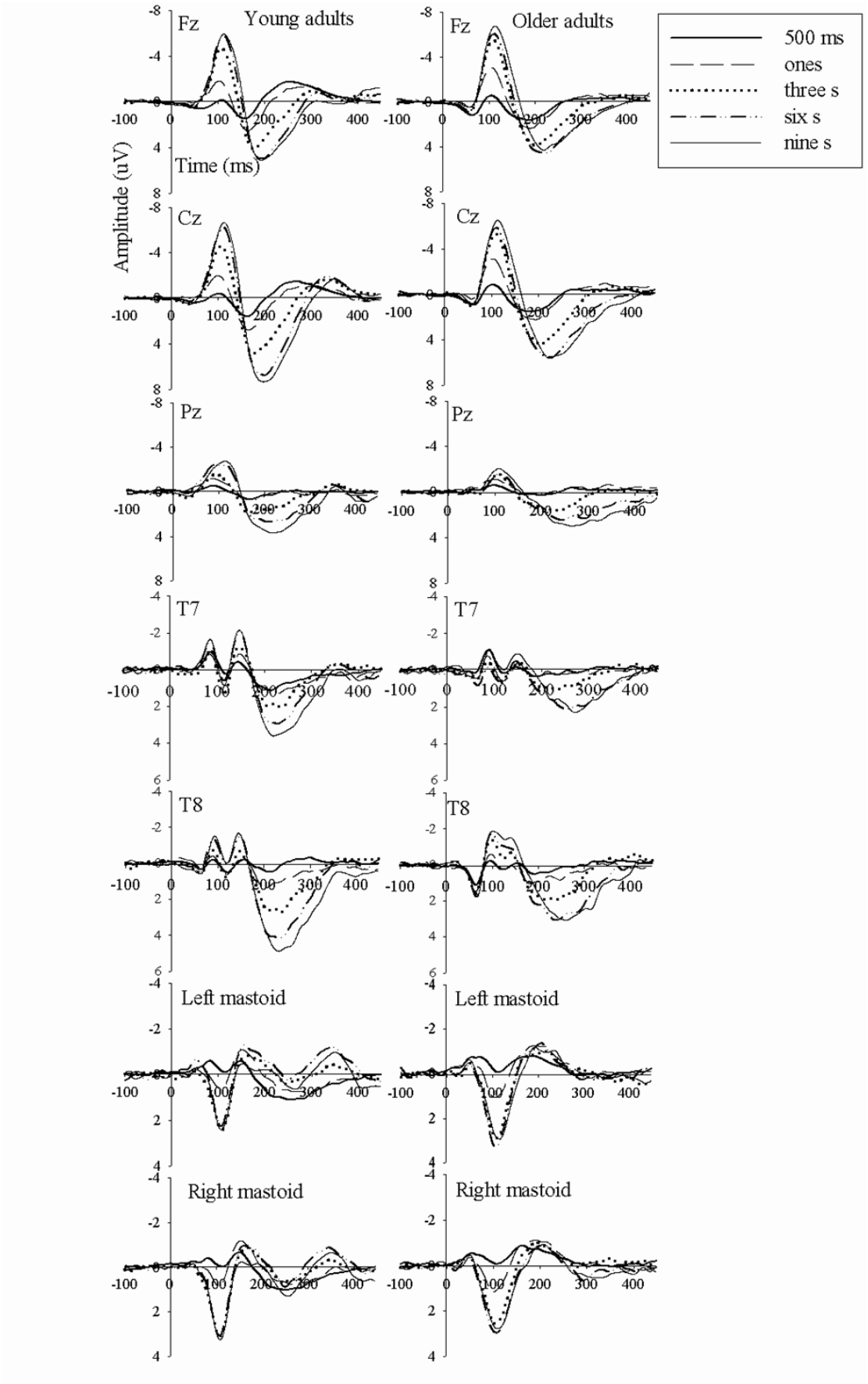
Young adults
Older adults
Fz
Cz
Pz
T7
T8
Left mastoid
Right mastoid
Amplitude (uV)
Time (ms)
500 ms
ones
three s
six s
nine s

Figure 1. Grand average waveforms for the young (left) and older group (right) at Fz, Cz, Pz, T7, T8, and the left and right mastoid. The five SOA conditions are overlaid. Negative amplitude is plotted upwards. Note midline, midtemporal, and mastoid sites are on different vertical (μV) scales.

N1 peak amplitude

The mANOVA conducted on N1 peak amplitude at Fz, Cz, and Pz showed a strong SOA effect ($F(4,40) = 82.255$, $p<.001$) indicating that N1 amplitude increased with increasing SOA. This result is evident in Figure 1 and Figure 2a. The analysis also revealed a strong main effect of electrode ($F(2,42) = 57.448$, $p<.001$) and an SOA x electrode interaction ($F(8,36) = 21.839$, $p<.001$). This interaction is explained by the fact that amplitude was similar at all three electrodes for the 500 ms SOA condition but as SOA increased, the N1 distribution became more anterior (i.e. amplitude at Fz and Cz was of similar magnitude and larger than at Pz for longer SOAs). There was an SOA x group interaction ($F(4,40) = 2.955$, $p<.05$) and an SOA x electrode x group interaction in the N1 data ($F(8,36) = 3.090$, $p<.01$) that remained after the data were rescaled ($F(8,36) = 2.747$, $p<.05$). To explore the three-way interaction further, unscaled N1 data from each of the three electrodes were individually submitted to mANOVA. The group x SOA interaction was significant at Cz ($F(4,40) = 3.416$, $p<.05$) and Pz ($F(4,40) = 3.292$, $p<.05$) but not Fz ($p = 0.164$). This suggested that the temporal profile of N1 differed between the age groups at Cz and Pz.

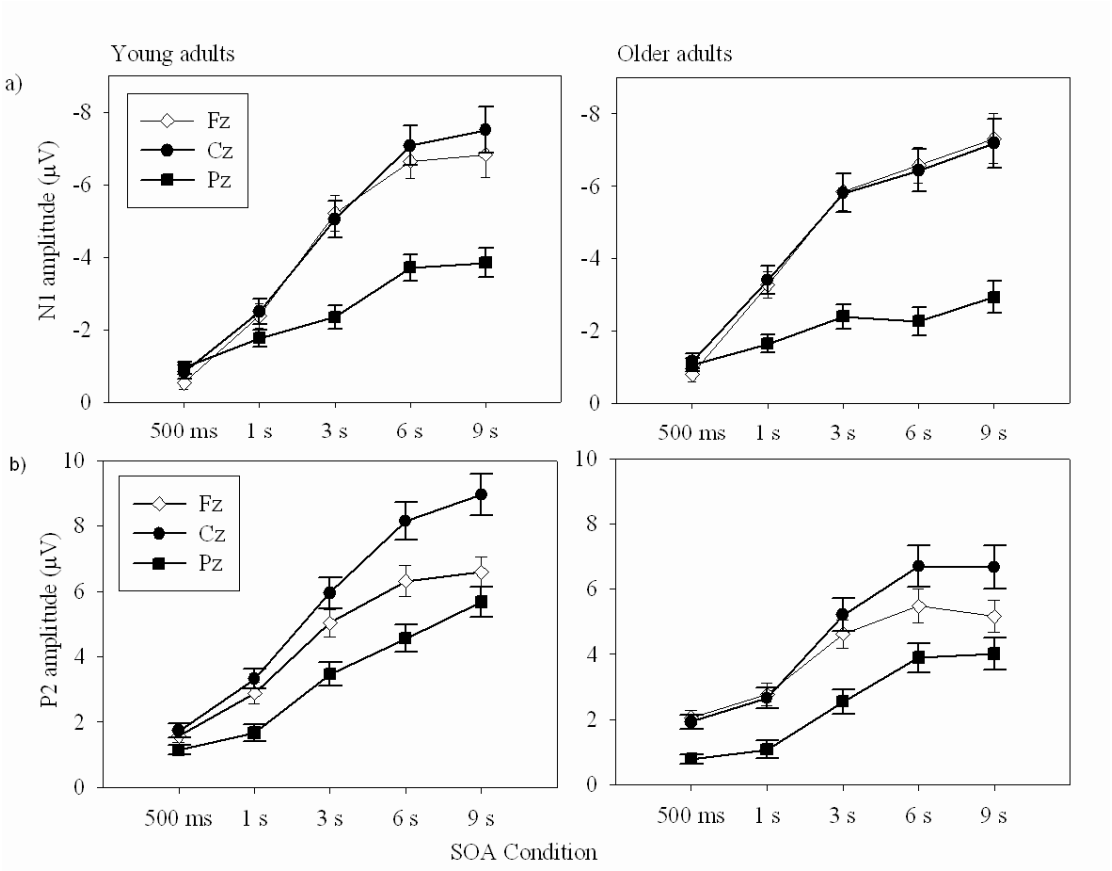

Figure 2. a) N1 peak amplitude for the young (left) and older group (right). Note that negative amplitude is plotted upwards. b) P2 peak amplitude for the young (left) and older group (right). Note that positive amplitude is plotted upwards. Error bars denote the standard error of the mean.

To explore the differences in the temporal profile of N1 between groups in more detail, we established that both groups showed a significant main effect of SOA at Cz (young: $F(2,20) = 40.096$, $p<.001$ and old: $F(4,17) = 29.192$, $p<.001$) and Pz (young: $F(4,20) = 16.022$, $p<.001$ and old: $F(4,17) = 5.482$, $p<.01$) and then conducted post-hoc pairwise comparisons (Bonferroni adjusted) between adjacent SOA levels for each group at Cz and Pz (see Table 2a). At Cz, we found that there was a significant difference between

N1 peak amplitude at the 500 ms and 1 s, and 1 s and 3 s SOAs for both groups. However, there was a significant difference between N1 amplitude at the 3 s and 6 s SOA for the young group only. The difference between N1 amplitude at the 6 s and 9 s SOA was not significant for either group. This provides evidence that N1 amplitude reached an asymptotic level at a shorter SOA in the older adults (3 s) compared to the young (6 s).

At Pz, the young adults showed a significant difference in N1 amplitude between the 500 ms and 1 s SOA and the 3 s and 6 s SOA, but not the 1 s and 3 s or 6 s and 9 s SOAs. However, the older adults did not show a significant difference in N1 amplitude between SOA levels for any of the four comparisons performed (Table 2a). This suggested that the older adults had a blunted response to the lengthening of the SOA compared to the young adults. Since these findings could account for previous reports of reduced N1 amplitude in older versus young adults at long SOAs, we additionally performed post-hoc independent samples t-tests at each SOA for electrode Cz and Pz. We found that older adults produced significantly smaller N1 amplitude at Pz at the 6 s SOA compared to young adults ($t(43) = -2.687$, $p = .01$).

Although we did not find evidence of increased N1 activity in older relative to young adults at the shorter SOAs, visual inspection of Figure 2a revealed that Fz and Cz became more differentiated from Pz at a shorter SOA in the older group (1 s) than in the young (3 s). This was evidenced by an electrode x group interaction at the 1 s SOA ($F(2,42) = 3.441$, $p<.05$) that did not occur at the other four SOAs. This finding suggests that N1 activity became more anterior at a shorter SOA in the older group relative to the young group.

Table 2

Bonferroni adjusted pairwise comparisons between adjacent SOA levels in each group for a) N1 amplitude at Cz and Pz and b) P2 amplitude at Fz and Cz.

a) N1 Comparisons	Young Cz	Older	Young Pz	Older
500 ms – 1 s	p<.001*	p<.001*	p = .004*	p = .244
1 s – 3 s	p<.001*	p<.001*	p = .564	p = .525
3 s – 6 s	p<.001*	p = .333	p = .001*	p = 1
6 s – 9 s	p = 1	p = 1	p = 1	p = .549
b) P2 Comparisons	Fz		Cz	
500 ms – 1 s	p = .002*	p = .087	p<.001*	p = .235
1 s – 3 s	p<.001*	p = .003*	p<.001*	p = .001*
3 s – 6 s	p = .031*	p = .163	p = .001*	p = .017*
6 s – 9 s	p = 1	p = 1	p = 1	p = .1

* significant difference in amplitude between SOA levels

N1 peak amplitude at the mastoids

As with the analysis conducted at midline sites, the mANOVA conducted on N1 amplitude at the mastoids showed a strong SOA effect ($F(4,38) = 53.082$, $p<.001$). However, at the mastoids, the main effect of SOA suggested that an increase in N1 amplitude occurred between the 500 ms and 3 s SOA, with little further increase in amplitude between the 3 s and 9 s SOAs (see Figure 1). The mastoid x group interaction ($F(1,41) = 6.450$, $p<.05$) showed that while amplitude at the right mastoid was larger than the left in young adults (simple main effect of mastoid: $F(1,22) = 10.81$, $p<.01$), amplitude at both mastoids was similar in the older group ($p =.601$).

N1 peak latency

There were no group differences in N1 peak latency. For N1 peak latency at Fz, Cz, and Pz, there was a main effect of SOA ($F(4,40) = 10.686$, $p<.001$). N1 latency increased with increasing SOA at these sites. Similarly, there was a main effect of SOA at the mastoids ($F(4,38) = 2.874$, $p<.05$) with an increase in latency visible between the 500 ms and 3 s SOAs but little further increase in latency between the 3 s and 9 s SOA conditions. These effects can be seen in Table 3.

Table 3

Latency of the N1 peak (ms ± standard error) by SOA, group, and electrode.

SOA	Group	Electrode			Mastoid	
		Fz	Cz	Pz	Left	Right
500 ms	Young	105 ± 4	99 ± 3	96 ± 5	106 ± 5	104 ± 5
	Older	103 ± 4	102 ± 4	106 ± 5	108 ± 5	98 ± 5
1 s	Young	104 ± 3	99 ± 3	101 ± 5	105 ± 3	105 ± 3
	Older	105 ± 3	103 ± 3	95 ± 5	108 ± 4	100 ± 4
3 s	Young	107 ± 2	106 ± 2	105 ± 4	108 ± 3	109 ± 3
	Older	109 ± 2	106 ± 2	111 ± 5	109 ± 3	107 ± 3
6 s	Young	114 ± 3	111 ± 3	114 ± 5	105 ± 3	107 ± 2
	Older	112 ± 3	112 ± 3	111 ± 5	107 ± 3	108 ± 3
9 s	Young	116 ± 3	113 ± 3	112 ± 4	105 ± 3	107 ± 2
	Older	115 ± 3	114 ± 3	114 ± 4	115 ± 3	108 ± 3

Ta and Tb mean amplitude[13]

We found a main effect of SOA at T7 and T8 when analysing Ta amplitude ($F(4,36) = 3.824$, $p<.05$). In general, mean amplitude was similar between the 500 ms and 3 s SOA conditions and then became increasingly more negative between the 3 s and 9 s SOA

[13] Note that a negative deflection in the ERP, known as N1a, preceded Ta and Tb in the 80 – 100 ms latency range. Analysis of N1a is not reported here as the results were similar to Ta.

conditions (see Figure 1). There was also a significant effect of electrode ($F(1,39) = 9.780$, $p<.01$) and an SOA x electrode interaction ($F(1,36) = 3.936$, $p<.01$). Mean amplitude of Ta was larger (more positive) at T7 than at T8, however this effect was more apparent at the long versus the shorter SOAs. There was a marginally significant effect of group ($F(1,39) = 3.443$, $p = .071$) and a group x electrode interaction ($F(1,39) = 4.836$, $p<.05$). In general, the young adults had larger Ta amplitude than the older adults, however when we analysed effects at each electrode separately, this group effect was significant at T8 ($F(1,40) = 7.678$, $p<.01$) but not T7 ($p = .699$). The factor SOA did not differentiate groups in the Ta data.

Similar to Ta data, Tb amplitude showed a significant SOA effect with larger (negative) amplitude produced at the long relative to the shorter SOAs ($F(4,36) = 7.158$, $p<.001$). As there was a group x electrode interaction ($F(1,39) = 6.119$, $p<.05$), we conducted a one-way mANOVA on T7 and T8 data separately. At T7 there was a marginally significant main effect of group ($F(1,42) = 3.787$, $p =.058$) indicating larger amplitude in the young than the old. The main effect of group at T8 was not significant ($p =.661$). The factor SOA did not differentiate groups in the Tb data.

P2 peak amplitude

The pattern of increasing amplitude with increasing SOA observed in N1 data was also noted for P2 peak amplitude ($F(4,40) = 88.499$, $p<.001$). In general, amplitude was largest at Cz followed by Fz then Pz, evidenced by the main effect of electrode ($F(2,42) = 79.43$, $p<.001$). There was also a main effect of group ($F(1,43) = 97.023$, $p<.05$) showing that P2 amplitude was larger in young than older adults overall. The SOA x group ($F(4,40) = 2.636$, $p<.05$) and SOA x electrode ($F(8,36) = 16.32$, $p<.001$) interaction were moderated by an SOA x electrode x group interaction ($F(8,36) = 2.293$, $p<.05$). As this interaction

remained after normalization ($F(8,36) = 2.541$, $p<.05$), we analysed effects at each electrode separately. There was a main effect of group ($F(1,43) = 6.764$, $p<.05$) at Pz, indicating that the older group generally had smaller P2 peak amplitude than the young group at this electrode. We found a significant group x SOA interaction at Cz ($F(4,40) = 2.832$, $p<.05$) and a trend towards this at Fz ($F(4,40) = 2.374$, $p=.068$) but not at Pz ($p = .306$). This suggested that the temporal profile of P2 differed between groups at Fz and Cz.

To explore the differences in the temporal profile of P2 between groups, we established that both groups showed a significant main effect of SOA at Fz (young: $F(2,20) = 42.619$, $p<.001$ and old: $F(4,17) = 22.964$, $p<.001$) and Cz (young: $F(4,20) = 38.576$, $p<.001$ and old: $F(4,17) = 42.134$, $p<.001$) and then conducted post-hoc pairwise comparisons (Bonferroni adjusted) between adjacent SOA levels for each group at Fz and Cz (see Table 2b). At Fz and Cz, we found that while there was a significant difference between P2 peak amplitude at the 500 ms and 1 s SOAs for the young group, this difference was not significant for the older group (although marginally significant at Fz). An age-related difference in the scalp topography of P2 activity could explain this result. Visual inspection of Figure 2b revealed that P2 amplitude was more anterior (larger at Fz and Cz relative to Pz) at the shortest SOA in the older group relative to the young. In support of this there was a significant electrode x group interaction at the 500 ms SOA ($F(2,42) = 4.082$, $p<.05$) but not at the other four SOAs.

At Fz, we also found that there was a significant increase in P2 peak amplitude between 3 s and 6 s SOAs for the young group but not the older group (although at Cz there was a significant increase in both groups). At Fz and Cz, the difference in P2 amplitude between the 6 s and 9 s SOA was not significant for either the young or older group. Therefore, we found evidence that P2 amplitude reached an asymptotic level at a shorter

SOA in the older adults (3 s) compared to the young (6 s) at Fz. Exploring these findings further, post-hoc independent samples t-tests conducted at each SOA for electrode Fz and Cz revealed that older adults produced significantly smaller P2 amplitude at Fz and Cz at the 9 s SOA compared to young adults (Fz: $t(43) = 2.095$, $p = .042$; Cz: $t(43) = 2.484$, $p = .017$).

P2 peak amplitude at the mastoids

At the mastoids, we found a main effect of SOA over the P2 period ($F(4,38) = 5.355$, $p<.01$). Pairwise comparisons (Bonferroni adjusted) on the factor SOA revealed that P2 amplitude increased significantly (in the negative direction) between the 500 ms and 1 s SOA condition ($p = .001$) but no significant differences were found between the 1 s and 3 s ($p = 1$), 3 s and 6 s ($p = 1$), or 6 s and 9 s SOA conditions ($p = 1$). We also observed a significant effect of mastoid ($F(1,41) = 9.966$, $p<.01$), and an SOA x mastoid interaction ($F(4,38) = 3.689$, $p<.05$). Overall, amplitude was larger at the left versus the right mastoid but this effect was primarily observable at the longer SOAs. We did not observe a group effect or an interaction between SOA and group at the mastoids over the P2 period.

P2 latency

Figure 3 depicts latency of P2 peak amplitude for the young and older group at Fz, Cz, and Pz. There was a significant main effect of group ($F(1,43) = 7.610$, $p<.01$) indicating P2 peak amplitude was delayed in the older group (211.04 ms $\pm$ 4.72) versus the young group (193.2 ms $\pm$ 4.42). As seen in Figure 3, P2 latency lengthened ($F(4,40) = 28.258$, $p<.001$) with increasing SOA. Pairwise comparisons (Bonferroni adjusted) for the factor SOA revealed that P2 latency increased significantly between the 500 ms and 1 s

(p<.001), 1 s and 3 s (p<.001), and 3 s and 6 s (p = .002) SOAs, but not between the 6 s and 9 s SOA (p = 1). P2 peak latency was similar at Fz and Cz but occurred later at Pz evidenced by the main effect of electrode (F(2,42) = 9.955, p<.001). There was also an SOA x electrode interaction (F(8,36) = 2.856, p<.05). The difference in latency between the fronto-central sites (Fz and Cz) and Pz was reduced at long relative to the shorter SOAs. There were no interactions with group.

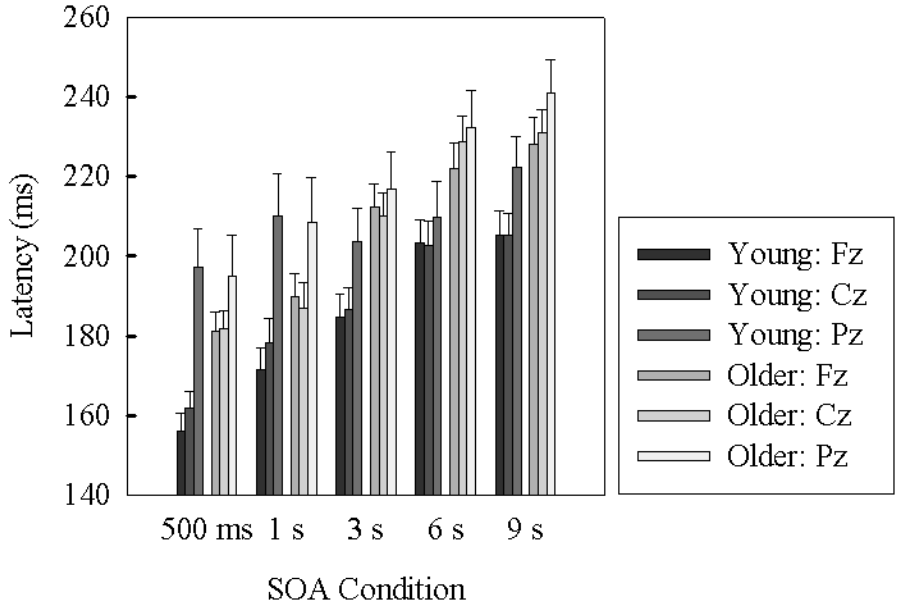

Figure 3. P2 peak latencies for the young and older group (from left to right per electrode and SOA condition). Error bars denote standard error of the mean.

At the mastoids, there was a main effect of SOA for the latency of the P2 peak (F(4,38) = 8.016, p<.001). However, unlike the pattern observed at midline sites, at the mastoids, pairwise comparisons (Bonferroni adjusted) for the factor SOA revealed that P2 latency increased significantly between the 500 ms and 1 s (p = .03), and 1 s and 3 s (p =

.035) SOAs, but not between the 3 s and 6 s (p = 1) or 6 s and 9 s SOAs (p = 1). The group effect was similar to that seen at midline sites; P2 latency at the mastoids was significantly delayed in the older group (195.0 ms $\pm$ 3.51) relative to the young group (167.36 ms $\pm$ 3.27; $F(1,41) = 33.267$, $p<.001$).

Correlations between hearing thresholds and N1 and P2 amplitude

In order to ascertain whether a relationship exists between hearing thresholds and N1 and P2 amplitude, we performed Pearson's correlations between hearing thresholds (at 0.5, 1, 2, 4, and 8 kHz) and N1 and P2 amplitude for the five SOA conditions. This was done within groups at Fz, Cz, Pz, and the left and right mastoid. Due to the large number of comparisons (125), we adjusted alpha to 0.001. None of the correlations were significant at this level except for one correlation in older adults. For older adults, there was a positive correlation between thresholds for the 2 kHz tone and P2 amplitude in the six second SOA condition ($r = .671$, $p = .001$). In this instance, larger P2 amplitudes were related to higher hearing thresholds.

Discussion

In the present study, age affected the relationship between amplitude and stimulus delivery rate for both the N1 and P2 waveforms of the auditory ERP. Specifically, the group x SOA interaction found at Cz and Pz for N1 amplitude, and at Fz (marginal) and Cz for P2 amplitude indicated that the temporal profile of N1 and P2 is affected by age at these sites. Although the majority of older adults in this study showed elevated auditory thresholds to high frequency sounds (a sign of presbycusis), it is unlikely that this factor contributed to our findings for two reasons. Firstly, auditory thresholds did not differ

between groups for the sound frequency (800 Hz) used in the study. Secondly, we did not find a consistent relationship between N1 or P2 amplitude and auditory thresholds in either group. Therefore, we attempt to explain our findings with reference to the literature proposing that multiple generators contribute to N1 and P2 activity recorded at the scalp.

As outlined in the introduction, Näätänen and Picton, (1987) proposed that there are at least three N1 generators and Budd et al. (1998) showed that N1 component 1 recovers over a 3 s period while N1 component 3 recovers over a 10 s period. By comparing N1 amplitude and latency data from mastoid and midline sites in the present study, we reach agreement with Budd et al.'s findings. Our mastoid data primarily increased between the 1 and 3 second SOA, while the midline data continued to increase up until the 6 or 9 second SOA. This highlights that N1 component 1 was primarily observed at the mastoids and that N1 component 3 contributes to N1 amplitude at midlines sites.

Age and SOA did not interact for N1 amplitude recorded at the mastoids. Our findings imply that the temporal profile of N1 component 1 does not differ with age. As mentioned in the introduction, it is possible that methodological differences between studies could account for the variability in previous results. For instance, we have found a trend in the direction of larger N1 amplitude in older versus young adults in another study in our laboratory where a mismatch negativity oddball paradigm was used (Cooper et al., 2006). Overall, the results of the current study do not suggest that N1 component 1 is greatly affected by age.

To examine age effects on N1 component 2, we assessed Ta and Tb amplitude at midtemporal electrodes, T7 and T8. Since Ta and Tb amplitude increased in the negative direction as SOA lengthened while N1 amplitude at the mastoids increased in the positive direction, the effect of SOA on N1 component 2 was in the opposite direction to that

described for N1 component 1. In agreement with our N1 component 1 data, no group x SOA interaction was found for Ta or Tb amplitude. However, we did observe some evidence of an age-related difference in N1 component 2. Young adults produced larger (more positive) Ta amplitude at T8 and larger (more negative) Tb amplitude at T7 (marginally significant) compared to older adults. As the only age-related difference reported for N1 component 1 was in the direction of older adults producing larger N1 component 1 amplitude than young adults, these findings relating to N1 component 2 are in the opposite direction to those of N1 component 1. Although Näätänen and Picton (1987) suggested that N1 components 1 and 2 could be indicative of similar processes, we found that our age and SOA effects for N1 component 1 and 2 differed. Therefore, while we cannot speculate on the meaning of the age-related findings with respect to N1 component 2 due to the lack of research into the functional relevance of this component, we can at least conclude that N1 components 1 and 2 are differentially affected by age.

To assess the effect of age upon N1 component 3, we concentrated upon data recorded from Cz and Pz. The main effect of SOA at Cz and Pz suggested that N1 amplitude increased as SOA lengthened, as previously reported (Hari et al., 1982). Furthermore, we observed a group x SOA interaction at Cz and Pz which (along with pairwise comparisons) suggested that N1 amplitude reached an asymptotic level at a shorter SOA in older (3 s) compared to young adults (6 s) at Cz and that older adults were less sensitive to SOA change than young adults at Pz. These findings could explain why others have reported reduced N1 amplitude in older versus young adults (Cooper et al., 2006; Kisley et al., 2005; Papanicolaou et al., 1984). However, our post-hoc independent t-tests revealed only one significant group difference; older adults produced smaller N1 amplitude than young adults at the 6 s SOA at Pz. From a functional perspective, while we could

interpret these data as evidence of a reduced arousal response in older adults, the evidence is not conclusive. More conclusive evidence of age-related differences in amplitude at the longer SOAs was forthcoming in the P2 data.

Although the P2 waveform has not been as widely studied as N1, our results suggest that there are at least two components contributing to P2 activity recorded at the scalp (e.g. Crowley & Colrain, 2004; Hari et al., 1982; Näätänen, 1992), one component dominant at shorter SOAs (see mastoid data) and one non-specific component dominant at longer SOAs (see midline data). We will refer to these P2 components as component 1 and 2, respectively. At the mastoids, P2 amplitude and latency increased primarily across the shorter SOAs, similar to N1 component 1. We did not observe a group effect or an interaction between SOA and group at the mastoids over the P2 period. Therefore, similar to N1 component 1, we can conclude that P2 component 1 was not greatly affected by age.

At midline sites, similar to our N1 data, we observed a significant main effect of SOA in P2 amplitude and latency data indicating that P2 amplitude increased and latency lengthened as SOA lengthened. Overall, P2 amplitude was smaller in older relative to young adults at midline sites. Since we observed a group x SOA interaction at Fz (marginal) and Cz, we found evidence that P2 amplitude reached an asymptotic level at a shorter SOA in the older versus the young group (as for N1). Therefore, while P2 component 1 shows little change with age, P2 component 2 does change with age. We interpret these results in much the same way as those for N1, that is, older adults may have an impaired arousal response to infrequently presented stimuli (e.g. see review Woodruff, 1985).

P2 peak amplitude occurred significantly later in older versus young adults at midline sites and at the mastoids, which is interesting considering that this latency

difference was not evident for N1 peak amplitude. The prolonged latency of P2 in older adults is in agreement with a prominent theory of cognitive aging which suggests that age-related cognitive impairment is a result of reduced processing speed (Salthouse, 1996). The age-related difference in latency of P2 but not latency of N1 highlights the independence of these waveforms and potentially shows that the processes contributing to these waveforms differ.

A finding that links N1 and P2 data is the shift in scalp topography of these waveforms that occurred as a function of age. For both N1 and P2, there was an anterior shift in amplitude at an earlier SOA in older compared to young adults. Although speculative, it is possible that this shift in N1 scalp topography with age represents greater activation of the proposed frontal N1 generator in the older adults. As the postulated frontal N1 generator has been related to an inhibitory influence over N1 (Knight et al., 1980; Sable et al., 2004), it may be that it is this inhibitory mechanism that is altered with age. The fact that we saw a similar pattern in the P2 data (also see Anderer, Pascual-Marqui, Semlitsch, & Saletu, 1998) suggests that a similar frontal influence could mediate P2 as well as N1 amplitude changes with age. Though there is little evidence to support this hypothesis, there is a literature suggesting that functions mediated by the frontal cortex are altered with age (i.e. the frontal hypothesis of aging; Moscovitch & Wincour, 1992; West, 1996; West, 2000).

In sum, we have been able to resolve the question of whether the timing of sound presentation influences the effect of age on N1 and P2 amplitude. We found evidence that the group x SOA interaction found for N1 and P2 waveforms of the auditory ERP can be attributable to independent age effects on N1 and P2 components operating at short SOAs versus components that dominate at longer SOAs. For example, we found little evidence of

change in N1 or P2 component 1. We did find evidence of age-related change in N1 component 2, N1 component 3, and P2 component 2. In addition, it is possible that a frontal component contributing to N1 and P2 alters with age. As our literature review in the introduction revealed that age effects on N1 and P2 amplitude have previously been observed (and these findings have often been reported in studies using a mismatch negativity oddball paradigm), the degree to which these age effects could be accounted for by another auditory ERP waveform, repetition positivity, that overlaps the latency period of N1 and P2 in oddball paradigms, remains unanswered (see Baldeweg, 2007; Baldeweg et al., 2004; Cooper et al., to be submitted a,b,c; Haenschel et al., 2005). Nonetheless, considering our results with respect to the effect of age on underlying components contributing to N1 and P2, we cannot rule out the possibility that the encoding of auditory information changes with age. However, since we did not observe evidence of age-related change in N1 component 1, we suggest that if age does affect the ability to encode sound properties into auditory sensory memory, N1 component 1 does not contribute to this outcome. Future research to determine the functional role of these underlying components with more precision is warranted.

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Chapter 3: study 2

The event-related potential reveals modeling of auditory repetition in the brain[14]

[14] This paper is to be submitted to the International Journal of Psychophysiology with authors Cooper, R.J., Atkinson, R.J., Clark, R.A., and Michie, P.T.

The event-related potential reveals modeling of auditory repetition in the brain

Auditory sensory memory describes a stage of auditory processing where sound features are encoded by the brain and integrated into a unitary representation which is briefly maintained (Cowan, 1984). Recently, Winkler (2007) has proposed that, in addition to sound features, the context in which sound occurs is encoded into auditory sensory memory traces. The effect of repetition of auditory stimuli on auditory sensory memory is of interest as it can inform us about how the brain encodes context into memory traces thereby modeling the auditory environment. The biological relevance of this modeling process stems from the fact that it could underpin our ability to ignore repetitive irrelevant auditory stimuli and quickly direct attention toward novel or relevant stimuli (e.g. Winkler, Karmos, & Näätänen, 1996). Two waveforms of the auditory event-related potential (ERP) responsive to repetition of auditory stimuli, mismatch negativity (MMN) and repetition positivity (RP), have been linked to aspects of this modeling process (Baldeweg, 2007).

MMN was first reported in 1978 (Näätänen, Gaillard, & Mäntysalo) and has generated a large body of literature detailing its association with auditory sensory memory (see reviews in Näätänen, 2007; Schröger, 2007; Winkler, 2007). In contrast, the 'MMN memory trace effect' is a relatively recently developed term that describes the increase in MMN amplitude that occurs as a function of auditory stimulus repetition (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004). In conjunction with developing this description of the MMN memory trace effect, Baldeweg et al. (2004) were the first researchers to identify RP, a waveform that also increases in amplitude as a function of auditory stimulus repetition. It has been claimed that RP and the MMN memory trace effect are related to auditory sensory memory trace formation (Baldeweg et al., 2004; Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005). However, as RP and the MMN memory trace

effect have only recently been described, the functional correlate of these two phenomena has been primarily inferred from the circumstance under which they are observed (i.e. a roving standard oddball paradigm; see detailed description below). In fact, to our knowledge, there is no published evidence exploring whether RP and the MMN memory trace effect are observed in any circumstance other than this[15]. Therefore the purpose of the present study was to investigate this issue in order to provide evidence to support or refute the claimed association between the repetition effects observed in the auditory ERP and auditory sensory memory trace formation.

Published studies recording RP and the MMN memory trace effect (Baldeweg et al., 2004; Baldeweg, Wong, & Stephan, 2006; Haenschel et al., 2005) have used an oddball paradigm with a roving standard. In general, the auditory oddball paradigm consists of a frequent, repeating, 'standard' tone that is infrequently replaced by a 'deviant' tone that differs from the standard in some respect (e.g. pitch, duration, intensity). However, in the roving standard oddball paradigm, the standard tone changes in pitch after the presentation of each deviant. The key difference between the roving standard paradigm and the traditional oddball paradigm (where a constant standard is used throughout) is that the memory trace of the standard tone must be established and strengthened over the course of each train only in the roving standard paradigm.

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[15] Prior to RP or the MMN memory trace being described, Cowan, Winkler, Teder, and Näätänen (1993) examined MMN amplitude as a function of auditory stimulus repetition in a roving standard oddball paradigm as well as a constant standard oddball paradigm. However, these researchers used long silent intervals between stimulus trains (11-15 s). Thus, although their data revealed the MMN memory trace effect, this result could have been influenced by the refractory properties of neuronal populations underpinning the N1 waveform. N1 recovers to full amplitude in approximately 10 s (see Davis, Mast, Yoshie, & Zerlin, 1966; Hari, Kaila, Katila, Tuomisto, & Varpula, 1982) and occurs within a similar latency range to RP and MMN.

In a roving paradigm, it has been found that the ERP to standards that occur late in a train is more positive in amplitude over the latency period approximately 100 – 200 ms post stimulus onset compared to the ERP to standards that occur early in a train (Baldeweg et al., 2004; Haenschel et al., 2005). When the ERP to standards occurring early in a train is subtracted from the ERP to standards occurring late in a train, the resultant positive amplitude waveform over this latency period (at frontal sites) has been labeled repetition positivity (RP; Baldeweg et al., 2004). It is the fact that RP grows in amplitude with increased repetition of auditory stimuli in a roving standard context (where the memory trace of the standard tone must be constantly updated) that has implicated RP in a process related to the establishment and strengthening of auditory sensory memory traces (Baldeweg et al., 2004; Haenschel et al.). If RP is a direct measure of the strength of the memory representation of the standard tone, MMN can be thought of as an indirect measure of this aspect of memory (Haenschel et al.).

The MMN is a negative amplitude waveform derived by subtracting the ERP for standard tones from the ERP for deviant tones. If this subtraction is performed for standards and deviants in different repetition conditions, it has been shown that MMN increases in amplitude as the number of repetitions of the standard tone increases (Baldeweg et al., 2004; Haenschel et al., 2005). As stated, this response to repetition defines the MMN memory trace effect. Therefore, both the response to repetition in the standard (i.e. RP) and deviant ERP could contribute to the MMN memory trace effect. Baldeweg et al. (2004) observed that negativity in the deviant waveform increased significantly with increasing repetition of the standard tone in a roving standard paradigm, while Haenschel et al. did not. That is, in Haenschel et al.'s study the primary contributor to the MMN memory trace effect was RP. It is in light of this fact that Haenschel et al. claim

that RP offers more direct insight into auditory sensory memory trace formation than MMN. A similar view on the relationship between RP and MMN will be outlined in the following discussion of the neural and theoretical bases of these waveforms.

As we alluded to in the introduction to this paper, both MMN and RP are associated with processes underpinning our ability to model the auditory environment. More specifically, MMN and RP have been linked to predictive coding models of stimulus processing (e.g. Baldeweg, 2007; Friston, 2005; Garrido et al., 2008). The predictive coding framework states that bottom-up sensory information travels upstream to aid in the formation of predictions about future stimulation and that top-down inferential information travels downstream to suppress predicted activity in lower levels. Whereas RP is thought to be more closely aligned to the process determining suppression of predicted activity, MMN is thought to represent the error signal which is propagated upstream when predictions do not match current stimulus input (Baldeweg, 2007). Baldeweg (2007) describes 'memory' as a property of these dynamic connections between higher and lower sensory levels. Indeed, there is evidence stemming from the cat auditory cortex of plasticity in the neural response to repeating sound (Ulanovsky, Las, & Nelken, 2003; Ulanovsky, Las, Farkas, & Nelken, 2004). Stimulus specific adaptation (SSA) describes the reduction in firing rate recorded in individual neurons in the cat primary auditory cortex when the same sound is presented frequently as opposed to rarely (also referred to as repetition suppression). As such, SSA has been referred to as a candidate mechanism for the establishment of auditory sensory memory traces (Baldeweg, 2007; Nelken & Ulanovsky, 2007; Ulanovsky et al., 2003; Ulanovsky et al., 2004). Both RP (Baldeweg et al., 2004; Haenschel et al., 2005) and MMN (Nelken & Ulanovsky, 2007; Ulanovsky et al., 2003; Ulanovsky et al., 2004) have been linked to SSA. As RP and SSA emerge over the period in which sound is repeated,

whereas MMN represents the differential response between novel and repeated sound, it is likely that RP and SSA contribute to the change in MMN amplitude which occurs as a function of repetition (i.e. the MMN memory trace effect).

We have stated that the notion that RP and the MMN memory trace effect are related to the establishment of auditory sensory memory traces has been inferred from the circumstance in which these repetition effects have been observed, that is, the roving standard oddball paradigm. The fact that the memory trace of the standard tone requires constant updating in the roving standard paradigm has been used as evidence that RP and the MMN memory trace effect represent memory updating processes such as the establishment and strengthening of auditory sensory memory traces. Given this viewpoint, we would not expect to observe RP or the MMN memory trace effect in a circumstance such as the traditional constant standard oddball paradigm as the memory trace of the standard tone does not require constant updating in this condition. However, given the theoretical perspective of the predictive coding framework outlined above, where auditory information is proposed to be automatically incorporated into a model of the auditory environment, it is unlikely that the process of modeling the auditory environment is entirely absent even under constant standard conditions. From this perspective, if the predictive coding model is the process that underpins RP generation and the MMN memory trace effect, then there may well be evidence of the modeling of repetition in the auditory ERP in a constant standard oddball paradigm. Therefore, in the present study, we contrasted the effect of repetition of the standard tone on the standard ERP in a roving standard and constant standard oddball paradigm to determine to what extent the repetition effects previously observed under roving standard conditions could be observed under traditional constant standard oddball conditions. In doing so, the primary aim was to enhance our

understanding of the functional correlate of repetition effects in the auditory ERP, particularly the proposed association between such repetition effects and the formation of sensory memory traces. To achieve this, we aimed to assess our findings in relation to the predictive coding framework and Baldeweg and colleagues' memory-based explanation of the repetition effects. If we were unable to explain our results within these parameters, it would necessitate a review of the functional correlate of the repetition effects under study.

Method

Participants

Ethics approval for the study was obtained from the University of Newcastle Human Research Ethics Committee. Twenty–four young adults (mean age 22.4 $\pm$ 5 years; 7 males) volunteered for the study. All were students at the University of Newcastle and all gave their written informed consent to participate. Participants were screened for neurological conditions, serious head injury, and hearing impairments. All participants reported having normal hearing.

Stimuli and procedure

Sounds were generated by Presentation ® software (Version 10, www.neuro-bs.com) and delivered over headphones. Before testing began, stimuli were calibrated to dB SPL using a Brüel and Kjaer sound level meter. Intensity was set at 80 dB SPL and tones were presented binaurally. The stimulus onset asynchrony (SOA) was 500 ms.

Two passive MMN oddball paradigms, one with a constant standard and one with a roving standard, were delivered to each participant. The order of presentation of the

constant standard and roving standard conditions was counterbalanced across participants. The number of standards presented in a train preceding a deviant was manipulated within subjects resulting in three repetition conditions: 4, 8, or 16 standards were delivered before a deviant was presented. The delivery of repetition conditions occurred pseudorandomly. In the constant standard condition, the standard tone was 1000 Hz (50 ms, 5 ms rise/fall) throughout. Trains of standard tones were followed by a 1000 Hz, 100 ms duration deviant (5 ms rise/fall). In the roving standard paradigm, standards changed in pitch from train to train (i.e. standards tones were identical within trains but differed in pitch between trains). Standards pseudorandomly cycled through 11 different frequencies across trains (700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, and 1200 Hz). The duration deviant (100 ms, 5 ms rise/fall) was presented at the same frequency as the preceding train of standards.

The constant and roving conditions took approximately 31 minutes each (broken into two 15.5 minute blocks). Short breaks were provided between blocks. As auditory stimuli were delivered, participants watched a silent video with subtitles. Participants were instructed to pay attention to the video and ignore the sounds coming through the headphones. The total number of tones presented in constant or roving conditions was 3720, including 3360 standards, 360 deviants. The entire appointment lasted approximately 2 hours.

EEG Recording

The EEG was recorded from 4 scalp channels (F3, F4, Fz, and Cz) and from both mastoids using an electrode cap (Electro-Cap International). Sites were located according to the 10/20 system and referenced to the nose. The vertical electro-oculogram (EOG) was recorded by electrodes above and below the left eye and the horizontal EOG by electrodes

at the outer canthi of each eye. Continuous EEG was digitized at 500 Hz with a gain of 75000. A bandpass filter 0.15 – 30 Hz and 50 Hz notch filter were applied. Scan 4.2 software was used to acquire data and Scan 4.3 for off-line analysis.

Data Analysis

Data were processed offline and movement artefacts were manually removed. Eyeblink artefact correction was utilised (Semlitsch, Anderer, Schuster, & Presslich, 1986). A 100 ms prestimulus baseline and 450 ms post stimulus period was used to epoch EEG data and epochs containing artefacts exceeding ± 100 μV were rejected.

Latency windows covering waveforms of interest are presented in Table 1 and were chosen by selecting a window surrounding peak amplitude in the grand average waveforms. We extracted mean amplitude for P1, N1, and P2 waveforms in the standard ERP. RP was calculated by separately subtracting the standard ERP for the 4 and 8 repetitions conditions from the standard ERP for the 16 repetitions condition. MMN difference waves were calculated by subtracting standard waveforms from corresponding deviant waveforms for repetition condition. For deviant and MMN waveforms, we extracted mean amplitude.

Table 1

Latency windows used to derive mean amplitude

ERP waveform	Latency window (ms)
Standard: P1	30 – 80
Standard: N1	85 – 135
Standard: P2	140 – 190
RP	100 – 200
Deviant	165 – 215
MMN	165 – 215

At Fz and the mastoids, we analysed mean amplitude derived from the latency windows shown in Table 1. These sites were chosen as MMN amplitude reverses in polarity at the mastoids relative to Fz, possibly reflecting activity from different MMN generators (see review in Deouell, 2007). Although Haenschel et al. did not find a repetition effect on the ERP for standards at the mastoids, data from our laboratory has shown a reversal in polarity of RP at the mastoids relative to Fz (Cooper, Todd, & Michie, to be submitted a). We analysed data at Fz using a 2 x 3 repeated measures mANOVA (Pillai's trace) with within subjects factors of presentation condition and repetition. For mANOVAs conducted on mastoid data, an additional within subjects factor, mastoid, with two levels was required.

Results

The ERP to standards

We analysed P1, N1, and P2 waveforms in the ERP to standards that occurred at the end of standard trains in the constant standard and roving standard conditions. Figure 1 presents the ERPs to standard tones in the three repetition conditions and two presentation conditions at Fz and the left and right mastoid. Although Figure 1 shows a trend for larger positivity in the standard ERP over the P1 period in the roving compared with the constant condition at Fz, there was no effect of condition ($p = .234$) nor repetition ($p = .719$) on P1 mean amplitude, nor was there an interaction between condition and repetition ($p = .162$).

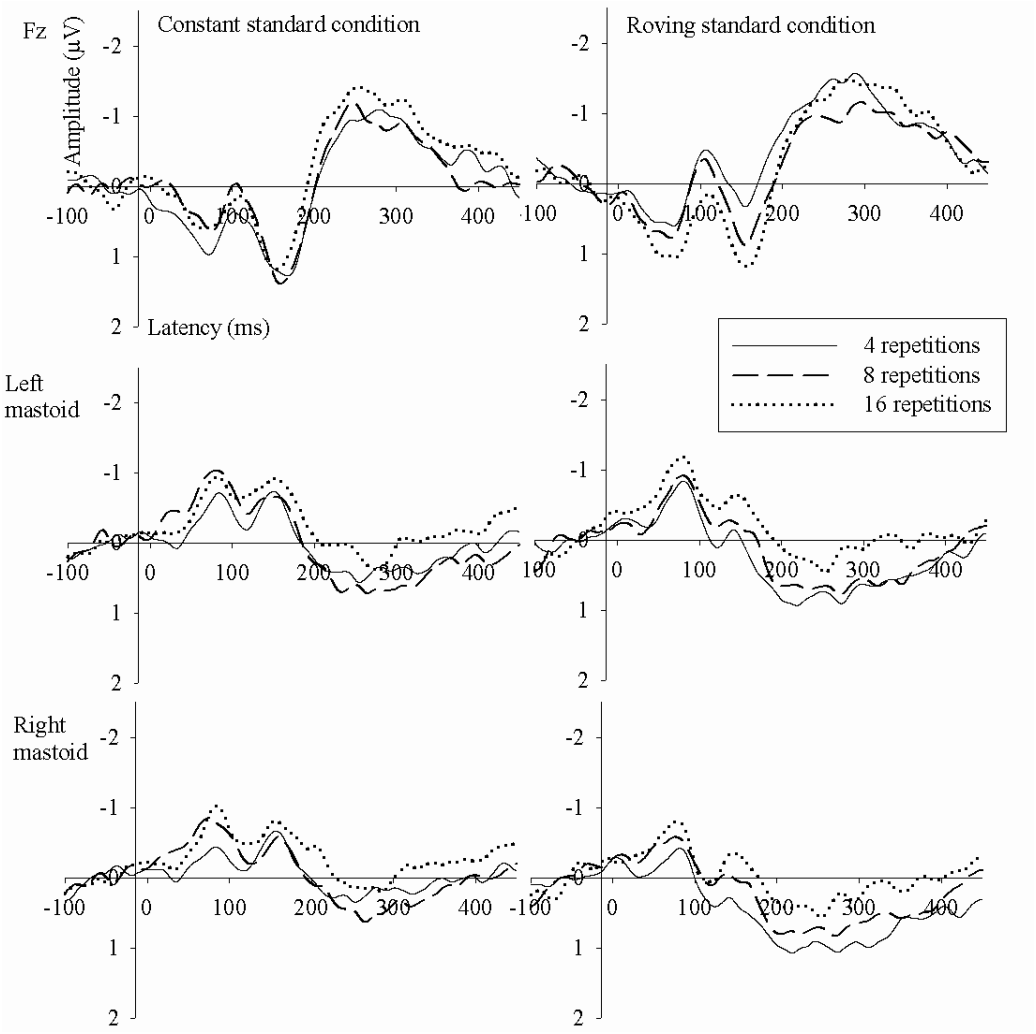

Figure 1. Grand average ERPs to standard tones in the constant (left) and roving (right) conditions at Fz (top row), the left mastoid (middle row), and right mastoid (bottom row). The three repetition conditions are overlaid.

For N1 mean amplitude at Fz, we found a main effect of condition ($F(1,23) = 4.66$, $p = .042$): N1 amplitude was smaller in the constant standard compared to the roving standard condition. There was no repetition main effect for the N1 data ($p = .228$), however, the interaction between condition and repetition approached significance ($F(2,22) = 3.00$, $p = .070$). There was a simple main effect of repetition in the roving ($F(2,22) =$

3.45, p = .05) but not constant condition (p = .489). In the roving condition, N1 amplitude decreased with increased repetition of the standard tone (i.e. in the direction of repetition positivity).

At the mastoids, over the N1 period, we observed a marginally significant main effect of condition ($F(1,23) = 3.97$, $p = .058$). As with N1 amplitude recorded at Fz, the reversal of N1 amplitude recorded at the mastoids was smaller in the constant standard than the roving standard condition. At the mastoids, there was a main effect of repetition ($F(2,22) = 3.54$, $p = .046$) but no condition x repetition interaction ($p = .997$). That is, N1 amplitude at the mastoids increased in the negative direction with increased repetition of the standard tone (i.e. reversal of polarity of repetition positivity) for both presentation conditions.

Analysis of P2 mean amplitude at Fz revealed a main effect of condition ($F(1,23) = 4.66$, $p = .042$) such that P2 amplitude was larger in the constant standard compared to the roving standard condition. There was no main effect of repetition ($p = .228$). However, there was a condition x repetition interaction ($F(2,22) = 6.13$, $p = .008$). As for N1 data at Fz, we found a significant simple main effect of repetition for the roving standard ($F(2,22) = 14.27$, $p<.001$) but not the constant standard condition ($F(2,22) = .76$, $p = .480$) for P2 mean amplitude. In the roving standard condition, P2 amplitude at Fz increased as a function of increased repetition of the standard tone.

At the mastoids, where P2 amplitude reversed polarity, there was a main effect of condition ($F(1,23) = 9.82$, $p = .005$) and a main effect of repetition ($F(2,22) = 5.02$, $p = .016$) but no condition x repetition interaction ($p = .432$). P2 amplitude at the mastoids was larger (more negative) in the constant than the roving condition and increased (in the negative direction) as a function of increased repetition of the standard tone for both

presentation conditions. For the means and standard deviations of N1 and P2 amplitude (and MMN amplitude) in the different presentation and repetition conditions, refer to Table 2.

Table 2

Means and standard deviations (in brackets) of N1, P2, and MMN amplitude (μV) in the two presentation conditions and three repetition conditions. Data from Fz, the left mastoid (LM), and right mastoid (RM) are shown.

		Constant standard repetition conditions			Roving standard repetition conditions		
Waveform	Site	4	8	16	4	8	16
N1	Fz	0.53	0.23	0.34	-0.25	-0.07	0.38
		(1.02)	(0.81)	(1.01)	(1.18)	(1.31)	(1.09)
	LM	-0.41	-0.67	-0.73	-0.23	-0.44	-0.67
		(1.40)	(1.04)	(0.88)	(0.87)	(1.07)	(0.89)
	RM	-0.23	-0.46	-0.65	0.12	-0.12	-0.19
		(1.40)	(0.90)	(0.91)	(0.85)	(0.87)	(0.99)
P2	Fz	1.09	1.10	0.86	-0.01	0.53	0.84
		(1.81)	(1.28)	(1.30)	(1.36)	(1.78)	(1.33)
	LM	-0.40	-0.44	-0.72	0.30	0.03	-0.38
		(1.15)	(1.32)	(0.90)	(1.16)	(1.13)	(1.01)
	RM	-0.44	-0.39	-0.67	0.53	0.20	-0.14
		(1.17)	(1.12)	(0.87)	(1.09)	(1.00)	(0.91)
MMN	Fz	-3.08	-3.08	-2.51	-1.63	-1.87	-2.47
		(1.83)	(2.39)	(1.61)	(1.89)	(2.36)	(2.04)
	LM	1.39	1.33	2.12	1.25	1.04	1.55
		(1.87)	(1.95)	(1.77)	(1.30)	(1.54)	(1.58)
	RM	1.73	1.60	2.56	1.02	1.01	1.52
		(2.05)	(1.76)	(1.44)	(1.49)	(1.63)	(1.44)

The repetition positivity

Figure 2 depicts repetition positivity (RP) in the constant standard and roving standard condition at Fz and the mastoids. To visualize RP, we subtracted the ERP for

standards in the shorter repetition conditions from the ERP for standards in the longest repetition condition in accordance with Haenschel et al. (2005). Figure 2 reveals that RP was significantly smaller in the constant condition relative to the roving condition at Fz ($F(1,23) = 4.75$, $p = .040$). There were no significant effects at the mastoids.

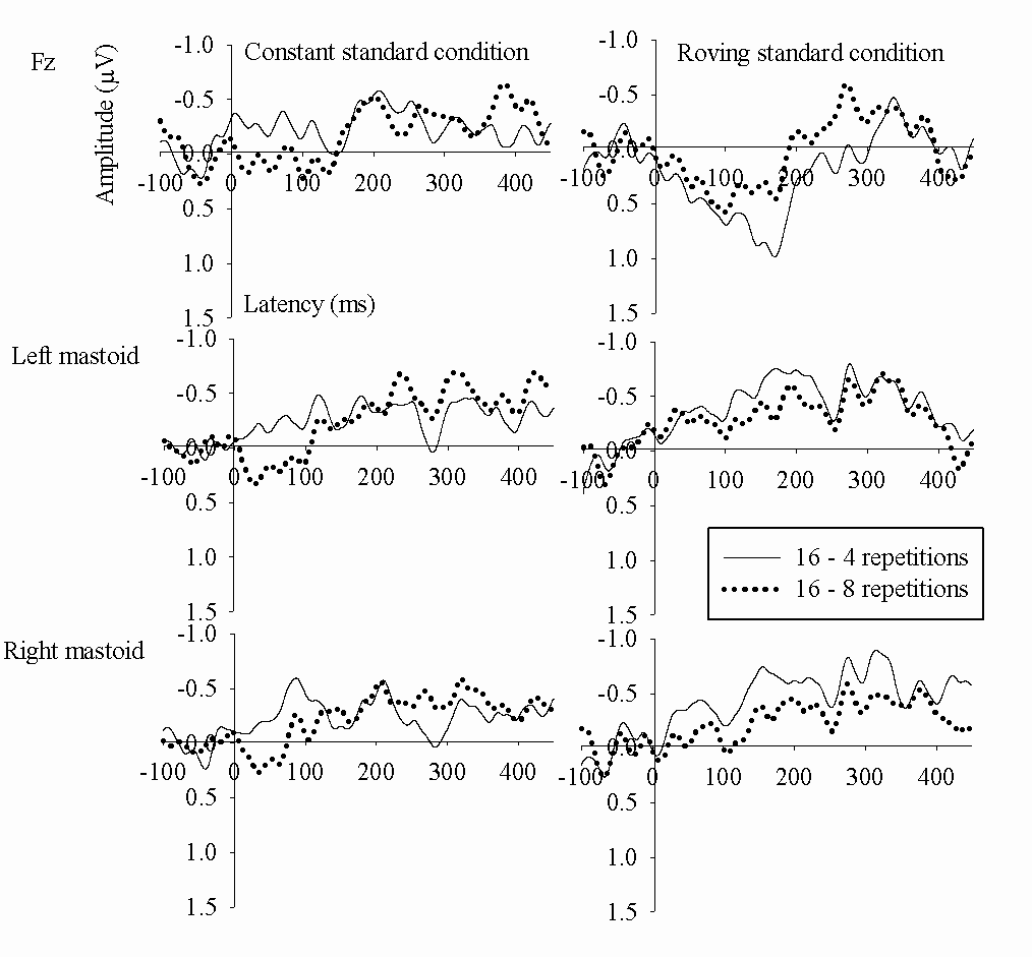

Figure 2. Repetition positivity (the ERP to standard tones in the 16 repetitions condition minus the ERP to standard tones in the shorter repetition conditions) in the two presentation conditions.

The ERP to deviants

Figure 3 depicts the ERP to deviants in the constant standard and roving standard condition. As Figure 3 suggests, there was no significant effect of condition or repetition on deviant waveforms at Fz ($p = .115$ and $p = .806$ respectively) or the mastoids ($p = .863$ and $p = .176$ respectively). There was no interaction between these factors at Fz ($p = .380$) or the mastoids ($p = .167$).

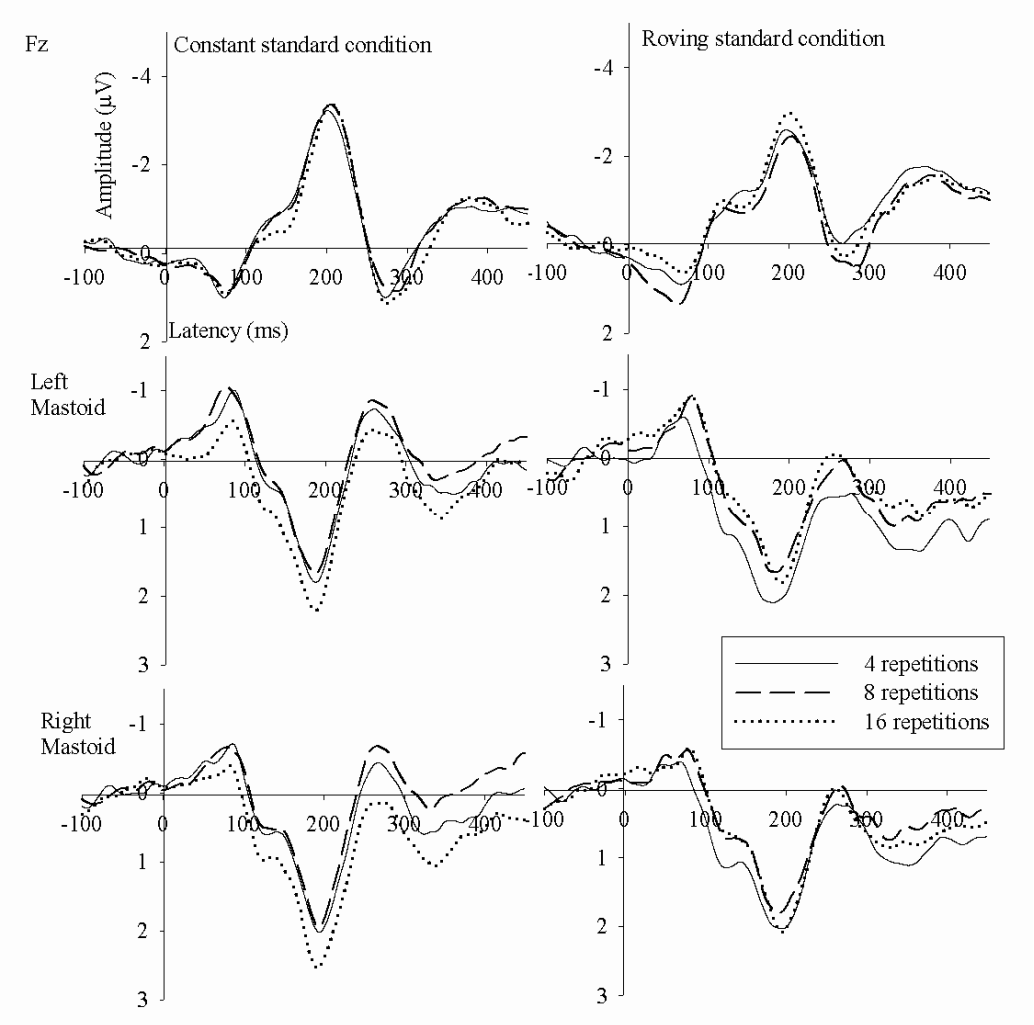

Figure 3. Grand average ERPs to deviant tones in the two presentation conditions and three repetition conditions. Note that data at Fz and the mastoids are presented at different scales.

The mismatch negativity

The MMN at Fz and the mastoids for the three repetition conditions and two presentation conditions is shown in Figure 4. At Fz, MMN was larger in the constant than the roving condition ($F(1,23) = 12.93$, $p = .002$) as can be seen in Figure 4. There was no repetition effect (MMN memory trace effect) at Fz ($p = .911$). Nor was there an interaction between condition and repetition ($F(2,22) = 2.57$, $p = .099$). However, since Figure 4 suggests that there is a trend towards the MMN memory trace effect in the roving but not the constant condition, we explored the repetition effect in each condition separately. The repetition effect was not significant in the constant ($p = .476$) or roving ($p = .206$) conditions.

At the mastoids, there was a marginal trend for MMN to be larger (more positive) in the constant versus the roving condition ($F(1,23) = 3.01$, $p = .096$). Unlike at Fz, at the mastoids, we saw a significant repetition effect ($F(2,22) = 3.94$, $p = .034$). MMN amplitude at the mastoids increased in the positive direction with increased repetition of the standard tone (reversal of polarity of MMN memory trace effect). However, there was no condition x repetition ($p = .702$) or condition x repetition x mastoids interaction ($p = .714$).

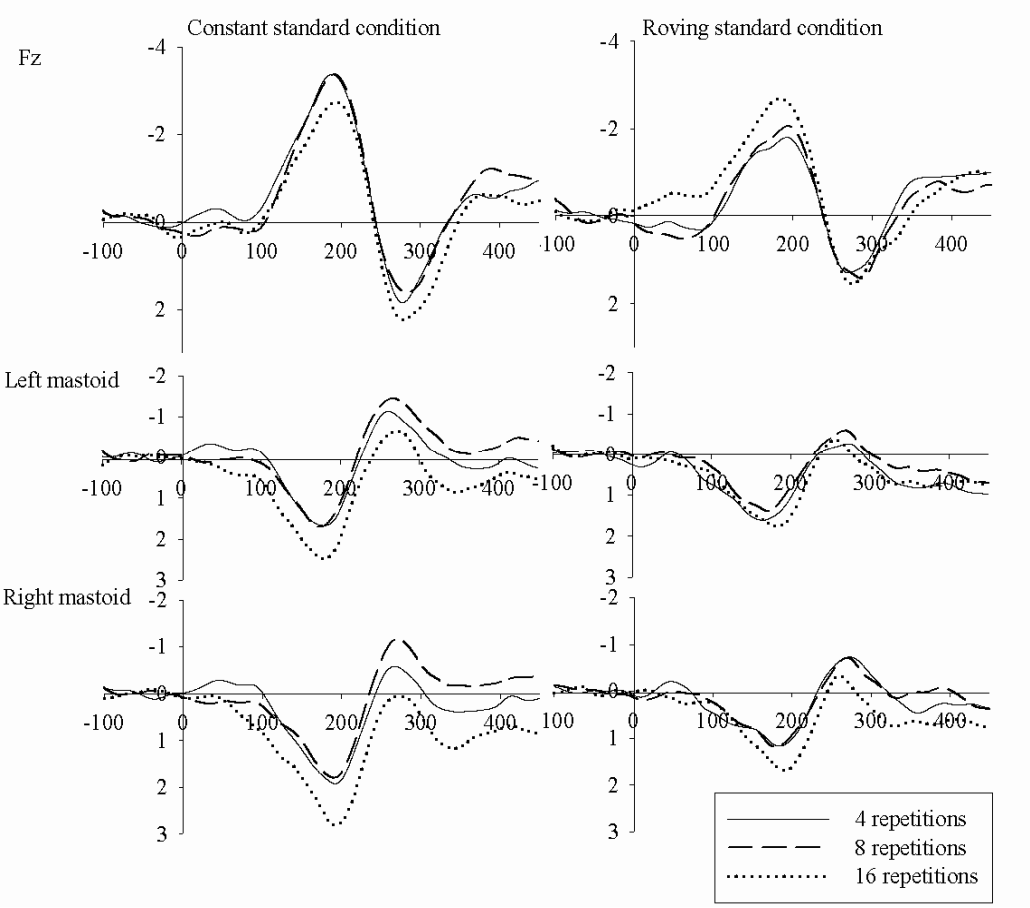

Figure 4. Grand average MMN waveforms in the two presentation conditions and three repetition conditions. Note that data at Fz and the mastoids are presented at different scales.

Discussion

In this study, we compared auditory ERP repetition effects in a constant standard versus a roving standard oddball paradigm to gain further insight into the functional correlate of these effects. More precisely, we were interested in reviewing the proposed relationship between the repetition effects observed in the ERP and the establishment and strengthening of auditory sensory memory traces. As we established a link between RP and the MMN memory trace effect in the introduction (such that RP is likely the primary

contributor to the MMN memory trace effect), we will firstly address results pertaining to RP and then assess whether or not the MMN data are in agreement with our conclusions.

In response to standard tones, we observed a repetition effect indicative of RP in the roving standard but not the constant standard condition at Fz over the N1 and P2 period. However, at the mastoids, an effect indicative of the reversal of polarity of RP was observed across both presentation conditions. In the MMN literature, different patterns of MMN activity have previously been observed at frontal and mastoid sites (e.g. Baldeweg, Williams, & Gruzelier, 1999; Jääskeläinen, Pekkonen, Hirvonen, Sillanaukee, & Näätänen, 1996; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000; Sato et al., 2002; Sussman & Winkler, 2001; Todd, Michie, & Jablensky, 2003) and this is thought to reflect the fact that different MMN generators could contribute to recordings at these sites (see review in Deouell, 2007). We believe it is possible to reconcile our contrasting findings from Fz and the mastoids with respect to RP by consideration of the fact that there may be at least two RP generators, one to which mastoid sites are most sensitive and another to which frontal sites are most sensitive (although we acknowledge that overlapping contributions from separate generators can be reflected in recordings across the scalp). Furthermore, if we consider that there may be a generator of RP in the auditory cortex which functions on a different time scale of adaptation relative to a more anterior generator of RP (possibly still located within the auditory cortex) then our seemingly discrepant findings in relation to the repetition effects observed across presentation conditions at mastoid and frontal sites can be explained. We will refer to these potential generators of RP as the auditory cortex and anterior generators respectively.

There are two lines of evidence that suggest that there may be separate generators of RP operating on different time scales of adaptation. In the introduction, we outlined that RP may represent a form of stimulus specific adaptation (SSA) that has previously been observed in the cat auditory cortex (Ulanovsky et al., 2003; Ulanovsky et al., 2004). Since SSA has been recorded operating on different time scales (Ulanovsky et al., 2004), it is plausible that generators of RP exist which function on different time scales of adaptation. In fact, Baldeweg (2007) has drawn this same conclusion. In addition, the differential sensitivity of RP generation to different pharmacological manipulations (of acetylcholine and the NMDA receptor system) also points to the fact that there may be RP generators operating on different time scales (see nicotine study by Baldeweg et al., 2006 and ketamine study by Baldweg, Moelle, Merle, & Born, in preparation, cited by Baldeweg, 2007, respectively). This conclusion was reached as the difference between placebo and drug conditions in the standard ERP was clearest after a larger number of repetitions in the nicotine study (greater than or equal to six; Baldeweg et al., 2006) than the ketamine study (less than or equal to six repetitions; see Baldeweg, 2007).

Accepting that RP represents a form of SSA, we will firstly discuss the proposed auditory cortex generator of RP. It is clear that in the roving standard condition, the adaptation process (SSA) begins anew at the start of each standard train due to the nature of the roving paradigm. In the constant standard condition, this adaptation may still be required if the auditory cortex generator of RP recovers quickly over the period in which a deviant tone rather than another standard is delivered. However, considering the fact that deviant sounds in the current study only differed from standards in duration (i.e. were of the same frequency as previously presented standards), our explanation suggests that the auditory cortex generator of RP may quickly recover following novel (deviant) stimulation.

It has previously been proposed that deviant stimulation heralds not only the mismatch between predicted and actual stimulation but also the updating of the model of the auditory environment (Winkler et al., 1996). Since the predictive coding model suggests that RP is a result of top-down suppression of the response to predicted stimuli, we propose that updating of the model of the auditory environment could involve the enforced recovery (due to withdrawal of top-down suppression) of neurons underpinning the auditory cortex RP generator. This hypothesis suggests that the auditory cortex RP generator reflects the response to repetition in the local as opposed to global auditory environment.

In contrast to the auditory cortex generator, we propose that the anterior generator of RP may demonstrate adaptation over a longer time course, enabling the system to retain information regarding stimulus history for a longer time period than the auditory cortex generator. This implies that the anterior RP generator reflects a global perspective of stimulus history relative to the local perspective exhibited by the auditory cortex generator. If this were the case, standard tones in all repetition conditions presented in the constant standard paradigm would be treated as previously heard stimuli, resulting in maximal adaptation (suppression) being maintained throughout the course of stimulation. This would explain the lack of a repetition effect in the constant standard condition at Fz (and the main effect of condition; see below). On the other hand, given that we used 11 different roving frequencies in the roving standard paradigm, we propose that in the roving condition, the anterior generator was able to recover by the time a repetition of a previously used standard frequency occurred (each frequency was used approximately once every 1.7 minutes on average). This would explain the effect of repetition observed in the roving standard condition at Fz. That is, since standards in consecutive trains in the roving standard condition were treated as new, adaptation occurred over the course of each train.

In addition, inspection of the results relating to the main effect of presentation condition reveals support for our proposal that two separate generators of RP exist that operate on different time scales of adaptation.

We observed significantly larger N1 and smaller P2 amplitude in the roving versus the constant condition at Fz and the mastoids in the standard ERP (although the effect was only marginally significant at the mastoids over the N1 period). In essence, we observed a positive shift in the standard ERP over the RP period in the constant versus the roving paradigm at Fz (and a negative shift at the mastoids). We take this as evidence that the mechanism underpinning RP was active in the constant as well as the roving condition, however, in the constant condition, the anterior RP mechanism resulted in overall suppression of the response to repeating sound regardless of the repetition condition. That is, in the constant standard condition, the identical standard tone that occurred in all repetition conditions may have been treated as though it were occurring in one 'long' repetition condition. There is a precedent for this suggestion as Baldeweg (unpublished observation, cited in Baldeweg, 2007) has reported that when a standard tone of one pitch occurs in a roving paradigm more often than standard tones of other pitches, there is larger RP for the more frequently presented tone. However, there is a problem with our explanation: why would the auditory cortex generator (which we have suggested reflects the response to repetition on a local time scale) also reflect an overall difference in amplitude between the constant and roving conditions (a difference that is defined on a global time scale)? This may be due to the fact that, as suggested earlier, mastoid and frontal sites do not reflect independent output from the auditory cortex and anterior RP generators respectively. That is, the suppression of the response to the standard tone that takes place within the anterior generator in the constant condition may be reflected at both

mastoid and frontal recording sites. In sum, we propose that, two different generators of RP operating on shorter and longer time scales of adaptation allow for separate coding of local and global aspects of auditory stimulation. As the theoretical underpinning of the repetition effect represented by RP involves modeling of the auditory environment (see earlier review of predictive coding framework), we argue that it is plausible that local and global stimulus properties are separately encoded in order to achieve efficient modeling.

The effects observed in our MMN data can be attributed to the influence of RP as there were no significant effects on deviant waveforms. MMN data was in general agreement with the patterns observed in RP data. For example, MMN was significantly larger in the constant compared to the roving condition at Fz in line with the suppression (i.e. RP) observed in the standard ERP in the constant relative to the roving condition (the condition effect was marginal at the mastoids, in line with the marginal result observed over the N1 period in standard waveforms at the mastoids). Secondly, in agreement with the repetition effect (i.e. RP) observed at the mastoids in the standard ERP across presentation conditions, we also recorded a repetition effect in MMN data at the mastoids across presentation conditions. This was in the direction of increasing positivity in MMN with increased repetition of the standard tone (i.e. reversal in polarity of the MMN memory trace effect at mastoid sites). However, in contrast to the significant effect of repetition (i.e. RP) observed in the standard ERP in the roving condition at Fz, there was not a significant MMN memory trace effect at Fz in the roving condition. We therefore argue that although MMN may be equally sensitive as RP to repetition effects mediated by the auditory cortex RP generator, RP may be more sensitive to repetition effects mediated by the anterior RP generator compared to MMN (likely due to the fact that MMN takes contributions from deviant as well as standard waveforms). This suggests, as mentioned earlier, that RP may

be a more direct indicator of the establishment of the contextual aspect of auditory sensory memory traces than MMN.

Conclusions

We have proposed that shorter- and longer-term memory for (local and global) stimulus history could be evident in RP recorded from mastoid and frontal sites respectively, as these sites may be sensitive to two separate generators of RP. We acknowledge that the hypothesis that there are two separate generators of RP acting on different time scales of adaptation is speculative. Despite this, we believe that our explanation is consistent with the neural and theoretical underpinnings that have thus far been proposed to account for the repetition effects (i.e. SSA and the predictive coding model). The predictive coding model suggests that RP represents modeling of auditory information in the brain. Our interpretation is that such modeling occurs in constant and roving standard conditions (underpinned by the action of at least two distinct RP generators). From this perspective, our data shows that RP reflects auditory sensory memory trace formation in a broader context (i.e. beyond the roving standard paradigm). Therefore, our findings remain compatible with the memory-based functional correlate of RP proposed by Baldeweg et al. (2004) and Haenschel et al. (2005) despite the fact that we found evidence of responsiveness to repetition in the auditory ERP in a traditional constant standard paradigm. In line with our primary aim, this study has enhanced our understanding of functional correlate of RP by more clearly identifying mechanisms contributing to RP.

We argue that the MMN memory trace effect conveys similar functional information as RP because RP primarily contributes to the MMN memory trace effect. However, RP may be more sensitive to repetition effects than MMN (due to the fact that

standard and deviant waveforms contribute to MMN) and therefore RP may be a more direct measure of trace formation than MMN. To further explore functional correlates of RP and the MMN memory trace effect, future research avenues include relating these effects to behavioural and neuropsychological data. This information could benefit clinical research exploring auditory sensory memory in, for example, schizophrenia (e.g. Baldeweg et al., 2004) and aging (e.g. Cooper, Todd, & Michie, to be submitted a,b).

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Chapter 4: study 3

Repetition effects on auditory sensory memory in young and older adults: an event-related potential study[16]

[16] This paper is to be submitted to Neurobiology of Aging by Cooper, R.J., Todd, J., & Michie, P.T.

Repetition effects on auditory sensory memory in young and older adults: an event-related potential study

Auditory sensory memory describes a period following auditory stimulation in which the brain analyses the properties of an auditory stimulus and integrates these to form a representation that is briefly retained (the auditory sensory memory trace; Cowan, 1984). An auditory event-related potential (ERP) waveform, the mismatch negativity (MMN), has been used to assess auditory sensory memory functioning in healthy aging (e.g. Alain & Woods, 1999; Cooper, Todd, McGill, & Michie, 2006; Fabiani, Low, Wee, Sable, & Gratton, 2006; Gaeta, Friedman, Ritter, & Cheng, 1998; Kisley, Davalos, Engleman, Guinther, & Davis, 2005; Pekkonen et al., 1996). However, recent studies suggest that 'the MMN memory trace effect' and a newly described ERP waveform, repetition positivity (RP), might be more direct indicators of auditory trace formation than MMN as these factors are more directly modulated by the repetition of auditory stimuli (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005). Thus, the present study was designed to assess auditory sensory memory trace formation in young and older adults using RP and the MMN memory trace effect. As the nature of the relationship between sensory processing and cognition with age remains a question of interest in the cognitive aging literature (e.g. Schneider & Pichora-Fuller, 2000), we were also interested in whether our ERP data would correlate with scores on an auditory verbal memory test (Rey Auditory Verbal Learning Test: RAVLT). In the following we explain how MMN is derived as a means to explore the concept of the MMN memory trace effect and RP in more detail.

The MMN is elicited by delivering a passive oddball paradigm where a repeating 'standard' tone is infrequently interrupted by the presentation of an acoustically different

tone, the ‘deviant’ (for recent reviews see Kujala, Tervaniemi, & Schröger, 2007; Näätänen, 2007; Schröger, 2007; Winkler, 2007). To derive MMN, the ERP generated to the standard tone is subtracted from the average ERP to the deviant tone. Baldeweg et al. (2004) and Haenschel et al. (2005) observed the MMN memory trace effect and RP by presenting ‘roving standard’ stimuli in the oddball paradigm. The roving standard, rather than remaining constant throughout an experiment, changes in pitch following each presentation of an infrequent deviant (e.g. Cowan, Winkler, Teder, & Näätänen, 1993). That is, roving standard tones are identical within a train but differ in frequency (Hz) between trains. Thus, in the roving standard oddball paradigm, the memory trace of the standard tone must be re-established following each presentation of a deviant tone. The MMN memory trace effect has been associated with this memory trace formation process as it describes the increase in MMN amplitude that occurs as a function of increased repetition of the standard tone under roving standard conditions (Baldeweg et al., 2004).

Moreover, Baldeweg et al. (2004) have proposed that the MMN memory trace effect provides a better indicator of memory function than MMN amplitude. They found that the MMN memory trace effect (the slope of MMN amplitude change as a function of increased repetition of the standard tone) correlated with memory functioning scores (Rivermead Behavioural Memory Test: RBMT) in a group of patients with schizophrenia, while MMN amplitude (averaged across repetition conditions) did not. However, a consideration to bear in mind is that due to the way in which MMN is derived, the MMN memory trace effect reflects the effect of repetition on the ERP to both standard and deviant stimuli. Since, Haenschel et al. (2005) found that the effect of repetition on the ERP to standard stimuli, labeled repetition positivity (RP), was the primary contributor to the MMN memory trace effect, it is possible that RP is more directly related to auditory

memory trace formation than MMN or the MMN memory trace effect (Baldeweg, Wong & Stephan, 2006; Haenschel et al.).

To study RP, Baldeweg et al. (2004) and Haenschel et al. (2005) analysed the ERP for standard tones at the end point of different length trains. RP emerged as a positive waveform (at Fz) superimposed upon the P1, N1, and P2 waveforms in the standard tone ERP (i.e. approximately 50 – 250 ms post stimulus onset). RP was larger in the ERP to standard tones that ended a long train of standards (e.g. 36 repetitions) compared to a short train (e.g. 2 repetitions). Therefore, since an update of the sensory memory trace of the standard was continually enforced by the nature of the roving standard paradigm and since RP amplitude increased over the repetition period, it has been proposed that RP indexes the formation (Haenschel et al.) and strengthening (Baldeweg et al., 2004) of auditory sensory memory traces. Furthermore, it has been suggested that at least two generators contribute to RP amplitude (Cooper, Atkinson, Clark, & Michie, to be submitted a). Cooper et al. (to be submitted a) showed that RP amplitude reverses in polarity at mastoid relative to frontal sites. It was proposed that an RP generator, to which mastoid sites are most sensitive, responds primarily to local features of auditory stimulation, while another generator, to which frontal sites are most sensitive, adapts to auditory stimulation over a longer time course (Cooper et al., to be submitted a).

Baldeweg et al. (2004) and Haenschel et al. (2005) have linked RP with a mechanism at the neuronal level that plausibly indexes auditory sensory memory trace formation, stimulus specific adaptation (SSA). SSA describes the reduction in firing rate recorded in individual neurons in the cat primary auditory cortex when the same sound is presented frequently as opposed to rarely (Nelken & Ulanovsky, 2007; Ulanovsky, Las, & Nelken, 2003; Ulanovsky, Las, Farkas, & Nelken, 2004). Ulanovsky et al. (2003) created a

difference signal by subtracting the neural response (spike count from peristimulus time histograms) to the standard stimulus from that to the deviant stimulus. These researchers related the difference signal recorded at the neuronal level to MMN recorded at the scalp in humans. Baldeweg et al. (2004) and Haenschel et al. however, drew a link between RP and SSA because adaptive change in RP is recorded over the repetition period of the standard tone. However, the association between SSA and RP remains speculative due to the fact that there is not a clearly established method of relating findings from single cell recordings to scalp recordings (e.g. Grill-Spector, Henson, & Martin, 2006; Ulanovsky et al., 2003). Nonetheless, it is plausible that SSA contributes to RP and that both factors contribute to MMN. For example, neural adaptation is thought to contribute to cortical threshold regulation (Ohzawa, Sclar, & Freeman, 1985) and increased cortical thresholds have been linked with positive ERP waveforms at the scalp (Elbert & Rochstroh, 1987).

RP and MMN have also been linked to a theoretical framework based on a predictive coding model of auditory processing (see Baldeweg, 2007; Friston, 2005; Garrido et al., 2008). The predictive coding framework states that bottom-up sensory information travels upstream to aid in the formation of predictions about future stimulation and that this top-down inferential information travels downstream to suppress predicted activity in lower levels. From this perspective, RP is thought to index the suppression of neuronal responses to predicted stimuli, while MMN is more closely aligned with detecting when predictions have not been met (Baldeweg, 2007). This is compatible with the view that the effect of repetition in standard waveforms (i.e. RP) is related to trace formation while the effect of repetition in deviant waveforms is associated with deviance detection (Baldeweg et al., 2006). Thus, attenuation of the MMN memory trace effect in certain

populations could be due to either or both of these mechanisms that contribute to the predictive coding process.

To our knowledge, the question of whether there are age-related differences in the MMN memory trace effect remains unanswered. In the current study we have addressed this question with young and older adults using a passive oddball paradigm with a roving standard and duration deviant. Though we would expect to see reduced MMN amplitude in older versus young adults in line with previous MMN studies (e.g. Alain & Woods, 1999; Alain, McDonald, Ostroff, & Schneider, 2004; Cooper et al., 2006; Gaeta et al., 1998; Kisley et al., 2005), this paradigm will allow us to asses whether there are age-related changes in the MMN memory trace effect and specifically whether any such changes are primarily driven by age-associated change in response to repetition in standard waveforms (i.e. RP), deviant waveforms, or both. Thus, an assessment of the mechanism(s) contributing to age effects in the response to repetition in auditory sensory memory will be possible with the current paradigm. As stated, we also investigated the correlation between adaptive measures responsive to repetition in auditory sensory memory (i.e. RP and MMN) and auditory verbal memory (RAVLT) scores. We did this to investigate whether these ERP measures thought to indicate auditory sensory memory trace formation are also related to memory for auditory information in general (e.g. Näätänen, 2007). If so, this would support Baldeweg et al. (2004) and Haenschel et al.'s (2005) claim that RP is associated with auditory sensory memory trace formation and also provide insight into a potential mediator of age-related cognitive change (specific to cognitive tasks reliant on auditory information).

Method

Participants

Twenty–five young (mean age 20 yrs ± 3; 3 males) and 25 older (mean age 64 yrs ± 8; 9 males) adult volunteers were recruited for the study. TheUniversity of Newcastle Human Research Ethics Committee granted ethics approval for the study and all participants provided their written informed consent to participate. A telephone screen was administered to participants prior to recruitment to screen for neurological and psychological disorders, serious head injury, drug abuse, and visual or hearing impairments. Those in the young group were first year psychology undergraduates who received course credit for their participation. Older adults were recruited from the Hunter Medical Research Institute research volunteer register and were reimbursed for their travel costs. The Mini-Mental State Exam (MMSE: Folstein, Folstein, & McHugh, 1975) was adminstered to older participants to screen for dementia (cut-off of 23 out of 30 for dementia; Crum, Anthony, Bassett, & Folstein, 1993). The mean MMSE score was 29 with a range of 27 to 30. We also used the Wechsler Test of Adult Reading (WTAR) and the Wechsler Abbreviated Scale of Intelligence (WASI; vocabulary and matrix reasoning subtests) to compare premorbid and current functioning between groups. Age-adjusted WTAR and WASI IQ estimates were 104.42 (11.56) and 113.88 (11.26) respectively for young adults and 107.28 (7.74) and 117.92 (11.08) respectively for older adults. There was no significant difference between groups on WTAR or WASI IQ estimates.

At the start of each appointment, auditory thresholds were tested in the left then right ear at five frequencies (0.5, 1, 2, 4, and 8 kHz) using a hand held audiometer with a

resolution of 5 dB. All participants had less than 20 dB difference between thresholds for each ear at each frequency except for four older adults at 4 kHz and two older adults at 8 kHz who had greater than 20 dB but less than 40 dB difference between ears at these frequencies. Mean auditory thresholds in dB HL are presented in Table 1 along with the mean difference between the young and older group. Young participants had auditory thresholds less than 25 dB HL for both ears at all frequencies tested. All older adults had thresholds below 25 dB HL at both ears for the 500 Hz and 1 kHz frequencies. At 2 kHz, two older adults showed thresholds greater than 25 dB HL (<45 dB HL). Twelve older adults showed elevated thresholds at 4 kHz (<70 dB HL), while 19 did at 8 kHz (<70 dB except for 6 individuals who could not hear the 8 kHz tone at the audiometer's limit of 70 dB HL). From this we can conclude that approximately 19 of our 25 older adults were experiencing the early signs of presbycusis, an age-related condition which is marked by elevated auditory thresholds at high frequencies. In an attempt to ensure equal auditory input to both groups we delivered low frequency tones in the experiment (between 700 Hz and 1200 Hz) and raised intensity 40 dB above individual threshold to a 950 Hz tone (midpoint of the 700 Hz and 1200 Hz tones) to compensate for any hearing losses in the older group.

Table 1

Auditory threshold data for the young and older group in dB HL (sd in brackets) and the difference between group means. Note the 5 dB resolution of the audiometer.

	0.5 kHz	1 kHz	2 kHz	4 kHz	8 kHz
Young	9.0 (4.7)	5.6 (4.8)	4.6 (4.7)	3.1 (4.4)	6.7 (7.0)
Older	12.7 (4.7)	9.9 (3.9)	13.4 (10.7)	28.2 (16.8)	44.3 (20.3)
Difference	3.7	4.30	8.8	25.1	37.6

Stimuli and procedure

Participants completed a series of assessments directly prior to the ERP experiment. These included a brief hearing test, Mini-mental state exam (older adults only), WTAR, WASI, and Rey Auditory Verbal Learning Test (RAVLT). The RAVLT taps into auditory verbal memory by requiring participants to listen to 15 item word lists and verbally recall as many words as possible at different delays. We derived several measures from the RAVLT: total score, initial recall, learning over trials, short term retention, and long term retention (see Ivnik et al., 1990 for details). Following neuropsychological testing, participants took part in the ERP experiment.

Sounds in the ERP experiment were generated by Presentation ® software (Version 10, www.neuro-bs.com) and delivered over KOSS TD60 headphones. Before testing began, stimuli were calibrated to dB SPL using a Brüel and Kjaer sound level meter. During the experiment, intensity was set at 40 dB above an individual's threshold to a 950 Hz tone. To determine an individual threshold, a PEST (parameter estimation by sequential testing) procedure (Taylor & Creelman, 1967) was employed with specifications as outlined in Treutwein's (1995) review. Participants were required to press a button on a response box every time they heard the 950 Hz tone played over headphones. The time between stimuli was jittered 1800ms $\pm$ 300ms and a miss was recorded if a response was not given within this time. The first three trials were practice trials with intensity set at 55dB SPL. Testing began with a step size of 8 dB after which Taylor and Creelman's heuristic rules determining the step size were implemented. We used the simplified Wald test as the decision rule defining when to change levels and employed a theta value of 0.75

(75% accuracy in responding required), and a 'w' value (deviation limit) of 1. PEST's MOUSE (minimum overshoot and undershoot sequential estimation) mode was used to determine the final threshold. That is, testing ended when the step size fell below 0.5 dB (experimenter defined) and therefore the last hit was the threshold recorded. This made the procedure accurate to within 1 dB. The mean intensity at which sounds were delivered in the experiment was similar ($t(48)=0.21$, $p=.84$) for the young group (84.4 ± 3.0 dB SPL) and older group (84.5 ± 2.4 dB SPL).

A passive MMN oddball paradigm with a 'roving' standard and duration deviant was implemented for the ERP experiment. Stimuli consisted of trains of binaural standard tones (50 ms, 5 ms rise/fall) separated by a 100 ms duration deviant (5 ms rise/fall). The 'roving' aspect of the paradigm arose from the fact that standards changed in pitch following the presentation of a duration deviant (i.e. standards tones were identical within trains and only changed in pitch following a duration deviant tone). Standards pseudorandomly cycled through 11 different frequencies across trains (700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, and 1200 Hz). Normative data shows that older adults should be capable of differentiating the minimum frequency difference (50 Hz) between standards in consecutive trains (Abel, Krever, & Alberti, 1990; König, 1957).

The number of standards presented in a train preceding a deviant was manipulated within subjects resulting in four repetition conditions. That is, 4, 8, 16, or 24 standards were delivered before a deviant was presented. Stimuli were delivered in four 15 minute blocks where each block consisted of 32 pseudorandom occurrences of the 4, 8, 16, and 24 repetitions conditions. The total number of tones presented was 7168 including 6656 standards and 512 deviants. The stimulus onset asynchrony (SOA) was 500 ms throughout. ERP recording time was approximately 60 minutes. During this period participants were

instructed to concentrate on a silent video with subtitles and ignore the sounds. The entire appointment lasted up to 3 hours.

EEG Recording

The EEG was recorded from 28 scalp channels (FP1, FP2, F3, F4, Fz, F7, F8, FC3, FC4, FCz, FT7, FT8, C3, C4, Cz, T7, T8, CP3, CP4, CPz, TP7, TP8, P3, P4, Pz, P7, P8, Oz) and from both mastoids using an electrode cap (Electro-Cap International) with sites based on the 10/20 system and referenced to the nose. The vertical electro-oculogram (EOG) was recorded by electrodes above and below the left eye and the horizontal EOG by electrodes at the outer canthi of each eye. Continuous EEG was digitized at 250 Hz with a gain of 75000. A bandpass filter 0.1 – 30 Hz and 50 Hz notch filter were applied. Scan 4.2 software was used to acquire data and Scan 4.3 for off-line analysis.

Data Analysis

Data were processed offline and movement artefacts were manually removed. Eyeblink artefact correction was utilised (Semlitsch, Anderer, Schuster, & Presslich, 1986). A 50 ms prestimulus baseline and 448 ms post stimulus period was used to epoch EEG data and epochs containing artefacts exceeding ± 100 μV (excluding EOG channels) were rejected.

Latency windows covering waveforms of interest are presented in Table 2 and were chosen by selecting a window surrounding peak amplitude in the grand average waveforms. We extracted a mean amplitude measure for P1 and N1 waveforms in the standard ERP. However we extracted peak amplitude of P2 rather than P2 mean amplitude to preserve the same latency search window for each group (there was a large difference in latency of P2

between groups). In order to quantify the latency difference in P2 between groups we extracted the latency of the P2 peak. RP was calculated by separately subtracting the standard ERP for the 4, 8, and 16 repetitions conditions from the standard ERP for the 24 repetitions condition. MMN difference waves were calculated by subtracting standard waveforms from corresponding deviant waveforms for each repetition condition. For deviant and MMN waveforms we extracted mean amplitude from an 'early' and 'late' period.

Table 2

Latency windows used to derive mean amplitude and peak (P2) amplitude

Area of interest	Latency Window (ms)
P1	30 – 80
N1	85 – 135
P2 (peak)	140 – 240
RP	100 – 200
Early deviant period	90 – 140
Late deviant period	170 – 220
Early MMN period	130 – 170
Late MMN period	170 – 220

At Fz and the mastoids we analysed mean amplitude measures and P2 peak amplitude and latency derived from the above windows using mixed design mANOVA (Pillai's trace) with factors repetition (within subjects) and group (for mANOVAs on mastoid data, an additional within subjects factor, mastoid, was required).

In order to explore whether there were any relationships between the ERP measures described above and neuropsychological test scores, we performed a correlational analysis on the ERP and neuropsychological data using Pearson's r. We correlated ERP amplitude and slope for RP and MMN (late period) with the RAVLT scores. We found the slope of

the regression line for MMN using data from the four repetition conditions. RP slope was calculated by using 8, 16, and 20 as the three levels of the independent variable repetition (corresponding to the three subtractions of repetition conditions used to derive RP, i.e. 24 – l6, 24 – 8, and 24 – 4). We used dependent variable values corresponding to MMN or RP mean amplitude over the latency periods stated in Table 2. To control for the large number of correlations performed, we reduced alpha to 0.001.

Results

Standards

Previously, Baldeweg et al. (2004) analysed predeviant standards, that is, standards occurring immediately prior to deviants. In order to increase the number of sweeps entering each average and thereby improve the signal to noise ratio at the individual level, we averaged clusters of standards from each repetition condition to represent the effect of increasing repetition on the standard ERP. For each repetition condition, we ensured an approximately equal number of sweeps entered each average by deriving our standard waveforms in the following way: we averaged the 4^{th} standard from each repetition condition; the 7^{th} and 8^{th} standard from the 8 repetitions condition with the 8^{th} standard from the 16 and 24 repetitions conditions; the 15^{th} and 16^{th} standard from the 16 and 24 repetitions conditions; and the 21^{st}, 22^{nd}, 23^{rd}, and 24^{th} standard from the 24 repetitions condition. To assess whether ERPs to standards derived in this manner (referred to as the standard) differed significantly from ERPs to predeviant standards we compared the two approaches in a 2 (type: standard, predeviant standard) x 4 (repetition) x 2 (group) mANOVA for P1 mean amplitude, N1 mean amplitude, and P2 peak amplitude. We found

a marginally significant effect of type for N1 ($F(1,48) = 3.30$, $p = .075$) and a significant effect of type for P2 ($F(1,48) = 21.68$, $p<.001$) suggesting that predeviant standard P2 amplitude was more positive than for standards (for P2: 1.33 μV ± .15 vs 1.03 μV ± .13 respectively; see Figure 1). However, no interaction with type reached significance for P1, N1, or P2. Given the lack of any interaction with type and the small overall amplitude difference between standards and predeviant standards, further analyses were conducted using standards.

Also of note in Figure 1 is the fact that older adults did not appear to produce a large second negative peak (N2) in the standard waveforms that was observed in young adult waveforms. As this difference was not the focus of this study, and as the functional significance of reduced N2 amplitude in older versus young adults is not well understood (see Bertoli & Probst, 2005 for a review of age-related N2 differences), we did not analyse the age-related N2 difference any further.

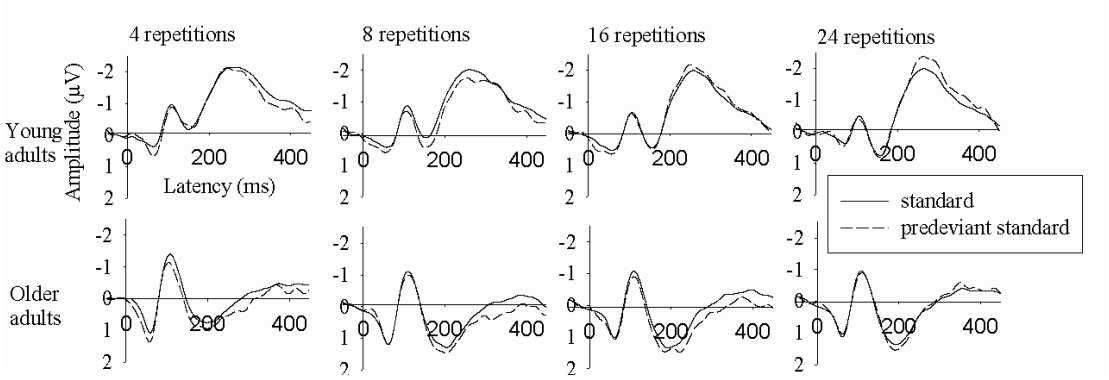

Figure 1. Standard and predeviant standard group average waveforms for the two groups (rows) and four repetition conditions (columns). Note that negative amplitude is plotted upwards.

In the following, we report group and repetition effects on P1 mean amplitude, N1 mean amplitude, and P2 peak amplitude in the standard ERP, firstly at Fz and then the mastoids. At Fz, a main effect of group was only observed for P1 ($F(1,48) = 12.24$, $p = .001$) and P2 data ($F(1,48) = 12.10$, $p = .001$) where the older group exhibited larger amplitude compared to the young group. A main effect of repetition was found only in the N1 ($F(3,46) = 6.58$, $p<.001$) and P2 data ($F(3,46) = 16.79$, $p<.001$). In general there was a decrease in N1 and an increase in P2 amplitude with increased repetition of the standard which could be interpreted as evidence of increased positivity across the N1/P2 latency range (i.e. repetition positivity). We found a significant repetition x group interaction in P2 data only ($F(3,46) = 3.43$, $p<.05$) as well as a repetition x group interaction in the linear contrast for P2 ($F(1,48) = 7.25$, $p = .01$).

We explored these interactions further by running a one-way mANOVA on P2 data separately for each group. We found a significant repetition effect in both young and older adult data ($F(3,72) = 16.99$, $p<.001$ and $F(3,72) = 6.07$, $p = .001$ respectively), however while the linear contrast of the repetition effect was significant in both groups (young: $F(1,24) = 54.85$, $p<.001$; older: $F(1,24) = 7.59$, $p= .011$), the quadratic contrast was significant only in the older group ($F(1,24) = 7.0$, $p = .014$). In both groups, the linear contrasts represented the effect of increasing positive amplitude with increasing repetition. The quadratic contrast in the older group indicated that the magnitude of amplitude change in response to repetition was reduced with increased repetition.

The repetition effects on the standards for each group are clearly evident in Figure 2 which depicts standard waveforms from each repetition condition. Whereas the repetition effect appears most robust over the P2 period at Fz in young adults, the older adults do not appear to differentiate between the 8, 16, and 24 repetitions conditions over this period. The

significant delay of approximately 40 ms in peak P2 amplitude in the older group (197 ms ± 4) relative to the young group (158.5 ms ± 4; $F(1,48) = 45.76$, $p < .001$) is also evident in Figure 2. The main effect of repetition at the mastoids over the N1 ($F(3,46) = 8.56$, $p < .001$) and P2 periods ($F(3,46) = 12.77$, $p < .001$) suggested that the polarity of RP reversed at these sites relative to Fz. However, the repetition x group interaction was not significant at the mastoids over the N1 ($p = .695$) or P2 ($p = .166$) period.

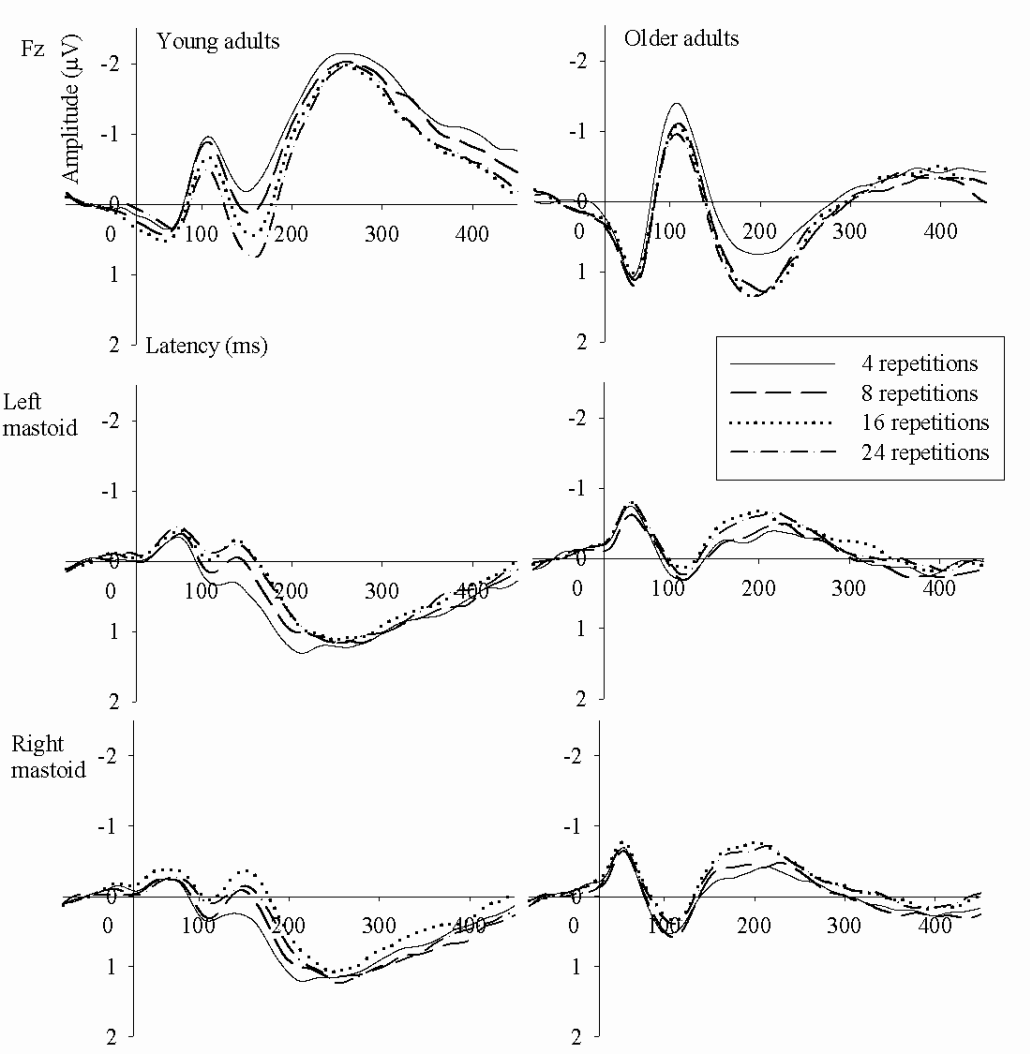

Figure 2. Standard waveforms for young (left) and older (right) adults at Fz (top row), the left mastoid (middle row), and right mastoid (bottom row). Repetition conditions are overlaid.

Repetition positivity

To visualize RP in a similar way to Haenschel et al. (2005), we subtracted standard waveforms for the shorter repetition conditions from the standard waveform for the 24 repetitions condition. The resulting difference waves depicting RP are shown in Figure 3. The morphology of RP suggests that it could represent an endogenous positivity superimposed on exogenous N1 and P2 waveforms in the standard ERP. A reversal in polarity of RP at the mastoids is also clearly evident.

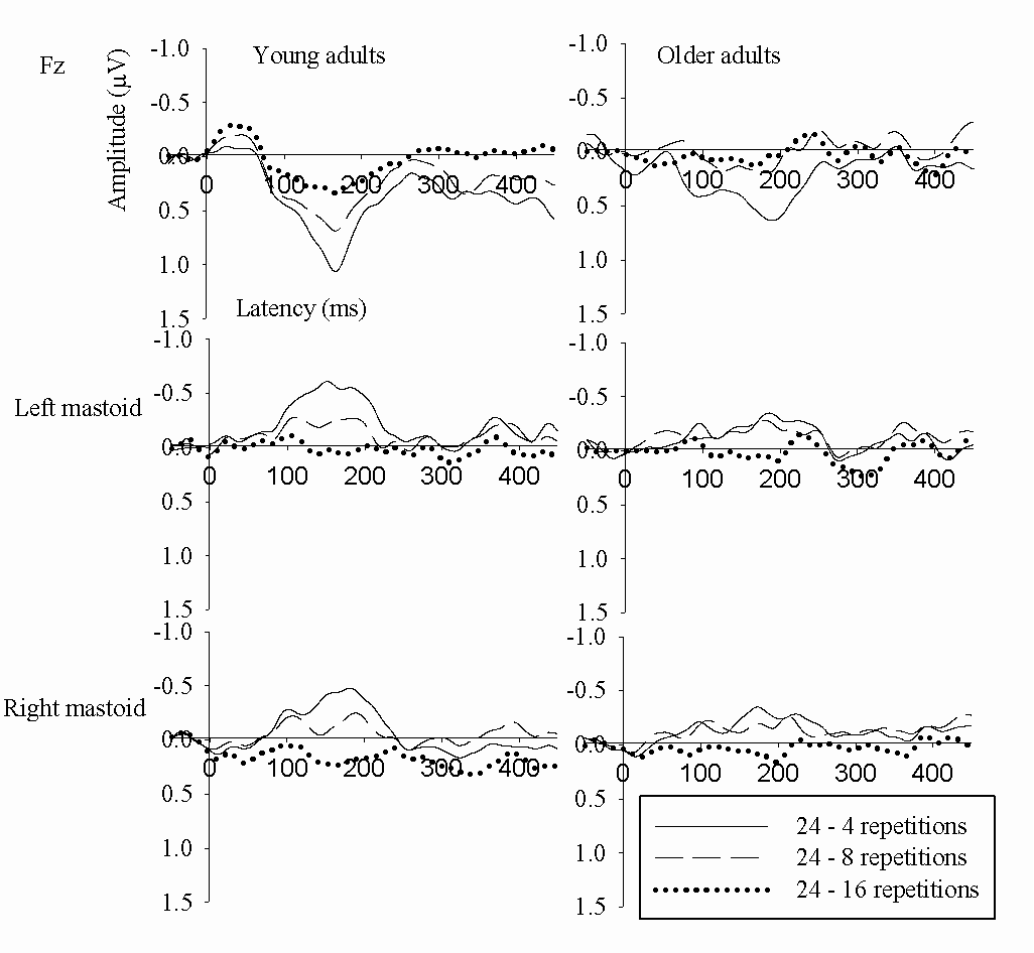

Figure 3. Repetition positivity difference waveforms for young (left) and older (right) adults at Fz (top row), the left mastoid (middle row), and right mastoid (bottom row).

To analyze RP data we examined mean amplitude over a window from 100 to 200 ms. At Fz and the mastoids we observed a main effect of repetition ($F(2,47) = 9.75$, $p<.001$) and $F(2,47) = 18.28$, $p<.001$ respectively) such that there was in general a larger difference in amplitude between the 4 repetitions and 24 repetitions conditions than between the 8 and 24 repetitions conditions and the 16 and 24 repetitions conditions. However, the repetition effect reversed polarity at the mastoids relative to Fz. That is, we observed RP as a positive waveform at Fz and a negative waveform at the mastoids. At Fz there was also a trend towards a main effect of group ($F(1,48) = 3.56$, $p=.065$) due to the fact that the young adults elicited larger differences between repetition conditions than older adults. The repetition x group interaction was not significant at Fz ($p=.573$) nor the mastoids ($p = .140$).

Deviants

Figure 4 depicts deviant waveforms from the four repetition conditions overlaid for the young and older group. The morphology of the waveforms in both groups suggests that there are two negative peaks, an earlier one peaking at approximately 100 ms and a second peaking at approximately 200 ms. However, the relative amplitudes of these two negative peaks is dependent on age; the second negative peak at Fz is larger than the first in the young adults whereas the opposite occurs in the older adults.

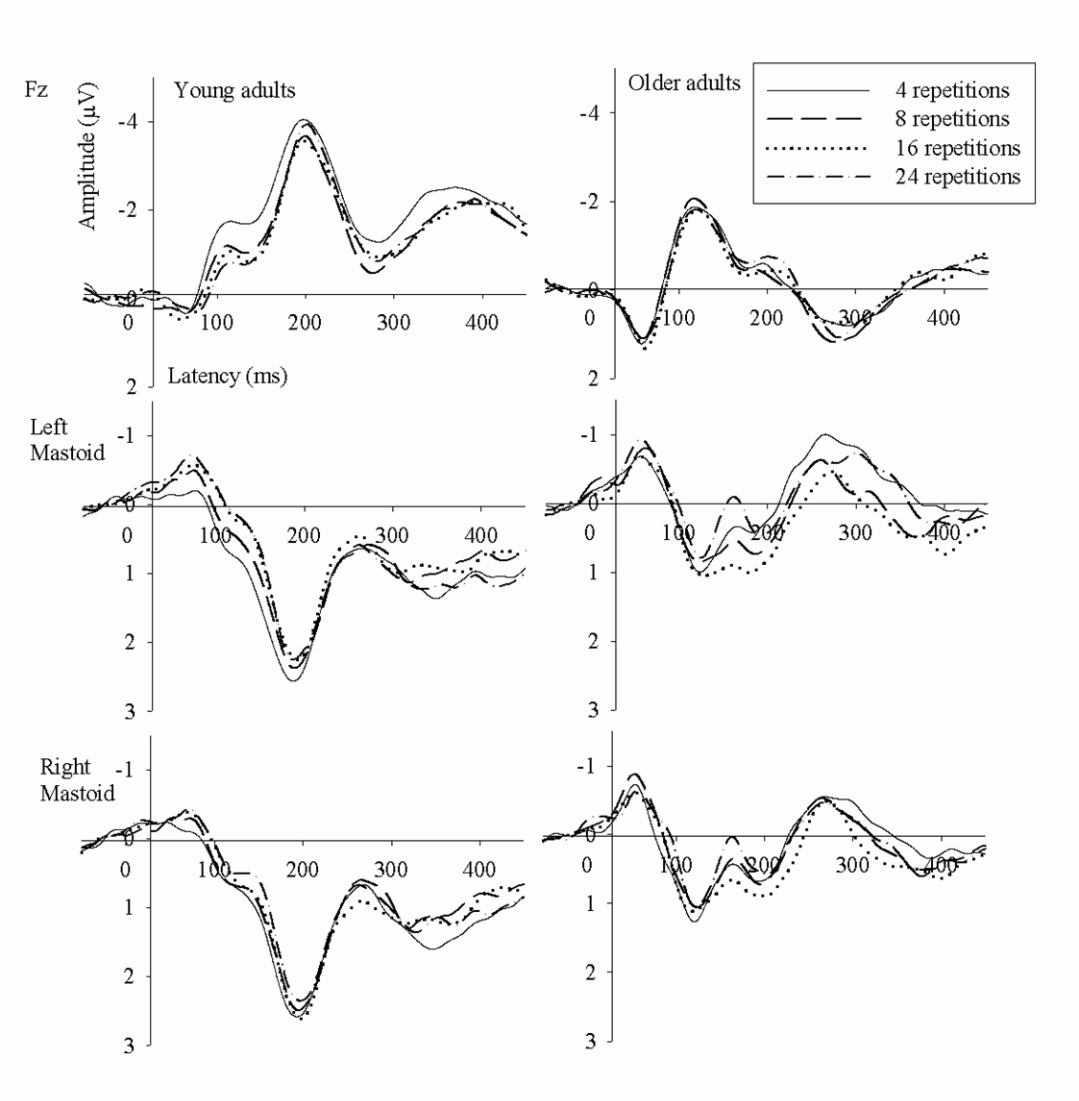

Figure 4. Deviant waveforms where the four repetition conditions are overlaid for the young group (left) and older group (right) at Fz (top), the left mastoid (middle), and right mastoid (bottom). Note that a different scale was used for Fz and mastoid data.

Over the early deviant period there was a main effect of group at Fz ($F(1,48) = 4.83$, $p = .033$) and a trend towards this at the mastoids ($F(1,48) = 3.64$, $p=.063$) whereby older adults showed larger early deviant amplitude than the young adults. The main effect of repetition at Fz ($F(3,46) = 3.18$, $p = .033$) indicated that overall there was a positive shift in

amplitude with increased numbers of standards preceding the deviant. Although this effect is clear only in the deviant waveforms for the young group (and suggests a carry-over effect of the RP into the early deviant period), the repetition x group interaction was not significant ($p = .241$). At the mastoids, there was a marginal trend towards reversal of the repetition positivity ($F(3,46) = 2.17$, $p=.104$).

The main effect of group was also significant over the late deviant period at Fz ($F(1,48) = 77.75$, $p<001$) and the mastoids ($F(1,48) = 37.56$, $p<.001$), however this result indicated that older adults elicited smaller late deviant amplitude relative to the young group. There were no repetition effects during the late deviant period at Fz or the mastoids. However, as we observed a significant repetition effect at Fz in the early deviant period (i.e. RP), it is possible that RP in the early deviant period masked an opposing repetition effect in the late deviant period at Fz. We therefore subtracted early deviant amplitude from late deviant amplitude in each individual and for each repetition condition at Fz in order to correct for the RP in the early deviant period. This adjusted measure of late deviant amplitude revealed a main effect of repetition ($F(3,46) = 5.38$, $p<.05$) at Fz such that amplitude increased in the negative direction with increased repetition. There was no interaction between repetition and group ($p=.847$).

Mismatch Negativity

We explored MMN data using an early (130 – 170 ms) and late period (170 – 220 ms). During the early MMN period there were no significant effects at Fz. However, at the mastoids, we observed a marginally significant effect of repetition ($F(3,46) = 2.55$, $p = .067$). In general there was an increase in positive amplitude with increasing repetition. Evident in Figure 6 is a main effect of group ($F(1,48) = 18.54$, $p <.001$) that was significant

over the late MMN period at Fz, showing that older adults (-1.59 μV ± 0.16) elicited smaller MMN amplitude than young adults (-2.59 μV ± 0.16). The main effect of repetition was marginally significant in the late MMN period at Fz ($F(3,46) = 2.62$, $p = .062$) suggesting that larger MMN amplitude was associated with greater repetition of the standard (i.e. MMN memory trace effect). Similarly, we observed a main effect of repetition at the mastoids ($F(3,46) = 5.04$, $p = .004$). In general, there was an increase in positive amplitude with increased repetition. There was no repetition x group interaction at Fz ($p = .412$) or the mastoids ($p = .632$).

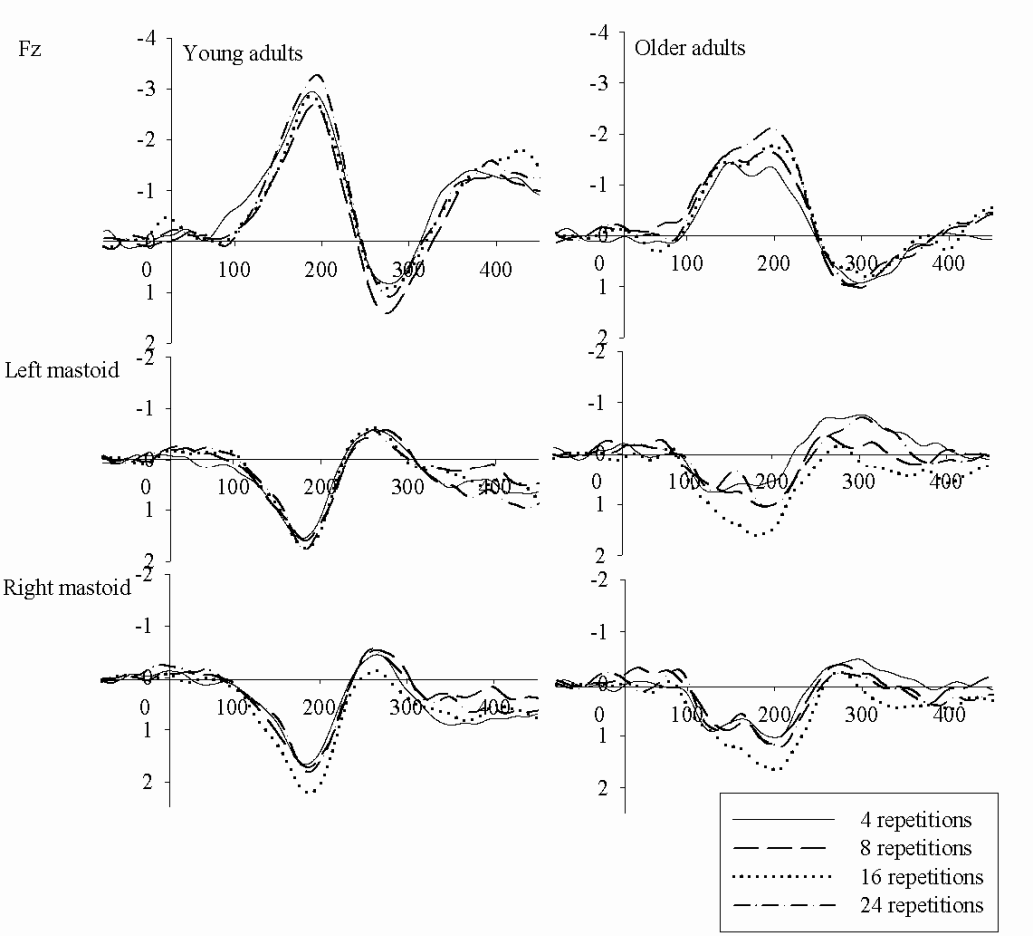

Figure 6. MMN difference waveforms for young (left) and older adults (right) at Fz (top row), the left mastoid (middle row), and the right mastoid (bottom row). The four repetition conditions are overlaid.

Neuropsychological test data and correlational analyses

Neuropsychological test scores differed significantly between the young and older group on all the measures presented in Table 3 except for RAVLT learning over trials.

Table 3

Young and older group mean scores for the Rey Auditory Verbal Learning Test (RAVLT; sd in brackets).

Neuropsychological test	Young group	Older group
initial recall	8.04 (1.9)	6.72 (1.72)*
total score	59.13 (7.85)	50.12 (10.47)**
learning over trials	1.5 (0.25)	1.5 (0.28)
short term retention	90 (11)	79 (16)*
long term retention	90 (13)	77 (14)**

* significant between group difference, $p<.01$
** significant between group difference, $p<.001$

To examine the relationship between ERP measures (see Table 4) and neuropsychological measures (see Table 3) we firstly averaged mean amplitude measures over repetition conditions for each ERP waveform. Correlations were performed within each group.

Table 4

ERP amplitude averaged over repetition conditions and the slope of the regression line for the young and older group (sd in brackets).

ERP measure	Young group	Older group
Average RP amplitude	.50 (.49)	.23 (.54)
RP slope	.04 (.07)	.03 (.06)
Average MMN amplitude	-2.6 (.86)	-1.6 (.77)**
MMN slope	-.02 (.07)	-.03 (0.7)

** significant between group difference, p<.001

No correlations were significant at alpha = 0.001. However, a marginally significant positive correlation between RP slope and long term retention emerged in the young group (young: r = .495, p = .012; older r = -.122, p = .561). Long term retention was assessed by measuring the percentage of words recalled from a 15 item word list approximately 20 minutes after the fifth presentation of the list relative to the number recalled directly following the fifth presentation (ERP set-up took place in the interim). Scatterplots of these data are presented in Figure 7. Correlations between neuropsychological variables presented in Table 3 and the other ERP measures presented in Table 4 were not significant.

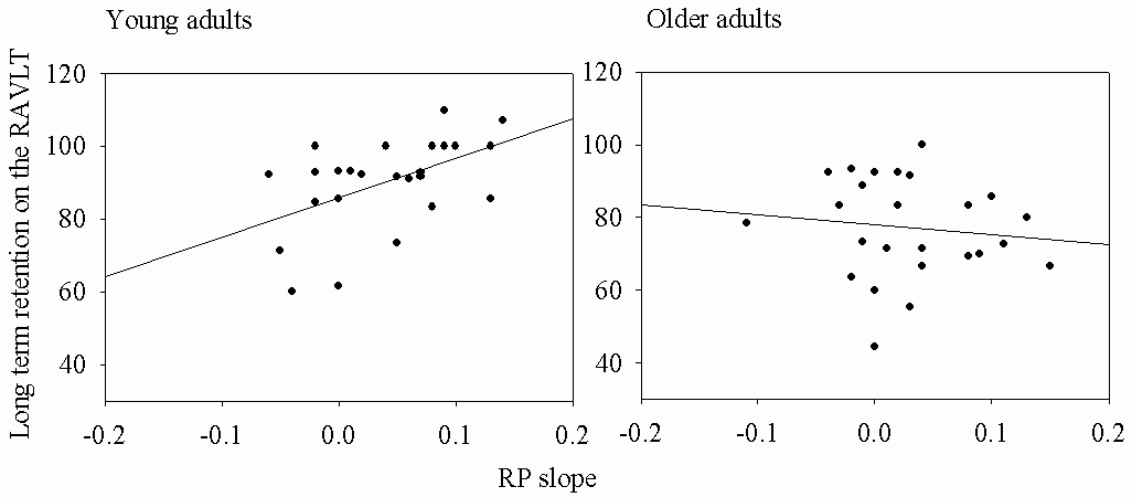

Figure 7. Scatterplots with regression lines for the young (left) and older group (right). The plot shows repetition positivity slope versus RAVLT long term retention scores.

Due to the fact that RP slope may have been a better indicator of memory function in the young than older adults (recall that we observed a quadratic fit to the P2 data in the standard waveforms), we decided to split the RP slope measure into an 'early' and 'late' repetition period. We calculated early RP slope by finding the slope between the 24 – 4 and 24 – 8 RP subtraction waveforms. Similarly, late RP slope was derived by calculating the slope between the 24 – 8 and 24 – 16 RP subtraction waveforms. As with our initial correlational analysis, in older adults, we did not find a significant relationship between early or late RP slope and any RAVLT variables. However, in young adults, we found that early RP slope correlated with long term retention ($r = .511$, $p = .009$) but not late RP slope ($r = .059$, $p = .780$).

Discussion

Using a passive oddball paradigm with a roving standard, we examined RP and the MMN memory trace effect in the auditory ERP of healthy adults. We extended previous work by investigating whether age affected these repetition effects.

A repetition effect in the direction of RP was evident over N1 and P2 periods in standard waveforms at Fz and the mastoids in both groups. At the mastoids, N1 and P2 amplitude shifted in the negative direction with increasing repetition, that is, RP reversed in polarity at the mastoids relative to Fz as seen previously (Cooper et al., to be submitted a). In standard waveforms there was only evidence of an age-related difference in RP over the P2 period at Fz, not the mastoids. At Fz, the standard ERP of young adults showed clear

differentiation between repetition conditions, whereas the standard ERPs in older adults showed little differentiation between the 8, 16, and 24 repetitions conditions over the P2 period (Figure 2). In the introduction, we presented previous research from our laboratory suggesting that at least two generators of RP exist, with frontal and mastoid sites being primarily sensitive to different RP generators (Cooper et al., to be submitted a). More specifically, we proposed that mastoid sites were most sensitive to a generator that encoded the local context of auditory stimulation (auditory cortex generator), and that frontal sites were most sensitive to an RP generator responsive to the global auditory context (anterior generator). Therefore, the present data would suggest that the auditory cortex generator of RP is intact in older versus young adults but that the anterior RP generator is compromised with age. From the above, we infer that a form of SSA represented by the auditory cortex RP generator is intact in older adults. Since in the theoretical (predictive coding) model proposed to explain RP generation, RP represents top-down suppression of the response to predicted stimulus input, it is possible that top-down influences acting on the anterior RP generator may be impaired in older compared to young adults. An age-related top-down processing deficit has previously been outlined by Gazzaley and D'Esposito (2007). Alternatively, less precise encoding of the features of auditory stimuli in old age (see Cooper et al., 2006) could mean that broader populations of neurons are stimulated in older than young adults in response to each of the roving standards (i.e. reduced frequency tuning with age). In turn, this could result in a build-up and subsequent saturation of the response to repetition. Since Winkler (2007) has stated that the context in which auditory stimuli occur is encoded into auditory sensory memory traces, one potential implication of our findings at Fz is that older adults may not encode the context of auditory stimulation as precisely as young adults.

In contrast to these interpretations, our data could also be viewed as more rapid encoding of repetition (to the point of saturation) in older compared to young adults. However, studies of the pharmacology of RP and of aging suggest that this is unlikely. NMDA receptors and the cholinergic system have been implicated in the process of RP generation as the RP is augmented by nicotine (a cholinergic agonist; Baldeweg et al., 2006) and reduced by ketamine administration (an NMDA receptor antagonist; Baldeweg, Moelle, Merle, & Born, in preparation, cited in Baldeweg, 2007). Since the cholinergic system is impaired with age (Araujo, Studzinski, & Milgram, 2005; Bartus, Dean, Beer, & Lippa, 1982; Muir, 1997; Terry & Buccafusco, 2003) and NMDA receptor concentration is reduced in aged primates (Gazzaley, Siegel, Kordower, Mufson, & Morrison, 1996), it is possible that the neurochemical system underpinning RP generation is impaired with age. That is, age-related change in the cholinergic system and possible changes in NMDA receptor density in older adults could explain reduced RP relative to young adults.

The age-related difference that we found in the response to repetition in the standard ERP was not present in our findings regarding the deviant ERP. In the early period of deviant waveforms at Fz, we found a significant repetition effect in the direction of RP (and a trend towards this at the mastoids). This is most likely explained by the fact that we used duration deviant stimuli that were only discernibly different from standards 50 ms post stimulus onset. Over the late deviant period, we observed a significant repetition effect in the opposite direction to RP (i.e. indicative of the MMN memory trace effect) only when we controlled for amplitude in the early deviant period (by subtracting amplitude in the early deviant period from the late deviant period). This finding, combined with the fact that two of three previous studies did not find evidence of a repetition effect on deviant waveforms (Haenschel et al., 2005; Cooper et al., to be submitted a; cf Baldeweg et al.,

2004), suggests that there is not a robust effect of repetition on deviant waveforms. Furthermore, unlike the age-related change in the response to repetition observed in the standard ERP, in the present study, the repetition effect over the late deviant period (after controlling for early deviant activity) was similar across groups. Therefore, with respect to repetition, our age-related difference was observed in the standard waveforms (over the P2 period at Fz) but not in deviant waveforms.

Since there was no repetition effect over the late deviant period in deviant ERPs unless we corrected for RP in the early deviant period, the marginal effect of repetition that we observed on late MMN amplitude (i.e. the MMN memory trace effect) was primarily due to RP over the P2 period in the standard waveforms which is in agreement with Haenschel et al. (2005) and Cooper et al. (to be submitted a). Given the lack of repetition x group interaction over the late MMN period at Fz or the mastoids, we suggest it is possible that RP over the P2 period is a more sensitive measure of age-related change in response to repetition than the MMN memory trace effect. In line with this view, Cooper et al. (to be submitted a) proposed that MMN recorded at Fz was not as sensitive to auditory stimulus repetition as RP recorded at Fz in a group of young adults. Both of these findings reflect the fact that MMN takes contributions from deviant as well as from standard waveforms. MMN therefore reflects more than simply the response to repetition in the standard waveform. Similarly, our correlational data provided further evidence that RP is more strongly related to memory functioning than the MMN memory trace effect.

Although Baldeweg et al. (2004) observed a relationship between the MMN memory trace effect and memory scores on the RBMT in patients with schizophrenia (correlations between RP slope and RBMT scores were not presented), in the current study, we only found a correlation in young adults between memory function on the RAVLT and

RP slope, not the MMN memory trace effect. In young adults, steeper RP slope (indicating greater differentiation between repetition conditions) correlated with better long term retention on the RAVLT. Further analyses conducted on early and late RP slope (i.e. RP slope derived from earlier compared to later repetition conditions) demonstrated that this relationship held true for early rather than late RP slope. We can therefore conclude that, in young adults at least, RP indexes a process related to memory performance. There are at least two ways to explain the lack of such a correlation in the older adult data. Firstly, it is possible that RP slope was a better indicator of memory function in young adults than in older adults due to the fact that, in older adults, a quadratic fit to the repetition effect was observed over the P2 period in standard waveforms. However, when we analysed early and late RP slope measures we still found no correlation with any RAVLT variables in older adults. Alternatively, it is possible that age-related differences that we observed in the RAVLT were mediated by age-related change in episodic memory (see review in Hoyer & Verhaeghen, 2006) more so than the implicit form of memory reflected by RP. Nonetheless, our results demonstrate that, in young adults, the dynamic response to repetition captured by RP slope is more closely related to memory (as proposed by Baldeweg et al., 2004 in relation to the MMN memory trace effect) than measures that mask this dynamic element (e.g. average RP or MMN amplitude). Our results also support the hypothesis that while MMN and the MMN memory trace effect may indirectly index the establishment and strengthening of auditory sensory memory traces, RP slope may be a more sensitive electrophysiological measures of sensory memory functioning (as previously proposed by Haenschel et al., 2005).

Before drawing conclusions from the results of this study, it is important to consider the hearing abilities of the older adults in this study. Although older adults in our study

showed signs of presbycusis, the fact that we used a lower range frequencies, raised intensity a set level above thresholds, and were primarily interested in repetition effects on the ERP rather than overall amplitude differences between age groups, suggests that presbycusis was not a major contributor to our findings. In fact, stimulus intensity did not differ significantly between groups, reflecting the fact that thresholds were more similar across groups at the lower than higher frequencies. Furthermore, since presbycusis is a condition that is virtually ubiquitous with age (Willott, 1991), our conclusions are generalisable to the older adult population.

Conclusions

In sum, we found an age-related difference in the response to repetition in standard waveforms (i.e. RP) but not in deviant or MMN waveforms. Given Baldeweg et al.'s (2006) description of the mechanisms governing the response to repetition in standard and deviant waveforms, we can conclude that the age-related difference in auditory sensory memory processing is specific to trace formation rather than deviance detection. However, significantly smaller late deviant amplitude and late MMN amplitude in older compared to young adults suggests that there is also an effect of age on deviance detection (which is potentially related to the sensitivity of older adults to the magnitude and dimension of deviance). In support of Baldeweg and colleague's assertion that RP is more directly related to auditory sensory memory trace formation than MMN or the MMN memory trace effect, we only found a relationship between a RAVLT variable and RP slope, not MMN amplitude or slope. However, we only observed this relationship for young, not older adults. Therefore, we did not find support for a relationship between age-related change in sensory memory trace formation and age-related change in a memory-based cognitive task.

Rather, our results in relation to the aging data suggest that the age-related change in RP amplitude is specific to a proposed anterior generator of RP, a finding which may represent evidence of a top-down suppression deficit (e.g. Gazzaley & D'Esposito, 2007) or reduced precision of feature encoding in older adults (e.g. Cooper et al., 2006). Moreover, this could mean that contextual features of auditory sensory memory traces are not encoded as precisely as in older compared to young adults. To further explore the relationship between RP, memory, and aging, future research could look at the functional correlates of RP by considering the relationship between RP and behavioural effects related to memory in young and older adults (e.g. Cooper, Todd, & Michie, to be submitted b).

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Chapter 5: study 4

In search of a behavioural correlate of repetition positivity in young and older adults[17]

[17] This paper is to be submitted to Biological Psychology by Cooper, R.J., Todd, J., and Michie, P.T.

In search of a behavioural correlate of repetition positivity in young and older adults

Although there is a wealth of literature concerning sensory decline with age (see review in Schneider & Pichora-Fuller, 2000) and age-related change in memory processes (see review in Hoyer & Verhaeghen, 2006), the literature concerning the effect of age on the sensory memory system that links sensory and cognitive domains is less abundant (Craik, 2000). In the auditory system, this intermediary processing stage is referred to as auditory sensory memory. Auditory sensory memory describes a period following auditory stimulation in which the features of sound are analysed, integrated, and briefly maintained (Cowan, 1984) in a representation that includes information about the auditory context in which sound is heard (Winkler, 2007). An understanding of the effect of age on auditory sensory memory could provide insight into a potential mediator of age-related change in higher order cognitive domains (e.g. auditory verbal memory). In recent years, researchers have identified a waveform of the auditory event-related potential (ERP), the repetition positivity (RP), that is thought to represent the establishment and strengthening of auditory sensory memory traces (Baldeweg, Klugman, Gruzelier, & Hirsch, 2004; Haenschel, Vernon, Dwivedi, Gruzelier, & Baldeweg, 2005). We have previously shown that there is a trend towards reduced RP amplitude with age (Cooper, Todd, & Michie, to be submitted b). Our data could be taken as evidence that older adults do not establish a precise memory trace of auditory information relative to young adults. However, given the fact that research into RP is still in its infancy, we believe that further investigation into RP and its functional correlates is warranted before a firm conclusion as to the significance of the age-related difference in RP can be drawn.

To elicit RP, an oddball paradigm with a ‘roving standard’ has generally been used (e.g. Baldeweg et al., 2004; Cooper et al., to be submitted b; Haenschel et al., 2005; cf.

Cooper, Atkinson, Clark, & Michie, to be submitted a). In the oddball paradigm, a frequent 'standard' sound is infrequently replaced by a 'deviant' sound that differs in some aspect from the standard (e.g. in frequency, intensity, or duration). The 'roving standard' refers to the case where standard tones are identical within trains (that are separated by deviant tones) but differ in pitch between trains. As the standard tone changes from train to train, the roving manipulation ensures that a memory trace of the standard tone must be established and strengthened over the course of each train. Using this paradigm results in the ERP to standards at the end of a train being more positive in amplitude (at Fz) than the ERP to standards earlier in a train over the latency period approximately 100 – 200 ms post stimulus onset. By subtracting the standard ERP for standards earlier in a train from the standard ERP for standards late in a train, RP emerges as a positive amplitude waveform which reverses in polarity at the mastoids. Previous work shows that there may be at least two generators of RP supported by neuronal populations that primarily encode either the local or global aspect of stimulus history (Cooper et al., to be submitted a). Cooper et al. (to be submitted a) suggested that an auditory cortex source of RP encodes and maintains a representation of auditory stimuli for a shorter time period than a more anterior generator of RP (possibly still located within the auditory cortex). In addition, there is evidence in the cat auditory cortex that neurons show stimulus specific adaptation (SSA; Ulanovsky, Las, & Nelken, 2003) on different time scales (Ulanovsky, Las, Farkas, & Nelken, 2004; whether different time scales of adaptation exist for different areas of the auditory cortex was not specifically examined). SSA essentially describes the reduction in neural firing which occurs as a function of stimulus repetition (repetition suppression) and thus may be a neural correlate of RP[18].

[18] Drawing a direct link between the response of single neurons and the pattern of activity

The conditions under which RP is elicited and the fact that RP increases with increasing repetition in the roving paradigm have promoted the idea that RP is related to sensory memory trace establishment. Since Winkler (2007) has recently argued that auditory sensory memory traces must contain information relating to the context in which auditory stimuli are heard, it is feasible that RP indexes the establishment of context into the auditory sensory memory trace. Another (complementary) way of interpreting RP is within the context of a predictive coding framework (e.g. Baldeweg, 2007; Friston, 2005; Garrido et al., 2008). The predictive coding framework states that bottom-up sensory information travels upstream to aid in the formation of predictions about future stimulation and that this top-down inferential information travels downstream to suppress predicted activity in lower levels. In this context, 'memory' is represented by the connections between higher and lower sensory levels (Baldeweg, 2007). RP forms part of this memory process by reflecting synaptic plasticity mediated by stimulus repetition. However, if a behavioural correlate of RP could be established, the argument that RP is related to the establishment of auditory sensory memory traces would be strengthened.

The type of memory most likely associated with RP, given that RP occurs under passive listening conditions, is an implicit form of memory referred to as priming. As mentioned, RP has been linked to SSA, a form of repetition suppression, and repetition suppression is thought to be a neural correlate of priming (Desimone, 1996). Priming

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observed in the ERP, which depends on the action of large populations of neurons, still poses difficulties (e.g. Grill-Spector, Henson, & Martin, 2006; Ulanovsky et al., 2003). Exactly how the increase in RP amplitude as a function of repetition could be related to the reduction in neural firing observed at the cellular level as a function of stimulus repetition is not clear. However, since neural adaptation contributes to cortical gain control (Ohzawa, Sclar, & Freeman, 1985) and since increased cortical thresholds have been linked with positive ERP waveforms at the scalp (Elbert & Rochstroh, 1987), it is plausible that SSA contributes to RP.

describes the change (improvement) in performance following repeated exposure to an item relative to when the item is novel (Schacter & Buckner, 1998). It has been suggested that repetition suppression is related to sharpened stimulus selectivity (see review in Desimone) which could explain the efficiency of responses to repeated stimuli (also see review in Grill-Spector et al., 2006). If RP is an ERP waveform related to this type of memory, we would expect to see a relationship between RP and the facilitation of responses to stimuli in longer versus short repetition conditions (akin to a priming effect).

Haenschel et al. (2005) attempted to establish a behavioural correlate of the repetition effects observed in the auditory ERP by implementing a roving oddball paradigm and asking participants to press a button whenever a deviant occurred. Although these researchers were able to record RP in the standard ERP, they found no repetition effect on the deviant ERP waveforms (unlike the consistent evidence of RP in standard waveforms, the evidence for a repetition effect in deviant waveforms is mixed). In addition, the researchers found no difference in time taken to detect the deviant as a function of the number of standards preceding the deviant. Since the RP is evident in the ERP of the standard rather than the deviant tone, we designed the present study in order to gauge participant responses to a question relating to standard rather than deviant tones.

If RP denotes a process relating to the establishment and strengthening of auditory sensory memory traces as has been proposed by others (Baldeweg et al. 2004; Haenschel et al. 2005) then a task which tests the precision of the memory trace of the standard in relation to the number of times the standard has been repeated would be the ideal way to assess whether a behavioural correlate of RP exists. In the current study, we modified the roving oddball paradigm such that after each deviant there was a silent pause followed by a 'probe' sound to which participants responded (see Figure 1). Fifty percent of the time the

probe sound was identical to standards in the previous train (same probe), while the other fifty percent of the time the probe differed from the previous standards in pitch (different probe). We asked participants whether the probe was the same or different to the previous train of standards and we recorded the percentage of correct responses and reaction time (for correct responses) following a short and a long train of standards.

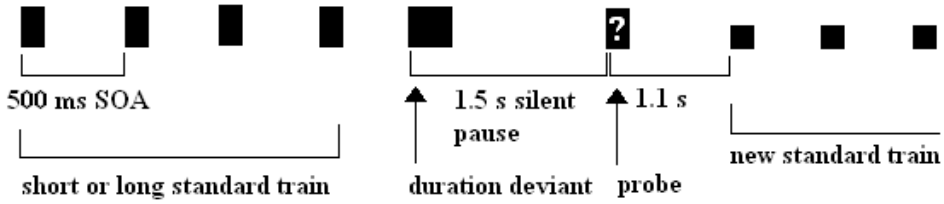

Figure 1. Paradigm for the current study. Standard and probe sounds were always 50 ms in duration whereas the duration deviant was always 100 ms. Height of rectangles reflects frequency (Hz) of the sounds; width reflects duration.

Although the paradigm we designed explicitly tests memory for the preceding set of sounds, the effect of repetition of the standard on responses to the probe can be viewed as an implicit process as the number of standards in the preceding train is not referred to in the question regarding the probe (although it should be noted that both explicit and implicit forms of memory could be active in the response to stimulus repetition; Bergerbest, Ghahremani, & Gabrieli, 2004). As stated, repetition suppression has been related to the implicit memory process that underpins behavioural priming effects (Bergerbest et al.; Desimone, 1996). If RP is an ERP correlate of this implicit memory process, then we should see that the larger the repetition effect (i.e. RP) in the ERP, the larger the repetition effect in the behavioural data (i.e. faster and more accurate identification of same probes

following long compared to short standard trains). Haenschel et al.'s null finding with respect to the effect of repetition on RT to detect deviants would suggest that the behavioural repetition effect would not extend to different probes. In support of the notion that the magnitude of RP could correlate with the magnitude of the behavioural repetition effect, Bergerbest et al. showed a correlation between a behavioural repetition effect (priming) to repeated auditory stimuli and repetition suppression (recorded by fMRI) in the superior temporal cortex and frontal regions of the brain.

In addition to exploring a potential behavioural correlate of RP, we were also interested in the possibility of replicating two of our previous findings in a new sample of adults: the age-related change in RP amplitude, and a relationship between RP and auditory verbal memory retention that was observed in young adults (Cooper et al., to be submitted b). Therefore, separately to the behavioural task, we recorded RP in young and older adults in a passive condition to allow replication of our previous findings. The interest in these research questions arose from the need to better determine the functional correlate of RP in order to understand the significance of age-related change in RP and its relation to auditory sensory memory functioning.

Method

Participants

Ethics approval for the study was obtained from the University of Newcastle Human Research Ethics Committee. Twenty–four young (mean age 19 yrs $\pm$ 3; 8 males) and 24 older (mean age 62 yrs $\pm$ 7; 7 males) adult volunteers were recruited for the study and all participants gave their written informed consent to participate. A telephone screen

was given to participants prior to recruitment to screen for neurological and psychological disorders, serious head injury, drug abuse, and visual or hearing impairments. Those in the young group were first year psychology undergraduates who received course credit for their participation. Older adults were recruited from the Hunter Medical Research Institute research volunteer register and were reimbursed for their travel costs. The Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975) was given to older participants to screen for dementia (cut-off of 23 out of 30 for dementia; Crum, Anthony, Bassett, & Folstein, 1993). The mean score on this test was 29 with a range of 27 to 30. We also used the Wechsler Test of Adult Reading (WTAR) and the Wechsler Abbreviated Scale of Intelligence (WASI; vocabulary and matrix reasoning subtests) to compare premorbid and current functioning between groups. Age-adjusted WTAR and WASI IQ estimates were 112.21 ($\pm$ 7.04) and 112.75 ($\pm$ 9.21) respectively for young adults and 110.04 ($\pm$ 10.70) and 124.20 ($\pm$ 8.37) respectively for older adults. There was no significant difference between groups for the WTAR ($p = .411$) but older adults scored significantly higher on the WASI IQ estimates than young adults ($t(46) = 4.508$, $p<.001$).

At the start of each appointment, auditory thresholds were tested in the left then right ear at five frequencies (0.5, 1, 2, 4, and 8 kHz) using a hand held audiometer with a resolution of 5 dB. All participants had less than 20 dB difference between thresholds for each ear for each frequency except for one older adult at 2 kHz, one at 4 kHz, and one at 8 kHz who had greater than 20 dB but less than 40 dB difference between ears at these frequencies. Mean auditory thresholds in dB HL are presented in Table 1 along with the difference between the young and older group. Young and older participants had auditory thresholds less than 35 dB HL for both ears at 500 Hz and 1 kHz frequencies. At 2 kHz one young adult and three older adults showed thresholds greater than 35 dB HL (<55 dB HL).

Eight older adults showed elevated thresholds at 4 kHz (<65 dB HL) and 14 at 8 kHz (<70 dB except for 4 individuals who could not hear the 8 kHz tone at the audiometer's limit of 70 dB HL). Thus approximately 14 of our 24 older adults showed signs of presbycusis, an age-related condition associated with elevated auditory thresholds at high frequencies. To account for this, we delivered low frequency tones in the experiment (between 700 Hz and 1200 Hz) and raised intensity 45 dB above individual threshold to a 950 Hz tone (midpoint of the 700 Hz and 1200 Hz tones).

Table 1

Auditory threshold data for the young and older group in dB HL (sd in brackets) and the difference between group means. Note the 5 dB resolution of the audiometer.

	0.5 kHz	1 kHz	2 kHz	4 kHz	8 kHz
Young	14.2 (5.9)	10.5 (6.0)	7.5 (8.6)	6.9 (7.1)	9.5 (10.2)
Older	14.7 (5.3)	12.6 (7.7)	15.0 (10.6)	23.2 (16.6)	36.4 (19.5)
Difference	0.5	2.1	7.5	16.4	26.9

Stimuli and procedure

Participants completed a series of assessments directly prior to the ERP experiment. These included a brief hearing test, Mini-mental state exam (older adults only), WTAR, WASI, and Rey Auditory Verbal Learning Test (RAVLT). The RAVLT taps into auditory verbal memory by requiring participants to listen to 15 item word lists and verbally recall as many words as possible at different delays. We derived several measures from the RAVLT: total score, initial recall, learning over trials, short term retention, and long term

retention (see Ivnik et al., 1990 for details). Following neuropsychological testing, participants took part in the ERP experiment.

Sounds in the ERP experiment were generated by Presentation ® software (Version 10, www.neuro-bs.com) and delivered over Sennheiser (HD280pro) headphones. Before testing began, stimuli were calibrated to dB SPL using a Brüel and Kjaer sound level meter. During the experiment, intensity was set at 45 dB above each individual's threshold to a 950 Hz tone. To determine an individual threshold, a PEST (parameter estimation by sequential testing) procedure (Taylor & Creelman, 1967) was employed with specifications as outlined in Treutwein's (1995) review. Participants were required to press a button on a response box every time they heard the 950 Hz tone played over headphones. Testing began at 55dB SPL with a step size of 8 dB after which Taylor and Creelman's heuristic rules determining the step size were implemented. We used the simplified Wald test as the decision rule defining when to change levels and employed a theta value of 0.75 (75% accuracy in responding required), and a 'w' value (deviation limit) of 1. The procedure was accurate to within 1 dB as testing ended when the step size fell below 0.5 dB. The mean intensity at which sounds were delivered in the experiment was higher ($t(35.9)= 2.9$, $p<.01$) for the older group (70.5 ± 4.2 dB SPL) compared to the young group (67.7 ± 2.4 dB SPL).

A variation on an oddball paradigm using a 'roving' standard and duration deviant was implemented for the ERP experiment (see Figure 1). Stimuli consisted of trains of binaural standard tones (50 ms, 5 ms rise/fall) which were followed by a 100 ms duration deviant (5 ms rise/fall). After the presentation of the deviant there was a silent 1.5 s pause whereupon a 'probe' sound was delivered (50 ms, 5 ms rise/fall). The next train of standards began 1.1 s following the onset of the probe. The 'roving' aspect of the paradigm arose from the fact that although standard tones were identical within trains, they differed

in pitch between trains. Standards pseudorandomly cycled through 11 different frequencies across trains (700, 750, 800, 850, 900, 950, 1000, 1050, 1100, 1150, and 1200 Hz). The number of standards presented in a train preceding a deviant was manipulated within subjects resulting in two repetition conditions; 4 or 16 standards were delivered before a deviant was presented. This occurred pseudorandomly. Within each standard/deviant train, the stimulus onset asynchrony (SOA) was 500 ms.

Half of the experimental stimuli were delivered in a passive condition where participants watched a silent video with subtitles while auditory stimuli were delivered over headphones. Participants were instructed to concentrate on the video and ignore the sounds. The other half of the stimuli were delivered as part of the behavioural task. Although we recorded the EEG during the behavioural task, the data are not reported here for two reasons. We observed artifacts in the ERP due to eyeblink activity associated with the button press made in the response period as well as the resolution of post-probe activity that resulted in slow positive drift of the ERP. The passive condition was always conducted first as it was thought that it would be more difficult to ignore the sounds once they had been attended to.

In the behavioural task, participants were told to attend to auditory stimuli and decide whether the probe sound after each 1.5 s silent pause was the same pitch or a different pitch to tones in the previous train. Fifty percent of probes were the same as standards from the preceding train (same probes). The other 50 percent of probes (different probes) differed in pitch to the preceding standards by 30 percent (for six standard frequencies, different probes were of higher pitch, while for the remaining five, different probes were lower). The left and right thumb were used to make responses and the hands used to respond ‘same’ or ‘different’ were counterbalanced across participants. Participants

were allowed 1 s to respond. Otherwise the trial was deemed incorrect. A computer screen prompted participants with the response mapping upon delivery of the probe (the labels 'same' and 'different' were also located above the appropriate response button) and provided feedback concerning whether answers were correct or incorrect. Practice was provided before the behavioural task began and lasted for as long as the participant required (several minutes on average). We collated behavioural data including: percentage correct responses and reaction times for correct responses for the two repetition conditions by the two types of probes. The passive condition and behavioural task took approximately 32 minutes each (broken into four 8 minute blocks). Short breaks were provided between blocks. In total, 3072 tones (including 2560 standards, 256 deviants, and 256 probes) were presented in the passive condition and in the behavioural task. The entire appointment lasted approximately 3 hours.

EEG Recording

The EEG was recorded from 15 scalp channels (F3, F4, Fz, FC3, FC4, FCz, C3, C4, Cz, T7, T8, CP3, CP4, CPz, & Pz) and from both mastoids using an electrode cap (Electro-Cap International) with sites located according to the 10/20 system and referenced to the nose. The vertical electro-oculogram (EOG) was recorded by electrodes above and below the left eye and the horizontal EOG by electrodes at the outer canthi of each eye. Continuous EEG was digitized at 250 Hz with a gain of 75000. A bandpass filter 0.1 – 30 Hz and 50 Hz notch filter were applied. Scan 4.2 software was used to acquire data and Scan 4.3 for off-line analysis.

Data Analysis

Data were processed offline and movement artefacts were manually removed. Eyeblink artefact correction was utilised (Semlitsch, Anderer, Schuster, & Presslich, 1986). A 50 ms prestimulus baseline and 448 ms post stimulus period was used to epoch EEG data. Epochs containing artefacts exceeding ± 100 μV in channels appart from EOG were rejected.

Latency windows covering waveforms of interest were chosen by selecting a window surrounding peak amplitude in the grand average waveforms. We extracted mean amplitude of N1 in the standard ERP (90 – 130 ms latency period). However we extracted peak amplitude of P2 (140 – 190 ms latency period) rather than P2 mean amplitude to preserve the same latency window for each group (there was a large difference in latency of P2 between groups). In order to quantify the latency difference in P2 between groups, we extracted the latency of the P2 peak.

As we have done previously (Cooper et al., to be submitted b), we averaged clusters of standards from each repetition condition to represent the effect of increasing repetition on the standard ERP. For each repetition condition, we ensured an approximately equal number of sweeps entered each average by deriving our standard waveforms in the following way: we averaged the 3rd and 4th standard from each repetition condition; the 7th, 8th, 9th, and 10th standard from the 16 repetitions condition; and the 13th, 14th, 15th and 16th standard from the 16 repetitions condition. We will refer to these averages as the 4, 8, and 16 repetition conditions respectively. RP was calculated by separately subtracting the standard ERP for the 4 and 8 repetitions conditions from the standard ERP for the 16 repetitions condition. We extracted RP mean amplitude over the period 100 – 200 ms post

stimulus onset. Deviant waveforms will not be presented here as they were not the focus of this study.

For the ERP to standard tones at Fz, we analysed N1 mean amplitude and P2 peak amplitude and latency derived from the aforementioned latency windows. We ran a 3 (repetition) x 2 (group) mixed design mANOVA (Pillai's trace). For RP mean amplitude we ran a 2 (repetition) x 2 (group) mANOVA. For mANOVAs on mastoid data, an additional within subjects factor, mastoid, was required. We also analysed behavioural data (percentage correct and reaction time) in a 2 (repetition) x 2 (probe) x 2 (group) mANOVA.

In order to perform a correlational analysis between the repetition effect in behavioural measures and the repetition effect in the standard ERP, we firstly found the slope of the regression line for RP amplitude as a function of stimulus repetition (RP slope). To do this, we used 8 and 12 as the two levels of the independent variable repetition (corresponding to the two subtractions of repetition conditions used to derive RP, i.e. 16 – 8 and 16 – 4). We used dependent variable values corresponding to RP mean amplitude in the 100 ms – 200 ms latency period for the two levels of repetition. We correlated RP slope with the difference in reaction time and accuracy between the short and long repetition conditions in the behavioural task. To explore the relationship between RP and memory performance, we correlated RP slope with RAVLT scores using Pearson's r. In order to control for the number of correlations performed, we adjusted alpha to 0.005.

Results

The ERP to standards in the passive condition

Over the N1 period at Fz, we observed a significant repetition effect in the direction of repetition positivity ($F(2,45) = 16.045$, $p<.001$) and a repetition x group interaction ($F(2,45) = 3.263$, $p<.05$). Although both groups showed a significant repetition effect in the direction of RP (young: $F(2,22) = 8.203$, $p =.002$; older: $F(2,22) = 10.044$, $p = .001$), Figure 2 shows that N1 mean amplitude was similar in the 4 and 8 repetitions conditions in the young group and the 8 and 16 repetitions conditions in the older group.

At the mastoids over the N1 period, we observed a main effect of repetition ($F(2,45) = 11.334$, $p<.001$). As repetition of the standard increased, so too did negativity at the mastoids. This highlights the reversal of polarity of RP at the mastoids. Unlike at Fz, the repetition x group interaction was not significant at the mastoids ($p = .380$).

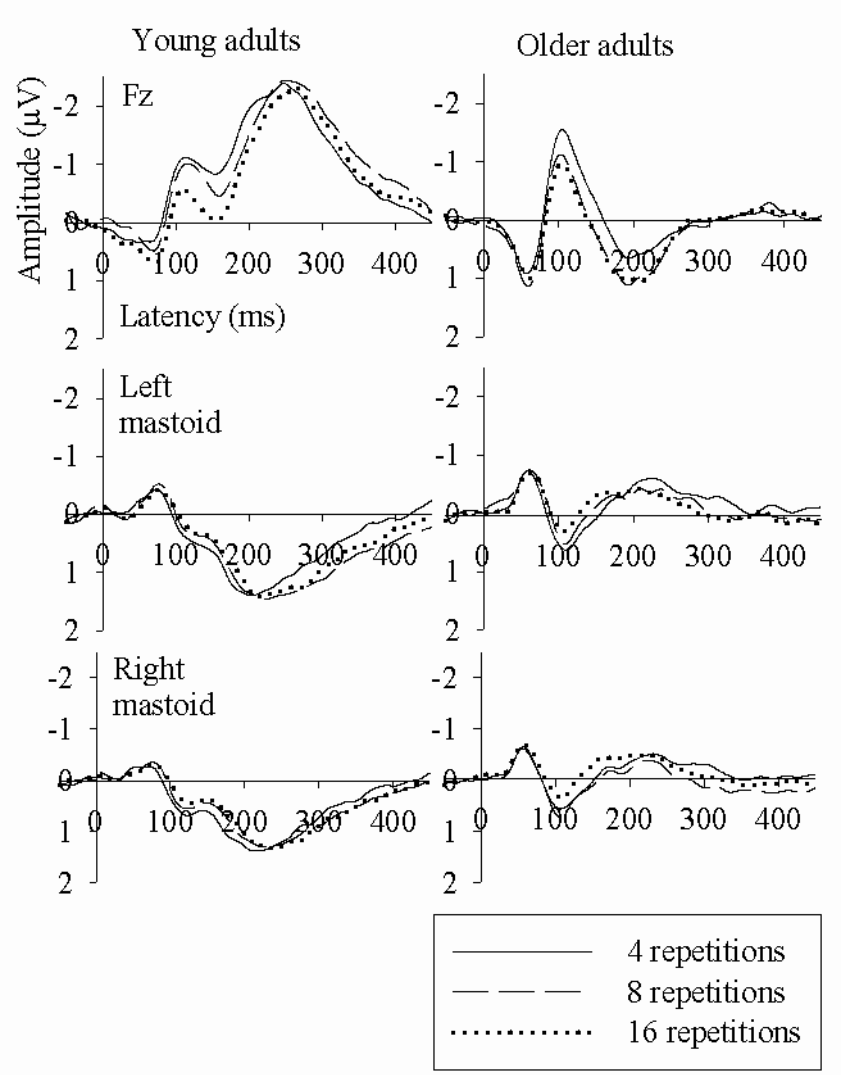

Figure 2. Passive condition standard waveforms for young and older adults at Fz (top row), the left mastoid (middle row), and right mastoid (bottom row). Repetition conditions are overlaid.

As with N1 amplitude, over the P2 period at Fz, we observed a significant effect of repetition ($F(2,45) = 23.480$, $p<.001$) in the direction of repetition positivity and a repetition x group interaction ($F(2,45) = 3.937$, $p = .027$). Although both groups elicited a

significant main effect of repetition (young: $F(2,22) = 16.186$, $p<.001$; older: $F(2,22) = 9.490$, $p = .001$), P2 amplitude was more clearly differentiated across repetition conditions in the young group than the older group (see Figure 2). In the older group, P2 amplitude for the 8 and 16 repetitions conditions was similar. There was an interaction between repetition and group for a linear ($F(1,46) = 4.030$, $p<.05$) and quadratic ($F(1,46) = 4.066$, $p<.05$) contrast. The repetition effect was best fit by a linear contrast in the young ($F(1,23) = 33.428$, $p<.001$) and by a linear ($F1,23) = 14.538$, $p <.001$) and a quadratic contrast ($F(1,23) = 5.712$, $p <.05$) in the old. The quadratic contrast was not significant in the young ($p = .445$). In both groups the linear contrasts represented the effect of increasing positive amplitude with increasing repetition. The significant quadratic contrast in the older group indicated that the magnitude of amplitude change in response to repetition was reduced with increased repetition. In addition, the main effect of group suggested that the older adult group had larger P2 peak amplitude than the young adult group ($F(1,46) = 28.120$, $p<.001$). P2 peak amplitude at Fz was also significantly delayed in older (194 ms $\pm$ 3) versus young (158 ms $\pm$ 3) adults ($F(1,46) = 55.805$, $p<.001$). Also note from Figure 2 that young adults show a second negative waveform at Fz that older adults do not appear to generate. This prominent negative waveform in young adults occurs in a similar latency window as the P2 occurs in older adults (and may therefore contribute to the age difference observed in P2 amplitude). For further information on this age-related difference refer to Bertoli and Probst (2005) as it will not be discussed further here.

At the mastoids, the effect of repetition for P2 peak amplitude was not significant ($p = .396$). The main effect of group remained significant ($F(1,46) = 53.140$, $p<.001$) with older adults showing larger reversal of P2 at the mastoids than young adults. Table 2

reveals means and standard deviations of N1 and P2 amplitude at Fz and the mastoids in the three repetition conditions for young and older adults.

Table 2

Means and standard deviations (in brackets) of N1 and P2 amplitude (μV) at Fz, the left mastoid (LM), and right mastoid (RM) in the three repetition conditions for young and older adults.

Waveform		Young adults			Older adults		
	Site	4	8	16	4	8	16
N1	Fz	-0.97	-0.82	-0.38	-1.26	-0.84	-0.68
		(0.92)	(0.90)	(0.90)	(1.24)	(1.21)	(1.12)
	LM	0.28	0.14	0.08	0.48	0.33	0.16
		(0.42)	(0.55)	(0.45)	(0.71)	(0.65)	(0.75)
	RM	0.48	0.34	0.21	0.44	0.52	0.19
		(0.46)	(0.49)	(0.54)	(0.65)	(0.64)	(0.62)
P2	Fz	-0.62	-0.29	0.24	0.89	1.34	1.36
		(1.26)	(1.22)	(1.06)	(0.91)	(0.67)	(0.74)
	LM	0.35	0.22	0.19	-0.87	-0.78	-0.77
		(0.41)	(0.57)	(0.58)	(0.83)	(0.72)	(0.71)
	RM	0.43	0.25	0.16	-0.77	-0.67	-0.89
		(0.64)	(0.61)	(0.52)	(0.70)	(0.57)	(0.60)

Repetition positivity in the passive condition

To visualize RP in a similar way to Haenschel et al. (2005), we subtracted standard waveforms for the shorter repetition conditions from the standard waveform for the 16 repetitions condition. The resulting difference waves depicting RP in the passive condition are shown in Figure 3. The morphology of RP suggests that it could represent an endogenous positivity superimposed on exogenous N1 and P2 waveforms in the standard ERP. We analysed RP over a window from 100 to 200 ms.

At Fz, there was a trend towards larger RP in young versus older adults ($F(1,46) = 3.335$, p .074). We observed a main effect of repetition at Fz ($F(1,46) = 20.459$, $p<.001$) indicative of the fact that RP increased as a function of increasing repetition of the standard tone. At the mastoids, where RP reversed polarity relative to Fz, the repetition effect was marginally significant ($F(1,46) = 3.371$, $p = .073$). The group effect was not significant at the mastoids ($p = .626$).

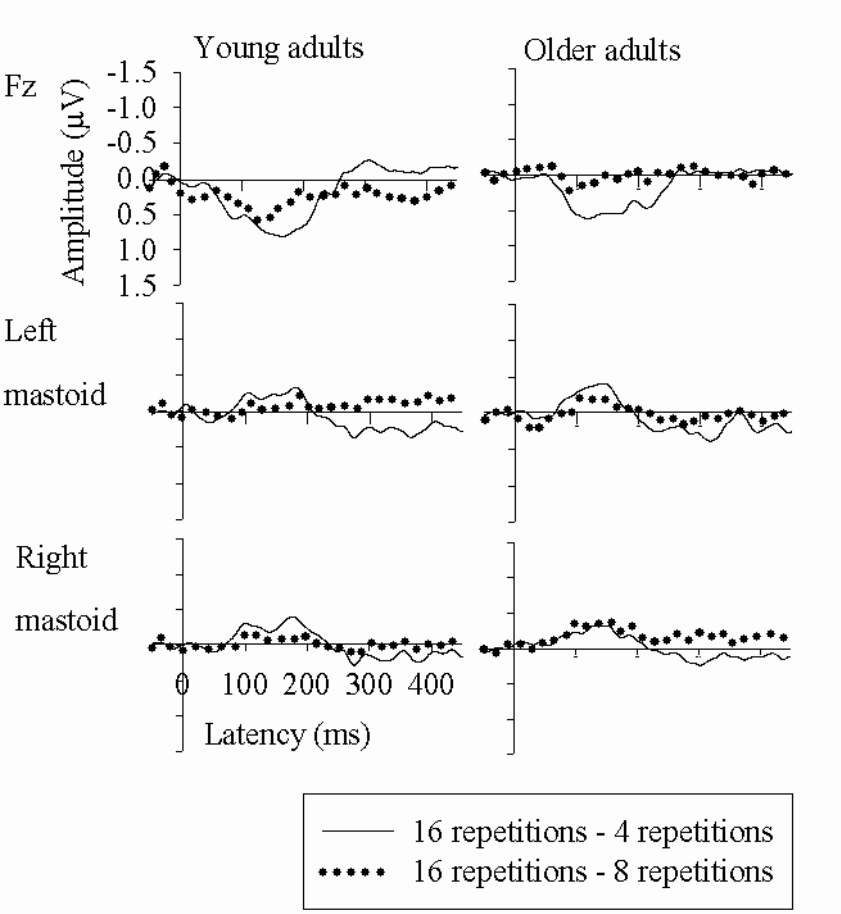

Figure 3. Repetition positivity difference waveforms for young and older adults in the passive condition at Fz (top row), the left mastoid (middle row), and right mastoid (bottom row).

Behavioural data from the active condition

For RT data, we found a main effect of probe ($F(1,46) = 14.608$, $p<.001$) which indicated that responses were faster in response to different probes over same probes. There was also a main effect of repetition ($F(1,46) = 23.484$, $p<.001$) and main effect of group ($F(1,46) = 8.875$, $p=.005$). Responses were faster in the 16 repetitions condition compared to the 4 repetitions condition (563 ms $\pm$ 10 vs 582 ms $\pm$ 10) and young adults were in general faster at responding to the probes than older adults (544 ms $\pm$ 14 vs 601 ms $\pm$ 14; see Figure 4).

Due to a ceiling effect in the accuracy data, the normality assumption underpinning ANOVA was violated. Hence, we used non-parametric statistical tests (Wilcoxon signed ranks tests to assess the repetition and probe effects, and Mann-Whitney tests to assess the group effects). As was the case for RT data, accuracy data revealed an effect of repetition for same ($z = -4.518$, $p<.001$) and different probes ($z = -2.808$, $p<.01$) and a group difference for same and different probes in the short and long repetition conditions ($z = -3.269$, $p<.001$; $z = -3.319$, $p<.001$; $z = -2.568$, $p<.01$; $z = -2.057$, $p<.05$ respectively). Accuracy was higher in the 16 repetitions condition relative to the 4 repetitions condition for same (92 % $\pm$ 1 vs 88 % $\pm$ 1) and different probes (92 % $\pm$ 1 vs 89 % $\pm$ 1), and young adults were in general more accurate than older adults (94 % $\pm$ 2 vs 86 % $\pm$ 2). Unlike in the RT data, we found no difference between same compared to different probes in the accuracy measure for the 4 repetitions ($z = -1.605$, $p = .108$) or 16 repetitions condition ($z = -.350$, $p = .726$). These effects can be seen in Figure 4.

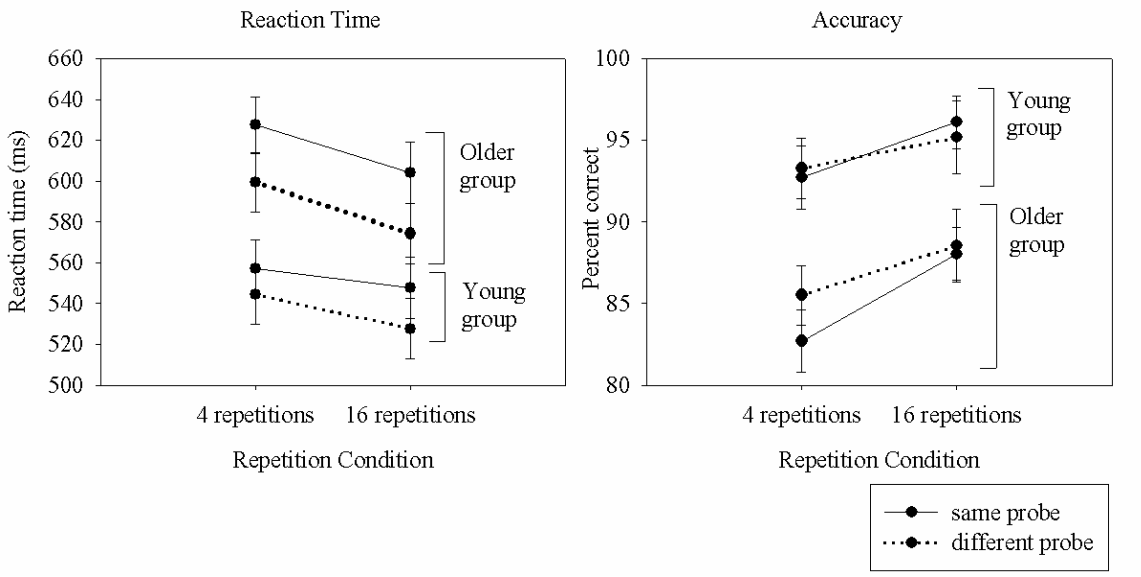

Figure 4. Reaction time (left) and accuracy (right) data for the behavioural task in the active ERP condition. The young and older adult group data are represented for same probes (solid line) and different probes (dotted line). Error bars represent SE.

Correlations between RP and behavioural measures

From the behavioural data we created four measures reflecting the behavioural effect of repetition in order to examine correlations with ERP data. That is, for accuracy and RT data for same and different probes we subtracted performance in the 4 repetitions condition from the 16 repetitions condition and correlated these with RP slope from the passive condition. We found that RP slope did not correlate with the behavioural effect of repetition for RT or accuracy in either the young or older group[19].

[19] We also looked at the correlation between the four behavioural measures and data from the standard waveform over the P2 period in the passive condition. Specifically, we used the difference between P2 amplitude in the 16 and 4 repetitions conditions as we concluded that this was most comparable ERP measure to the behavioural measures. None of the correlations were significant in either group.

Correlations between RP and auditory verbal memory measures

Table 3 reveals that the only significant difference between age groups on the RAVLT occurred for the initial recall trial ($t(46) = 2.769$, $p<.01$) and the RAVLT total score ($t(46) = 3.747$, $p<.01$). Young adults outperformed older adults on these two measures. The same pattern of results was revealed when we used WASI IQ scores as a covariate.

Table 3

Young and older group mean scores for the RAVLT (sd in brackets).

RAVLT measure	Young group	Older group
initial recall *	8.6 (1.5)	7.3 (1.9)
total score*	61.5 (5.9)	53.6 (8.5)
Learning over trials	1.5 (0.22)	1.5 (0.29)
short term retention	95 (9)	90 (15)
long term retention	92 (11)	92 (16)

* significant between group difference, $p<.01$

We were interested in examining the correlation between repetition positivity slope and scores on the RAVLT. Mean RP slope for the young was 0.07 ($\pm$ 0.16) and for older adults was 0.11 ($\pm$ 0.12). The difference was not significant ($p = .321$). None of the within-group correlations were significant at alpha = 0.005. However, in the young group, we observed a marginally significant correlation between repetition positivity slope and scores on the initial recall trial of the RAVLT ($r = .447$, $p = .029$). This correlation indicates that steeper RP slope (indicative of greater differentiation between repetition conditions) is associated with better recall of items on the first trial of the RAVLT. The correlation was

not significant in the older group (r = .004, p = .986). Scatterplots showing this relationship are presented in Figure 5.

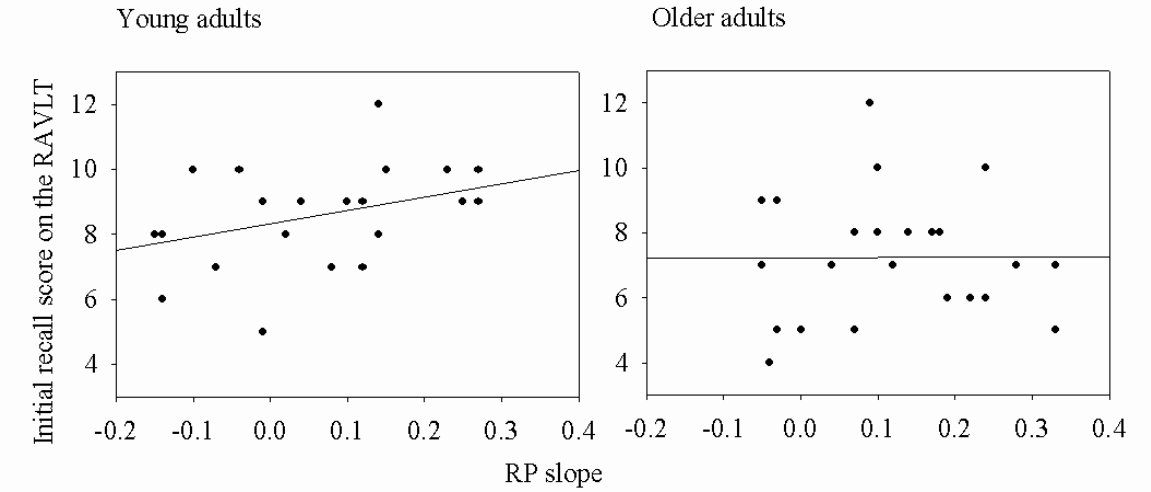

Figure 5. Scatterplots with regression lines for the young (left) and older group (right). Plots show repetition positivity slope (x-axis) versus scores on the initial recall trial of the RAVLT (y-axis).

In a previous study (Cooper et al., to be submitted b), we highlighted that RP slope might be a better indicator of memory function in young than older adults, since we observed a quadratic fit to the P2 data in the standard waveforms in that study. We also observed a quadratic fit to P2 data in the present study. In our previous study we addressed this concern by generating RP slope from an early and late repetition period. However, we were unable to replicate this procedure here due to the reduced number of repetition conditions used in the current study. Therefore, we analysed P2 slope in an early and late repetition period. Early P2 slope was calculated as the slope of P2 between the 4 and 8 repetition conditions, while late P2 slope was derived by calculating the slope of P2

between the 8 and 16 repetition conditions. Similarly to Cooper et al. (to be submitted b), we found that the correlation between RP slope and a RAVLT variable (in this case, initial recall score) observed in young adults was primarily determined by activity from the early rather than late repetition conditions. That is, in young adults, we observed a marginally significant correlation between early P2 slope and initial recall score ($r = .381$, $p = .066$) but not late P2 slope and initial recall score ($r = -.132$, $p = .540$) in young adults. Interestingly, in older adults, we observed a negative correlation between late P2 slope and short term retention on the RAVLT ($r = -.566$, $p = .004$). As P2 slope was not analysed in our previous study, we conducted a re-analysis of P2 data from that study. This also revealed that, in older adults, there was a negative correlation between late P2 slope (late P2 slope calculated using 16 and 24 repetitions conditions) and initial recall score on the RAVLT ($r = -.509$, $p = .009$). The correlation that we previously observed between early RP slope and long term retention in young adults was replicated in the re-analysed P2 data: we observed a correlation between early P2 slope and long term retention ($r = .409$, $p = .043$). In sum, across two studies, it appeared as though steeper P2 slope calculated from the late repetition period was related to poorer auditory verbal memory performance in older adults. This relationship was in the opposite direction to that observed between RP slope (from an early repetition period) and RAVLT variables in young adults across the same two studies. Figure 6 presents scatter plots showing the negative correlation between late P2 slope and RAVLT variables in older adults from Cooper et al. (to be submitted b) and the current study.

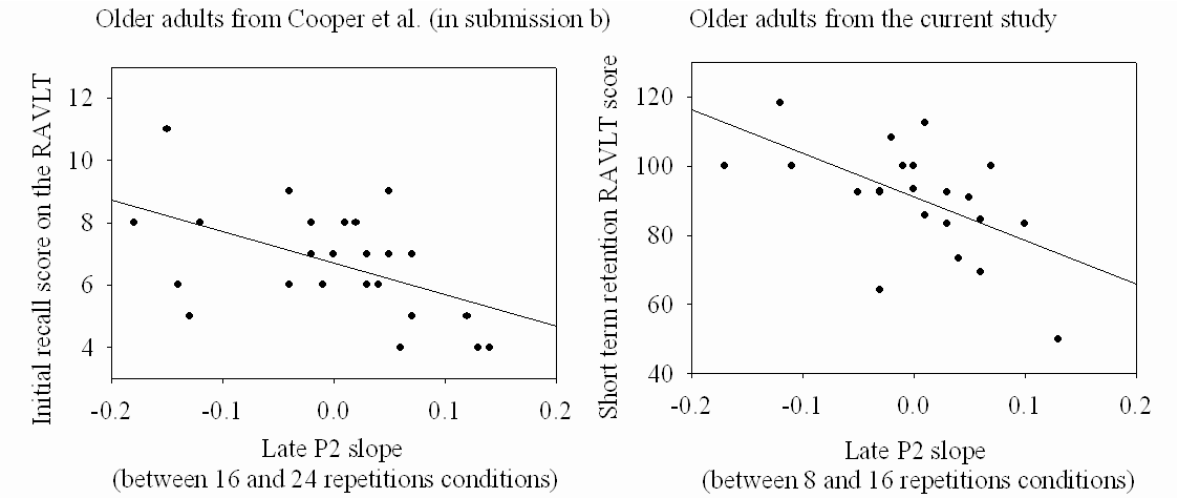

Figure 6. Scatterplots with regression lines for the older group from Cooper et al. (to be submitted, b; left) and the current study (right). Plots show late P2 slope (x-axis) versus scores on the initial recall trial of the RAVLT (y-axis; left) and the short term retention RAVLT task (y-axis; right).

Discussion

The effect of repetition on the auditory ERP

In the passive condition, young adults showed a clear effect of repetition (RP) in standard waveforms, especially over the P2 period at Fz. Although older adults showed evidence of RP between the 4 repetitions condition and the longer repetition conditions at Fz, the standard ERP for the 8 and 16 repetitions conditions was similar. In effect, we replicated the repetition x group interaction in P2 amplitude (at Fz) that we have previously observed (Cooper et al., to be submitted b). In our previous study, this resulted in a trend for smaller RP amplitude in older compared to young adults, a result also seen in the present study. Given the similarity of the results across two different samples, we can be

confident that the age-related difference in response to repetition in the auditory ERP is a robust finding.

As outlined in the introduction, it is likely that RP represents neural adaptation (SSA) occurring within a predictive coding system and that, as such, RP indexes the establishment of context into the auditory sensory memory trace. Thus, the age-related difference in the response to repetition observed in our standard waveforms at Fz in the passive condition could be interpreted as indicating that older adults have reduced capacity to differentiate between repetition conditions and encode contextual information relative to young adults. The alternative explanation is that older adults show an increased capacity to quickly establish repetition suppression. We argue that the former interpretation is supported by literature on the neurochemistry of RP and of aging.

The RP is augmented by nicotine (Baldeweg, Wong, & Stephan, 2006) and reduced by ketamine administration (Baldeweg, Moelle, Merle, & Born, in preparation, cited in Baldeweg, 2007). These findings implicate NMDA receptors and the cholinergic system in the process of RP generation (NMDA receptors are modulated by acetylcholine; Baldeweg, 2007). Yu and Dayan (2002) have proposed that acetylcholine levels regulate the balance between bottom-up sensory and top-down predictive information, in essence reflecting the certainty of predictions contained in top-down information. Therefore, a compromised cholinergic system could impair plasticity in context dependent situations (Baldeweg, 2006), such as in the roving-standard oddball paradigm. The cholinergic hypothesis of aging, formulated over two decades ago (Bartus, Dean, Beer, & Lippa, 1982), implicates impaired cholinergic functioning as a causal agent mediating memory deficits that occur with age (e.g. Araujo, Studzinski, Milgram, & 2005; Muir, 1997; Terry & Buccafusco, 2003). In addition, it has been shown that NMDA receptor concentration is reduced in aged

primates (Gazzaley, Siegel, Kordower, Mufson, & Morrison, 1996). Since increased RP occurred via a cholinergic agonist (nicotine) and decreased RP via an NMDA receptor antagonist (ketamine), a compromised cholinergic system and possible changes in NMDA receptor density in older adults could affect cortical plasticity and explain reduced RP relative to young adults.

The preceding discussion of the age-related difference in the response to repetition focused on data recorded at Fz. At the mastoids, we did not record an interaction between age group and repetition over the N1 or P2 period in this or our prior study. Given our outline of two possible RP generators in the introduction, we can conclude that older adults are not impaired in terms of the RP generator that responds to local features of auditory stimulation but that there is an age-related difference in the more anterior generator of RP that is proposed to operate on a longer time scale of adaptation (see Cooper et al., to be submitted a). Although we established that there is an age-related difference in RP, we also wished to determine how age-related change in RP might affect behaviour.

Is there a behavioural correlate of RP?

Older adults were slower and not as accurate on the behavioural task relative to young adults (Figure 4). However, both groups showed faster RT and higher percent correct for the 16 repetitions condition relative to the 4 repetitions condition. The similarity of the behavioural repetition effect across groups is not unexpected given that the behavioural task compared the 4 and 16 repetition conditions and the older adults did show differentiation between these repetition conditions in the standard ERP in the passive condition. In addition, the behavioural effect of repetition was in the expected direction, that is, we saw facilitation of responding to probes following greater repetitions of the

standard tone. Unexpectedly, the behavioural effect of repetition was observed in response to both the same and different probes in RT and accuracy measures. The behavioural repetition effect for same probes can be interpreted as a priming effect. However, the repetition effect for different probes cannot directly represent a priming effect (although the duration of different probes was primed we would not expect this to cause a repetition effect as the same duration standards and probes were used across the entire experiment). It appeared as though the repetition of the standard tone not only facilitated responding to that tone but also facilitated responding to other tones[20]. Upon closer inspection, these findings are compatible with the predictive coding framework used to describe the process generating RP.

Predictive coding suggests that top-down suppression of neuronal responses to predicted stimuli explains RP. Novel stimuli violate predictions and therefore generate an error signal thought to be represented in the ERP by mismatch negativity (MMN; Baldeweg, 2007). There is evidence that MMN increases as a function of repetition of the standard tone (Javitt, Grochowsky, Shelley, & Ritter, 1998) thus implying that the strength of the error signal is related to the preceding number of repetitions of the standard. This suggests that novelty detection could be influenced by repetition suppression (see also Desimone, 1996). Therefore, it is plausible that, the larger the amplitude of RP (i.e. in response to greater numbers of repetitions), the larger the facilitation of responses to novel

[20] RTs were also faster overall to the different probe than the same probe in both groups. Such an effect has previously been observed by Bindara, Williams, and Wise (1965). Bindara, Donderi, and Nashisato (1968) claim that 'different' responses will be faster than 'same' responses in cases where stimuli can only be differentiated in a relative sense (e.g. tone frequency). Bindara et al. (1968) proposed that the opposite effect (i.e. same responses faster than different) will occur when the differences between stimuli are absolute (e.g. letters). The mechanism explaining these findings has not been clearly identified (see review in Farell, 1985).

stimuli. Thus, we could conclude that the behavioural effect of repetition observed in both the same and different probes provides indirect evidence that there is a behavioural correlate of RP. This does not explain why Haenschel et al. (2005) did not observe the behavioural effect of repetition in their study where the task was to detect whether a deviant was higher or lower in frequency than the preceding standards. The only explanation we can offer is that, since participant mean RTs were generally faster in our study than in Haenschel et al.'s study (544 ms versus approximately 620 ms respectively for young adult samples), perhaps methodological differences between the two studies (e.g. the silent interval prior to probes and the response time-limit of 1 s imposed on our participants) encouraged faster responding in our study and allowed us to observe the behavioural repetition effect for different probes.

An alternative possibility is that the behavioural effect of repetition is explained by the predictability of occurrence of the probes. That is, there was a 50 percent chance that a probe would occur after 4 repetitions of the standard, whereas the probe occurred 100 percent of the time following 16 repetitions of the standard. On the other hand, it could be argued that any attempt to test the behavioural effect of increasing repetition will, by definition, also involve manipulating the predictability of a required response. In future, predictability could be reduced by jittering the occurrence of probes such that probes could occur at any position in a train. Thus, while we were able to observe the expected effect of repetition on behaviour, we cannot rule out the possibility that factors other than RP contributed to the behavioural effect. For example, Bergerbest et al. (2004) and Desimone (1996) suggest that repetition suppression is a passive response to repetition while the opposite effect, repetition enhancement, is more closely related to active memory processes

(although note that Haenschel et al., 2005, previously recorded RP in an ignore and attend condition).

Therefore, it is possible that the behavioural repetition effect could have been caused by repetition suppression (i.e. RP), repetition enhancement, predictability of probes, or a combination of factors. Since we have shown that the implicit coding of stimulus repetition is represented by RP, it remains plausible that the behavioual repetition (priming) effect that we observed is a behavioural correlate of RP even though we were not able to demonstrate a correlation between RP slope with the behavioural repetition effect. In addition, the behavioural repetition effect can be explained by the predictive coding model, a model which we believe best explains the nature of RP generation.

The relationship between RP and auditory verbal memory

We saw that in young adults only, RP slope correlated with the initial recall score on the RAVLT and that this was primarily due to changes occurring across early rather than late repetition conditions. In our previous study, we observed a correlation between RP slope and long term retention on the RAVLT in young adults that also appeared to be driven by activity in early rather than late repetition conditions. The relationship between RP and auditory verbal memory in young adults shows that functioning in a low-level form of memory (auditory sensory memory) could potentially influence functioning in a higher order test of memory. Hence, one could argue that age-related change in RP could influence cognitive change in older adults. However, the lack of a relationship between RP slope and the RAVLT in older adults suggests otherwise. This could be due to the fact that RP slope is a good indicator of the response to repetition in young adults where the response to repetition is linear, but a poor indicator of the response to repetition in older

adults where the response to repetition in the ERP can be fitted by a quadratic function (see P2 data). We tested this hypothesis by examining P2 slope from early and late repetition conditions. Surprisingly, we found that there was a negative correlation between late P2 slope and short term retention in older adults. Furthermore, in a re-analysis of data from a previous study (Cooper et al., to be submitted b), we found a similar negative correlation between late P2 slope and initial recall score on the RAVLT in young adults. In light of these findings, we suggest that the saturation of the response to repetition that we observe in older adults may reflect a compensatory mechanism. That is, perhaps there is a benefit to older adults that accrues from not differentiating between repetition conditions; although this may disrupt their ability to distinguish the precise temporal context in which information was encountered, it may also result in a stronger memory that an event has occurred. It is possible that this type of compensatory mechanism (acting on implicit memory) could arise in order to counteract the well documented change in the explicit memory system of older adults (e.g. see review in Hoyer & Verhaeghen, 2006). That is, with age, content may come to be valued over context in implicit memory. There is some evidence that age-related change in explicit memory results in a form of compensation. For example, when older adults perform recognition memory tasks, they are more reliant than young adults on methods other than explicit recollection (such as familiarity; see review in Fabiani & Wee, 2001; Prull, Dawes, Martin, Rosenberg, & Light, 2006).

Potential caveats

Although we relate findings from our older adult group to the process of aging, there are several aspects of our older adult group worth mentioning. The majority of adults in the older group showed signs of presbycusis and since sound intensity was raised a set

level above threshold, the older adult group heard louder stimuli than the young. This said, it is thought that a degree of hearing loss is virtually ubiquitous with age (Willott, 1991) which means that the current results are generalisable to the older adult population. Since the results regarding the age-related difference in the response to repetition in the standard ERP were similar to our previous study (Cooper et al., to be submitted b) where auditory input was not significantly different between the age groups, we suggest our findings are not related to differential sound intensity between groups. In addition, while we did not test the pitch discrimination abilities of older adults, we do not believe that age-related change in pitch discrimination explains our results. Although pitch discrimination ability deteriorates with age (Abel, Krever, & Alberti, 1990; König, 1957), the older adults should have been able to distinguish the minimum frequency difference (50 Hz) between standards in consecutive trains according to König and Abel et al.'s normative data on the topic. Also, the fact that we saw discrimination between our shortest and the longer repetition conditions in the ERP suggests that older adults could discriminate between the roving frequencies (i.e. if the older adults could not discriminate between the roving frequencies, we should not have seen any repetition effect in the ERP at Fz for this age group). Therefore, we believe that the similarity between the standard ERP for the longer repetition conditions in older adults is indicative of an altered response to repetition rather than an inability to distinguish the roving frequencies. However, it is plausible that reduced capacity to encode sound features precisely with age contributes to the build-up (and saturation) of RP with age (as suggested by Cooper et al., to be submitted b). This could occur if the roving standard stimulated a broader population of neurons in older compared to young adults (see Figure 7). Similarly, we have previously shown that in young adults, RP saturates at Fz when a constant rather than a roving standard is delivered (Cooper et al.,

to be submitted a). Cooper et al. (in preparation b) also suggested an age-related top-down suppression deficit (see Gazzaley & D'Esposito, 2007) as an alternative explanation to the encoding deficit hypothesis. Finally, the fact that older adults in this study were high functioning (as indicated by significantly higher WASI IQ scores relative to young adults) suggests our results were not due to age-related deficits in current functioning.

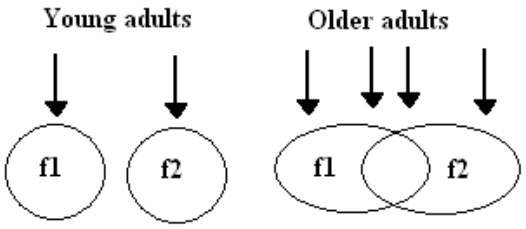

Figure 7. Arrows represent repetition suppression acting on a population of neurons responsive to a single roving standard frequency (e.g. f1 or f2). A broader population of neurons may be stimulated by each roving standard in older adults (right) relative to young adults (left).

Conclusions

Three main findings inform conclusions about this study. Firstly, we replicated our previous finding that older adults do not differentiate between longer repetition contexts in the ERP in the same manner as young adults, and established this age-related difference as a robust finding. This age-related difference is restricted to a generator of RP which maintains auditory sensory memory representations pertaining to global stimulus history. Secondly, we established a potential behavioural correlate of RP, akin to a priming effect. However, the fact that we had difficulty recording RP in conjunction with a behavioural task meant it was difficult to directly relate RP to the observed behavioural repetition

effect. An avenue for future research would be to see whether we could replicate the age-related blunting of the repetition effect observed in the ERP in a behavioural task (by using a greater range of repetition conditions than those used in the current behavioural task). Thirdly, we found that RP slope correlated with performance on an auditory verbal recall task (RAVLT) in young adults as we have seen previously. Therefore, combined evidence from this study and from study of the theoretical and neurochemical bases of RP suggests that RP is related to memory formation and that this process is disrupted in older adults. Our research does, however, highlight that the change in RP amplitude with age could represent a compensatory mechanism due to the fact that we observed a negative correlation between P2 slope and short term retention in older adults. This research could have implications for theories of cognitive aging as age-related change in auditory sensory memory may be a potential mediator of age-related change in aspects of cognition that rely on implicit processing of auditory information. It would be interesting to see whether a task tapping contextual aspects of stimulation, such as a frequency estimation task, is related to RP. It has been shown that, relative to young adults, older adults have difficulty estimating the number of times that an item has recently been presented when the number of repetitions increases above approximately five (Freund & Witte, 1986; Hasher & Zacks, 1979; Mutter & Goedert, 1997).

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Chapter 6

General Discussion

General Discussion

Summary of the research studies

The research that I have conducted and report within this thesis has been primarily concerned with i) the effect of age on auditory sensory memory and ii) the relationship between such age effects and age-related change in other types of memory for auditory information. To achieve this, I assessed how the presentation rate and repetition of auditory stimuli affects the auditory ERP of young and older adults by examining several auditory ERP waveforms, N1, P2, MMN, and RP. More specifically, study 1 examined the effect of age on N1 and P2 amplitude for different stimulus delivery rate (SOA) conditions. In study 2, we investigated the conditions eliciting two repetition effects, RP and the MMN memory trace effect, in the auditory ERP of young adults. Study 3 was concerned with the effect of age on RP and the MMN memory trace effect as well as the relationship between repetition effects in the auditory ERP and explicit memory for auditory information. Finally, in study 4, we re-examined the effect of age on RP. Furthermore, we looked at the relationship between RP and implicit memory for contextual information in addition to explicit memory for auditory information. In the following, I will summarise and integrate results from the four studies to support conclusions regarding the nature of age-related change in auditory sensory memory, whether a relationship exists between age-related change in auditory sensory memory and other types of memory for auditory information, and how these findings relate to theories of cognitive aging. Due to the manner in which the studies of this thesis have been presented (journal article format), I will also reiterate the links between the studies.

Age-related change in auditory sensory memory and the auditory ERP

Hearing sensitivity of older adults across studies

In the discussion section of each study, we have argued that our ERP findings are not explained by age-related differences in peripheral hearing mechanisms, even though the majority of older adults in studies 1, 3, and 4 showed signs of presbycusis, an age-related condition defined by a loss of hearing sensitivity, particularly for high frequency sound. Therefore, the hearing sensitivity of older adults in our studies will not be discussed further in this section.

A note on P1 and N2 waveforms

Although P1 and N2 waveforms were not the focus of the research presented in this thesis, there are several points worth mentioning in relation to these waveforms. In agreement with previous research on P1 (Amenedo & Diaz, 1998b; Fabiani et al., 2006; Pfefferbaum et al., 1979) and N2 (Bertoli & Probst, 2005; Čeponiene et al., 2008), figures from studies 1, 3, and 4 suggest that P1 was larger and N2 was smaller in older compared to young adults. Moreover, while not all of these findings were reported in the body of the thesis, we analysed P1 and N2 differences in studies 1 and 3 and found that the age related differences in P1 and N2 were significant[21] (due to the consistency of these results we did

[21] In study 1, P1 at Fz (over a 40 - 60 ms time window) was marginally larger in older versus young adults across SOAs ($F(1,43) = 3.95$, $p = .053$) but significantly larger at the 500 ms SOA ($t(43) = 2.38$, $p<.05$). This agrees with the age effect on P1 reported in study 3. Due to the latency shift in N2 with increasing SOA in study 1, we used a different 40 ms search window for each SOA condition to analyse N2 (500 ms: 240 – 280 ms; 1 s: 280 – 320; 3 s: 310 – 350; 6 s: 310 – 350; 9 s: 330 – 370) and found that young adults produced significantly larger N2 than older adults at Fz ($F(1,43) = 14.16$, $p = .001$). Similarly, in study 3, the age difference in N2 was significant over a 250 – 300 ms search window at Fz ($F(1,48) = 118.62$, $p <.001$).

not conduct such analyses in study 4). In the introduction, I indicated that the direction of age-related change in P1 and N2 waveforms could represent a reduced capacity to inhibit processing of irrelevant auditory stimuli. However, without data specifically testing this interpretation, I cannot speculate further on the extent to which this conclusion is justified with respect to the current studies.

Nonetheless, the question remains, to what extent inefficient inhibitory processing (as potentially demonstrated by older adults) could affect auditory sensory memory. In fact, there is evidence that this form of attentional disregulation could be beneficial to memory performance in particular circumstances. For example, it has been shown that, compared to young adults, older adults exhibit greater priming of words previously presented as distracters in another task (Rowe, Valderrama, Hasher, & Lenartowicz, 2006; for a similar type of result see Gazzaley & D'Esposito, 2007). This finding is in contrast with previous literature showing a small but significant advantage to young over older adults on priming tasks. To understand such a result, it helps to consider the following: while a reduced capacity to inhibit irrelevant stimuli could certainly lead to poorer performance on a primary task involving relevant stimuli, memory benefits may emerge if seemingly irrelevant stimuli later become relevant (arguably an ecologically valid circumstance). Therefore, attentional disregulation as potentially indicated via P1 and N2 waveforms in older adults could result in changes in sensory memory processing that are beneficial to implicit memory. Although this hypothesis requires further investigation (we did not manipulate relevance of stimuli in the studies of this thesis), I have included these points as they contribute to a theme that I will return to and expand upon in a later section on 'the issue of compensatory brain activity'.

N1 and P2 waveforms

In study 1, we established that the previous lack of agreement in the literature regarding the effect of age on N1 and P2 waveforms of the auditory ERP may well be due to the differences in stimulation rate (SOA) used in various studies. That is, we found that age differentially affected the underlying components contributing to N1 and P2 amplitude recorded at the scalp. As the functional relevance of age-related change in N1 component 2 and the proposed frontal N1 and P2 components could not be established, we could not rule out the possibility that there are changes in the way that older adults encode auditory information into auditory sensory memory. However, since we did not observe evidence of age-related change in N1 component 1 (thought to reflect encoding of sound properties; Näätänen & Picton, 1987) we concluded that if age does affect the ability to encode sound properties into auditory sensory memory, N1 component 1 is not the mechanisms through which this occurs.

As we did not find evidence of larger N1 in older compared to young adults at faster stimulation rates in study 1, even though we have previously observed a trend in this direction in an oddball paradigm (Cooper et al., 2006), we suggested that the age effect on N1 may also be affected by the type of paradigm used (i.e. oddball versus the single tone presentation delivered in study 1). That is, our prior result (Cooper et al., 2006) may have been mediated by a waveform observed over the N1/P2 period in the oddball paradigm, RP (e.g. Baldeweg et al., 2004; Haenschel et al., 2005). RP may be more likely to occur in oddball than single tone presentations considering that the predictive coding model thought to underpin RP generation (e.g. Baldeweg, 2007) is likely to be more active under oddball than single tone conditions (i.e. probabilistic versus monotonous stimulation). Furthermore,

if RP occurring under oddball conditions were delayed in older adults, this could potentially result in larger N1 and P2 in older compared to young adults when the oddball paradigm in used (see below). Given the hypothesis that RP may be affected by age, and since it was claimed that RP may provide a direct measure of auditory sensory memory trace formation (Baldeweg et al., 2004; Haenschel et al., 2005), we continued our investigation of the relationship between age and auditory sensory memory by focusing on RP in studies 2, 3, and 4.

In studies 3 and 4 we found more support for our assertion that the type of paradigm implemented can influence the age effect on N1 and P2 amplitude. Despite finding no age difference in P2 amplitude at a short (500 ms) SOA in study 1, we found significantly larger P2 amplitude in older versus young adults using the same short SOA in studies 3 and 4. While we did not observe significantly larger N1 amplitude in older compared to young adults in study 3 or 4, the figures from both studies suggest a trend in this direction. As stated, these results could be indicative of age-related delay in RP. Although not reported in the body of this thesis, we attempted to test this claim. We chose the RP waveform with the best signal-to-noise ratio, namely the 24 - 4 RP waveform from study 3, to assess whether RP latency differs as a function of age. For the same reason, we used a jackknifing procedure outlined by Miller, Patterson, and Ulrich (1998). Jackknifing involves computing for each individual a group average without that individual's data. A correction is then applied to inferential statistics used with jackknifed data. Using jackknifed data, we found that young adults produced faster RP peak latency (166 ms) compared to older adults (189 ms). On implementing the correction procedure outlined by Miller et al., we found this difference approached significance ($t(48) = 1.7$, $p<.1$). Therefore, we have evidence, albeit weak, that RP latency increases with age.

In sum, while SOA and the type of paradigm implemented (oddball versus single stimulus delivery) can influence the age effect on N1 and P2 amplitude, RP may mediate such age-related change in oddball paradigms.

Repetition positivity

Since research into RP is in its infancy, study 2 was designed to improve our understanding of the mechanisms contributing to RP in an effort to evaluate the claim that RP is related to memory trace formation (e.g. Baldeweg et al., 2004; Haenschel et al., 2005). We found support for this claim, arguing that the mechanisms underpinning RP are elicited in both a constant standard and roving standard oddball paradigm via two RP generators. An auditory cortex and an anterior RP generator were proposed to reflect encoding of local and global aspects of stimulus history, respectively. We assessed our results from two perspectives, i) the predictive coding model which states that RP represents the top-down suppression of responses to predicted stimuli (e.g. Baldeweg, 2007; Friston, 2005; Garrido et al., 2008) and ii) stimulus specific adaptation (SSA), a form of repetition suppression observed in the cat auditory cortex (Nelken & Ulanovsky, 2007; Ulanovsky et al., 2003; Ulanovsky et al., 2004). Although it has not previously been suggested that SSA is under top-down control, the predictive coding framework suggests that this may be the case. In addition, Ulanovsky et al. (2004) have stated that a "network effect may be necessary to explain SSA" (p. 10453). In sum, study 2 showed that neurons underpinning RP are active in modeling the auditory environment and that this plausibly occurs via SSA and predictive coding. We therefore concluded that RP represents trace formation and the establishment of context into the auditory sensory memory trace. This characterization of RP highlighted it as an ideal tool to study auditory sensory memory

trace formation in older adults. We chose the roving standard oddball paradigm to record RP in studies 3 and 4 as this paradigm offers the best opportunity to view the response to repetition indicative of RP at both frontal and mastoid sites.

In studies 3 and 4, we found very similar results with respect to the effect of age on RP. Across the two studies, we found that age affects the response to repetition in the standard ERP at a frontal site, Fz, but not at mastoid sites. The fact that this occurred with different adults participating in the two studies indicates the robust nature of these age effects. With what we learnt from study 2, we concluded that age affects the anterior RP generator that encodes auditory information from a global stimulus history perspective but does not affect the auditory cortex RP generator that represents local stimulus history information. We offered two possible explanations to account for the age effect at Fz. Firstly, it is possible that as frequency discrimination is impaired with age (e.g. Abel et al., 1990; König, 1957), the representation of frequency information in the brain is not as precise in older compared to young adults. This could cause repetition suppression (i.e. RP) to build-up and saturate at Fz over the course of the roving paradigm in older adults in a similar manner to the way in which RP saturates at Fz in a constant standard relative to a roving standard paradigm (e.g. study 2; however, recall that in study 2, a positive shift in the ERP over the N1 and P2 period occurred in the constant versus the roving paradigm in young adults, whereas a positive shift over the P2 but not N1 period occurred in older compared to young adults in studies 3 and 4. This is consistent with the hypothesis that the suppression process may be delayed with age, as argued earlier). A second possibility is that top-down influences change with age causing the age effect on RP. This notion is supported by evidence presented in the introduction that there are numerous top-down connections to the auditory cortex. Furthermore, Gazzaley and D'Esposito (2007) have

identified that older adults have a top-down suppression deficit that they defined as a reduced capacity to suppress task irrelevant information.

Given these possibilities, why is it that we only observe the effect of age at Fz and not the mastoids? Again we offer two reasons. If the age effect is the result of age-related change in the neural representation of frequency within the brain, data from Jääskelainen et al. (2004; 2007) could offer one explanation of our findings. Jääskelainen and colleagues suggest that neurons in the posterior auditory cortex are less finely tuned for frequency than those in a more anterior region of the auditory cortex. If the anterior RP generator is located within the auditory cortex, it is possible that the age-related difference in RP is only observed at Fz because older adults are not capable of encoding the fine tuning of frequency required at more anterior positions within the auditory cortex relative to young adults. That is, the age-difference in RP might only emerge when a more precise encoding of frequency is required (the role of the anterior region of the auditory cortex) compared to when less precise frequency tuning is required (the role of the posterior region). As stated, the alternative to this viewpoint is that the age difference in RP may be mediated by a top-down rather than bottom-up factor. If the age difference in RP is explained by a top-down mechanism, the time scale over which stimuli are encoded may influence the difference in findings from Fz and the mastoids. Since it is possible that two neuromodulators (nicotine and ketamine) regulate RP generation on distinct time scales (see review in Baldeweg, 2007), it is plausible that the neurochemical underpinnings of RP elicitation may differ between the anterior and auditory cortex RP generator. Thus, the fact that we saw an age effect at Fz but not the mastoids could be due to a differential age-related effect on the neurochemistry underpinning RP generation. At this stage, both of our suggestions for why we observe an age effect at Fz but not the mastoids are speculative. However, our data from

study 2 implying that there are two RP generators allows us to be confident that the difference in the age effect at mastoid and frontal sites represents independent age effects on separate RP generators.

In sum, combined RP data from studies 2, 3, and 4 suggest that RP is related to auditory trace formation and that this process is altered with age. We next asked whether this age-associated change could affect memory for other forms of auditory information. For example, in study 4, we examined the relationship between RP and implicit memory by assessing whether there is a behavioural correlate of RP.

Although we found that young and older participants responded more quickly and accurately to tones that followed a longer rather than shorter number of repetitions, we were not able to directly relate RP slope to the behavioural priming effect that was observed. There is, however, other evidence that argues in favour of a relationship between RP and implicit memory. For instance, Bergerbest et al. (2004) have shown a correlation between a behavioural repetition effect (priming) and repetition suppression (recorded by fMRI) using auditory stimuli. Researchers have also demonstrated that MMN, which receives contributions from RP, is related to an implicit form of memory that influences behaviour (van Zuijin, Simeon, Paavilainen, Näätänen, & Tervaniemi, 2006). Therefore, despite not finding direct evidence for this in our own data, we argue that since neurons underpinning the RP waveform are responsible for encoding the repetition context, it is plausible that RP is the mechanism that informs implicit contextual memory.

Before discussing the relationship between RP and explicit memory, I will present a discussion of MMN findings in order to consider the association between RP and explicit memory in conjunction with that between MMN and explicit memory.

MMN and the MMN memory trace effect

We reported on the response to repetition in MMN waveforms in studies 2 and 3, providing information on the conditions eliciting the MMN memory trace effect and the effect of age on the MMN memory trace effect, respectively. Given the robust nature of the effect of repetition on standard but not deviant waveforms, we concluded that RP primarily contributes to the repetition effect in MMN data (the MMN memory trace effect). However, there was not a direct correspondence between results pertaining to the effect of repetition on RP and MMN waveforms (i.e. RP but not the MMN memory trace effect was affected by presentation condition in study 2 and age in study 3), most likely due to the fact that MMN takes contributions from deviant as well as standard waveforms. In agreement with Haenschel et al. (2005), we take this data as evidence that RP may be a more direct indicator of the establishment of auditory sensory memory traces than MMN. In addition, our conclusions are supported by data pertaining to the relationship between RP, MMN, and explicit memory, which we will address presently.

The relationship between sensory and cognitive processing with age

Our aim in comparing auditory sensory memory performance and performance on other types of memory tasks was to draw some conclusions regarding how the relationship between sensory and cognitive processing develops with age. The relationship between auditory sensory memory and explicit memory was examined in studies 3 and 4. The only correlations between ERP data and RAVLT variables were found using RP (or P2) slope, not the slope of MMN change with repetition (i.e. the MMN memory trace effect) or average RP or MMN (averaged over repetition conditions). This supports our previous assertion that RP is more directly related to memory trace formation than the MMN

memory trace effect and measures of RP and MMN that mask the effect of repetition of the standard tone.

In studies 3 and 4, we observed a relationship between RP slope and RAVLT scores in young but not older adults. In young adults, RP slope correlated with RAVLT long term retention scores in study 3 and with RAVLT initial memory scores in study 4. Further analyses showed that the correlations that we observed between RP slope and RAVLT variables in studies 3 and 4 in young adults were mostly driven by activity from the early rather than late repetition conditions. We interpret these findings as evidence that in young adults, steeper RP slope (indicative of greater differentiation between repetition conditions, especially early repetition conditions) is related to one's ability to remember explicit auditory verbal information. Importantly, although this correlation does not necessarily imply causation (i.e. that the type of memory indicated by RP directly influences explicit memory for auditory information), it is possible that implicit memory could influence performance on explicit memory tasks (and vice versa; Jennings & Jacoby, 1993).

In older adults, we found a relationship between P2 slope and RAVLT variables, albeit in the opposite direction to the relationships observed in young adults. That is, we found a negative correlation between late P2 slope and scores on the initial recall trial of the RAVLT (study 3) and short term retention scores (study 4) in older adults. We suggest that we were able to observe such correlations in older adults using P2 slope rather than RP slope due to the fact that P2 slope preserves information relating to the full range of repetition conditions (i.e. the RP subtraction waveform reduces the number of such observations by one). This facilitated the analysis of early and late repetition periods, especially in study 4 where this division was not possible with RP data. Since standard as opposed to RP subtraction waveforms also have a greater signal to noise ratio, we would

recommend using P2 rather than RP slope to perform correlations with other variables in future (also recall that similar results were observed in young adults whether we used RP or P2 slope; see study 4). Our interpretation of these findings will be outlined in the following section on age-related compensatory brain activity.

The issue of compensatory brain activity

In the introduction to this thesis, I discussed a dilemma facing researchers interested in the cognitive neuroscience of aging. That is, I highlighted the fact that age-related changes in brain activity could reflect compensatory mechanisms (see also Cabeza et al., 2005; Daselaar & Cabeza, 2005; Prull et al., 2000). The question remains as to whether or not the age-related changes in the auditory ERP observed in the studies presented in this thesis could be accounted for by compensatory mechanisms. Our findings in relation to the negative correlations observed between late P2 slope and RAVLT variables in older adults suggest that a form of compensatory activity could be influencing RP in older adults.

We suggest that there could be a benefit to older adults reaching saturation of the RP mechanism (which is what seems to occur over the longer repetition conditions in older adults); although this may disrupt their ability to distinguish the precise temporal context in which information is encountered (a factor not directly tested within this thesis), it may also result in a stronger memory that an event has occurred at some point in the past. While this explanation is not likely related to conscious compensatory activity, it is possible that this type of compensatory mechanism could arise in order to adjust for age-related changes in the explicit memory system of older adults. In other words, a greater reliance on the implicit memory system might emerge with age and this may result in age-related change in implicit memory. Although we do not have direct evidence for this supposition, the

remember/know task (e.g. Tulving, 1985) has been utilised to demonstrate that the contribution of recollective and familiarity processes to episodic memory is altered with age. In the remember/know paradigm, participants perform a recognition task where they classify items as either distinctly remembered from the study list (remember) or as familiar and likely to have been encountered in the study list (know). Prull et al. (2006) have shown that older adults classify a greater number of hits as know items than young adults whereas young adults classify a greater number of hits as remember items than older adults (although older adults have a higher number of false alarms than young adults for remember and know items). This demonstrates that due to age-related difficulty in remembering episodic information, older adults may (consciously or not) rely on other sources of information from which to discern whether items have been previously encountered. Therefore, older adults may rely more on the implicit memory system to compensate for change in explicit memory and this reliance may alter the manner in which the implicit memory system works (i.e. content may be valued over context)[22].

We mentioned earlier that there is some evidence that attentional disregulation in older adults might result in memory benefits in ecologically valid situations where stimuli are not readily classified as relevant or irrelevant. Our interpretation of the negative correlations that we observed between RP slope and RAVLT variables in older adults uses a similar logic in that we are suggesting that the age-related difference in RP amplitude could be detrimental or beneficial depending on the task at hand (i.e. whether the task concerns memory for items or temporal context of items). This remains an interesting

[22] While it is possible that age-related change in implicit memory contributes to the development of age-related change in explicit memory, we have taken the opposite stance due to the fact that the age-related change in implicit memory is more subtle than the clear differences in explicit episodic memory described in the cognitive aging literature.

avenue for future research as does the question of whether identifiable factors contribute to the adoption of successful compensatory strategies with age (e.g. whether education or intelligence play a role; see review in Fabiani & Wee, 2001). While not reported in the body of this thesis, we did evaluate whether WASI IQ, years of education, or chronological age could account for the negative correlation observed between late P2 slope and RAVLT variables in older adults. We hypothesised that older individuals who did not show signs of compensatory activity (i.e. older adults with P2 slopes more similar to young adults), might have lower IQ, fewer years of education, or younger age than those who did show evidence of compensatory activity. However, in studies 3 and 4, we found no correlation between WASI IQ, years of education, or chronological age and P2 slope (early or late) in either age group. Given combined findings from studies reported in this thesis, there are conclusions that can be drawn with respect to current theories of aging.

Theories of aging supported by the research

Our correlational data demonstrated that there is a complex pattern relating age-associated change in RP to auditory verbal memory. Our results provide some support for Anstey et al.'s (2003) proposal that cognitive dedifferentiation does not occur with age (i.e. relationships between different abilities do not necessarily increase with old age). Rather than simply observing an increase in the relationship between RP slope and auditory verbal memory with age, we saw that the relationship was strongest for the early repetition conditions in the young and the later repetition conditions in older adults. Furthermore, the relationship between RP slope and RAVLT variables was in the opposite direction with age! Although our data does not specifically answer whether or not there is a common cause to the age-related changes that we have observed across the current studies, this

section will highlight that there may be multiple contributions explaining age-related change in different domains.

We hypothesized that either broader frequency tuning with age or a top-down mechanism could mediate the age-related difference in RP. These two explanations potentially map to two theories outlined in the introduction, the information degradation hypothesis and frontal hypothesis of aging, respectively. The information degradation hypothesis (e.g. Schneider & Pichora-Fuller, 2000) states that age-related changes in the quality of sensory information disrupt cognitive processing while the frontal hypothesis states that processing mediated by the frontal cortex is likely compromised with age (e.g. Moscovitch & Wincour, 1992; West, 1996; 2000). Although, as stated in the introduction, the frontal cortex is not the sole source of top-down connections in the cortex, the frontal hypothesis has previously been used to explain an age-related top-down suppression deficit (Gazzaley & D'Esposito, 2007). Gazzaley and D'Esposito (2007) proposed an amalgamation of the frontal hypothesis with the inhibitory deficit hypothesis of aging (e.g. Hasher & Zacks, 1988) as an explanation of the age-related top-down suppression deficit since they contended that the frontal cortex likely mediates inhibitory processes such as top-down suppression of irrelevant stimuli. The fact that we have interpreted negative correlations between RAVLT variables and RP activity as potential evidence of age-related compensatory activity might suggest that we favour the frontal hypothesis over the information degradation hypothesis. However, it is possible that these hypotheses are not mutually exclusive options. We discuss methods of evaluating the information degradation and frontal hypotheses in the following concluding section.

In addition to the theories of aging discussed above, studies 1, 3, and 4 provide support for the speed of processing theory of aging (e.g. Salthouse, 1996). In study 1, we

found that P2 peak amplitude but not N1 peak amplitude was delayed with age. Similarly, studies 3 and 4 revealed the delay in P2 peak amplitude with age. As such, the age-related delay in P2 amplitude presents as a robust finding and points to the fact that speed of processing slows with age. This delay in the neural response to sound presentation has the potential to affect later processing stages in the manner described by Salthouse (1996; i.e. the limited time mechanism and simultaneity mechanism). That is, delayed P2 in older adults may mean that later processing stages do not receive adequate information to function efficiently. For example, a meta-analysis of 32 studies has previously shown that P3 latency increases with age (Polich, 1996); if one accepts Salthouse's views, it is possible that the delay in P2 affects subsequent processes such as those indexed by P3 latency (i.e. attention allocation and memory updating; Polich).

In a similar vein, Schneider and Pichora-Fuller (2000) have discussed the consequence of reduced neural synchrony in old age. It is possible that a reduction in neural synchrony is responsible for the delay in P2 peak amplitude. For example, just as faster P2 latency observed in young adults as a function of training has been interpreted as evidence of increased neural synchrony with learning (e.g. Reinke et al, 2003), the delay in P2 in older adults could be a result of reduced neural synchrony with age. In this thesis, we have not focused on the age-related delay in processing of auditory information and its potential relationship to cognitive decline[23]. Having shown that the age-related delay in P2 peak amplitude is a robust finding, its relationship to cognitive functioning in old age is an avenue for future research.

[23] Although not reported in study 4, we found no relationship between average P2 latency (averaged across repetition conditions in the passive paradigm) and average RT (averaged across the factors probe and repetition) in either age group.

In addition to the relationship between our findings and cognitive theories of aging, our data converge with the neuroimaging literature outlined in the introduction to this thesis. For example, our hypothesis that the age-related change in RP may be due to a top-down suppression deficit is in agreement with the notion that neural networks rather than specific regional changes in brain activity may provide the best explanation of what is occurring in the aging brain (e.g. Gazzaley & D'Esposito, 2005; 2007; Grady, 2005; 2008). Moreover, it has been suggested that deficient neuromodulation may play a role in regulating neural networks (Bäckman & Farde, 2005; Li, 2005). We have proposed that age-related change in NMDA receptor and cholinergic systems could mediate age-related change in RP. Interestingly, there is also evidence that deficient NMDA receptor functioning could have contributed to age-related change in N1 amplitude reported in study 1. That is, a similar pattern of change in N1 amplitude to that observed as a function of age in study 1 has been documented in awake monkeys who received an NMDA receptor antagonist (phencyclidine: PCP; Javitt, Jayachandra, Lindsley, Specht, & Schroeder, 2001). Javitt et al. delivered click stimuli at five SOAs (150 ms, 450 ms, 1.5 s, 4.5 s, and 9 s, in separate blocks) similar to those used in study 1 and observed preserved N1 amplitude at short SOAs combined with reduced N1 amplitude at longer SOAs after PCP administration. Given this and the fact that NMDA receptor concentration is reduced in the aged primate brain (Gazzaley, Siegel, Kordower, Mufson, & Morrison, 1996), our study 1 data suggest that NMDA functioning may also be compromised in aged humans and may contribute to age-related change in N1 amplitude at longer SOAs.

As outlined in the introduction to this thesis and demonstrated in this summary, it is possible that multiple causes rather than a common cause best explain age-related decline.

This conclusion is supported by the fact that we have found several theories of aging that plausibly fit our data.

Conclusions and future directions

In this thesis, we have aimed to reduce the gap in our understanding of age effects in auditory sensory memory (e.g. Craik, 2000) by recording N1, P2, MMN, and RP waveforms of the auditory ERP. In line with one of the stated goals of the cognitive neuroscience of aging, the broad aim of the research presented in this thesis was to use ERP waveforms to link electrophysiological and cognitive changes associated with aging. We achieved this by examining the relationship between RP and MMN and other types of memory for auditory information (implicit and explicit).

We concluded that i) age affects auditory sensory memory, ii) the relationship between auditory sensory memory and implicit memory for auditory information requires further investigation (see below), and iii) there is a relationship between auditory sensory memory and explicit memory for auditory information that is altered with age. That is, we concluded that RP occurring in the N1/P2 and MMN latency period indicates memory trace formation and that age affects RP amplitude (restricted to an anterior RP generator that encodes global stimulus history information). Despite not finding direct evidence of a relationship between RP and implicit contextual memory (priming), we argued that this relationship remains plausible. Across two studies, we found a positive correlation between the response to repetition in the ERP (due to RP activity) and explicit auditory verbal memory in young adults but a negative correlation in older adults. Therefore, although age-related change in RP could affect the capacity of older adults to encode the context of auditory stimulation, this potentially reflects compensatory activity. We concluded that RP

was a more precise indicator of memory trace formation than MMN because MMN takes contributions from standard and deviant waveforms (i.e. two mechanisms contribute to MMN). Furthermore, data from study 3 suggested that RP is more closely related to memory for explicit information than MMN. Across our aging studies, we also found a consistent delay in P2 latency in older versus young adults. In sum, our research provided support for several cognitive theories of aging such as the information degradation hypothesis, the frontal hypothesis of aging (incorporating the inhibitory deficit hypothesis), and speed of processing hypothesis. Clearly, a combination of factors may be affecting the aging brain.

As mentioned throughout this discussion section, there are various lines of investigation that arise from the results of the studies presented in this thesis. For example, the functional relevance of age-related change in P1 and N2 waveforms, in the components underlying N1 and P2 waveforms, and in P2 latency, all require further explanation. However, as age-related change in auditory sensory memory functioning reflected by RP was focused upon in the studies comprising this thesis, I will concentrate on outlining three potential research directions related to this specific context. For detail on more general questions arising from RP research, see Appendix 1.

First of all, in the current research we could not determine whether bottom-up or top-down influences primarily contributed to the effect of age on RP. One way of assessing the validity of the bottom-up explanation would be to increase the separation between roving frequencies (e.g. broaden the frequency range from 600 to 1600 Hz and use 100 Hz separations), thereby reducing the possibility that an overlapping population of frequency specific neurons would be stimulated by successive roving standards in older adults. If older adults displayed the same pattern of RP activity observed in the current studies, this

would suggest that top-down influences control the age-related change in RP. Alternatively, if older adult RP data became more similar to that of young adults, the implication would be that age-related changes in frequency tuning contributed to the present RP results. Similarly, if roving standards with reduced frequency separation were delivered to young adults, or if young adults with poor frequency discrimination for their age were tested with the current roving paradigm, and we saw RP results similar to older adult data in the present studies, this could also provide evidence for the bottom-up explanation of age-related change in RP. While this research question is of importance in determining the cause of age-related change in RP and, by extension, auditory sensory memory, it is possible that bottom-up and top-down explanations are not mutually exclusive options. Therefore, ways of assessing top-down contributions to RP should also be sought, such as conducting source analysis of ERP data recorded with a high density montage. If a source of RP activity is located outside of the auditory cortex, this may help clarify whether there are top-down influences on RP.

Secondly, although we argued in study 4 that a relationship between RP and implicit memory for contextual information plausibly exists, we were not able to provide definitive evidence that this is the case. One way to follow-up on this issue would be to elucidate whether an age-related difference in the behavioural effect of repetition observed in study 4 (i.e. priming) was evident over a wider range of repetition conditions (i.e. 4, 8, and 16, rather than 4 and 16 repetitions). If older adults showed no behavioural effect of repetition for those repetition conditions for which there was no differentiation in the ERP (i.e. the 8 versus 16 repetition conditions) while at the same time young adults showed a behavioural repetition effect across all repetition conditions, then we would have much stronger evidence that RP has a behavioural correlate and that RP is an indicator of implicit

memory (e.g. priming). Such evidence could also be obtained in a different way, if we were to extend our work in the manner outlined next.

A third research direction involves gathering more evidence to clearly evaluate our hypothesis that the age-related change in RP may be beneficial for item memory but detrimental for contextual memory in older adults. I envisage that this could be investigated by firstly assessing whether RP is elicited by stimuli classifiable in absolute terms (e.g. spoken words or pictures; see Appendix 1 for more information regarding this possibility) rather than relative terms (such as the tones used in the present studies). If RP were elicited to such stimuli, we could compare RP (or P2) slope to implicit and explicit memory measures recorded using the same set of stimuli. For instance, explicit item memory could be tested by delivering a recognition memory test of stimuli presented in different repetition conditions during an RP recording and implicit contextual memory could be assessed by comparing reaction times recorded in separate repetition conditions of the recognition memory test. By collating this data in the one set of participants using the one stimulus set, and given results from studies 3 and 4 of this thesis, we would expect that older adults with flatter late P2 slope would outperform older adults with steeper late P2 slope on the item-based explicit memory task whereas the opposite outcome might occur on the context-based implicit memory task (i.e. reduced differentiation between RTs from separate repetition conditions in older adults with flatter compared to steeper late P2 slope). In young participants, we would expect that steeper P2 slope would be beneficial for both item and context memory aspects of the task. Given that this type of design has clear potential to highlight the implications of age-related change in RP and auditory sensory memory for other types of memory, this would represent an advance upon the current studies where different tasks were delivered to elicit RP and explicit memory measures.

Finally, more general research avenues arising from the current studies concern the manipulation of factors that affect RP as well as consideration of the relationship between RP and other measures of repetition suppression recorded at the neuronal level and using fMRI (see Appendix 1 for a broader discussion of these issues). This type of research has the potential to associate data from various neuroimaging techniques and thus increase our understanding of the way in which the brain models the environment and stores information for later use. By looking at factors such as those outlined above, we may be better able to distinguish the relationship between age-related change in different types of memory such as sensory memory, implicit memory, and explicit memory. Researchers in the field of cognitive neuroscience are well placed to answer such questions in the future and thus extend on current theories of cognitive aging.

Appendix 1

Issues remaining with respect to RP

One question that has not been specifically addressed to the best of our knowledge is whether RP would be elicited in response to the build-up of auditory memory traces beyond those determined by the roving frequency paradigm. For instance, would we see RP in a paradigm where the roving element was an auditory feature other than frequency, such as duration, intensity, or where the repeating feature was an abstract pattern? If RP at the scalp is a reflection of SSA at the neural level, then it could be predicted that RP may be elicited to repetitions of other auditory features, since SSA has been observed in response to repetition of intensity as well as frequency (Ulanovsky et al., 2003). However, further evidence comes from ERP paradigms in which repetition was examined for purposes other than directly examining RP. For example, Bendixen, Prinz, Horváth, Trujillo-Barreto, and Schröger (2008), whilst looking at the rapidity of regularity extraction as determined by MMN, have shown a positive shift in the ERP over the RP period in standard tones as a function of repetition (the ERP for the 5^{th} and 10^{th} standards in a train was averaged and compared to an average of the 15^{th} and 20^{th} standards in a train). Interestingly, the regularity that was repeated was an abstract pattern where the duration of sound predicted the direction of the pitch shift of the following sound. The roving aspect of this paradigm was defined by changes in the relationship between the duration of tones and the direction of the pitch shift of following tones. This is tentative evidence that RP is elicited by the build-up of the representation of abstract patterns. Similarly, Snyder, Alain, and Picton (2006) have observed a positive waveform that reverses in polarity at temporal sites in the latency range of RP. This waveform increased in size as a function of repetition of an ABA

tone pattern over a 10.8 s period. The authors related this waveform to the process of forming auditory objects. We propose that this waveform may be equivalent to RP (see also figures in Snyder and Alain, 2007, that show an age effect on their repetition-related waveform similar to age effects on RP reported in this thesis).

Is it plausible that RP would occur to repetition of abstract patterns as well as concrete auditory features? If the parallel between RP and repetition priming is correct, then RP occurrence to abstract pattern repetition might be expected, since exact stimulus correspondence is not necessary for priming to occur (the size of an object does not affect visual priming; e.g. see review by Desimone, 1996) and the words delivered by a voice do not appear to affect auditory voice priming (e.g. Schweinberger, 2001).

In addition, there is evidence that a positive shift in the ERP occurs with a single repetition of visually presented words (Rugg, Mark, Gilchrist, & Roberts, 1997). However, this shift occurs somewhat later than RP, with an onset at approximately 250 ms and an approximate duration of 300 ms. The relatively greater complexity of processing words compared to simple tones may have delayed an ERP component that is otherwise similar to RP. However, repetition effects similar to those seen in Rugg et al.'s (1997) study were also observed in a study of object repetition (Henson, Rylands, Ross, Vuilleumeir, & Rugg, 2004). Henson et al. (2004) found repetition suppression (fMRI data) in combination with a positive shift in the visual ERP over a similar period as that seen in Rugg et al.'s (1997) study but there was additional evidence of the repetition effect in the visual ERP over the earlier P1 and N1 period. This suggests that an RP like effect may have been present in these studies but that other aspects of the tasks (i.e. the added complexity relative to passive auditory tasks) delayed or prolonged such a repetition effect. In fact, Henson (2003) has suggested that semantic priming may affect the latency of the repetition effect. The Rugg et

al. (1997) and Henson et al. (2004) studies highlight that repetition effects similar to those we have observed (i.e. RP) extend to the visual as well as auditory domain.

One instance where RP has not been observed as a function of repetition of sound comes from Ylinen and Houtilainen (2007). These researchers specifically reexamined data from an earlier study (Houtilainen, Kujala, & Alku, 2001) in order to assess whether RP was present as a function of repetition of vowels and vowel-like sounds. In fact, they found the opposite pattern to RP. That is, at frontocentral sites over the P1 and N1 period, they found a negative shift in the ERP to standard sounds as a function of repetition. While it is possible that the repetition conditions that Ylinen and Houtilainen used to examine RP were not ideal to observe a repetition effect (an average of the ERP to the 3rd and 4th standards were compared to an average of the 5th and 6th standards), this does not explain the negative shift in the ERP in response to repetition. The key difference may lie in the fact that vowels possess long term representations in memory. Even vowel-like sounds may have stimulated long term representations of the vowels that they were similar to. There is fMRI evidence that having pre-existing memory traces of stimuli can affect the direction of a repetition effect (Henson, Shallice, & Dolan, 2000). However, whereas Henson et al. (2000) argued that repetition suppression was most likely to be observed using stimuli with pre-existing representations in memory and repetition enhancement for stimuli without such representations, RP data from Baldeweg's group and Ylinen and Houtilainen suggest the opposite, that stimuli without pre-existing representations in memory elicit repetition suppression (i.e. RP) while stimuli with pre-existing memory representations may induce the opposite of RP (i.e. repetition enhancement or repetition negativity in the ERP over the N1/P2 period at Fz).

In contrast, others argue that repetition suppression is a result of passive responding to stimuli and repetition enhancement a sign of more active responding to repeated stimuli (Bergerbest et al., 2004; Desimone, 1996). For example, repetition suppression might occur on implicit but not explicit tasks (Bäckman & Almkvist, 1997: PET study; Busch, Groh-Bordin, Zimmer, & Herrmann, 2008: EEG; Henson, Shallice, Gorno-Tempini, & Dolan, 2002: fMRI). In a similar vein, Gazzaley and D'Esposito (2007) argue that repetition suppression can be observed in response to repetition of irrelevant information whereas repetition enhancement is likely to occur in response to repetition of relevant information. Henson (2003; 2004) also highlights the role of the particular task used at encoding and testing of memory (i.e. match or mismatch of tasks) in controlling suppression and enhancement effects in response to repetition. To disentangle these conflicting data, there is certainly a need for further research into repetition effects (in the ERP, BOLD signal, and at the neuronal level) where attention, familiarity of stimuli (i.e. whether stimuli are likely to be represented in long-term memory), type of stimulus repetition (i.e. exact repetitions of all stimulus features or repetitions of patterns of stimuli), and number and timing of repetitions are controlled for.

With respect to the timing of repetition, Henson (2003) suggests that the effect of repetition seen for immediate repetitions (as have been used to deliberately elicit RP) may engage a different mechanism to that engaged for longer-lag repetitions (e.g. those used in Rugg et al., 1997) and may be more closely linked to short-term than long-term potentiation. While this remains a possibility, there are also data suggesting that repetition effects recorded at different lags might not differ qualitatively (Henson et al., 2004). Henson et al. (2004) showed that lag affected ERP repetition effects in a quantitative (i.e. smaller repetition effect with increasing lag) rather than in a qualitative way (i.e.

topography of repetition effects remained similar as a function of lag). A similar issue involves the question of how long repetition effects such as RP might endure. It has been suggested that the time course of adaptation in response to a repeating stimulus may be dynamic and related to stimulus history (Fairhall, Lewen, Bialek, & de Ruyter van Steveninck, 2001). However, Bendixen, Roeber, & Schröger's (2007) study where RP was not seen in response to pitch repetitions with a 1300 ms SOA suggests that RP might only be seen at shorter SOAs (although it is possible that other factors may have contributed to the lack of RP in this study). As stated, these questions warrant further investigation. Whether the age effect that we have observed in relation to RP would remain the same or would alter under some of the different stimulus conditions described above also remains to be determined.

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