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**Nicotine And The Mismatch Negativity
In Alzheimer's Disease**

Christopher Engeland

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**A thesis submitted to the
Department of Psychology
in partial fulfillment of
the requirements for the degree of
M.Sc. (Psychology)**

**Carleton University
Ottawa, Ontario, Canada**

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ABSTRACT

Mismatch negativity (MMN), a time-locked negative event-related potential which is elicited by a deviant stimulus in a set of standard stimuli, was elicited by changes in auditory frequency in patients with mild-moderate Alzheimer's disease (AD). In study I, MMN peak amplitude occurred later in AD subjects ($n=13$) than in healthy age-matched controls ($n=13$) ($p<0.01$). Additionally, MMN average amplitude was greater in AD subjects when elicited by a 1 second than a 3 second interstimulus interval. This was not seen in control subjects and suggests that MMN is sensitive to differences between the two groups. In study II, placebo or an acute oral dose of nicotine (2.0 mg) in gum was given after a baseline recording session on each of two test days. AD subjects were either free of medication (non-THA, $n=6$) or at a maximally tolerated dose of tacrine (THA, $n=6$). Peak amplitude was smaller post-placebo than either pre-placebo ($p<0.01$) or post-nicotine ($p<0.05$) in the non-THA group. Means of THA subjects were in the same direction but not significant. This effect was best seen 150-200 msec post-stimulus ($p<0.01$). For all subjects combined ($n=12$), peak latencies were longer post-placebo compared to either pre-placebo ($p<0.01$) or post-nicotine ($p<0.05$). Post-pre difference scores between test days also differed for latency ($p<0.05$). Overall, these results indicate that a small acute dose of nicotine prevented MMN attenuation, which was likely due to lowered mental arousal, and was more effective in AD subjects not currently undergoing cholinergic therapy. As MMN is likely an indirect measure of auditory sensory memory, nicotine may have therapeutic value in the treatment of memory impairment in AD.

Nicotine And The Mismatch Negativity In Alzheimer's Disease

Chris Engeland

Each year the number of elderly people across the globe increases. As a result, Alzheimer's disease (AD) is quickly becoming a major burden of health to our society. Currently, AD is the fourth leading cause of death after heart disease, cancer and stroke. It afflicts more than 1% of the population and as many as 9-10% of individuals over the age of 65 (Wisniewski & Wisniewski, 1992). Over 4 000 000 people in the USA and 300 000 in Canada currently have Alzheimer's (Utal & Coleman, 1995), 7000 AD victims live in the Ottawa region and 10 000 Canadians die from the disease each year (Ottawa Alzheimer's Society, Personal Correspondence, 1995).

Research in AD is limited within certain boundaries for a variety of reasons. The disease is specific to the human brain, which limits the use of animal models in studying AD and has greatly hindered our understanding of it. What is known about AD is largely from serial biopsies and post-mortem analyses of affected brain tissue. Additionally, the progression of Alzheimer's is extremely slow. As a result the disease in its early stages is not clinically detectable and this prevents the development of drug treatments that might inhibit or reverse the progression of AD early on. By the time AD is diagnosed irreversible brain damage has already occurred and is usually quite extreme. Thus, it is important to have a basic understanding of how AD affects and physiologically alters various brain regions and their associated mental functions.

Neuropathological Correlates Of Alzheimer's Disease

Many physical changes occur in the brain of a person suffering from AD. There is an overall loss of 20-30% of brain cells due to shrinkage and death. As a result of such severe neuronal loss, the ventricles become increased in size and overall brain weight is significantly decreased (Whitehouse, 1991).

Alzheimer's does not affect all areas of the brain equally. The temporal lobes show the first and most severe loss of neurons. This helps to explain the deficits in memory, comprehension, speech execution and language seen early on in AD (Carlson, 1986; Whitehouse, 1992). The parietal lobes are also affected which produces deficits in recognition and coordinated movements (Carlson, 1986). Late in the disease the frontal lobes show neuronal dysfunction and loss. A severe loss of motor control begins to occur at this stage (Nicholls, Martin & Wallace, 1992). Throughout the disease only the occipital lobes are left relatively intact.

Damage caused by AD is specific to individual brain structures. The hippocampus is one of the main structures affected. Neuronal loss in this area often exceeds 50% in advanced cases of the disease (Whitehouse, 1991). Damage to this structure or to its efferent connections produces severe memory deficits, in particular the encoding and consolidation of new information (Squire, 1992).

The loss of neurons in the hippocampus is mainly cholinergic. This is primarily due to the severe cell loss which occurs in the nucleus basalis of Meynert (NBM) (Whitehouse, 1991). The NBM is located at the base of the forebrain and projects to all areas of the cerebral cortex (Schröder, Giacobini, Wevers, Birtsch & Schütz, 1995). This structure

provides most of the cholinergic inputs to the neocortex as well as to the hippocampus (Whitehouse, 1991; Goldman & Côté, 1991; Schröder et al., 1995). The cell bodies are located in the NBM and the axons extend into both of these areas providing a rich supply of acetylcholine (ACh). A deficiency of ACh occurs early in AD and correlates more strongly with the severity of the disease than does any other transmitter (Nicholls et al., 1992).

It is believed that this gross cholinergic deficiency is primarily due to cell death that occurs in the NBM. The greatest cognitive impairments found in AD may be attributed to this neuronal loss (Schröder et al., 1995). Post-mortem analyses show that cell death averages 79% in this area (Carlson, 1986). The NBM plays an important role in integrating subcortical activity due to its numerous inputs and outputs. It is also believed to play a crucial role in sustained and spatial attention (Lawrence & Sahakian, 1995) and in reinforcement and learning (Carlson, 1986).

Due to the fact that the neocortex receives most of its cholinergic inputs from the NBM, severe cell loss also occurs here due to AD. The pre-synaptic terminals degenerate first and eventually much of the cortical grey matter deteriorates. The neurons first lose their dendritic spines and then the smaller cells die off, followed in time by the larger ones (Kolb & Whishaw, 1990). This area is involved with higher mental processes such as intellect and social skills. It also plays a role in long-term memory (LTM) and learning (Carlson, 1986; Schröder et al., 1995).

Other regions of the brain are also greatly affected by AD. The amygdala, another part of the limbic system, plays a role in the regulation of emotions and undergoes severe

neuronal degeneration due to AD (Kolb & Whishaw, 1990). Within the limbic system, the entorhinal cortex is affected the earliest and to the most severe degree. It is glutaminergic in nature, serves as the major source of input to the hippocampus and is the main relay between this and the neocortex (Squire, 1992). In advanced AD these two areas become essentially isolated from each other due to the destruction of this pathway (Kolb & Whishaw, 1990). Dopamine (DA) levels of the substantia nigra are also reduced. Psychotic features common to AD may be related to such mesocortical deficiencies, especially in the ventral tegmental area (VTA) which is the area most deficient in DA due to Alzheimer's (Schröder et al., 1995).

Other neurotransmitter levels are affected in a similar fashion. Serotonin (5-hydroxytryptamine: 5-HT) levels in the Raphé nucleus are significantly lower in AD and abnormally low levels of neuropeptides (eg. somatostatin, Neuropeptide Y, Substance P, etc.) are found throughout areas of the cortex (Goldman & Côté, 1991). Decreased overall norepinephrine (NE) levels in some AD patients have also been reported (Forstl, Levy, Burns & Luthert, 1994). This loss is primarily due to neuronal degeneration in the locus coeruleus, which plays a role in cognition and emotion (Carlson, 1986). These cells are rich in NE and losses in this area and in the Raphé nucleus have been correlated with the occurrence of depression, a common symptom of AD (Schröder et al., 1995). This follows the biological amine theory of depression which suggests decreased levels of NE and 5-HT can result in clinical depression.

The severe cell loss seen in AD is associated with, and likely caused by, abnormal protein formations in the brain. These are the presence of neurofibrillary tangles (NFTs)

found within neurons and senile plaques of amyloid which form in the extracellular spaces around neurons. These formations occur in several disorders but only in AD and Down's syndrome do they appear together (Goldman & Côté, 1991).

Cholinergic Deficiencies And Treatments In Alzheimer's Disease

Due to the severe cholinergic deficiencies in Alzheimer's disease, therapeutic research has concerned itself mainly with agonizing the cholinergic system in AD treatment. Several key findings validate this line of thinking. The clinical severity of AD is correlated with a decline in choline acetyltransferase (CAT) which is an enzymatic marker of cerebral cholinergic activity (Sahakian, Jones, Levy, Gray & Warburton, 1989; Christensen, Maltby, Jorm, Creasey & Broe, 1992; Warburton, 1992). Biopsy studies indicate losses of CAT in Alzheimer's are greatest in the cortex and hippocampus where they total 60-90% (Whitehouse, 1991).

Alzheimer's severity is also correlated with low levels of ACh synthesis and with a loss of subcortical cholinergic cell bodies in the basal forebrain (Sahakian et al., 1989; Warburton, 1992). As a result, the cognitive and memory deficits associated with AD have been chiefly attributed to deficient cholinergic transmission (Christensen et al., 1992).

Additionally, cholinergic antagonists such as scopolamine produce anterograde memory impairment in both healthy young and elderly subjects and worsen existing memory problems in AD patients. Furthermore, the memory deficits seen in healthy individuals due to scopolamine "blockade" mimic those of mild Alzheimer's patients (Christensen et al., 1992).

For years therapeutic treatment strategies have focused upon stimulating the cholinergic system in AD. Early studies used precursors of ACh, such as choline and lecithin, but cognitive improvements were minimal (Warburton, 1992). Direct infusions of ACh were also given orally to increase overall cholinergic brain levels but these results were again inconclusive.

The most successful treatment strategy to date has been with AChE inhibitors (eg. physostigmine). Physostigmine has been shown to enhance memory and learning in animal studies and in some patients (Harrell, Callaway, Morere & Falgout, 1990). However, a short half-life and adverse side-effects have been major drawbacks of this treatment.

Tacrine (Tetrahydroaminoacridine: THA) is a non-competitive and reversible AChE inhibitor which serves to prolong the time ACh remains in the synaptic cleft. In 1986 Summers, Majovski, Marsh, Tachiki and Kling reported that THA produced cognitive improvement in 14 of 17 AD patients treated with THA. The methods and procedures used were heavily criticized but the results of their study promoted other THA research in the late 1980's and early 1990's, most of which also produced negative results, albeit with small samples and low doses.

More recently, four large-scale double blind, placebo controlled multi centre studies (Davis et al., 1992; Farlow et al., 1992; Knapp, Knopman, Solomon, Pendlebury & Davis, 1994; Watkins, Zimmerman, Knapp, Gracon & Lewis, 1994), with hundreds of patients each, have shown that THA can have a beneficial effect upon AD, especially in the earlier stages of the disease. Sahakian and Coull (1993) also reported that THA has a cognitive enhancing effect in mild to moderate AD. However, these positive effects were

restricted to certain aspects of attentional functioning rather than memory.

THA is currently the only viable drug treatment for AD. The two countries who have fully approved its use are the USA (approved in 1993) and France. In 1994, in the USA, THA (Cognex®) was prescribed to between 60 000 and 70 000 Alzheimer's patients (Wilcock, 1994). In Canada, THA is in phase three of drug development. It is being evaluated in clinical situations to assess for efficacy, safety, proper dosage, side effects, variability of response, etc. However, it is not yet available for broad use by physicians.

The drawback with THA is that it has a low therapeutic index. Several side effects are common, the worst being hepatotoxicity. An increase in the level of the hepatic enzyme alanine aminotransferase (ALT) is the most common occurrence related to this side effect (Davis et al., 1992). Looking across studies, one third to one half of patients taking THA will experience hepatotoxicity of varying degrees.

Evidence indicates that up to one third of Alzheimer's patients with mild to moderate dementia may exhibit cognitive improvement from the use of THA. For treatment inclusion it is recommended that patients score between 10 (Woo & Lantz, 1995) and 23 (Lezak, 1995) on the Mini-Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975) as this is one scale often used to define mild to moderate dementia, although some researchers have argued scores below 18 are indicative of severe cognitive impairment (Tombaugh & McIntyre, 1992).

Nicotine-Cholinergic Links In Alzheimer's Disease

Two types of cholinergic receptors exist: nicotinic and muscarinic. These are aptly

named, as nicotine and muscarine specifically activate these receptors respectively. Drugs which are specific to post-synaptic muscarinic receptor sites have been considered for treatment of AD, such as arecoline and RS86. Despite some claims that global functioning and affect are slightly improved by these substances, no significant improvements have been seen on tests of cognitive function (Warburton, 1992).

Widespread cholinergic stimulation has also not been very effective in the majority of AD patients. Moreover, the four areas of greatest cell loss in AD are the NBM, ventral tegmental area (VTA), locus coeruleus and the Raphé nucleus, all which possess nicotinic receptors (Schröder et al., 1995). Consequently, it seems sensible to explore more specific substances such as nicotine, or a subclass of nicotinic agonist, as a therapeutic option for AD.

Nicotine is the only active drug present in cigarette smoke and inhalation is, by far, the most popular route of nicotine administration (Julien, 1995). Over 95% of nicotine in cigarette smoke is absorbed and passes into the brain in about ten seconds (Revell, 1988). Regardless of how the drug is administered (egs. oral, intravenous, subcutaneous, transdermal, nasal aerosol), once in the blood nicotine easily crosses across cell membranes due to its lipophilicity and is readily absorbed into all body areas. Nicotine has an effect on every physiological system in the body (Le Houezec & Benowitz, 1991) but this study will primarily concern itself with effects upon the central nervous system (CNS).

The half-life of nicotine is approximately 120 minutes. Roughly 80-90% of the drug is metabolized by the liver and 5-10% is excreted unchanged by the kidney (Le Houezec & Benowitz, 1991). Nicotine readily crosses the blood brain barrier, both by

diffusion and active transport by the choroid plexus. Its distribution is throughout the entire brain with highest concentrations in the hippocampus, hypothalamus, thalamus, midbrain, brainstem and some areas of the cerebral cortex (Le Houezec & Benowitz, 1991). Cotinine, the main metabolite of nicotine, does not pass through the blood brain barrier to any significant degree (Nordberg, 1995).

The primary effect that nicotine has on the CNS is its stimulation of the cholinergic system. The active form of nicotine is a positively charged ion whose molecular structure resembles ACh in its spacing of positive and negative charges. However, it is a less flexible molecule and can only bind to nicotinic receptor types, whereas ACh also binds to muscarinic receptors (Le Houezec & Benowitz, 1991).

The nicotinic receptor is a ligand-gated ion channel composed of five subunits (Decker, Brioni, Bannon & Arneric, 1995). Two main subtypes of this receptor exist and these are classified by the chemicals which selectively block them. The first subtype, called C_6 nicotinic receptors, are selectively blocked by mecamylamine in both the peripheral nervous system (PNS) and the CNS and by hexamethonium in the PNS only. The second subclass, called C_{10} nicotinic receptors, are selectively blocked by decamethonium at the neuromuscular junction. The receptors of primary interest in this study are the C_6 receptors of the CNS (Le Houezec & Benowitz, 1991).

The first treatment strategies for AD were quite general and aimed at inhibiting AChE (eg. THA). Newer therapeutic research is beginning to target nicotinic receptors specifically (Schröder et al., 1995) and recent research suggests there may be a number of different types in the CNS (Decker et al., 1995).

Nicotine acts both pre-synaptically and post-synaptically. Activation of post-synaptic nicotinic receptors causes a direct and rapid change in permeability of cell membrane to both Na^+ and Ca^{++} (Zhang & Nordberg, 1995), depolarizing the post-synaptic cell. Activation of the pre-synaptic receptors causes a release of ACh (Sahakian et al., 1989; Wilson et al., 1995) which further enhances these excitatory effects post-synaptically.

Nicotine affects many neurotransmitter systems including dopamine, norepinephrine, epinephrine, serotonin, glutamate and GABA along with several amino acids and neuropeptides, and may serve to neuromodulate several hormonal pathways in the CNS (eg. growth hormone) (Le Houezec & Benowitz, 1991; Nordberg, 1995; Wilson et al., 1995). However, the most direct effect nicotine has on the brain is as a cholinergic agonist and this is its main mechanism of action in the CNS.

Nicotinic receptors are more widely distributed in the brain than muscarinic receptors and appear to be affected to a greater extent by AD (Nordberg, 1995). The NBM is one of the areas of the human brain most dense in nicotinic receptors (Newhouse & Hughes, 1991) and it undergoes more neuronal loss in AD than any other cerebral region. The deterioration observed in this structure and its ascending pathway primarily involves nicotinic receptors. Muscarinic receptors are also present in the NBM but these remain stable in both number and function over the course of the disease (Warburton, 1992). Moreover, there is a consistent and severe loss of nicotinic receptors throughout the cerebral cortex in AD (Whitehouse et al., 1986; Benwell, Balfour & Anderson, 1988; Nordberg, 1995), whereas reports of muscarinic receptor losses due to the disease have

been ambiguous (Whitehouse et al., 1986).

In vitro analyses of AD victims has shown that there is a shift from high to low affinity nicotinic binding sites in the temporal cortex compared with age-matched controls. Neurochemical studies upon autopsy indicate this is due to a selective loss of high affinity nicotinic receptor types (Nordberg, 1995). These findings of decreased binding sites and lowered receptor affinities for nicotine have been confirmed repeatedly in AD patients (Schröder et al., 1995) and are associated with the pathological effects of the disease (Whitehouse et al., 1988; Van Duijn & Hofman, 1991).

Despite these facts, the primary theoretical and therapeutical focus up to now in AD has concerned muscarinic receptors (Newhouse et al., 1988; Wilson et al., 1995). THA, along with most other cholinergic agents, has been presumed to chiefly affect this muscarinic system. However, Nordberg et al. (1992) used positron emission tomography (PET) scans to illustrate that the changes induced by THA in the AD brain parallel those associated with nicotinic receptor restoration. Furthermore, research indicates that unique binding sites specific for AChE exist on nicotinic receptors (Nordberg, 1995). Thus, non-competitive inhibition of the nicotinic system exists in the presence of AChE. This strongly suggests that treatments aimed at AChE inhibition (eg. THA) directly affect nicotinic as well as muscarinic systems.

PET studies have shown that improvements seen in early AD patients taking THA are correlated with both an increase in glucose metabolism and an up regulation of nicotinic receptors. Recent studies have utilized the radioisotope C¹¹-nicotine. This is nicotine labelled with carbon 11, a radioactive emitter of positrons. A lower than normal

uptake of C^{11} -nicotine is evident in early AD, especially in the temporal association and parietal cortices, suggesting a downregulation of the nicotinic system as a whole (Nordberg et al., 1997). Moreover, there is a significant increase in the cerebral uptake of this radioisotope after three weeks (Nordberg, 1995) or three months (Nordberg et al., 1997) of THA treatment.

The two types of cholinergic systems are markedly different. Nicotinic receptors act directly on the post-synaptic cell through ion channels they are directly coupled with. Conversely, muscarinic receptors are coupled with G-proteins and affect the post-synaptic cell through secondary action (Wilson et al., 1995). Autoreceptors also exist in the nicotinic system, but not in the muscarinic system, which cause further synthesis and release of ACh when they are stimulated (Wilson et al., 1995). Additionally, nicotinic autoreceptors enhance glutaminergic transmission in the hippocampus (Gray, Rajan, Radcliffe, Yakehiro & Dani, 1996) which is essential for explicit memory (Squire, 1992).

Moreover, chronic stimulation generally causes nicotinic receptors to upregulate themselves in two ways: (1) by an increase in number, and (2) by a shift in proportion from low to high affinity binding sites (Nordberg, 1995). Nicotinic upregulation has been seen in both animals and humans (Benwell & Balfour, 1985; Benwell et al., 1988) and is likely due to nicotine-induced receptor desensitization (Wilson et al., 1995). These effects occur in several brain regions including the cortex and striatum (Wilson et al., 1995). Specifically, smoking causes most gray matter in the brain to undergo increased nicotinic binding (Benwell et al., 1988).

Smoking studies suggest this up regulation is due to increased receptor density

rather than increased binding affinity, although the newly created receptors generally have high affinity binding sites (Benwell et al., 1988). These results match those seen in animals that have been administered nicotine chronically (Benwell et al., 1988). Conversely, muscarinic receptors react differently and may even downregulate themselves when overstimulated (Levin, 1992). This may explain why muscarinic therapy of AD has been largely unsuccessful and suggests that targeting the nicotinic system may be more beneficial to patients for long-term therapy.

Of particular interest to this study is the finding that there is a reduced incidence of AD in elderly smokers versus elderly non-smokers (Mattson, 1994). Epidemiological studies have repeatedly evidenced a protective effect of cigarette smoking on the development of various neurodegenerative diseases, in particular Parkinson's Disease (PD) and AD (Baron, 1986; Van Duijn & Hofman, 1991; Friedland, 1994; Fagerström, Pomerleau, Giordani & Stelson, 1994). Evidence from animal models further suggests that nicotine protects against PD (Clemens, Baron, Coffey & Reeves, 1995).

Smokers are at approximately half the risk of non-smokers for developing PD and various studies suggest that nicotine is responsible for this effect (Baron, 1986). Furthermore, the risk for AD in smokers may be as low as 35% that of non-smokers and is dose dependent, with the heaviest smokers at the lowest risk for Alzheimer's (Friedland, 1994).

A study by Van Duijn and Hofman (1991) also found a strong inverse relationship to exist between AD and cigarette smoking. Specifically, the risk of developing AD decreased with an increasing number of cigarettes smoked daily before disease onset.

Moreover, individuals who inherited the disease as an autosomal dominant disorder developed the condition significantly later in life if they were smokers than if they were non-smokers. When data was pooled from all prior formal studies (eight total), most which had previously yielded conflicting results, a significant inverse relationship was again found between AD and smoking. A more recent study by Salib and Hillier (1997) also supports these findings and indicates this inverse relationship applies to Alzheimer's disease but not to dementia as a whole.

A possible explanation for this inverse relationship is that the same genetic factors which decrease susceptibility to AD also increase the resistance against the negative effects of tobacco (Mattson, 1994). An alternate explanation might be that up regulation of nicotinic receptors caused by chronic smoking helps compensate for receptor loss due to the disease, allowing smokers to either resist or delay the deleterious effects of Alzheimer's disease. Some recent evidence also suggests that nicotine may inhibit amyloidosis, thereby slowing down or blocking senile plaque formation (Cohen, 1996; Salomon, Marcinowski, Friedland & Zagorski, 1996).

Whether or not these findings are correct, nicotine should be thoroughly explored as a potential treatment for AD as an inverse relationship between the two appears to exist. Many of the same areas of cognition that are deficient in AD appear to be enhanced by nicotine in healthy individuals and current research suggests nicotine enhances some of these qualities in AD patients.

Memory, Aging And Alzheimer's Disease

Current views generally regard memory to consist of multiple processes or systems rather than being a single entity (Craik, 1990; Squire, 1992; Carlesimo & Oscar-Berman, 1992; Cowan, 1995; Lawrence & Sahakian, 1995). For example, explicit memory consists of the memories we can bring to conscious awareness. Conversely, implicit memory is involved in priming, simple conditioning and the learning of skills and habits. Through this memory system, an organism's ability to function in the world is increased through experience but not conscious recollection (Squire, 1992). These memory systems also deviate in topographical origin, as damage to the hippocampus proper or surrounding cortical structures (ie. entorhinal, perirhinal and hippocampal) greatly affects explicit but not implicit memory (Squire, 1992; Carlesimo & Oscar-Berman, 1992). Further evidence of this comes from functional neuroimaging studies which have shown that implicit memory processes are anatomically distinct from explicit memory processes. For example, explicit memory processes related to encoding are electrophysiologically distinct from implicit memory processes related to priming (Squire, 1992).

Explicit memory is affected in several ways by aging. Short-term memory (STM) is generally preserved, though working memory often exhibits deficits (Craik & Rabinowitz, 1984; Morris, Gick & Craik, 1988; Craik, 1990; Morris, Craik & Gick, 1990). These deficits are due to increased task complexity rather than increased load. For example, increasing the complexity of a word list is more likely to cause performance decrements in the elderly than simply increasing list size (Morris et al., 1988). Supporting this, a division of attention is detrimental to working memory in the aged only if task

difficulty also increases (McDowd & Craik, 1988). Thus, it appears to be active processes rather than passive holding processes which are affected by age (Morris et al., 1988). Additionally, LTM typically declines slowly with age (Craik & Rabinowitz, 1984; Craik, 1990; Morris et al., 1990). Conversely, implicit memory shows little or no change due to aging (Craik, 1990).

Explicit memory is extremely affected by AD. A loss of memory is frequently the first symptom reported by AD patients and is often regarded as a necessary element for diagnosis of this disorder (Carlesimo, Fadda, Bonci & Caltagirone, 1993). The disease has a profound effect on both STM and LTM (Morris, 1986; Hulme, Lee and Brown, 1993), although the dementing process impairs LTM to a greater extent (Carlesimo, Fadda, Lorusso & Caltagirone, 1994). AD patients are especially deficient in encoding processes, largely due to hippocampal injury (Carlesimo & Oscar-Berman, 1992; Hulme et al., 1993). Due to damage in mesial temporal and diencephalic structures, which are needed for early memory consolidation, AD patients appear to suffer from either early decay of the memory trace (Carlesimo & Oscar-Berman, 1992; Carlesimo et al., 1993) or from the trace being refreshed less efficiently (Hulme et al., 1993). This results in particularly poor and often faulty memory consolidation in the first ten minutes after being exposed to a stimulus (Carlesimo & Oscar-Berman, 1992; Carlesimo et al., 1993).

Conversely, implicit memory is relatively unaffected in AD. For example, priming associated with the visuomotor system and various sensory systems is generally unaffected by the disease, likely because primary motor and sensory cortices and the basal ganglia are relatively spared in AD (Carlesimo & Oscar-Berman, 1992). However, some deficiencies

have been reported in monitoring the frequency and modality of words and pictures (Grafman et al., 1990). Additionally, some verbal and visuo-perceptual skills, assessed by repetition priming, have been found to be partially deficient in AD patients. These deficiencies are most apparent in tasks which depend on accessing the lexical-semantic features of the stimuli (Carlesimo & Oscar-Berman, 1992). The neural substrates for this semantic memory system lie in the tempoparietal associative cortex in the left hemisphere, an area consistently and severely damaged in AD (Carlesimo & Oscar-Berman, 1992). Thus, it may not be implicit memory which is defective in these tasks but other systems which implicit memory may be occasionally dependent upon.

Nicotine Effects On Cognitive Function

(i) Effects In Animals

Animal studies of nicotine have bypassed many of the problems that are inherent with studying the drug's effects upon humans. Animals can be assigned randomly to treatment groups and it is possible to administer chronic doses of nicotine to animals that have no previous experience with the drug.

Most studies to date have indicated that nicotine improves learning and memory performance in a variety of animal species (Levin, 1992; Warburton, 1992). Conversely, there are a number of studies that have found the drug elicits no effect or a negative one on these same cognitive qualities. This discrepancy between findings is likely due to a variety of factors including differences in drug dose, variations across species or strains of the same species, task complexity and the amount of training an animal receives (Levin,

1992).

Various studies have illustrated that nicotine improves the performance of normal rodents on tasks such as the Morris water maze, the T-maze and both inhibitory and active avoidance (Levin, 1992). Both acute and chronic nicotine administration causes an improvement in working memory on the radial-arm maze in rats (Levin, Rose & Abood, 1995). Other studies have also indicated that nicotine can improve learning and memory in both young and aged rats (Levin, 1992; Levin et al., 1995; Socci, Sanberg & Arendash, 1995). Erickson (1971) has reported that improved avoidance acquisition stems from the facilitation of LTM consolidation rather than from attentional stimulation.

Wilson et al. (1995) chronically administered nicotine to rats for a three week period and tolerance did not develop for cognitive effects. Furthermore, the performance of these rats was superior to normals four weeks after withdrawal, despite the two hour half-life of the drug. A possible explanation for this is the up regulation of nicotinic receptors which occurs during chronic receptor stimulation (Wilson et al., 1995).

In normal aged and young monkeys delayed matching to sample improved when nicotine was given (Decker & Majchrzak, 1993; Wilson et al., 1995). Enhancements in choice accuracy were also seen in aged rhesus monkeys with drug administration (Levin, 1992). Improvements persisted 24 hours or more after injection (Wilson et al., 1995). These tests are essentially measures of STM. It is critical to note that the above performances were impaired when the nicotinic receptor antagonist mecamylamine was administered rather than nicotine (Decker & Majchrzak, 1993). Moreover, nicotine reversed deficits caused by mecamylamine when the two drugs were co-administered

(Levin, 1992). Many animal studies have yielded similar results and mecamylamine also slowed cognition in humans (Levin, 1992).

These findings suggest that the cognitive enhancing effects of nicotine stem from its stimulating effects in the CNS. Nicotine has been shown to cause *in vitro* release of ACh in the cerebral cortex of rats. More recent *in vivo* studies (microdialysis) have supported these findings (Schröder et al., 1995). Furthermore, intravenous injection of nicotine caused increased ACh release throughout rat cortex for at least two hours. Endogenous measurements of drug levels in the brain further suggest that ACh synthesis was increased (Schröder et al., 1995), most likely due to activation of nicotinic autoreceptors.

Animal studies found that acute nicotine administration reversed cognitive deficits produced by the ablation of cholinergic projection systems in the forebrain, probably by increasing the ability to attend to environmental stimuli (Hodges, Allen, Sinden, Lantos & Gray, 1990). Specifically, nicotine reversed the cognitive deficits caused by the lesioning of the NBM (Newhouse et al., 1988) which is a proposed animal model of AD. Chronic nicotine administration also reversed lesions of the fimbria or the basolocortical projection, which each affect the working memory in rats (Levin, Christopher, Briggs & Rose, 1993). Deficits from septal lesions (on the Morris water maze) have also improved with nicotine administration and have still been apparent 15 days later (Decker, Majchrzak & Anderson, 1992).

Research is now beginning to turn towards unique nicotinic ligands in hopes they might possess therapeutic value in AD. Levin et al. (1995) recently reported that a

specific dimethylaminoethyl compound (DMAE II), which stimulates nicotinic receptors, produced similar effects to nicotine in rats. With either substance the animals exhibited significant improvements in working memory performance on the radial arm maze. No additive effects of the drugs were seen when administered together.

GTS-21 is another selective nicotinic agonist which has produced effects in rats similar to nicotine. Both drugs improved general learning, increased LTM and enhanced the acquisition of active avoidance to the same extent (Arendash, Sengstock, Sanberg & Kem, 1995). This new drug also improved passive avoidance in rats when they were pretreated with GTS-21 before undergoing lesions of the nucleus basalis (Arendash et al., 1995). GTS-21 is less toxic than nicotine and may possess future therapeutic value in AD and other neurodegenerative disorders if nicotinic agonists prove useful.

Studies have also shown that deleterious effects of nicotine, such as nausea and dizziness, fade with chronic treatment. Furthermore, research with animals has found the drug's cognitive benefits persist or improve over time (Levin, 1992). This suggests that chronic exposure to nicotine may be more beneficial therapeutically than acute dosing.

(ii) Effects In Healthy Adults

Systemic administration of nicotine has been reported to augment cognitive processes in a large number of human studies (Schröder et al., 1995). Although some studies have reported deficits, no effects or ambiguous findings from nicotine administration (Levin, 1992), the majority of studies performed have demonstrated that nicotine enhances cognition in a variety of ways, especially attention and memory

functioning (Warburton, 1992; Levin et al., 1995).

Nicotine is also capable of affecting other cognitive functions such as improving perceptual speed (Katayama et al., 1995) and simple motor responding (Wilson et al., 1995). Other studies indicate that nicotine may improve LTM and produce state-dependent learning (Newhouse et al., 1988). Nicotine has also been seen to counteract some of the cognitive deficits seen in the elderly due to normal aging (Levin, 1992). However, the strongest and most consistent findings so far have been drug-related improvements in rapid information processing and vigilance, both measures of attentional processing (Levin, 1992). The effects of nicotine on attention have been reported often and it is plausible that other drug-related cognitive improvements (eg. memory) stem from attentional enhancement.

Attention

Nicotine, administered by gum or oral tablets, has been found to improve performance on repeated administrations of the Stroop test (a test of attentional interference) in non-smokers (Provost & Woodward, 1991; Le Houezec et al., 1994). Furthermore, oral doses of both 1.0 and 2.0 milligrams (mg) of nicotine reduced the Stroop effect in both smokers and non-smokers (Warburton, 1992). This reduced Stroop effect has been primarily attributed to nicotinic enhancement of attention (Provost & Woodward, 1991), which suggests the drug enhances selective attention towards relevant information and suppresses irrelevant information (Warburton, 1992).

Several studies have reported that nicotine enhances performance on rapid information processing tasks (Wesnes & Warburton, 1984; Hasenfratz, Michel, Nil &

Battig, 1989; Warburton, 1992), producing dose-related enhancements on both speed and accuracy measures (Wesnes & Warburton, 1984; Warburton, 1992). Le Houezec et al. (1994) reported enhanced information processing on a choice reaction time task in 12 non-smokers administered 0.8 mg nicotine subcutaneously. There was no trading of speed for accuracy and overall performance was superior in the drug condition versus saline. The authors concluded that augmented attention due to nicotine best explained these results. Wesnes and Revell (1984) failed to replicate these findings but they did report that nicotine tablets ingested by non-smokers reversed the negative effects of scopolamine on both a choice reaction time task and the Stroop test.

Measures of attention switching and selective attention have also shown improvements with nicotine administration (Warburton, 1992). Furthermore, nicotine tablets have prevented commonly occurring decrements in sustained attention and visual vigilance tasks in both smokers and non-smokers (Warburton, 1992; Le Houezec et al., 1994), and smoking has had similar effects on visual and auditory vigilance tests (Revell, 1988).

Peeke and Peeke (1984) reported that cigarette smoking augmented short-term verbal recall. Immediate recall of unrelated words was significantly improved for 50-word lists in the drug condition. Similar results have been found using 48-word lists and nicotine tablets (Rusted, Graupner & Warburton, 1995). However, attention played a larger role with longer lists (Warburton, 1992) and studies have repeatedly shown that memory improvement due to nicotine is positively correlated with list length. For example, on a test of immediate free recall ingestion of 1.5 mg of nicotine enhanced recall

on a 30 word list but not on a 10 word list (Warburton, 1992). Rusted et al. (1995) reported similar results. This indicates nicotine may affect cognition (eg. memory) primarily through enhanced attention.

Memory

Studies concerning the effects of nicotine on memory have been contradictory. Using a syllable list, Andersson and Post (1974) reported a drop in learning and of correct recollection when a cigarette with 2.1 mg nicotine was smoked versus a nicotine-free cigarette. However, in a follow-up study Andersson and Hockey (1977) found weak evidence that smoking may enhance encoding if it is known the information will have to be recalled at a later point. Furthermore, smokers were shown to perform significantly worse than non-smokers on measures of incidental memory. Possibly nicotine enhances selective attention to relevant information only.

Indeed, it is likely that increased attention is partially responsible for any memory enhancements seen with the drug. Additionally, Peters and McGee (1982) reported that cigarette smoking can produce state-dependent memory effects. They concluded this is likely due to the arousal which is produced by nicotine. Warburton (1992) also reported this effect in several studies.

However, Warburton (1992) reported that on blocks of word lists nicotine administration enhanced recall of the earlier blocks more than the later blocks. As attention was presumed to be maximal at the beginning of this long test, it was concluded that nicotine enhanced consolidation to some degree. Warburton (1992) also found that long-term recall of word-lists was significantly improved when nicotine was taken prior to

learning but not prior to recall. This suggests the drug enhanced encoding but not retrieval. Overall, it is clear that LTM can be enhanced by the drug and several studies suggest that nicotinic facilitation occurs more with LTM than STM (Warburton, 1992). Possibly a greater attentional component is needed at the time of encoding when one is required to remember things for longer periods of time.

Sherwood, Kerr and Hindmarch (1992) administered nicotine gum to smokers and observed an enhancement of STM on a recognition task, as well as faster motor reaction times and improved compensatory tracking performance. Improvements were continuous across multiple doses of the gum, which suggests that acute nicotine tolerance does not develop quickly for psychomotor effects (Sherwood et al., 1992).

Some studies have found that post-trial nicotine administration can have a positive effect on material to be memorized (Warburton, 1992; Rusted et al., 1995). Memory improvements seen with post-trial administration illustrate the relationship that exists between nicotine and memory consolidation (ie. STM to LTM) (Colrain, Mangan, Pellett & Bates, 1992). Colrain et al. (1992) used a memorization task of associated pairs and found that low doses (0.6 mg) of post-trial nicotine significantly reduced errors. However, Peeke and Peeke (1984) found no such effects when free recall of unrelated words was tested under similar post-trial smoking conditions. This suggests that post-trial smoking has a greater cognitive effect on associated memories than on unrelated words (Rusted et al., 1995).

Rusted et al. (1995) performed a series of studies examining the effects of pre- and post-trial nicotine administration using both minimally deprived smokers (one hour) and

non-smoker control subjects. To varying degrees, improvements were seen for the smoking group on both associative and free recall tasks throughout the experiment. Additionally, drug administration enhanced the memory of associated words more than unrelated words. The authors concluded that nicotine does improve memory, that associative memories are more susceptible to nicotinic effects than the free recall of unrelated words and the drug augments memory more when it is administered pre-trial rather than post-trial.

Effects Of Drug Dosage

The dose of nicotine is important in determining cognitive effect, as dose functions tend to be U-shaped (Peeke & Peeke, 1984). In general, low doses produce greater facilitation than high doses, which may have little to no effect or even impair functioning (Colrain et al., 1992). Various animal studies, which tested a range of cognitive abilities, have supported this contention (Levin, 1992). For example, nicotine improved working memory in aged rats given acute but not chronic doses. Furthermore, chronic infusion increased the beneficial effects of subsequent acute dosing (Levin & Torry, 1996). This suggests that nicotine may be useful in treating age-related memory impairments but only using specific dosing regimens.

Colrain et al. (1992) tested the effects of post-trial smoking of low (0.6 mg) and medium (1.12 mg) dose cigarettes on memory in humans. The low dose of nicotine was associated with significantly fewer errors overall than the no smoking and zero nicotine conditions. The medium dose of nicotine produced results part way between the low nicotine and no smoking conditions. Again, this illustrates that nicotine is sometimes more

effective in lower doses.

(iii) Effects In Alzheimer's Disease

Alzheimer's disease is associated with a wide range of memory impairments and has a profound effect on both STM and LTM (Hulme et al., 1993), although the dementing process impairs LTM to a greater extent (Carlesimo et al., 1994). As nicotine seems to have a positive effect on both of these memory types and also counteracts cognitive deficits caused by antagonism or lesions of the cholinergic system nicotine may be a viable treatment for AD.

To date, six studies have examined the effects of nicotine in AD patients. Newhouse et al. (1988) analysed the effects of two different doses of intravenous nicotine (0.125 and 0.25 $\mu\text{g/kg/min}$) on 6 nonsmoking patients with probable AD. All exhibited moderate dementia. When the patients were assessed by cognitive tests (free recall and category retrieval), immediate free recall was seen to improve with the higher dose of nicotine (0.25 μg). This was mainly due to a decrease in intrusion errors and supported the suggestion by Fuld, Katzman, Davies and Terry (1982) that intrusion errors are common in AD, possibly more so than in other types of neurodegenerative disorders. Furthermore, Fuld et al. (1982) have claimed that this type of error may be related to the degree of cholinergic damage suffered by the brain. Additionally, a trend towards long-term recall consistency was noted. The authors viewed this as representing enhanced acquisition or encoding rather than consolidation, due to the fact that this trend was only seen for words presented during drug infusion and not before. Possibly this improvement

was due to augmented attention which nicotine may have produced (Sahakian et al., 1989; Warburton, 1992; Le Houezec et al., 1994).

In 1989, Sahakian et al. observed the effects of three subcutaneous nicotine doses (0.4, 0.6 and 0.8 mg) on 7 mild to moderate AD patients. Nicotine significantly improved attention and information processing more than placebo in both AD patients and healthy young adults. Furthermore, the output and vigour of response rates improved, as seen by an increase in reaction times. This second finding was attributed to nicotine's agonistic effect on catecholamine release and turnover, specifically dopaminergic release in the nucleus accumbens. It should be noted there was no effect of the drug on STM.

A larger follow-up study was performed by Jones, Sahakian, Levy, Warburton and Gray (1992) using 22 mild to moderate Alzheimer's patients. Nicotine was administered subcutaneously in doses of 0.4, 0.6 or 0.8 mg. The results indicated that nicotine administration significantly improved perception, sustained visual attention, rapid visual information processing and reaction time. This confirmed and extended the earlier findings by Sahakian et al. (1989) and, similar to that study, visual and auditory STM showed no improvement upon nicotine administration. The investigators suggested that nicotine may be useful in treating attention and information processing deficits in AD due to the increase in vigilance and discrimination produced by the drug.

Recently, Wilson et al. (1995) examined the effects of sustained nicotine administration on 6 mild to moderate AD patients. The subjects were exposed to 7 days of placebo given transdermally (via a patch), 8 days of nicotine given transdermally and 7 days of washout respectively. Daily evaluations of learning, memory and behaviour were

conducted. The treatment patch contained 22 mg of nicotine and was changed daily. This allowed approximately 0.9 mg/hr of nicotine to be delivered over a 24 hour period. Thus, a steady drug state was achieved in the blood. This was regarded to be an intermediate level of administration when compared with previous intravenous studies using nicotine. The drug was well tolerated and no significant toxicity was noted. Significant improvement was noted on a learning task (repeated acquisition) during the nicotine condition which persisted through the washout phase.

Newhouse et al. (1988) reported impaired learning on a similar task of repeated acquisition when mecamylamine was administered to healthy human subjects. The same pattern of errors occurred in AD patients in this study and disappeared upon nicotine administration. Despite this, Wilson et al. (1995) reported that measures of memory and global cognition, assessed with the Dementia Rating Scale (DRS) (Hughes, Berg, Danzinger, Coben & Martin, 1982; Berg, 1988), and measures of behaviour were not significantly affected by the drug. However, it should be noted that the DRS is not validated as being sensitive to cognitive changes induced by drugs.

Katayama et al. (1995) also administered nicotine chronically via transdermal patch to mild to moderate demented patients, including an AD subgroup. A daily dose of 35 or 52.5 mg was given daily over a four week period. Both perceptual speed and level of arousal were increased compared with pre-drug baselines. This was viewed as an overall improvement in cognitive processes and further suggests that nicotine may have therapeutical benefits for cognitive disorders and disease.

Conversely, another recent study (Snaedal, Johannesson, Jonsson & Gylfadottir,

1996) reported dermal plasters containing nicotine were no better than placebo dermal patches in treating short-term memory, attention, psychomotor speed or word fluency in mild to moderate AD patients. However, in this study a dose of 21 mg/day of nicotine was given over a four week period and only 75% of the patients (18/24) were able to tolerate this dose for so long. This may have confounded the end results.

The Mismatch Negativity Potential

Mismatch negativity (MMN) is a time-locked negative event-related electrical potential (ERP) which is recorded from the scalp surface and is elicited by a deviant stimulus in a sequence of standard homogeneous stimuli. It has a peak latency (the time lapse after stimulus onset before amplitude is maximal) of 150 milliseconds (ms) on average, which ranges from 100-250 ms (Javitt, Steinschneider, Schroeder, Vaughan Jr. & Arezzo, 1994; Pekkonen, Jousmäki, Reinikainen & Partanen, 1995; Schröger, 1997), regardless of gender (Pekkonen, Jousmäki, Partanen & Karhu, 1993). In general, the size of the mismatch response is proportional to the amount of difference between the standard stimuli and deviant stimulus (Schröger, 1997).

Auditory-elicited MMNs have been clearly and repeatedly demonstrated using scalp recordings, even when stimulus change is slight or occurs very frequently (Näätänen, Paavilainen, Tiitinen, Jiang & Alho, 1993; Näätänen & Alho, 1995c). The MMN response has also been detected for visual (Näätänen, 1992; Alho, Woods, Algazi & Näätänen, 1992; Pekkonen et al., 1993) and somatosensory stimuli (Hari et al., 1990; Näätänen, 1992; Näätänen & Alho, 1995c), though these findings are controversial and rather weak.

Perhaps these processes cannot be recorded from the scalp as easily. For the purpose of this study only auditory-elicited MMNs will be discussed.

Recent research strongly suggests the mismatch response exists in neonates before they reach full term. Cheour-Luhtanen et al. (1996) administered repetitive vowel sequences with occasional oddballs to healthy infants born prematurely 30-35 weeks after conception. This elicited a brain response very similar to the MMN seen in adults and represents the ontogenetically earliest discriminative response of the human brain ever recorded. Conversely, in humans, some of the other ERP components are not fully developed until puberty (Csépe, 1995).

In research, the auditory deviations used to elicit an MMN are most commonly changes in the duration, intensity or frequency (ie. pitch) of the sound (Näätänen et al., 1993; Pekkonen et al., 1993). Both increments and decrements of these elements elicit MMNs (Näätänen & Alho, 1995a). Although considerable variation exists between individuals, fairly good test-retest stability of MMN amplitude has been shown for changes in either frequency or duration with various ISIs (Pekkonen, Rinne & Näätänen, 1995; Escera & Grau, 1996).

This current study is primarily concerned with MMN elicited by frequency change, the variable which appears to be least affected by the subject's level of conscious awareness (Loewy, Campbell & Bastien, 1996). However, deviations in numerous other variables may also evoke similar mismatch responses. These include variations in the time interval between sounds (also called the interstimulus interval - ISI) (Böttcher-Gandor & Ullsperger, 1992), or in spatial location (Paavilainen, Karlsson, Reinikainen & Näätänen,

1989; Pekkonen et al., 1993; Schröger, 1995), in complex tones and patterns (Schröger, Näätänen & Paavilainen, 1992; Schröger, 1994) including speech (Lang et al., 1995), in phonetic structure (Sams, Aulanko, Aaltonen & Näätänen, 1990; Pekkonen, Jousmäki et al., 1995), or in frequency glides (Sams & Näätänen, 1991). Gender only seems to influence MMN elicited by complex stimuli, in which case females exhibit longer latencies (Lang et al., 1995).

Recent research has demonstrated MMN occurrence due to deviances in tone pairs or serial tone patterns (see Näätänen & Alho, 1995a for review) and a change in a continuous tone can also elicit the mismatch response (Lavikainen, Huotilainen, Ilmoniemi, Simola & Näätänen, 1995; Winkler & Schröger, 1995). Additionally, Schröger (1995) found that deviating an auditory stimulus in two dimensions (eg. a change in both frequency and spatial location) resulted in larger MMN amplitudes than by changing either dimension alone.

The omission of a stimulus is also capable of eliciting MMN, although Nordby, Hammerborg, Roth and Hugdahl (1994) found that the mismatch response is less sensitive to omissions than to inclusions of a stimulus element. When a stimulus element is removed MMN still occurs but with a longer peak latency and smaller amplitude than when the same stimulus element is added. Possibly an organism finds changes to be more significant when something “new” has been added rather than when something “known” has been removed from its environment (Nordby et al., 1994).

In 1992, Schröger showed that intensity played little effect on the frequency-elicited MMN. He varied intensity over a 40 dB/SPL range. None of the mismatch

responses produced by 50 Hz frequency changes were significantly different. This suggests that the frequency-elicited MMN is sensitive to the specific type of change rather than changes in the overall amount of stimulus energy (Schröger, 1994).

Two chief interests in recording MMN are the measures of amplitude and peak latency. Both should be assessed and analysed separately as the two are not strongly correlated in normal-hearing adults and, thus, seem to represent different central mechanisms (Lang et al., 1995). The main factors which amplify MMN amplitude are decreases in either ISI or stimulus change probability, or increases in the difference between deviant and standard tones (Pekkonen et al., 1993). These same characteristics decrease MMN latency (Näätänen & Alho, 1995c).

Näätänen (1992) found that deviant stimuli with a 2% probability of occurrence elicited significantly greater amplitude MMNs than stimuli with a 10% chance of occurrence. Additionally, Sams, Hari, Rif and Knuutila (1993) presented two auditory tones with equal probabilities of occurrence to subjects and recorded their ERPs. When one tone was presented a number of times in a row, the amplitude of the MMN elicited by the other tone substantially increased. Thus, the probability of the deviant stimulus and MMN amplitude were inversely correlated. The lower the chance of deviation the greater the size of the mismatch response when it did occur. Sokolov (1975) suggested this may be an orienting reflex to auditory changes in the surrounding environment.

Mismatch amplitude is also larger when stimuli are presented rapidly in short ISIs between 100-600 ms (Loewy, 1996) or when deviations from the standard set are large (Sams, Paavilainen, Alho & Näätänen, 1985; Novak, Ritter, Vaughan Jr. & Wiznitzer,

1990; Näätänen & Alho, 1995c). This is problematic for electrophysiological recordings because given the right combination of the above characteristics the MMN may become so large it temporarily overlaps an earlier negative (N100) component of the ERP (Näätänen, 1982) which usually peaks at 80-100 ms (Pekkonen, Jousmäki, Reinikainen & Partanen, 1995). Moreover, the N100 may also increase in amplitude if deviances are very large (Lavikainen et al., 1995; Näätänen & Alho, 1995c). Additionally, MMN latency decreases with increasing deviance from the standard stimuli (Javitt et al., 1994). This further increases the chance of overlap with N100 and has been demonstrated with both changes in the frequency (Sams et al., 1985; Novak et al., 1990) and the spatial location of a stimulus (Paavilainen et al., 1989).

If N100/MMN overlap occurs then MMN amplitude will be artificially increased in value (Näätänen & Alho, 1995c). Thus, when overlap between the N100 and MMN components occurs a larger than normal negative wave appears in the ERP. This overlap can be teased out by decreasing the difference between the deviant stimulus and the standard set.

Another common MMN recording problem is overlap with additional negative (N200b) and positive (P300) components of the ERP, which peak on average at 200 ms and 300 ms respectively (Javitt et al., 1994; Kropotov et al., 1995; Pekkonen, Jousmäki et al., 1995). These are endogenous potentials as they are not elicited by the physical characteristics of the stimulus, as MMN is, but stem from brain activation when a decision has been reached or a response has been made (Picton, Lins & Scherg, 1995). These two components generally occur during stimulus/task conditions involving voluntary active

attention. For this reason most MMN studies use “ignore” conditions (eg. read a book) simply to prevent their possible overlap with the mismatch response.

Taking such overlaps into account, attention generally plays no role on MMN generation. It has been demonstrated repeatedly that MMN amplitude and latency are identical whether subjects ignore or attend to auditory tones (Näätänen, Gaillard & Mäntysalo, 1978; Sams et al., 1985; Alho, Sams, Paavilainen, Reinikainen & Näätänen, 1989; Näätänen et al., 1993; Alho, Woods & Algazi, 1994). Variations in the degree of attention (assessed by task difficulty) do not seem to affect the magnitude of the MMN either (Näätänen et al., 1993). Moreover, the mismatch response still occurs: (1) when individuals are preoccupied with other stimuli or tasks (Näätänen & Alho, 1995c), (2) under anaesthesia (King, McGee, Rubel, Nicol & Kraus, 1995; Csépe, 1995), (3) during certain stages of sleep (Csépe, 1995; Loewy et al., 1996), and (4) without conscious perception of stimulus change (Näätänen & Gaillard, 1983).

Despite these findings, MMN elicited by difficult to detect stimulus change (egs. very small frequency changes, short random ISIs) is slightly enhanced with auditory attention (Alho et al., 1992; Woods, Alho & Algazi, 1992; Winkler, Lukkarinen, Alho, Teder and Näätänen - see Näätänen et al., 1993). Furthermore, the amplification of MMN may be reduced by strong redirection of attention away from the stimulus change (Woldorff, Hackley & Hillyard, 1991) or by white noise masking to the contralateral ear (Salo, Lang & Salmivalli, 1995), although the generation of the mismatch response is independent of attentional factors (Näätänen et al., 1993). When redirected attention occasionally affects MMN, it is primarily by decreasing amplitude (Näätänen et al., 1993).

It is important to note that a threshold exists which the stimulus change must surpass before MMN can be elicited. Such thresholds commonly vary between individuals (Pekkonen, Rinne & Näätänen, 1995) and evidence suggests they are unaffected by attention (Näätänen et al., 1993).

In 1983, Näätänen and Gaillard determined the MMN thresholds for individual subjects by using frequency changes upwards from 1000 Hz. On average, MMN appeared at 1010 Hz. This supported the idea that a threshold of detecting stimulus change must be reached before MMN can occur. Sams et al. (1985) also used various frequency deviants to determine what minimal frequency change from 1000 Hz was needed to trigger an MMN. A small amplitude MMN occurred with an 8 Hz frequency change and larger amplitudes were seen for 16 and 32 Hz changes. As the deviation of pitch increased peak latency was seen to decrease. Furthermore, the elicitation of MMN by specific frequency changes was found to correlate strongly with the individual's ability to discriminate if a change in pitch had occurred (Sams et al., 1985). Thus, a positive relationship exists between MMN occurrence and the discriminatory threshold for auditory frequency change. Recently, it has been found that smaller frequency changes of 5 Hz can sometimes elicit a late and very small MMN (Tiitinen, May, Reinikainen & Näätänen, 1994).

To sum, MMN is an ERP which is quite resilient to the effects of attention and appears to represent the physical attributes of a stimulus precisely. Exogenous ERPs are those which are mainly affected by the physical attributes of the eliciting stimulus. Therefore, they are not affected much by either the mental state of the individual or the

psychological characteristics of the stimulus. Conversely, endogenous ERPs are chiefly affected by these latter characteristics and largely unaffected by the physical characteristics of the eliciting stimulus. It appears that MMN is more endogenous than exogenous in nature, though it does possess characteristics of each type.

Memory Trace Theory Of The MMN

Näätänen et al. (1993) proposed that a cortical representation of the standard tone exists when the deviant tone is presented. The new tone is then automatically compared to this representation and MMN occurs if a difference is detected. An elicitation of MMN may then result in a switch of attention to, and conscious perception of, the stimulus change (Näätänen et al., 1993).

Sensory memory is a memory type of limited capacity in which a sensory representation of a stimulus remains “fixed” for a very short duration (several seconds). This representation is an exact match of the stimulus and is lost in a process of decay, a gradual deterioration of the neuronal trace, unless first stored into STM. Two criteria differ sensory memory from other memory types: (1) it is an exact representation of the stimulus that has not been manipulated, transformed or categorized in any way; and (2) it is specific to one modality only (eg. auditory) (Cowan, 1995). Therefore, MMN may be representative of sensory memory as it fits both these defining criteria.

Numerous studies have shown that MMN amplitudes and latencies (measured in the “ignore” condition) correlate with the amplitudes and latencies of N200b and P300 ERP components and with behavioural performances (see for reviews Lang et al., 1995;

Schröger, 1997). For example, Winkler, Reinikainen and Näätänen (1993) found a strong positive correlation to exist between the recognition of deviant tones (a behavioural measure) and MMN amplitude (an electrophysiological measure). Furthermore, forward and backward masking are commonly used in perceptual auditory tasks to study sensory memory. In this study, as masking was presented closer to the test tone both performance and MMN amplitude declined. A variety of other studies have shown that when healthy subjects actively discriminated between tone pitches or between vowels their performance scores correlated with MMN amplitudes. Moreover, those with poorer discrimination needed larger frequency deviations to elicit an MMN (Lang et al., 1995).

Given these points, and also that the range of maximal separation between tones that produces MMN (approximately 10 seconds) (Böttcher-Gandor & Ullsperger, 1992; Sams et al., 1993) is about equal to the range of being able to discriminate between tones in behavioural tests, it has been suggested that the cortical representation of each tone is sensory in nature (Lang et al., 1995). Specifically, it appears MMN probes the neural representation of the standard stimulus and, thus, it should provide a reasonable measure of this memory trace (Näätänen & Alho, 1995c). Additionally, it is unhampered by attentional, motivational and performance-related components.

Moreover, MMN occurs very early in stimulus processing and whether stimulus change is predictable or random the mismatch response is equal in amplitude and latency (Ritter, Deacon, Gomes, Javitt & Vaughan Jr., 1995). None of these criteria are true for the N200b or P300 responses. Taken together, these characteristics suggest the MMN is an automatic, preattentive response which is rarely influenced by higher order cognitive

processes but instead provides a simple straightforward probe of the “memory trace” it depends upon (Ritter et al., 1995; Näätänen & Alho, 1995a, 1995c). This trace is part of an implicit memory system which cannot be brought into conscious awareness. Memory trace theory states this trace must exist or a comparison of the two stimuli will not be possible and MMN will not occur.

The alternative to memory trace theory is that MMN is elicited by a neuronal release from refractoriness. This hypothesis suggests that a population of neurons are put into a refractory state when stimuli are unchanging. When a deviation from the norm finally occurs these cells are released from their state of unresponsiveness and this change elicits the MMN component of the ERP. However, studies strongly suggest that MMN is not simply a response by a new set of neurons to an infrequent stimulus which occurs among a standard set. Several points of evidence make this quite clear.

First, MMN rapidly decreases in amplitude with increasing ISIs. Mäntysalo and Näätänen (1987) recorded ERPs from subjects using a standard MMN oddball paradigm with ISIs of one, two, four and eight seconds. The MMN was strongest for ISIs of one second, attenuated for two seconds and non-existent for four and eight seconds. Thus, an MMN will not occur if ISIs are exceptionally long. This evidence supports the argument that a memory component is involved in MMN. Assumedly the neuronal trace decays over a short period after which MMN can no longer be elicited by a deviant stimulus.

Second, if the deviant stimulus is the first or second in a sequence MMN will not occur (Sams et al., 1985). Sams et al. (1993) presented two auditory tones with equal probabilities of occurrence to subjects and recorded their ERPs. MMN occurred for a

stimulus change only if the standard stimulus had been previously presented at least twice (Sams et al., 1993). This suggests that at least two standard tones must occur for a neuronal trace to exist. At this point new stimuli can be compared to the trace and MMN will occur if a difference is detected.

Third, a decrease in the intensity or duration of either tone-length or ISI elicits the mismatch response (Woldorff et al., 1991). Even the omission of a tone or the second of a pair of tones can cause the MMN to occur (Nordby et al., 1994; Näätänen & Alho, 1995a). Thus, stimulus change does not have to occur for an MMN to appear. Identical tones presented with varying time intervals can elicit the same response.

Last, the MMN responds to very small stimulus change. This is not typical of normally responding neuronal groups to new stimuli (Näätänen & Alho, 1995c). Otherwise, a vast network of unique neuronal populations would have to exist in a small area to account for every possible stimulus change which could occur. Taken together, a memory trace likely exists and is likely to be very complete since a deviation in any physical feature of simple or complex sound patterns can elicit an MMN (Schröger et al., 1992; Alho, Woods, Algazi, Knight & Näätänen, 1994).

Some studies suggest the neuronal trace may persist for even longer than 10 seconds. In an experiment by Cowan, Winkler, Teder and Näätänen (1993) subjects listened to two short blocks of auditory tones. A deviant stimulus was presented as the second stimulus of the second block. This was only found to elicit an MMN when the previous stimulus (of the same block) matched the standard stimuli presented in the first block. The inter-block interval varied from 11-15 seconds. Thus, a deactivated form of

the memory trace may be present for fifteen seconds or longer at which point an identical tone is still able to reactivate it, allowing the MMN to again be elicited (Näätänen & Alho, 1995b). This effect was also observed using an inter-block interval of 9.5 seconds, during which 6 tones of random frequencies were presented to eliminate the carryover of sensory storage (Winkler, Cowan, Csépe, Czigler & Näätänen, 1996).

The neuronal trace can also be modified. By deviating segments of a complex auditory pattern, a stronger MMN response can sometimes be achieved with practice (Schröger et al., 1992). Additionally, individuals who showed attenuated MMN amplitudes and poor discrimination were able to improve both with practice (Lang et al., 1995), suggesting that performance and MMN are positively correlated. It should be noted that such adaptive changes are dependent upon attention. Overall, it appears that auditory sensory memory is capable of undergoing adaptive change and is not simply a "raw acoustic record of the input" (Näätänen & Alho, 1995b). Rather, this form of memory is constantly modified by new auditory stimuli and long-term neuronal traces in a deactivated form may also influence it.

Implicit Memory, MMN And Alzheimer's Disease

There are several systems of implicit memory which have been studied in relation to AD. Some have shown no deficits in the presence of the disease (egs. priming of the visuomotor and sensory systems), whereas others have been affected to a degree (egs. priming of verbal and visuo-perceptual skills). However, these deficiencies may be due to the effects of AD on external systems which implicit memory is occasionally dependent

upon, rather than disturbances of implicit memory itself.

The most thoroughly studied system of implicit memory has been that of the articulatory loop. This is a buffer store of verbal material which subserves the central executive system (CES), the control centre of working memory. The loop stores information of one modality for a short duration and operates at a level below conscious awareness (Morris, 1984, 1986). In these respects it possesses properties similar to those of MMN.

The articulatory loop consists of two parts. The first is an articulatory rehearsal mechanism which is an active process coordinated by the CES. Its function is to refresh the memory trace of the second part of the loop which is a passive phonological store. Various studies have found the articulatory loop still functions normally in elderly individuals and AD patients (Morris 1984, 1986; Gick et al., 1988; Carlesimo et al., 1994). However, in early AD there is an apparent decline of CES resources (Morris, 1986; Carlesimo et al., 1994). As a result, there was a notable decrement in AD patients' abilities to remember consonant trigrams when a non-verbal distraction task (tapping) was presented (Morris, 1986). This occurred due to a reduced functioning of the CES. This, in turn, caused deficits in the articulatory rehearsal mechanism which is essential for maintaining information in STM stores.

This is another example of an implicit memory system attenuated by AD. However, these disturbances were due to the decreased functioning of an external mechanism (the CES) which the implicit system occasionally relies upon. It is not known whether or not external mechanisms outside of the areas of MMN generation affect MMN

elicitation and size. Regardless, sensory memory appears to be a specific type of implicit memory which is less prone to the effects of interference, attention and motivation than other types of implicit memory (eg. priming). This may explain why MMN is relatively unaffected by such factors except under extreme conditions of focused attention or decreased vigilance (eg. sleep). It seems as if MMN measures a memory system which is “more” implicit or further removed from consciousness than these other systems. Possibly auditory sensory memory does not depend on external systems for support and, as a result, only under very extreme conditions is reduced functioning seen.

Mismatch Negativity Generators

Reason dictates that there are two auditory representations present during MMN: (1) R' which contains the features of the standard stimuli, and (2) R which contains the features of the new deviant stimulus. The representation R' is assumed to be part of the long auditory store which, like MMN, lasts up to about 10 seconds, is capable of holding several pieces of information, represents the temporal pattern of the stimulus and undergoes decay over time (at the point of full stimulus resolution) (Schröger, 1997). The new stimulus R is likely part of the short auditory store which typically lasts 100-200 msec (Schröger, 1997).

MMN usually peaks about 100-250 msec post-stimulus, which is possibly the terminating phase of the short auditory store. Perhaps this is the point at which R' is updated and MMN may then occur if a deviance is detected by a comparator mechanism. Supporting this, it has been shown that the formation of R must occur for MMN to be

elicited. If the deviant stimulus is followed by masking within 25 msec this does not happen, even when the representation R' has been previously established (Schröger, 1997). Thus, it appears that MMN may be a measure of the output of either the comparison process between these two auditory representations or it may reflect the adaptation of this neural model to auditory change. Regardless, MMN seems to be an indirect measure of this long auditory memory store.

It has been further suggested that MMN consists of two separate components which are generated in distinct areas of the brain: (1) the supratemporal plane of the auditory cortex and (2) the frontal cortex (Näätänen & Michie, 1979). Supporting this, Giard, Perrin, Pernier and Bouchet (1990) recorded ERPs using current source density analysis during a selective attention task. Subjects were presented with a standard set of tones and an occasional variant which differed in pitch. The above two areas of MMN generation were confirmed and found to differ in peak latency.

The first component (auditory) was found to produce an early sensory-specific wave. This was larger in the hemisphere contralateral to the ear of stimulation. The second component (frontal) produced a non-specific wave that occurred slightly later. This was always larger over the right hemisphere, regardless of the ear of stimulation or direction of attention, and was related to the orienting response (Giard et al., 1990). Although scalp distributions of MMN differ depending upon what change is made upon the standard stimulus (Alho, 1995), similar findings have been reported for changes in intensity and duration (Paavilainen et al., 1991). Hemispheric differences were smallest for frequency-elicited MMNs.

Alho, Woods, Algazi et al. (1994) recorded MMN amplitudes to non-attended deviant tones in patients with dorsolateral prefrontal lesions of the cortex. Amplitudes were attenuated compared with controls, especially for tones recorded above the lesioned hemisphere, further supporting the hypothesis that the frontal cortex is involved in MMN elicitation. It should be noted that this area of cortex is especially involved in attentional processes and with orienting functions (Paavilainen, Alho, Reinikainen, Sams & Näätänen, 1991).

Recently Molnár, Skinner, Csépe, Winkler and Karmos (1995) presented further evidence suggesting the presence of a frontal MMN generator using mathematical tools based on chaos theory. Magnetoencephalograms (MEGs) recorded in humans and EEGs recorded in animals have also suggested that a major generator of MMN is located in this area (Kropotov et al., 1995). Furthermore, Javitt et al. (1994) localized MMN-like activity in monkeys to the primary auditory cortex, specifically to the supragranular laminae. Intracranial MMN recording in non-primates suggests that, in some species, MMN may also be generated in subcortical structures such as the thalamus and hippocampus (Csépe, 1995; Alho, 1995). Kropotov et al. (1995) did not find this to be true in humans.

Schröger (1995) found that the simultaneous change of both frequency and spatial location elicited a larger MMN amplitude than a change in either stimulus alone. Additionally, he showed that this two dimensional change could be temporally and topographically modelled by adding the one dimensional changes together. Schröger (1996, 1997) also found similar results using duration and intensity changes, duration and

frequency changes or interaural time and level differences to elicit MMNs. This is strong evidence that separate generators exist for the elicitation of MMN. It seems these effects resulted from the independent activity of separate neural populations, each which generated in parallel its own MMN response to a specific aspect of stimulus change.

Supporting this, Kropotov et al. (1995) recorded frequency-elicited MMNs intracranially directly from the temporal cortex. The study found that MMN was generated from a small area in the primary cortex which was spatially separate from the generators of the attention-dependent N200b and P300 ERP components. Additionally Sams, Kaukoranta, Hämäläinen & Näätänen (1991) measured magnetic ERPs and found that MMN generators were anterior to the source of the N100 wave suggesting that different neural populations were involved in the generation of each. Thus, it seems that neural generators of MMN are located in auditory cortex and are unique from the areas which generate the N100, N200b and P300 ERP components.

To sum, it is generally accepted that the areas of MMN elicitation are found bilaterally in or around the primary auditory cortex on the supratemporal plane (Paavilainen et al., 1991; Sams et al., 1991; Pekkonen et al., 1993; Näätänen & Alho, 1995a) and probably in the right frontal cortex (Winkler et al., 1993; Näätänen & Alho, 1995a). Additionally, a generator also likely exists in the right lateral temporal cortex (Näätänen & Alho, 1995a). These generators are usually distinct from each other as well as from other components of the ERP.

In 1979, Näätänen hypothesized that the auditory (caudal) component of MMN is necessary for detection of stimulus change and is not perceived consciously. Conversely,

the frontal component is associated with an involuntary switching of attention towards the stimulus change (Alho, 1995) and is necessary for conscious knowledge that a change has occurred. Furthermore, Näätänen (1991, 1992) suggested the auditory component of MMN as a whole might possess a threshold which, if surpassed, triggers the frontal component. This in turn allows for conscious discrimination of the stimulus change to occur. Näätänen further postulated the MMN is necessary but not sufficient on its own for the conscious perception of such a change. Paavilainen et al. (1991) supported these theories and further hypothesized that the frontal component may form a link between sensory-specific cortex and the areas which generate the N200b and P300 responses. It has been shown that when deviating tonal pitch in an attentional situation, the MMN produced is time-locked to the subsequent N200a and P300 components that follow (Novak et al., 1990).

Näätänen and colleagues (Näätänen, 1991; Näätänen et al., 1993; Näätänen & Alho, 1995a) have postulated that the early auditory component of MMN may be further divided into two subcomponents: (1) computational / informational and (2) amplifying / modulating. Theoretically, the function of the first of these subcomponents is to detect the stimulus change and elicit an MMN. The second subcomponent then reacts to the physical characteristics of the new stimulus (eg. how much it deviates from the standard) and, by doing so, determines the strength of the MMN. Thus, it amplifies the reaction of the first subcomponent.

It is known that MMN amplitude is affected by various drug states (Jaaskelainen, Lehtokoski et al., 1995; Jaaskelainen, Pekkonen et al., 1995; Serra, Escera, Sanchez-Turet,

Sanchezsastre & Grau, 1996). For example, stimulants increase and sedatives decrease MMN amplitude (Näätänen, 1995; Lang et al., 1995). Theoretically, this is because these substances affect the amplifying / modulating subcomponent of the MMN, a system which is dependent upon the state of vigilance of the individual (ie. awake, asleep, medicated, etc.).

Thus, it is possible the auditory component of MMN is derived from both computational and amplifying subcomponents. The first reacts to stimulus change automatically and the second amplifies this signal. Vigilance and drug-state affect this amplification. If the auditory component's threshold is surpassed, the frontal component of MMN then responds and conscious awareness that stimulus change has occurred becomes possible.

Recent evidence suggests the MMN, absent in deep coma, can predict the return to consciousness of comatose patients with severe traumatic brain injury. The appearance of MMN was seen to precede an improvement in scores on the Glasgow Outcome scale (Kane et al., 1996), further suggesting that vigilance severely affects MMN amplitude and latency.

Mismatch Negativity And Aging

Changes in the topography of MMN origin have been reported with age. Woods (1992) found that MMN amplitude was maximal over the right hemisphere in middle aged individuals and over the left hemisphere in the elderly. This was felt to be indicative of an age-related reduction in the cerebral mechanisms involved with detection of stimulus

change in the right hemisphere. Similar declines in other right hemisphere processing abilities, such as visuospatial and constructional, were also seen with age.

The wave characteristics of MMN also change with age. Woods (1992) used a dichotic listening condition and observed that the average MMN response in elderly subjects (age 60-74 years) was weaker than in middle aged individuals (age 26-53 years) when changes in duration occurred. Specifically, the amplitude of the MMN was lower and the peak latency greater in elderly adults. Other studies (Verleger, Neukäter, Kömpf and Vieregge, 1991; Czigler, Csibra & Csontos, 1992; Karayanidis, Andrews, Ward & Michie, 1995) have observed a similar age-related lowering of mismatch amplitude when frequency deviants were used. Overall, MMN appears to be less prominent in the elderly.

Memory trace theory assumes that a decrease or loss of MMN amplitude is due to impaired comparison abilities (Näätänen, 1990), possibly due to memory trace decay. Supporting this notion are the findings that MMN is gradually lost in young subjects as the ISI increases and this effect is enhanced in the aged (Pekkonen et al., 1993, 1996).

MMN, measured by wave area for frequency deviants, was stable across all ages for frequency changes when using ISIs of 0.5 or 1.0 seconds (Pekkonen et al., 1993, 1996). However, increasing the ISI from one second to three seconds significantly decreased the MMN wave area in the aged (Pekkonen et al., 1993). Only when the ISI reached five seconds was this effect seen in young adults. Pekkonen et al. (1996) also found that ISIs of 4.5 seconds attenuated MMN amplitude to a greater extent in older than in younger subjects. These results were interpreted as a shortening of human auditory sensory memory with aging, likely because the neuronal trace decays faster in the

elderly. Additionally, when the results of 0.5 and 1.0 second ISIs were combined, changes in duration elicited lower MMN amplitudes in older individuals compared with younger controls (Pekkonen et al., 1996).

It appears that age-related variations of the MMN do occur. Specifically, as one ages duration-elicited and frequency-elicited MMNs become attenuated, the first to a greater degree. Moreover, ISI length has an age-related effect. Pekkonen et al. (1993) proposed this may reflect a shortening of the duration of auditory sensory memory with increasing age. If this is true then one might expect to see even greater attenuation of the MMN in patients with severe memory problems (eg. Alzheimer's).

Mismatch Negativity, Neuropathology And Dementia

MMN attenuation is seen in many different neuropathological conditions. Recently, Alho et al. (in press, see Näätänen & Alho, 1995c) found reduced MMNs in patients with unilateral lesions of the dorsolateral frontal cortex. They proposed this attenuation was due to either decreased activity of the MMN generator in the frontal lobes or from ipsilateral lesions which affected input to this area from the auditory cortex.

Reduced MMN amplitudes have also been illustrated in schizophrenics (Näätänen & Alho, 1995c; Javitt, Doneshka, Grochowski & Ritter, 1995). Kathmann, Wagner, Rendtorff and Engel (1995) did not find this but did observe a significant increase in MMN peak latency in both medicated schizophrenic patients and detoxified chronic alcoholics compared to untreated individuals with similar conditions. Recently, increases in MMN latencies and attenuated MMN amplitudes have been reported in patients with

non-insulin-dependent diabetes mellitus (Vanhanen et al., 1996) or with PD (Stam et al., 1993; Pekkonen, Jousmäki et al., 1995). Of particular interest, PD patients suffering from dementia exhibited decreased MMN amplitudes when an ISI of 1 second was used (Lang et al., 1995) suggesting a shortening of the memory trace in dementia.

Until recently, ERP investigations in AD have primarily focused on the P300 component, which has generally been shown to be reduced in amplitude (suggesting deficits in the deployment of attentional resources) and delayed in latency (suggesting a slowing of stimulus evaluating processes) in this disorder (Kügler, Taghavy & Platt, 1993; Katayama et al., 1995; Holt et al., 1995; Yokoyama, Nakashima, Shimoyama, Urakami & Takahashi, 1995). Increased P300 latency and decreased glucose metabolism have both been correlated with dementia severity (Szelies, Mielke, Grond & Heiss, 1995).

Auditory sensory memory is linked to STM and also may draw upon LTM (Cowan, 1995), both which are deficient in AD (Hulme et al., 1993). Given that MMN is likely an indirect measure of auditory sensory memory in humans (Näätänen & Alho, 1995a, 1995c), that memory deficits are a core characteristic of AD (Carlesimo et al., 1993) and that MMN is sensitive to sensory memory decay (Pekkonen et al., 1993), it seems likely that measures of MMN in AD patients may yield valuable insights into the disorder. Moreover, unlike the P300, MMN is largely unaffected by attentional processes which are deficient in AD. Thus, measurements of MMN in AD are simple to obtain, as rigorous and confounding attentional requirements are not placed upon patients during recording. Also, assuming MMN provides a measure of auditory sensory memory, it is easier to infer its presence in the brain than other more abstract types of memory (eg.

LTM).

Only three studies to date have examined MMN in AD. Yokoyama et al. (1995) found that MMN latency was delayed on Pz in AD patients compared with age-matched controls. MMN amplitude did not significantly differ between groups. Verleger, Kömpf and Neukäter (1992) also reported that the MMN/N200b complex as a whole had a greater latency in AD patients but they attributed this solely to a late N200b component. They too reported that MMN amplitude was not significantly different between AD patients and the control group.

Several problems arise with these conclusions due to experimental designs. First, the mismatch response in both studies was measured in an attend condition. As a result, it is likely that other complexes overlapped the MMN such as the N100 and, in particular, the N200b. Second, a physical response was made to the deviant tones (raising a finger or pushing a button). These evoked motor potentials may have further confounded the results. Moreover, the ISIs used were 1.5 seconds or 2 seconds (Verleger and Yokoyama studies respectively). As the MMN assumedly measures a transient memory trace, it is possible that significant mismatch differences between these groups will only be apparent for longer ISIs (eg. 3 seconds).

A follow-up study by Pekkonen, Jousmäki, Könönen, Reinikainen and Partanen (1994) also found no mismatch differences between AD patients and age-matched controls using short ISIs of 1 second. However, using ISIs of 3 seconds the responses of both groups were attenuated. Furthermore, this attenuation was greater in AD patients than in controls (measuring MMN across F3, Fz, F4 this result was significant at Fz and

approaching significance at F3). MMN latency was not measured. Overall, these results suggest that the automatic detection of stimulus change still occurs in AD patients.

However, the memory trace associated with this detection appears to decay faster in these individuals than in age-matched controls. In AD there is a significant degeneration of neurons in the superior temporal gyrus where MMN is partially generated according to neuromagnetic studies (Sams et al., 1991). Assuming the memory trace is stored in the same area where it is generated, the decreased memory trace seen in AD may reflect neuronal damage and loss of plasticity in this region of the temporal lobe (Pekkonen et al., 1994).

Mismatch Negativity, Alzheimer's Disease And Hearing

Many AD patients are unable to selectively attend to one ear and, as a result, they do very poorly on dichotic listening tasks. However, it is likely that poor performance on such tasks is not due solely to an overall deficit in central auditory processing or peripheral hearing loss (egs. cochlear or eighth nerve damage), as accuracy and attentional allocation may be lost but processing capacity and depth are generally maintained (Grimes, Grady, Foster, Sunderland & Patronas, 1985; Mohr, Cox, Williams, Chase & Fedio, 1990). The hearing deficits that AD patients sometimes experience likely stem from a breakdown of cortical mechanisms linked with the selective allocation of attention (Mohr et al., 1990). Thus, the reports of poor performances by AD patients on some dichotic auditory tasks are likely related to attentional capabilities rather than hearing problems. As the MMN does not require one's attention, it appears to be an ideal probe to circumvent such

problems when conducting tests involving audition in AD patients.

Nicotine, EEG And ERPs

Examination of the acute effects of nicotine on electrocortical activities has primarily been approached through the quantitative analysis of background EEG rhythms following cigarette smoke inhalation (eg. fast Fourier transform analysis yielding power spectrums). The general consensus of these reports, observed both in review articles (egs. Church, 1989; Knott, Hooper, Lusk-Mikkelsen & Kerr, 1995) and several key studies (egs. Knott, 1988; Knott, 1989a; Knott, 1989b; Domino & Matsuoka, 1991; Domino, Riskalla, Zhang & Kim, 1992), indicate that EEG activity following acute smoking of one or two cigarettes typically portrays a desynchronized electrically activated brain profile. This is characterized by an acceleration of the dominant frequency and a shift in spectrum activity, accompanied by power suppression in slow frequency bands and power augmentation in fast frequency bands. These profiles, observed mainly in young adult samples, have been shown to be equally evident in the elderly (> 60 years of age) (Knott & Harr, 1996). Similar EEG profile changes have been reported after chewing nicotine gum in 2 and 4 mg doses (Pickworth, Herning & Henningfield, 1986) and, more recently, with chronic transdermal application of nicotine at a dose of 21 mg (Bosman, 1995).

Reviews of smoke inhaled nicotine effects on ERPs have generally concluded that cigarette smoking increases the intensity of brain responsiveness to sensory input (Knott, 1989c; Knott, Kerr, Hooper & Lusk-Mikkelsen, 1995). Smoke-inhaled nicotine has been shown in some but not all reports (Houlihan, Pritchard & Robinson, 1996) to augment the

deployment of attention and to speed the evaluative processing of task stimuli. This is evidenced by smoking induced increments in P300 amplitudes and reductions in P300 latencies respectively. Different ERP components, such as the P300, have been shown to reflect attentional/cognitive processes (eg. Picton, 1992).

Chronic applications of the transdermal nicotine patch have been shown to produce shortened P300 latencies in AD patients (Katayama et al., 1995). Similar attentional/cognitive effects have been observed in non-smokers following subcutaneous nicotine injections (Le Houezec et al., 1994).

To sum, various routes of nicotine administration act to stimulate the human brain electrophysiologically and to a similar degree. These findings suggest that cognitive studies which examine the effects of nicotine, given via cigarette smoking or by other means (egs. gum, patch), are valid and comparisons can be made between them.

Study Rationale

Both cigarette smoking and other forms of nicotine administration have been shown to alter memory processes and to enhance attention which may in turn impact on memory. Nicotine's primary mechanism of action in producing such effects appears to be by direct stimulation of cholinergic neurons in the CNS, the transmitter system most deficient in AD.

Given that memory defects are a core characteristic of AD and that MMN is sensitive to certain aspects of memory processing (ie. sensory memory decay), this thesis aims to explore the relationship between nicotine and MMN in AD. Specifically, the

relationship between these components will be explored in two separate studies, with one being directed at examining differences in MMN profile between AD patients and age-matched controls. The second study will examine the acute effects of nicotine on MMN in AD patients. The differences in MMN between THA-treated and non-THA-treated AD patients will also be examined

Although this thesis is considered to be mainly exploratory in nature to provide empirical data for the generation of testable hypotheses, it is generally predicted that AD patients will exhibit smaller MMN amplitudes and longer MMN latencies (especially with longer ISIs) than healthy elderly controls. Furthermore, nicotine will increase these amplitudes and shorten these latencies in AD patients in general but more so in the THA-treated patients than in the non-THA-treated patients.

METHODS

STUDY I: A Comparison Of MMN In AD Patients And Age-Matched Controls

1. Subjects

The MMN recordings of thirteen medication-free mild to moderate AD patients (8 males, 5 females; mean age 73.4 yrs; range 68-82 yrs) were obtained from a previously run drug trial protocol. These subjects were interviewed and screened by a neurologist prior to testing. All met the inclusion/exclusion criteria outlined in Appendix A. Thirteen elderly sex-matched controls (mean age 68.4 yrs; range 58-75 yrs) were also recruited on a voluntary basis to participate. Controls were awarded \$30 for their time in this study. Prior to ERP recordings, the MMSE was administered (mean score 19.7; range 13-22) to AD subjects.

2. Stimulation

MMN was elicited by two auditory "oddball" stimulus conditions presented through headphones to the subject's right ear using stimulus features identical to Pekkonen et al. (1993). A total of 400 random tone pips (70 msec duration) of 800 Hz (the standard tone, 85% probability) and 552.4 Hz (the deviant tone, 15% probability) were delivered in three separate blocks (200 tones in the first block using an ISI of 1 second; 100 tones in each of the other two blocks using an ISI of 3 seconds). ISIs were calculated from onset to onset of subsequent tones. Blocks were always presented in the same order and there were at least two minutes between blocks in which subjects rested. Pitches below 1000 Hz were used as hearing for low frequency tones is lost later in life than for high frequency tones (Hickish, 1989). Tones were of 84 msec duration (including 7 msec rise and decay times) and were delivered in random order, so that at

least two standard tones occurred between deviant tones. Sound intensity was kept constant at 60 dB/SPL

3. Recording

Cerebral electrical activity was recorded from the frontal scalp sites of F3, Fz and F4 (left, central and right frontal respectively) using the standard 10-20 electrode system illustrated in Figure 1 (Jasper, 1958). Scalp sites were referenced to linked earlobe sites for monopolar

Insert Figure 1 about here

recordings and a mid-forehead electrode was used as ground. Electro-oculographic (EOG) activity was recorded from the outer canthus of the right eye and referenced to another electrode one centimetre above the same eye. This permitted the recording of both vertical and horizontal eye movements on a single recording channel. All electrode impedances were less than 5.0 kOhms.

EEG and EOG raw signals were recorded with a high frequency amplifier filter setting of 30 Hz and a time constant of 0.2 seconds. Electrical recordings were monitored online and analog-to-digital samplings began 50 msec prior to stimulus onset, to measure prestimulus baseline and noise level, and continued afterwards for 450 msec. A total of 256 data points were digitized for each recording channel (ie. a sample was taken every 2.15 msec). Single stimulus trial data were stored on hard disk for later offline analyses.

4. Procedure

Subjects attended one testing session, during which they sat in a comfortable reclining

Electrode Montage

Figure 1. Electrode placement for ERP recordings, based on 10-20 system

chair in a sound-attenuated electrically shielded chamber. A video camera mounted in the recording chamber allowed the experimenter to view the subject on a monitor in the adjacent control room. Subjects were instructed to close their eyes and ignore any sounds coming from the headphones while electrical MMN recordings were carried out.

5. Analysis

Prior to peak amplitude/latency measurements, each channel was visually examined to ensure no mechanical problems occurred with the equipment. Offline analysis involved de-artifacting of electrical signals. This included the automatic rejection of single trials with EEG or EOG amplitudes exceeding $\pm 100 \mu\text{V}$ (due to head, facial or eye movements) followed by an ocular correction of individual EEG trials using a standard linear correction procedure (Woestenburg, 1994). The responses from the two 3-second block ISIs were averaged together. Average waveforms were then computed for each stimulus type, within each ISI sequence, per channel (ie. F3, Fz, F4) and for each subject.

Averaged waveforms were digitally filtered with a zero-phase shift low pass filter set at 17 Hz and grand averaging was performed for the purpose of visualizing group mean ERP components. The MMN was best observed in a "difference" wave which was computed by digitally subtracting, point-by-point, the standard from the deviant waveforms for each channel in each ISI sequence condition. Employing the measurement methodology of Näätänen and colleagues (egs. Alho, Paavilainen, Reinikainen, Sams & Näätänen, 1986; Alho et al., 1989), the average negative amplitude of these "difference" waveforms was calculated across the 50-250 ms post-stimulus sweep in consecutive 50 ms windows (ie. 50-100 ms, 100-150 ms, 150-200 ms and 200-250 ms). In addition, the average of all data points in the 50-250 ms window was computed

yielding an average MMN amplitude measure. Peak latency and peak amplitude values (ie. the time point and amplitude of the largest negative peak between 100-300 ms) were also extracted from these difference waveforms, per channel, for each individual. Peak latency was defined as the time elapsed from stimulus presentation to peak amplitude.

A few peak amplitude/latency values were selected by the computer which obviously reflected either the N100 component or late negativity appearing after an easily recognizable MMN peak. These values were manually corrected in as conservative a manner as possible. Manual corrections which affected amplitude values were required for less than 20% of the averaged waveforms.

6. Statistics

Data points were found to be normally distributed (ie. z-scores were no greater than ± 3 and skewness and kurtosis scores were not greater than ± 2) for measures of peak amplitude and peak latency. As a result, the analyses for these two measures were performed parametrically using a univariate analysis of variance (ANOVA) with repeated measures. Specifically, each MMN measure was subjected to a separate 2 (Group: control, AD subjects) X 2 (Interval: 1, 3 seconds) X 3 (Channel: F3, Fz, F4) ANOVA. Any interactions found to be significant were followed up with a simple effects analysis. The measure of average amplitude was not normally distributed and, as a result, was analysed non-parametrically. Between-group differences were assessed using Mann-Whitney U-tests and within-group differences were assessed with the Wilcoxon Matched-Pairs Signed-Ranks Statistic. Correlations between MMN values and MMSE scores were assessed using Pearson's r (parametric) for measures of peak amplitude/latency and Spearman's coefficient (non-parametric) for the measure of average amplitude.

STUDY II: The Acute Effects Of Nicotine On MMN In AD Patients

1. Subjects

Twelve patient volunteers (mean age 71.1 yrs; range 53-82 yrs) diagnosed with mild to moderate Alzheimer's disease were recruited from the outpatient population at the Royal Ottawa Hospital. All were previously interviewed and screened by a neurologist, had passed a medical exam which included an electrocardiogram (EKG) and blood sampling (for routine biochemical/haematological screening) and met the inclusion/exclusion criteria outlined in Appendix B. Six of the AD subjects (2 males, 4 females; mean age 73.9 yrs) had not received any pharmacological treatments with CNS agents for at least a one month period. The other six (5 males, 1 female; mean age 68.3 yrs) were receiving ongoing treatment of THA (mean treatment time 10.2 mos; range 6-12 mos) and had been at their maximally tolerated dose (mean maximal dose 153 mg/day (qid); range 120-160 mg/day) for six weeks or longer. All subjects were classified as non-smokers (ie. had not smoked in the past ten years).

During an orientation session the rationale and procedures of the study were explained and demonstrated to each subject and a consent form signed (see Appendix C) by both subject and caregiver. Individuals were then verbally questioned (see Appendix D) concerning their history of health and CNS drug use (smoking and cholinergic drugs in particular). Hearing intensity thresholds were determined and the MMSE then administered to assess degree of cognitive impairment.

The MMSE is a commonly used standardized examination of mental status. It assesses orientation, registration, attention, calculation language and recall (Wiederholt et al., 1993). Administration of the test typically takes 5-10 minutes (Lezak, 1995) but times may be longer for

severely demented individuals. Scores on the test can range from 0-30. In AD subjects there is an expected decline of 2-5 points on the MMSE per year (Tombaugh & McIntyre, 1992). Test scores below 24 are generally indicative of dementia (Lezak, 1995). In the majority of studies, MMSE scores of less than 23 have been associated with dementia 79% of the time (Tombaugh & McIntyre, 1992).

In this study, the average MMSE score was 25.1 (range 15-30) classifying the group on the whole as being cognitively non-impaired. However, the test by itself is not sensitive to mild cognitive change (Tombaugh & McIntyre, 1992; Tombaugh, McDowell, Kristjansson & Hubley, 1996) and false negatives are fairly common (Lezak, 1995), especially in the higher educated (Tombaugh & McIntyre, 1992; Tombaugh et al., 1996). For this reason, all subjects used had been previously diagnosed with Alzheimer's disease using larger test batteries (ie. Clinical Dementia Rating Scale and each fulfilled the DSM-IV criteria for mild to moderate dementia of the Alzheimer's type). The main purpose of using the MMSE as a screening tool in this study was to identify and screen out individuals with "severe" cognitive impairments. None of the AD subjects used in this study fit this criterion (ie. no MMSE scores were below 10; mean score was 25.1; range was 15-30).

2. Stimulation

MMN was elicited by two auditory "oddball" stimulus conditions presented through headphones to the subject's right ear using stimulus features identical to Pekkonen et al. (1993). A total of 400 random tone pips (70 msec duration) of 800 Hz (the standard tone, 85% probability) and 552.4 Hz (the deviant tone, 15% probability) were delivered in three separate blocks (200 tones in the first block using an ISI of 1 second; 100 tones in each of the other two

blocks using an ISI of 3 seconds). ISIs were calculated from onset to onset of subsequent tones. Blocks were always presented in the same order and there were at least two minutes between blocks in which subjects rested. Pitches below 1000 Hz were used as hearing for low frequency tones is lost later in life than for high frequency tones (Hickish, 1989). Tones were of 84 msec duration (including 7 msec rise and decay times) and were delivered in random order, so that at least two standard tones occurred between deviant tones. Sound intensity was set at 60 dB/SPL above the individual's hearing threshold for the right ear. Thresholds were determined by a descending methods of limits procedure involving the presentation of an initial tone of 50 dB/SPL which was stepped down in increments of 5 dB/SPL or less until undetectable.

3. Recording

Cerebral electrical activity was recorded from the frontal scalp sites of F3, Fz and F4 (left, central and right frontal respectively) using the standard 10-20 electrode system illustrated in Figure 1 (Jasper, 1958). Scalp sites were referenced to linked earlobe sites for monopolar recordings and a mid-forehead electrode was used as ground. Electro-oculographic (EOG) activity was recorded from the outer canthus of the right eye and referenced to another electrode one centimetre above the same eye. All electrode impedances were less than 5.0 kOhms.

EEG and EOG raw signals were recorded with a high frequency amplifier filter setting of 30 Hz and a time constant of 1.0 second. Electrical recordings were monitored online and analog-to-digital samplings began 50 msec prior to stimulus onset, to measure prestimulus baseline and noise level, and continued afterwards for 450 msec. A total of 256 data points were digitized for each recording channel (ie. a sample was taken every 2.15 msec). Single stimulus trial data were stored on hard disk for later offline analyses.

It should be noted that measures of quantitative EEG (QEEG) and P300 were also assessed on separate tasks in this study. However, these fall beyond the scope of this paper and will not be dealt with here.

4. Design

Subjects attended the laboratory for two test days during which measurements were collected before and after randomized, double-blind, acute administration of nicotine or placebo. MMN amplitudes between test days have been shown to correlate significantly (Lang et al., 1995). Nicotine gum was administered in a pseudorandomized manner so that half of the subjects within each grouping (ie. THA and non-THA subjects) received a 2.0 mg dose of nicotine in gum (Nicorette[®], Pharmacia AB, Sweden) on day 1 and placebo gum (0 mg nicotine) on day 2. The remaining participants received placebo on day 1 and nicotine on day 2. The placebo was a commercial gum which approximated Nicorette[®] in size and texture. Test sessions were separated by a 2-5 day interval.

Subjects were required to refrain from tobacco, caffeine and CNS affecting drugs (eg. aspirin), with the exception of the THA group which took THA on the morning of testing with breakfast. Additionally, no alcohol was consumed 24 hours prior to testing. Studies show that even a low dose of alcohol (0.5 g/kg) can reduce MMN amplitude by more than 60% and increase latency (Jaaskelainen et al., 1995; Jaaskelainen, Pekkonen, Hirvonen, Sillanaukee & Näätänen, 1996).

5. Nicotine

To mask the taste differences between Nicorette[®] and placebo participants wore noseplugs when chewing and a drop of mint oil was placed on each piece. This hindered taste perception so

that the subject had no idea which gum they were chewing on a given day. Tabasco[®] sauce has been used in other studies (Sherwood et al., 1992) but mint oil has a less aversive aftertaste and disguises the taste equally well. Subjects were instructed to close their eyes and the gum was placed on their tongues so that visible differences between gums was not a factor.

Subjects were instructed to follow the chewing instructions for Nicorette[®] gum (ie. take two bites every minute for a period of 20 minutes). A taped voice recording reminded them when to chew and the investigator was present to ensure that chewing was performed correctly. Afterwards, the subject disposed of the gum and chewed a strong commercial mint gum for two minutes before removing the noseplugs.

Ten minutes after chewing finished post-gum measurements were collected. The chewing of nicotine gum in this manner is estimated to produce a peak blood nicotine level of 5.0 µg/ml at approximately 25 minutes from the initiation of chewing (Russell, Feyerabend & Cole, 1976). The elimination half-life of nicotine in plasma is estimated to be 120 minutes (Le Houezec & Benowitz, 1991).

6. Procedure

On test days, subjects were instructed to eat a light breakfast and arrived at the laboratory 1.5 - 2.0 hours afterwards. Thus, testing sessions began between 8:30 - 10:00 am and were identical on both days. Subjects sat in a comfortable reclining chair in a sound-attenuated electrically shielded chamber. A video camera mounted in the recording chamber allowed the experimenter to view the subject on a monitor in the adjacent control room.

Following electrode hookup and the assessment of heart rate and blood pressure, subjects were instructed to watch a neutral video (on mute) and told to ignore the tones while electrical

MMN recordings were carried out. The normal procedure with studies of MMN is to have individuals read a text of their choice but many AD patients no longer read for pleasure.

Watching television is an easier task to perform, it keeps subjects mentally alert and it has been used in a previous study of MMN in AD (Pekkonen et al., 1994).

The gum was then chewed in the manner previously described, heart rate and blood pressure were reassessed and MMN was again recorded using the identical procedures. At the end of each test day subjects completed an adverse symptoms report, administered verbally, to determine the presence and degree of any negative side effects exerted by the gum (see Appendix E).

7. Analysis

Prior to peak amplitude/latency measurements, each channel was visually examined to ensure no mechanical problems occurred with the equipment. Offline analysis included the automatic rejection of single trials with EEG amplitudes exceeding $\pm 100 \mu\text{V}$ (due to head or facial movements). EOG artifact was expected to be larger in Study II as the subjects' eyes were open, whereas in Study I they were closed. As a result, EOG amplitudes greater than $\pm 200 \mu\text{V}$ (rather than $100 \pm \mu\text{V}$) were rejected. This was followed by an ocular correction of individual EEG trials using a standard linear correction procedure (Woestenburg, 1994). The responses from the two 3-second block ISIs were averaged together. Average waveforms were then computed for each stimulus type, within each ISI sequence, per channel (ie. F3, Fz, F4) and for each subject.

Averaged waveforms were digitally filtered with a zero-phase shift low pass filter set at 17 Hz and grand averaging was performed for the purpose of visualizing group mean ERP

components. The MMN was best observed in a “difference” wave which was computed by digitally subtracting, point-by-point, the standard from the deviant waveforms for each channel in each ISI sequence condition. Employing the measurement methodology of Näätänen and colleagues (egs. Alho, Paavilainen, Reinikainen, Sams & Näätänen, 1986; Alho et al., 1989), the average negative amplitude of these “difference” waveforms was calculated across the 50-250 ms post-stimulus sweep in consecutive 50 ms windows (ie. 50-100 ms, 100-150 ms, 150-200 ms and 200-250 ms). In addition, the average of all data points in the 50-250 ms interval was computed yielding an average MMN amplitude measure. Peak latency and peak amplitude values (ie. the time point and amplitude of the largest negative peak between 100-300 ms) were also extracted from these difference waveforms, per channel, for each individual. Peak latency was defined as the time elapsed from stimulus presentation to peak amplitude.

A few peak amplitude/latency values were selected by the computer which obviously reflected either the N100 component or late negativity appearing after an easily recognizable MMN peak. These values were manually corrected in as conservative a manner as possible. Manual corrections which affected amplitude values were required for less than 9% of the averaged waveforms.

8. Statistics

Data points were found to be normally distributed (ie. z-scores were no greater than ± 3 and skewness and kurtosis scores were not greater than ± 2) for all measures (ie. peak amplitude/latency and average amplitude). As a result, all analyses were performed parametrically using univariate ANOVAs with repeated measures. Specifically, each MMN measure was subjected to a separate 2 (Group: non-THA, THA) X 2 (Trial: pre-drug, post-drug) X 2 (Drug:

placebo, nicotine) X 2 (Interval: 1,3 seconds) X 3 (Channel: F3, Fz, F4) ANOVA. Any interactions found to be significant were followed up with a simple effects analysis. Correlations between MMN values and MMSE scores were measured using Pearson's r . Specifically, correlations were assessed between: (1) MMSE and baseline values (ie. MMN values from the first pre-drug session performed), and (2) MMSE and post-pre differences obtained on the nicotine treatment day.

RESULTS

Study I

Figure 2 displays the group averaged MMN subtracted waveform at each recording

Insert Figure 2 about here

channel for 1 and 3 second ISI conditions respectively. The waveforms elicited with 1 second ISIs did not show a clear single MMN component for either group. Rather, they indicated two separate negative peaks, both which occurred within the traditionally accepted MMN window (ie. 100-250 msec). It appears the earlier negativity, which peaked at about 110 msec, reflects variation in the N100 component, whereas the later negativity, which peaked approximately 210 msec post-stimulus, seems to be the actual MMN somewhat delayed. This delay was expected as subjects were elderly and suffered from AD.

With the 3 second ISI condition, a single MMN component was apparent within the 300 msec cutoff for the control group, although attenuated. AD subjects still exhibited two separate peaks, the first at about 110 msec and the second at about 260 msec. Again, this first peak likely reflects variation in the N100 component.

Although intraindividual variability was high, the MMN peak was quite apparent for each individual subject for all measures. It is important to note that the waveforms displayed in Figure 2 represent group averages. However, the statistics for this study were not calculated from group averages but from peak/latency scores and average amplitude scores which were derived from

Figure 2. Group (AD patients and controls) averaged MMN waveforms at each recording channel for the 1 and 3 second ISI conditions

individual averages. Thus, the aforementioned group averaged waveforms are chiefly for display purpose and do not exactly illustrate the statistical findings of this study.

Peak Amplitude/Latency

Means for both groups were clearly in the expected directions, as the average MMN peak amplitude was greater and the average latency was shorter with an ISI of 1 second rather than 3 seconds at all channels in each group. Though these findings were non-significant, they suggest that typical MMN recordings were obtained in this study.

The parametric analysis of peak amplitude revealed no significant differences between the various groups, intervals or channels used. However, a main effect of group existed for the measure of peak latency, as control subjects displayed significantly shorter peak latencies than AD subjects ($F(1,24) = 8.50, p < 0.01$).

Average Amplitude

The non-parametric analysis of average amplitude (Mann-Whitney U-tests) found no between-group differences for the post-stimulus interval of 50-250 msec. However, as shown in Figure 3, a within-group analysis (Wilcoxon) found that the average amplitude was more

Insert Figure 3 about here

negative with an ISI of 1 second rather than 3 seconds in the AD group. This was significant at Fz ($p < 0.01$) and F4 ($p < 0.05$) and approached significance at F3 ($p < 0.09$). Though the 1 and 3 second ISI mean average amplitudes of control subjects were not statistically different, they were clearly in the same direction as the means of AD subjects (ie. 1 second < 3 second) at all channels.

Figure 3. Group (AD patients and controls) average amplitude during the 50-250 msec post-stimulus interval at F3, FZ and F4

Individual Amplitude Windows

Similarly, no between-group differences were found for the individual amplitude windows of: (1) 50-100 msec, (2) 100-150 msec, (3) 150-200 msec, and (4) 200-250 msec. However, within the AD group, the amplitudes of window 2 (F_4 , $p < 0.05$) and window 4 (F_z , $p < 0.05$; F_4 approached significance, $p < 0.06$) both exhibited more negative values with an ISI of 1 second compared to 3 seconds. Means at all other channels were clearly in the same direction but non-significant, as were all means for windows 1 and 3. The means of the control group were not significantly different, yet were clearly in the same direction as the means of the AD group (ie. 1 second < 3 seconds) at all channels.

Behavioural Correlations

Using Pearson's r for the measure of peak amplitude/latency and Spearman's correlation coefficient for the measure of average amplitude (both averaged and individual amplitude windows), the relationship between MMSE scores of the 13 AD patients and MMN values were assessed. No significant correlations were found.

Study II

All 12 subjects completed the two study sessions and no ill effects from nicotine administration were reported by anyone. One female subject reported mild light-headedness at the end of the nicotine testing session but, as testing overlapped lunch hour, she felt this was due to mild hunger.

Figure 4 illustrates the averaged pre- and post-gum MMN subtracted waveform at each

Insert Figure 4 about here

recording channel for placebo and nicotine, for both the 1 and 3 second ISI conditions. Figures 5-6 display the same waveform, comparing non-THA and THA treated groups for 1 and 3

Insert Figures 5-6 about here

second ISI conditions respectively. All waveforms exhibited a clear single MMN component within the normally accepted post-stimulus time window of 100-250 msec.

Again, it is important to note that the waveforms displayed in Figures 4-6 represent group averages. However, the statistics for this study were derived from individual averages. Thus, the group averaged waveforms are chiefly for display purpose and do not exactly illustrate the statistical findings of this study.

Peak Amplitude

Means for both groups were clearly in the expected directions, as the average MMN peak amplitude was greater and the average latency was shorter with an ISI of 1 second rather than 3 seconds at all channels in each group. Though these findings were non-significant, they suggest that typical MMN recordings were obtained in this study.

A 2-way interaction of Trial x Drug ($F(1/10) = 10.23, p < 0.01$) and a 3-way interaction of Trial x Drug x Group ($F(1/10) = 5.77, p < 0.05$) were observed for measures of peak amplitude. Follow-up post-hoc analyses of the Trial x Drug x Group interaction were first used to explore

Figure 4. Averaged pre- and post-gum MMN waveforms at each recording channel for the 1 and 3 second conditions

Figure 5. Group averaged waveforms comparing non-THA treated patients with THA treated patients pre- and post-gum administration for the 1 second ISI condition

Figure 6. Group averaged waveforms comparing non-THA treated patients with THA treated patients pre- and post-gum administration for the 3 second ISI condition

for group differences in response to placebo and nicotine treatment. To test for possible drug effects, each test session was evaluated for differences before (pre-) and after (post-) placebo/nicotine administration. As seen in Figure 7, two significant differences within the non-

Insert Figure 7 about here

THA group were revealed. First, the peak amplitude was more negative pre-placebo than post-placebo ($F(1/5) = 17.59, p < 0.01$). This was not found in the THA group, though the means were clearly in the same direction. Second, the peak amplitude was more negative post-nicotine than post-placebo ($F(1/5) = 8.18, p < 0.05$). Again, this was not statistically significant in THA subjects but means were similar.

In order to further contrast the differential effects of drug treatments on MMN, pre-drug values were subtracted from post-drug values and the resulting net effect change scores were subjected to one-way ANOVAs for each channel. On the placebo treatment day, both groups exhibited a smaller peak amplitude post-placebo compared to pre-placebo. Examining the difference scores in Figure 8, one can see this drop in amplitude was greater in non-THA than in

Insert Figure 8 about here

THA patients ($F(1/10) = 8.24, p < 0.05$). Conversely, on the nicotine treatment day, the means of THA subjects pre- and post-nicotine were identical, whereas non-THA subjects exhibited a greater peak amplitude post-nicotine (non-significant). Within the non-THA group, these post-

Figure 7. Group (THA and non-THA) averaged peak amplitudes pre- and post-gum administration for each treatment day

Figure 8. Average peak amplitude difference scores (post-pre) for non-THA and THA subjects on placebo and nicotine treatment days.

pre differences scores were significantly different between placebo vs. nicotine treatment test days ($F(1/5) = 20.89, p < 0.01$).

Peak Latency

A Trial x Drug interaction ($F(1/10) = 5.57, p < 0.05$) was found. Follow-ups revealed, as indicated in Figure 9, that latencies were greater post-placebo compared to pre-placebo ($F(1/11)$

Insert Figure 9 about here

$= 11.31, p < 0.01$). Conversely, latencies were smaller post-nicotine compared to pre-nicotine, though this difference was not statistically significant. Thus, the peak latency of subjects significantly increased after placebo but non-significantly decreased after nicotine treatments when compared with pre-drug (baseline) values. The post-pre latency difference scores were also significantly different between treatment days ($F(1/10) = 5.57, p < 0.05$). Additionally, peak latency was greater post-placebo compared to post-nicotine ($F(1/11) = 7.15, p < 0.05$). No differences were seen when comparing pre-drug values across placebo vs. nicotine treatment test days.

Average Amplitude

The analysis of average amplitude during the amplitude window of 50-250 msec (windows 1-4 combined) yielded both Interval x Group ($F(1/10) = 6.00, p < 0.05$) and Drug x Interval x Group ($F(1/10) = 8.40, p < 0.05$) interactions. As shown in Figure 10, follow-ups found

Figure 9. Average peak latencies pre- and post-gum administration for both placebo and nicotine treatments (n=12)

Insert Figure 10 about here

that the mean MMN amplitude of non-THA subjects was more negative when subjects were presented with an ISI of 3 seconds rather than 1 second ($F(1/5) = 8.13, p < 0.05$). This was especially seen on the placebo treatment day ($F(1/5) = 7.02, p < 0.05$), whereas THA subjects on this day exhibited a more negative average amplitude when using an ISI of 1 second rather than 3 seconds ($F(1/5) = 9.79, p < 0.05$). This was significantly more negative than the average amplitude of non-THA subjects with an ISI of 1 second ($F(1/10) = 11.31, p < 0.01$). No differences were observed between 1 and 3 second ISI amplitudes in either group on the nicotine treatment day.

Individual Amplitude Windows

During window 1 (50-100 msec) a significant Drug x Interval x Group effect was seen ($F(1/10) = 8.48, p < 0.05$). Follow-ups revealed that non-THA subjects displayed a more negative amplitude, during this time interval on the placebo treatment day, when an ISI of 3 seconds was used rather than 1 second ($F(1,5) = 6.91, p < 0.05$). The means for THA subjects were in the opposite direction but non-significant. On the nicotine treatment day, no differences between ISIs were apparent for either group.

No significant main or interaction effects were observed with average amplitude during window 2 (100-150 msec). A main effect of trial was seen during window 3 (150-200 msec), as the average amplitude during pre-drug sessions was significantly more negative than during post-drug sessions ($F(1/10) = 5.79, p < 0.05$). An additional exploratory analysis found that the average amplitude during this interval was more negative pre-placebo than post-placebo ($F(1/11) = 13.18,$

Figure 10. Average amplitude during the 50-250 msec post-stimulus interval.

$p < 0.01$). No differences were seen on the nicotine treatment day.

During window 4 (200-250 msec) significant Interval $\times$ Group ($F(1/10) = 6.07$, $p < 0.05$) and Drug $\times$ Interval $\times$ Group ($F(1/10) = 5.47$, $p < 0.05$) interaction effects were seen. Follow-ups revealed similar findings to those found when all four windows were combined. The average amplitude of non-THA subjects was more negative when an ISI of 3 seconds was used rather than 1 second ($F(1/5) = 9.30$, $p < 0.05$). This was especially seen on the placebo treatment day ($F(1/5) = 14.87$, $p < 0.05$). Conversely, the means of THA subjects, though non-significant, were in the opposite direction (ie. more negative with an ISI of 1 second). Additionally, a more negative amplitude was seen for the non-THA group than for the THA group with an ISI of 3 seconds on the placebo treatment day ($F(1/10) = 10.10$, $p < 0.01$). On the nicotine treatment day amplitudes were non-significant for both groups when compared between ISIs.

Behavioural Correlations

Using Pearson's r for the measures of peak amplitude/latency and average amplitude (both averaged and individual amplitude windows), the relationship between MMSE scores of the 13 AD patients and MMN values were assessed. No significant correlations between MMSE scores and any of these MMN measures were found.

DISCUSSION

Study I

This study basically replicated research done by Pekkonen et al. (1994) who found that MMN amplitudes, of both elderly AD subjects and age-matched controls, attenuated when the ISI was increased from 1 to 3 seconds. Furthermore, this difference in amplitude was greater in the AD group than in the control group, though this finding was relatively weak as it was only evident at Fz (and approached significance at F3).

In this study, the averaged group waveforms did not appear to be ideal, as double negative peaks were sometimes apparent in the traditionally accepted post-stimulus time window (100-250 msec). However, the MMN was analysed using individual averages, rather than group averages, and significant between-group and within-group differences were found.

Although the MMN peak did not differ in amplitude between groups, it did occur later in elderly AD subjects than in healthy age-matched controls. This suggests that, in AD, either the auditory sensory comparison mechanism was not functioning as quickly or the neural circuitry took longer to adapt to auditory change, as MMN appears to be a measure of one of these processes. Such deficits were likely a result of large neuronal loss associated with AD and may have been related to decay of the sensory memory trace.

No between-group differences were observed when measuring MMN by average amplitude. However, AD subjects exhibited greater negativity with an ISI of 1 second compared to 3 seconds during the time intervals of 100-150 msec and 200-250 msec. Most importantly, this was also seen during the overall interval of 50-250 msec, suggesting that MMN was not simply

displaced into another time interval but an overall reduction in negativity did occur. No differences in negativity were seen between ISIs during any time interval in the control group, further indicating that there was a reduction, rather than a displacement, of negativity in the AD group. Possibly the sensory memory trace in AD subjects fades quicker than in healthy elderly subjects, which may have resulted in the reduction in MMN amplitude seen in the AD group when a longer ISI (ie. 3 seconds) was used. Again, these deficits were likely due to the vast neuronal damage associated with the disease.

In the AD subjects, no relationship existed between the electrophysiological measure of MMN and the rating scale measure of the MMSE. This does not mean that MMN is not related to any cognitive/behavioural functions. Likely, more sensitive measures are needed which tap into the same or related processes which are being measured by MMN.

Unlike the study by Pekkonen et al. (1993) the controls in this study did not exhibit MMN differences, for any measure, when comparing between 1 and 3 second ISIs. However, this study used measures of peak and average amplitude, whereas Pekkonen et al. (1993) measured amplitude by wave area. This difference in measurement techniques may account for the difference in results. Possibly wave area is a more sensitive MMN measure.

Despite this, the results of this study were in concordance with two other studies (Verleger et al., 1992; Yokoyama et al., 1995) which also found increased MMN latency in AD subjects compared with age-matched controls. Additionally, unlike these other studies, subjects in this study did not attend to the tones or make a motor response to target stimuli. This strengthens these findings, as the mismatch response remains cleaner (ie. less noise) and easier to isolate when the above actions are not performed.

The results of this study were also similar to those of Pekkonen et al. (1994), who also reported that AD patients exhibited greater negativity with an ISI of 1 second compared to 3 seconds. They assessed MMN with a measure similar to that of average amplitude which was used in this study. Possibly the measure of average amplitude is more sensitive than that of peak amplitude. When assessing the effects of age or neuropathology on MMN, sensitive measures are surely needed. Therefore, the inclusion of average amplitude as a measure in future MMN studies of this type is highly recommended.

One drawback, which might have reduced the measurement sensitivity of this study and increased between group variability, was that intensity levels were set at 60 dB/SPL regardless of hearing ability. As the electrical signals produced by sound from the inner ear attenuate with age, cortical ERP responses may have been lower because of this (Pekkonen et al., 1996). Future studies should measure individual hearing thresholds and adjust sound intensity levels for each subject accordingly. This was done in study II.

Study II

Nicotine was well tolerated by all 12 AD subjects and no ill effects were reported. It was originally hypothesized that THA subjects would show a greater MMN improvement than non-THA subjects when given nicotine, as THA has been shown to upregulate nicotinic receptors after only three weeks of treatment (Nordberg, 1995). However, nicotine had more of an effect in non-THA subjects who were not undergoing cholinergic therapy, though its effects on both groups were often similar.

For instance, both groups clearly exhibited greater MMN peak amplitudes pre-placebo

than post-placebo, though this was only significant in the non-THA group. Thus, MMN amplitude was attenuated in the late part of the test session, most likely due to decreased mental alertness/arousal in the subjects. It appears that THA subjects were less susceptible to declines in mental alertness than non-THA subjects. This was probably due to ameliorated cholinergic functioning as a result of THA therapy, which allowed THA subjects to sustain mental alertness for longer durations.

Mental alertness (different from attention) modulates the amplitude of the mismatch response, with greater alertness being positively correlated with greater amplitude (Näätänen, 1995; Lang et al., 1995). Recent research indicates that the maximum duration of a recording session in children and the elderly should be one hour, in order to avoid these effects. Even in younger adults, MMN will begin to attenuate after 1-2 hours (Lang et al., 1995). Although the presentation of test stimuli was relatively brief in duration, the test sessions themselves were quite long (3-4 hours), especially considering that subjects suffered from AD. In fact, towards the end of testing a few subjects commented that they found the testing long and were getting tired or hungry. This further indicates that some subjects were less mentally alert, and likely explains why MMN amplitude decreased, late on the placebo treatment day.

Conversely, an attenuation of MMN peak amplitude was not seen late on the nicotine treatment day. Rather, the THA group exhibited no change and the non-THA group displayed a slightly greater amplitude post-nicotine compared to pre-nicotine, though non-significant. Moreover, the post-pre difference scores between treatment days were significantly different within the non-THA group. Also, non-THA subjects displayed greater MMN amplitudes post-nicotine compared to post-placebo. This last difference (between post-drug amplitudes) appears

to be due to nicotine treatment, as there were no differences in pre-drug amplitudes across test days.

Taken together, these results suggest that an acute oral dose of nicotine countered the normal decline in vigilance that untreated AD subjects seemingly experience during long test sessions. Possibly this was accomplished by altering diffuse CNS arousal functions, which may have served to strengthen or refresh neuronal memory traces resulting in a more sensitive automatic detection of stimulus deviance. However, this contention that nicotine's effects on MMN were chiefly due to alterations in diffuse alertness/arousal processes is speculative. It is, in part, reinforced by neuroelectric evidence showing that nicotine increases EEG arousal in both young and elderly adults (Knott & Harr, 1996). This is particularly relevant for AD patients, who typically exhibit an EEG pattern of excessive slow waves (ie. delta, theta) which are characteristic of lowered CNS arousal states (Knott & Harr, 1996).

The THA group clearly exhibited peak amplitude means in the same direction as the non-THA group but no significant differences were found. Thus, THA subjects did not seem to experience decreases in mental alertness as severely as non-THA subjects did during the post-placebo trial. This was likely due to a recovery or improvement of cholinergic functioning as a result of THA therapy. Moreover, the MMN amplitudes of THA subjects were not enhanced to the same degree as were the amplitudes of non-THA subjects after chewing nicotine gum. Possibly there was less room for improved nicotinic functioning in THA subjects as their cholinergic systems were likely less deficient than untreated AD subjects (due to THA therapy). Alternatively, nicotine may have been less effective in THA subjects because THA therapy results in a larger available store of ACh, which competes with nicotine at the synapse. Likely, both of

these reasons combined accounted for the reduced effect nicotine had on THA subjects.

Measures of peak latency found that the MMN occurred significantly later post-placebo than pre-placebo. Conversely, on the nicotine treatment day the MMN occurred earlier post-nicotine than pre-nicotine, though this was not significant. However, the post-pre difference scores between treatment days were significant and the MMN peak occurred significantly later post-placebo than post-nicotine. Again, there were no differences in pre-drug performances across testing days suggesting that post-drug differences were due to nicotine treatment. No between-group differences existed.

Other studies have only reported an attenuation of MMN amplitude due to decreased arousal caused by long test sessions. However, this study indicates that lowered arousal caused a lengthening of peak latency in both groups. Furthermore, nicotine seemingly prevented this and did so equally in both non-THA and THA subjects. Perhaps peak latency is a more reliable measure than peak amplitude, as it appeared more capable of detecting the effects of nicotine within both groups. Supporting this, peak latency has been shown to be less variable than peak amplitude (Lang et al., 1995).

The MMN seems to have chiefly occurred between 150-250 msec post-stimulus, as these were the time intervals when significant differences existed for measures of average amplitude. These results were expected, as MMN typically peaks around 150 msec (Javitt et al., 1994; Pekkonen et al., 1995) and often occurs later in elderly and demented individuals (Woods, 1992; Verleger et al., 1992; Pekkonen et al., 1993).

The average amplitude exhibited 150-200 msec post-stimulus possessed greater negativity pre-drug than post-drug on the placebo treatment day. This is further evidence that decreased

mental arousal likely occurred late in the test sessions. Again, nicotine seems to have countered lowered alertness, as this effect was not seen on the nicotine treatment day.

On the placebo treatment day the average MMN amplitude of the THA group exhibited a profile similar to that observed in other studies involving young and elderly adults, as greater negativity was apparent with 1 second than with 3 second ISIs (Pekkonen et al., 1993, 1996). Conversely, the average amplitude of non-THA subjects was greater with the longer 3 second ISI, an unexpected finding. However, on the nicotine treatment day, neither group exhibited a difference in negativity between ISIs.

Possibly nicotine lessens the mismatch difference seen between 1 and 3 second ISIs, as the difference between them was always greatest on the day when placebo was given. The key point seems to be that on the nicotine treatment day these differences disappeared and both groups performed similarly with no amplitude differences apparent between ISIs. In this respect, after nicotine was given AD subjects performed similarly to younger healthy subjects, in whom MMN amplitude does not typically decrease as a function of ISI for values of 3 seconds or less (Pekkonen et al., 1993).

These effects, due to ISI, were seen during the 50-250 msec time interval and similar results were also apparent during the 50-100 msec and 200-250 msec time intervals. As MMN was not expected to occur until at least 100 msec after stimulus onset, and because the 100-150 msec interval exhibited no significant MMN effects, the negativity changes seen 50-100 msec post-stimulus were likely due to variations of the N100 peak which typically occurs 80-100 msec post-stimulus (Pekkonen et al., 1995). Occasionally, an N100/MMN interaction or overlap can occur (Näätänen, 1982; Sams et al., 1985; Novak et al., 1990; Näätänen and Alho, 1995c). To

some degree this may have happened in this study, as the N100 appeared to have exhibited similar properties to the component of the MMN which seemingly occurred between 200-250 msec post-stimulus.

Across all 12 AD subjects, no correlations existed between the electrophysiological measure of MMN and the rating scale measure of the MMSE. Again, this does not mean that MMN is not related to any cognitive/behavioural functions. More sensitive measures may be needed which tap into the same or related processes that MMN taps into. The effect of nicotine on MMN, judged by post-pre difference scores between test days, was also not correlated with MMSE scores. THA has been previously correlated with MMSE but only in chronic doses (Sahakian & Coull, 1994).

Overall, it seems that nicotine had a positive enhancing effect on MMN in AD subjects. Specifically, the drug appears to have prevented the MMN attenuation which occurred during long test sessions, likely the result of lowered mental alertness/arousal. This is in line with previous evidence that nicotine's main effect on cognition is the increase of mental vigilance and attention, which has been repeatedly reported in both healthy adults (Provost & Woodward, 1991; Levin, 1992; Warburton, 1992; Le Houezec et al., 1994; Rusted et al., 1995) and in AD patients (Sahakian et al., 1989; Jones et al., 1992; Sahakian & Coull, 1994; Katayama et al., 1995).

Nicotine-induced enhancements of MMN amplitude were not seen in THA subjects to the same extent as they were in non-THA subjects. Despite this, both groups benefited equally from acute nicotine treatment when assessed by measures of peak latency. This suggests that nicotine did have a positive enhancing effect on MMN in THA subjects but these effects were less

noticeable than in non-THA subjects. Possibly the less variable measure of peak latency was required to detect them (Lang et al., 1995).

Alternatively, peak amplitude and peak latency may measure slightly different, though related, processes. Possibly the amplification of MMN is chiefly affected by the strength of the memory trace. Thus, during states of decreased mental vigilance or with long ISIs this trace may become weaker causing amplitude to attenuate. However, a separate factor may determine when the MMN occurs (ie. peak latency), such as the speed that the comparator mechanism is operating at or how quickly the neural model adapts to sensory change. It seems that MMN is an indirect measure of one of these two processes. Although this memory trace and comparator mechanism are assumed to be both involved with auditory sensory memory and collocated, it may be possible to quantitatively measure each separately. Possibly the MMN measures of amplitude and latency assess these two processes respectively, which could explain why different results often occur between these measures in MMN research.

It is important to bear in mind that Alzheimer's disease is multi-faceted and involves severe degeneration of the brain in many different areas. Despite this, a minute and acute oral dose of nicotine (2.0 mg) was able to improve the electrophysiological response to stimuli change in the brains of mild-moderate AD patients, seemingly preventing decreased vigilance late in the test day. This causes one to wonder what effects a higher and/or chronic dosing regime of nicotine would have on these patients, especially knowing that the nicotinic system upregulates itself when severely stimulated (Nordberg, 1995).

These findings based on MMN suggest that nicotine may be a useful treatment of mild-moderate AD when used alone. Its acute effects do not appear to be additive with those of THA.

Recent research with cholinergically deficient rats (aged or nucleus basalis lesioned) suggests that THA may be more effective with concurrent severe losses in other transmitter systems such as dopamine, norepinephrine and especially serotonin but nicotine may be more effective when there have not been severe losses in these particular systems (Riekkinen, Sirvio & Riekkinen, 1994; Riekkinen & Riekkinen, 1995; Riekkinen, Aroviita, Kivipelto, Taskila & Riekkinen, 1996). This further implies that, in the earlier stages of AD, nicotine is at its peak effectiveness and may be more effective than THA. Additionally, AD patients who cannot tolerate THA may possibly still benefit from nicotine therapeutically, as might patients undergoing non-cholinergic therapy for AD.

Considerations For Future Studies

i) It would be interesting to see if nicotine administered immediately after hookup would yield significantly higher peak amplitudes than placebo (ie. no baseline session used). A potential follow-up study to this one might involve two groups of untreated AD subjects, and possibly two groups of age-matched controls. Each group would be given either placebo or nicotine and then undergo a single MMN testing session. This would help elucidate if nicotine enhances MMN beyond baseline levels or just prevents its decline due to lowered arousal levels, as only one test session would be given and deficits in vigilance should not occur. Additionally, a 4.0 mg dose of nicotine chewing gum might serve as an alternate drug dose to expand this study further. Finally, as intensity-elicited MMN is more affected by ISI than frequency-elicited MMN (Schroger, 1997), it might be prudent to use intensity variants when trying to determine if fine group differences exist. The drawback of this proposed study is that nicotine's effects could only be assessed with

between-group rather than within-group analyses, causing intraindividual variation to become a larger factor.

ii) It is possible that MMN might be enhanced equally by any stimulant, even one which is not specific to the cholinergic system in its actions. This could be addressed by testing various other stimulants, such as amphetamine and methylphenidate (Ritalin), to determine if the effects produced by nicotine on MMN in AD are greater than those produced by non-cholinergic stimulants. If so, then agonizing the cholinergic system would appear to be beneficial in AD patients, in that arousal and attention appear to be increased. This, in turn, would likely enhance other cognitive processes, such as memory, which operate better under conditions of high mental alertness.

iii) Various other nicotinic receptor agonists exist which should also be examined for possibly beneficial cognitive effects in AD. Unlike nicotine, GTS-21 has little effect on nicotinic receptors at the neuromuscular junction yet affects those in the CNS. Studies suggest this substance produces cognitive effects equal to nicotine (Arendash et al., 1995; Bjugstad, Mahnir, Kem, Socci & Arendash, 1996) and it may stimulate upregulation of nicotinic alpha 4 beta 2 binding sites to a greater degree (Bjugstad et al., 1996). Thus, it may be a good alternate treatment as side-effects in the periphery are minimal with this substance.

Another nicotinic agonist is metanicotine (RJR-2403) which is also specific to alpha 4 beta 2 nicotinic receptor subtypes. This drug enhances cognition equally to or better than nicotine and is less potent than nicotine in increasing heart rate and blood pressure and in causing physiological

depression (Lippiello et al., 1996a, 1996b). Other similar nicotinic receptor agonists to consider include DMAE II (Levin et al., 1995) and ABT 418 (Decker et al., 1995).

iv) It is not known if MMN will ever play a role in the diagnostic criteria of individual patients as it exhibits large intraindividual variability and is positively correlated with one's state of mental vigilance (Näätänen, 1995; Lang et al., 1995). Both these factors decrease the reliability of the measure (Lang et al., 1995).

Even when using groups of subjects sensitive measures are often needed to observe subtle changes in MMN. For example, MMN is attenuated by alcohol in a dose-dependent manner (Jaaskelainen et al., 1995). Low doses of ethanol (0.55 g/kg) have been shown to attenuate MMN amplitude with an ISI of 2.4 seconds but not 0.8 seconds, whereas higher doses of ethanol (0.85 g/kg) have suppressed MMN for both intervals (Jaaskelainen, Pekkonen, Hirvonen, Sillanauke & Näätänen, 1996). Although MMN is a very resilient ERP to changes in mental state, by varying the ISI length the effect of reduced vigilance (from alcohol) upon MMN was determined.

Increasing ISI length always causes an eventual attenuation of the mismatch response (Pekkonen et al., 1996). Thus, ISIs seem to be one of the best and easiest variables to use in assessing MMN deterioration. Possibly this is also a means to measure the gradual decay of the auditory sensory memory trace in different individuals. Moreover, by varying the length of the ISI it seems one can vary the sensitivity of MMN. This may help in determining group differences from a variety of causes (egs. various drug states, aging, neuropathology, etc.). Regardless, ISI variation is a valuable and essential tool for MMN studies of the future.

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APPENDIX A

Inclusion Criteria (Study I):

1. Sex And Age

Patients could be of either sex and < 85 years of age.

2. Probable AD

The patient must have been diagnosed with probable AD. This diagnosis was based on the guidelines provided by the NINCDS-ADRDA work group on clinical diagnosis of Alzheimer's disease (McKahn et al., 1984). The patient must have shown cognitive decline. This must have had a gradual onset and been progressive over at least 6 months. It must have had the following characteristics:

- (I) Sustained deterioration of memory in an alert patient
- (II) Impairment in at least one of the following five areas:
 - (i) orientation
 - (ii) judgement and problem solving
 - (iii) functioning in community affairs
 - (iv) functioning in home and hobbies
 - (v) functioning in personal care

3. Mini-Mental State Examination (MMSE) Score Between 14 And 22

The patient must have scored between 14 and 22, extremes included, on the Mini-Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975), showing deficits in at least two areas.

4. Other Inclusion Criteria

The patient must:

- Have learned to read and write and been judged to be sufficiently proficient in the language used in this study
- Been able to attend out-patient clinics
- The patient must have given his/her informed consent or witnessed oral consent before entering into the study

Exclusion Criteria (Study I):

1. Clinically Active Cerebrovascular Disease (CVD)

As evident by transient ischemic attacks, reversible ischemic neurological deficit or ischemic stroke within the past 12 months.

2. CVD According To NINDS-AIREN Criteria (Roman et al., 1993)

Any one of the following findings on CT or MRI scan led to exclusion:

- Multiple (≥ 2) large vessel infarcts
- A single strategically-placed infarct in the angular gyrus, thalamus, basal forebrain, posterior cerebral artery or anterior cerebral artery territories
- Multiple (≥ 2) basal ganglia and white matter lacunas
- Extensive (ie. involving $\geq 1/4$ of the white matter) periventricular white matter hypodensities unless this was the abnormal finding on CT or MRI scan in patients ≥ 70 years of age

3. Multiple Focal Neurological Signs

4. Specific Findings On CT scan (Or MRI scan)

- Tumour
- Fresh hemorrhage
- Chronic subdural hematoma

5. History Of:

Mental retardation, Down's syndrome, stroke, brain trauma, intoxication, CNS-infection (incl. viral, fungal or syphilitic etiology) or other neurological conditions resulting in cognitive impairment, prior to or coincident with the onset of dementia. A history of non-cognitive (eg. purely motor) neurological deficits did not necessarily exclude the patient.

6. Diagnosis Of Any Neurological Disorder Other Than AD

Disorders that could produce cognitive deterioration including, but not limited to, epilepsy, Pick's disease, Creutzfeldt-Jacob's disease, normal pressure hydrocephalus, Huntington's or Parkinson's disease. However, mild extrapyramidal signs for which no treatment was required did not exclude the patient. Such signs may have been either parkinsonian or choreatic (eg. buccofacial dyskinesia).

7. Patients With Current Psychiatric Diagnosis According To DSM-III-R (American Psychological Association, 1987)

Substance abuse, or dependence, anxiety disorder, major depression or schizophrenia.

8. Patients With Behavioral Problems Requiring Neuroleptics At Entry

Or who had received neuroleptics to treat behavioral problems for more than one episode or for more than one continuous week in the last 3 months prior to entry. Patients receiving neuroleptics only at night to control minor sleeping disorders for whom the dose has not been changed over the last 3 months prior to entry were not excluded.

APPENDIX B

Inclusion Criteria (Study II):

1. Sex And Age

Patients can be of either sex and must be < 85 years old

2. Mild To Moderate AD

Patients must meet criteria for mild to moderate probable AD according to both the DSM-IV (American Psychological Association, 1994) and the Clinical Dementia Rating (CDR) Scale (Hughes et al., 1982; Berg, 1988).

Exclusion Criteria (Study II):

Any of the following criteria excluded a patient from the study:

1. Patients with clinically significant psychiatric disorders including neurological disorders other than AD.
2. Patients with abnormal EKG and blood pressure readings.
3. Patients with concomitant disorders according to DSM-IV criteria (eg. depression, substance dependency).
4. Patients with a history of serious head injury.
5. Potential contraindications to nicotine such as active, untreated gastric or duodenal ulcers, liver disease or uncontrolled hypotension.
6. Patients being treated with CNS drugs including new investigational compounds and cholinesterase inhibitors other than tacrine.
7. Patients receiving beta blockers.
8. Patients with auditory impairments severe enough to preclude ERP testing.
9. Patients without a working knowledge of english or french.

APPENDIX C

INFORMED CONSENT STATEMENT FOR PATIENTS TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

TITLE OF PROPOSAL:	Effects of Acute Nicotine Administration on Brain Electric (MMN) Function and Cognition in Dementia of the Alzheimer's Type
PRINCIPAL INVESTIGATOR:	V. Knott, D.Phil.
ASSOCIATE INVESTIGATORS:	V. Ilivitsky, M.D., T. Mendis, M.D.
RESEARCH ASSISTANT:	Chris Engeland, B.Sc.(Hons)
RESEARCH NURSE:	R. Julien-Bimm, R.N., B.Sc.N.

Brief Description of Project:

Dementia of the Alzheimer type (DAT) is associated with impairments in memory and a number of cognitive functions including attention, abstract thinking and judgement. A number of biological research studies have found associations between DAT and reduced levels of acetylcholine in the brain. Acetylcholine is a brain chemical which is known to be important for normal, optimal memory and cognitive functions. Many of the drugs used to treat DAT are meant to increase the levels of Acetylcholine in the brain so that memory and cognition may be improved. Some of these drug treatments have produced only a modest improvement in some mental functions and research continues to look for more effective drugs in the treatment of dementia.

Nicotine, which is commonly found in tobacco and cigarettes, is known to increase the release of acetylcholine in the brain and some studies have shown that a smoking history reduces the risk of acquiring DAT. When nicotine is administered in a single dose by injection or as a tablet to smokers and nonsmokers it results in improved memory and better performance on a range of cognitive tasks. Initial studies have shown that a single dose of nicotine administered to DAT patients by way of intravenous injection or skin patch can improve certain aspects of attention, alertness and mental processing.

Nicotine gum also improves various aspects of memory and mental processing in non-patient volunteers. This study will attempt to examine the effects of nicotine gum in DAT patients by measuring changes in brain response and in various performance tasks measuring attention, memory and cognition.

Procedures Involved:

The study will require you to attend the laboratory for one practice session and two morning test sessions which will begin anytime between 9-11 a.m.. You will be asked to abstain from smoking, caffeine, alcohol and drugs (e.g. Aspirin) 12 hours before each test session. If you are a patient who is already taking tacrine as a study drug here at the Royal Ottawa Hospital you will be asked to take the morning tacrine dose with your breakfast on the two testing days and then come to the lab 1½ hours later. Test sessions will be separated by 1-3 days.

During the test sessions you will be given a single piece of gum to chew in a prescribed manner shown to you by the research assistant. In one of the sessions the gum will contain 2 milligrams of nicotine and the gum in the other session will be a placebo and will contain no nicotine or any active drug. The order of the test sessions will be random so that neither you nor the research staff directly involved in the study will know which you are chewing in any given session.

Testing will take place before and after gum chewing. Brain function will be assessed by placing sensors on your scalp to record the EEG (electroencephalogram). These brain waves will be examined during an eyes-closed resting period and again during tests which will require you to sometimes ignore sounds and sometimes attend to sounds. Tests will also assess your memory and your response speed to sounds and numbers presented by a computer. You will also be asked to complete very brief questionnaires which will assess your mood and your physical reaction to the gum chewing. Each test session will take approximately 3 hours to complete.

Possible Risks Involved:

The risks are very minimal. Nicotine chewing gum is frequently used as a treatment to help smokers stop smoking. Chewing 2 milligrams of nicotine on a single occasion raises blood nicotine to levels obtained with smoking a single cigarette. The main side effects which may be experienced include nausea, salivation, abdominal pain, vomiting, diarrhea, cold sweat, headache, dizziness, disturbed hearing and vision, mental confusion, weakness, fainting, respiratory difficulty and increased, weak and irregular heart rate. It should be realized that while this list of side effects experienced by some patients is quite extensive, they are temporary (usually not lasting more than 24 hours) and are more typically seen in subjects who chew 10-20 pieces per day. Although the frequency of appearance of these symptoms tends to be higher in nonsmokers, who have not built up a tolerance to nicotine, it is unlikely subjects in this study will experience all of the symptoms and it is quite possible that none of them will be experienced.

The EEG monitoring is very similar to that carried out in general hospitals except that it is analyzed by a computer. The sensors placed on your scalp and skin may cause a mild and temporary irritation and redness of the skin which will disappear in a few hours. The cap which positions the electrodes may feel snug and will be kept on throughout the 3 hour period.

Participation:

Your participation is voluntary and you will be free to withdraw from the study at any time without penalty or loss of any benefits you are otherwise entitled. No direct personal benefit may result from taking part in this study but knowledge may be gained that will benefit others.

OTHER INFORMATION

1. Confidentiality: When results of this study are reported you will not be identified by name. Only authorized study investigators will have access to your records from this study.

2. Payment: You will not be paid for your participation but any transportation/parking and associated costs will be covered by the study.

3. Problems or Questions: The principal investigator is Dr. Verner Knott. You may contact him, or Chris Engeland (the research assistant) if you have any problems or questions about this study. For routine calls please call Chris at 722-6521, ext. 6254. The address is the Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, Ontario, K1Z 7K4.

If you have any questions about your rights as a patient, or if you have complaints about the study, you may speak to a patient representative. The patient representative is not associated with the research. To contact a patient representative call 724-6530.

Please keep a copy of this document for your personal records

CONSENT FORM

Study Name: **Effects of Acute Nicotine Administration on Brain
Electric**
the **(QEEG/ERPs) Function and Cognition in Dementia of
Alzheimer Type.**

A. Patient's Consent.

I have read the explanation and had the opportunity to discuss it and to ask questions. I consent to take part in this study.

_____	_____	_____
Name of Patient	Signature of Patient	Date

B. Caregiver's Permission.

I have read the explanation and had the opportunity to discuss it and to ask questions. I consent to my ward's participation in this study.

_____	_____	_____
Name of Caregiver	Signature of Caregiver	Date

C. Statement of Investigator's Responsibility.

I have explained the nature, purpose, procedures, benefits, risks of, and alternatives to this research study. I have offered to answer any questions and have fully answered such questions. I believe that the patient, guardian or legal representative fully understands my explanation and has freely given informed consent.

_____	_____	_____
Name of Investigator	Signature of Investigator	Date

_____	_____	_____
Name of Witness	Signature of Witness	Date

APPENDIX D

Questionnaire For Smoking/Drug/Alcohol History Nicotine Gum Study Participants

Patient Name:	D.O.B.
Patient Code:	Gender:
Caregiver:	Handedness:

History of Hypertension (Y/N):
If so, how long?

Current medication (dose, # daily doses, reason):

Does the patient drink [coffee /day, tea /day, colas /day]?

Does or did the patient smoke? (Y/N)

Age started smoking:	Age of quitting:	Difficulty?
Amount smoked per day:		
Preferred cigarette brand (Name, strength, size):		

Lived for an extended period of time with a smoker?
How long and when did this end?

Does the patient have a history of substance abuse? If so, how much & for how long?
Defined by more than 3 drinks/day for more than 2 months. Drug problems include regular & continuous use or addiction to prescription or non-prescription drugs for a period longer than 2 months.

Any active liver disease?

Active untreated ulcers?

History of mental illness (depression, schizophrenia)?

Previous head injury? Defined as having to see a specialist for it (eg. neurologist).

Taking tacrine? Dosage, # daily doses and for how long?

Taken tacrine previously? How long ago & reason for stopping?

APPENDIX E**Adverse Symptoms Report**

Administered by experimenter at the end of each test session.

Patient:

Session:

Date:

Notes _____

SYMPTOMS**PRESENT**

Dizziness

—

Weakness/Faintness

—

Headache

—

Ringing in Ears

—

Palpitations

—

Nausea

—

Cramps

—

Chest Pain

—

Difficulty Breathing

—

Numbness (limbs/face)

—

Vomiting

—

IMAGE EVALUATION TEST TARGET (QA-3)

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