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Acute nicotine effects on auditory sensory memory in tacrine-treated and nontreated patients with Alzheimer's disease An event-related potential study

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Abstract

The auditory mismatch negativity (MMN) event-related brain potential (ERP) reflects the storage of information in acoustic sensory memory. Thirteen patients with Alzheimer's disease (AD), 6 receiving treatment with the cholinesterase inhibitor, tacrine [tetrahydroaminoacridine (THA)], and 7 receiving no treatment, were administered 2 mg of nicotine polacrilex and placebo. MMNs were recorded with 1- and 3-s interstimulus intervals (ISIs) during pre- and post-placebo/nicotine administration. Amplitudes decreased from pre- to post-placebo recordings in nontreated patients but remained stable in THA-treated patients. Comparison of pre- and post-nicotine MMNs found amplitude increases with nicotine in nontreated but not in THA-treated patients. MMN latencies were shortened by nicotine in both treatment groups. These exploratory findings suggest that nicotine-improved strength of acoustic sensory memory traces and speed of acoustic sensory discrimination in AD are differentially affected by chronic tacrine treatment.

Keywords: Nicotine; Tacrine; Sensory memory; Alzheimer's disease; ERPs, Event-related potentials; MMN, Mismatch negativity; Acetylcholine

1. Introduction

The seminal reporting of selective loss of cholinergic receptors (Chr) in brains from deceased patients with Alzheimer's disease (AD) (Davies and Mahoney, 1976), together with the early follow-up work in AD linking decreased cholinergic markers and nicotinic Chrs to cognitive decline (Perry et al., 1978, 1997; Whitehouse et al., 1981, 1982), stimulated the cholinergic hypothesis of AD (Bartus et al., 1982) and provided the initial momentum for the past two decades of research attempting to design specific pharmacologic approaches for the treatment of this disease (Rainer and Mucke, 1998). Of the many strategies exploited for the modulation of cholinergic neurotransmission, only inhibitors of the catabolic enzyme, acetylcholinesterase, aimed at increasing the concentration of acetylcholine in the neuronal cleft to levels sufficient for effective signal transmission, have shown the therapeutic potential required for approval as an efficacious symptomatic treatment AD (Rainer and Mucke, 1998). The best documented clinical efficacy of these inhibitors are studies of tacrine [tetrahydroaminoacridine (THA)], which evidences symptomatic improvement with short-term (2–3 months) treatment (Giacobini, 1994), and clinical trials have shown a rather similar magnitude of improvement with a number of second-generation inhibitors (Giacobini, 1997).

However, given that these treatments, which can be limited by side effects, have shown only modest improvements and only in a subset of AD patients, suggested strategies for maximizing and prolonging any positive acetylcholinesterase inhibitor effects have involved combinations with other cholinergic drugs such as muscarinic or nicotinic Chr agonists (Giacobini, 1997). Selective activation of remaining central nicotinic Chrs has itself been advocated as a promising approach to the treatment of AD (Sjöberg et al., 1998) and a recent Phase II trial in AD evidencing cognitive-enhancing effects of the novel nico-

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tinic agonist ABT-418 has lent support to this approach (Potter et al., 1999). In addition, repeated administration of the nicotinic agonist, nicotine, has been shown to increase the synthesis and release of acetylcholine (Summers et al., 1994) and acetylcholine binding in the cerebral cortex, hippocampus and median raphe nucleus by approximately 25% (Schwartz and Kellar, 1983). In addition to increasing nicotinic Chr density (Benwell et al., 1988), nicotine has been found to induce a shift in the proportion of low- to high- affinity nicotinic Chr binding sites (Romanelli et al., 1988). Behaviorally, nicotine administration has been shown to improve the deteriorating memory of aged rodents and monkeys (Buccafusco and Jackson, 1991; Widzowski et al., 1994) and has been found effective in attenuating cognitive deficits in animal models mimicking cholinergic deficiencies observed in AD (Levin, 1992). Both smoking and nicotine administration have exerted performance-enhancing effects in adult smokers (Widzowski et al., 1994; Wesnes and Warburton, 1983; Heishman et al., 1994; Pritchard and Robinson, 1998) and nonsmokers (Foulds et al., 1996; Lehouezec et al., 1994). Also, acute nicotine administration, although highly variable in its effects, has been reported to improve sensory acuity, attention, information processing and psychomotor vigilance functions in AD patients (Katayama et al., 1995; Newhouse et al., 1988, 1990; Sahakian et al., 1994).

The suggestion that a combination of direct and indirect cholinergic treatment strategies may work in an additive fashion to augment cholinergic function is partially reinforced by the observation that brain uptake of acutely administered nicotine is increased in patients receiving chronic tacrine treatment (Nordberg et al., 1992). In view of the purported cholinergic hypersensitivity shown in AD patients (Sunderland et al., 1998), this investigation explored the differential central effects of a small dose of nicotine, as administered by 2 mg of nicotine polacrilex, in medication-free AD patients and in AD patients receiving ongoing THA treatment.

Scalp-recorded late (>50 ms) endogenous event-related potentials (ERP), extracted from scalp-recorded electroencephalographic (EEG) activity and reflecting a variety of psychological processes such as attention, memory and processing speed, have been proposed as unique markers in human psychopharmacological research, being well suited for the noninvasive probing and temporal tracking of perceptual cognitive processes altered by centrally acting agents (Münte et al., 1986), including cognitive-enhancing agents (Delacour et al., 1994) and agents with Chr actions (Dierks et al., 1994). The mismatch negativity (MMN) component of the ERP, exhibiting a frontal maximum amplitude with a modal latency of between 50 and 200 ms and a duration of $\sim$100–200 ms, is elicited by physical "deviant" (e.g., in pitch, intensity, duration and location) acoustic stimuli embedded in a homogenous sequence of "standard" stimuli, irrespective of whether the stimuli are attended to or not (Näätänen and Picton, 1982; Näätänen et al., 1978). The physical features of the repetitive standard auditory stimuli are purported to be fully analyzed and encoded as neural traces in short-term echoic memory (i.e., the sensory register or preattentive store, characterized by a large-capacity passive system with a rapid decay of raw sensory data; Deutsch, 1975), and the MMN is believed to be automatically elicited each time any afferent auditory input features fail to match the features encoded in the prevailing neuronal representation (Näätänen, 1984, 1992). The MMN, stemming from this automatic comparator process, is elicited only if the prevailing neuronal trace of the standard stimuli has not decayed by the time of deviant stimulus onset. MMN studies varying interstimulus intervals (ISIs) have shown auditory traces to be sustained up to 10 s in young healthy adults (Böttcher-Gandor and Ullsperger, 1992).

Aging has been found to alter trace decay in the human auditory system as MMNs are attenuated more with increasing ISIs in healthy elderly vs. young adult subjects (Pekkonen et al., 1993, 1996). AD patients appear to exhibit relatively normal robust MMNs with short ($\sim$1 s) ISIs (Kazmerski et al., 1997; Gaeta et al., 1999) but exhibit faster trace decay with increasing ($\sim$3 s) ISIs than do elderly controls (Pekkonen et al., 1994). In previous studies utilizing relatively short ($\sim$1 s) ISIs, smoke-inhaled nicotine has not consistently altered MMN amplitudes in young adults (Knott et al., 1995), while in AD patients, acute THA administration has attenuated MMNs (Riekkinen et al., 1997). This current exploratory study examined the effects of acute nicotine in nontreated and THA-treated AD patients using both short and long ISIs to elicit MMNs.

2. Method

2.1. Subjects

Thirteen (7 males) patients (mean age 71.1 years, range 53–82 years) meeting DSM-IV (American Psychiatric Association, 1994) criteria for probable AD were included in the study once informed consent was obtained. A complete medical history was recorded and laboratory (including an EKG and blood and urine analysis), neurological (including computed tomography scans to rule out other possible causes of dementia) and psychiatric screens were performed before entry. Subjects were required to have no history of alcohol/drug abuse, head trauma, concurrent or past CNS disease other than dementia, severe physical illnesses or hypertension or history of presence of other psychiatric disorders. Seven (five males) patients had not received any pharmacological treatments with CNS agents for at least a 1-month period (nontreated group). These patients were being recruited for an independent clinical trial, which required a minimum of 30-day drug-free period as an inclusion criteria. The other six (five males) patients were receiving tacrine treatment (THA-treated group) and had been at their maximally tolerated dose (mean 140.0 mg/day,

range 80–160 mg/day) for 6 months or longer (mean 11.6 months, range 6–15 months). The mean and range of Mini-Mental State Examination (MMSE; Folstein and McHugh, 1975) rating scores for the patients were 23.8 and 4–30, respectively. The average MMSE score (25.5) in the six THA-treated patients at the time of this study had not substantially changed from the average MMSE score (26.3) assessed at the beginning of their tacrine treatment. MMSE scores of THA-treated patients did not differ from scores of nontreated patients.

2.2. Design

Patients attended the laboratory for one "orientation" session for familiarization with study procedures and for two additional "test" sessions in which they received either placebo or nicotine within a repeated-measures, pseudorandomized, double-blind, cross-over design. Half of the subjects in each grouping (THA-treated and nontreated) received nicotine on the first test session and then received placebo in the second session. The remaining patients received the treatments in the reverse order. Test session was separated by a 2–5-day interval.

2.3. Procedure

Recording sessions were carried out in the morning following overnight abstinence of alcohol, caffeine (none of the patients reported a history of smoking) and CNS-acting drugs, with the exception of tacrine (in the THA-treated group), which was taken in the morning, in accordance with the patients' daily schedule. Patients were instructed to eat a light breakfast and were tested 1.5–2.0 h afterwards (between 8:30 and 10:30 a.m.). The THA-treated patients took their morning tacrine dose with their breakfast. Each session followed a structured timetable. Upon arrival at the laboratory, electrode hook-up was initiated and was followed by a baseline MMN recording and assessment of supine vital signs. The pretreatment baseline testing was followed by the administration of the treatments and a nicotine absorption period, after which time the same pretreatment assessments were carried out again. In addition to the MMNs and vital signs, patients were questioned with regards any adverse drug (nicotine) effects.

2.4. Treatments

Nicotine was administered orally in the form of nicotine polacrilex (Nicorette; 2 mg). The placebo was a commercial gum approximating Nicorette in size, color and texture. To eliminate the effects of any visible differences between placebo and nicotine gums, patients were instructed to close their eyes and the gum was placed on their tongues. To make any taste differences between Nicorette and placebo, a drop of mint oil was placed on each gum and patients were required to wear nose plugs when chewing. Patients were instructed to follow the Nicorette chewing instructions, requiring that they take two bites every minute for a period of 20 min. A taped voice recording reminded them when to chew and an investigator was present to ensure that chewing was performed correctly. After the 20-min chewing period, the patient disposed of the gum and chewed a strong commercial mint gum (to mask nicotine/placebo gum tastes) for 2 min before removing the nose plugs. Patients waited for an additional 10-min absorption period before posttreatment assessment was initiated. Compared to the smoking of a single cigarette, which results in a range of peak blood nicotine levels from 15 to 35 mg/ml, the chewing of nicotine (2 mg) gum in this prescribed manner is estimated to produce a peak blood nicotine level of 5.0 mg/ml at approximately 25 min from the initiation of chewing (Russell et al., 1976). This nicotine polacrilex dose has been shown to be psychoactive, producing task performance improvements in both smokers (Sherwood et al., 1992) and nonsmokers (Provost and Woodward, 1991). Patients were questioned with a checklist at the end of each study period with regards to adverse effects (e.g., nausea, dizziness and agitation) that are commonly experienced with nicotine gum.

2.5. Stimuli

ERP recordings were carried out in a sound-attenuated, electrically shielded chamber situated adjacent to the control room housing the computers, monitors, amplifiers and recorders. During the recording session, subjects sat upright in a chair and, as with previous studies attempting to control attention (Gaeta et al., 1999) levels, watched a silent video on a TV screen during the presentation of auditory stimuli used to elicit MMNs. They were instructed not to attend to the auditory stimuli.

ERPs were elicited with the presentation of 400 sinusoidal "oddball" tone stimuli (70-ms duration, 7-ms rise per decay) delivered in three separate blocks: 200 tones in one block using an ISI of 1 s (onset-to-onset) and 100 tones in each of the other two blocks using an ISI of 3 s. Each stimulus block consisted of standard (85%) and deviant (15%) tones with frequencies of 800 and 552 Hz, respectively. Tones were delivered in pseudorandom order so that at least two standard tones occurred between deviant tones. Tones were presented to the right ear at 60 dB above hearing threshold, with thresholds being 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 or less. Questioning of participants after the test sessions, regarding the content of the videos, indicated that all had attended to the videos and were not aware of any tone frequency (800 vs. 552 Hz) differences.

2.6. ERPs

As with previous work (Pekkonen et al., 1996), ERPs were extracted from activity recorded from three frontal

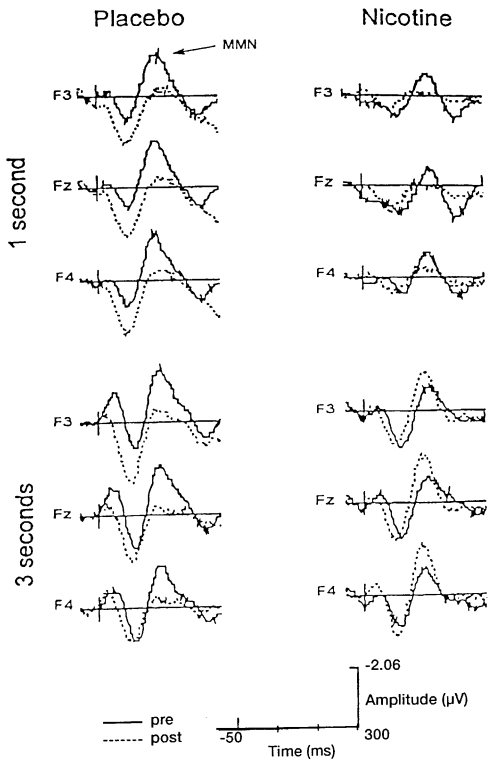

Fig. 1. Grand averaged 1- and 3-s MMN "difference" waveforms of combined THA-treated and nontreated AD patients recorded during pre- and post-placebo/nicotine administration.

(Fz, F3 and F4) sites, where MMNs exhibit maximal amplitude. Scalp sites were referenced to linked earlobes and an additional electrode was placed on the forehead to serve as ground. Electrodes, placed on the supraorbital ridge and canthus of the right eye, recorded vertical (VEOG) and horizontal (HEOG) electrooculographic activity. Electrode impedances were kept below 5 kΩ. Signals were amplified using a 1.0-s time constant and a 30-Hz filter. Analog-to-digital sampling, time locked to each stimulus, was carried out on-line at 512 Hz for 350 ms (beginning 50 ms before stimulus onset).

Off-line analysis of computer stored digitized data involved rejection of individual epochs with EEG, VEOG and HEOG voltages exceeding ±100 μV. Nonrejected epochs were subjected to ocular correction using regression-based weighing coefficients (Semlitsch et al., 1986). Final averages were collated for each stimulus type at each of the three recording sites. The MMN "difference" waveform component was derived from the "subtraction" procedure whereby digitized values of standard waveforms were subtracted from digitized values of deviant waveforms. The MMN measures for each average were amplitude and latency. Peak amplitude was defined as the maximum negative voltage between 50- and 250-ms poststimulus onset, measured in relation to the average prestimulus baseline voltage. Latency was defined as the time to reach maximum (peak) negative voltage from stimulus onset.

2.7. Statistics

MMN amplitudes and latencies were analyzed by separate split-plot 2 (Group: THA vs. non-THA) × 2 (Drug: nicotine vs. placebo) × 2 (Trial: pre- vs. post-drug) × 2 (ISI: 1 vs. 3 s) × 3 (Site: Fz, F3 and F4) parametric, univariate, repeated-measures analysis of variance (ANOVA) procedures. The repeated-measures effects (drugs, trial, ISI and site) were adjusted by the Greenhouse–Geisser Epsilon correction. Significant ($P<.05$) interactions were followed up with simple main effects analysis.

3. Results

None of the 13 subjects reported nausea, dizziness or any of the common adverse symptoms associated with the chewing of nicotine gum, and no significant Drug, Trial or Drug × Trial changes were observed with vital sign (blood pressure and heart rate) indices.

Statistical analysis of amplitudes yielded significant Drug × Trial ($F=10.23$, $df=1/10$, $P<.005$) and Drug × Trial × Group ($F=5.17$, $df=1/10$, $P<.05$) interactions. Follow-up simple main effect analysis confirmed the impression of post-placebo amplitude reduction but, as shown in Fig. 2, was significant only in the nontreated group ($F=17.81$, $df=1/5$, $P<.01$). Similarly, only the nontreated group evidenced significant nicotine-induced MMN alter-

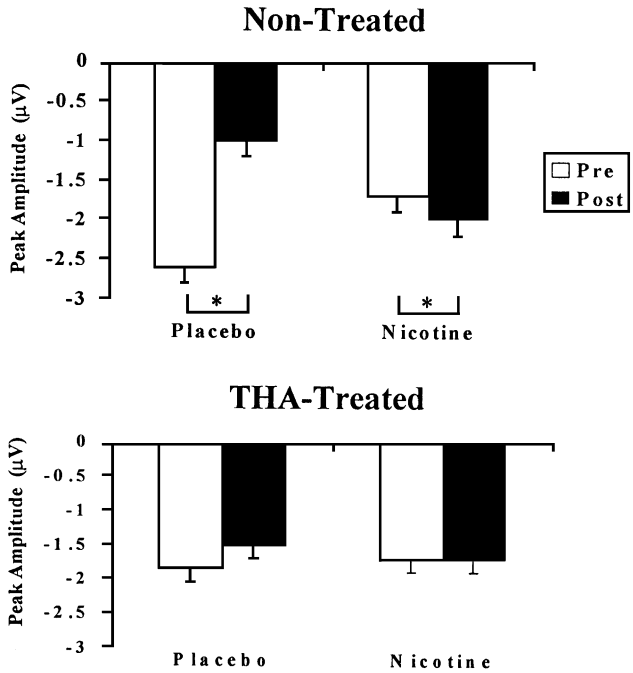

Fig. 2. Mean ± S.E. MMN amplitude values (averaged across electrode sites as well as the 1- and 3-s ISI conditions) for THA-treated and nontreated AD patients recorded during pre- and post-placebo/nicotine administration (asterisks indicate significance as described in text).

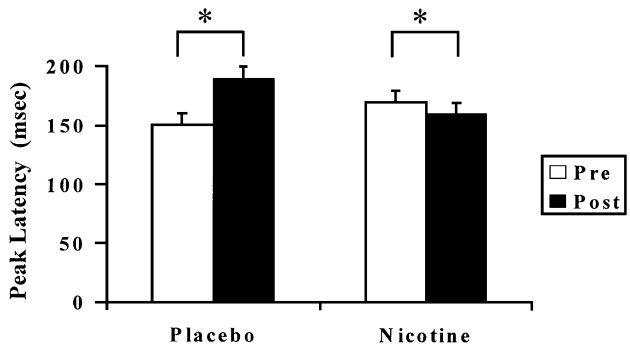

Fig. 3. Mean ± S.E. MMN latency values (averaged across electrode sites as well as the 1- and 3-s ISI conditions) of combined THA-treated and nontreated AD patients recorded during pre- and post-placebo/nicotine administration (asterisks indicate significance as described in text).

ations, with amplitudes increasing post-nicotine administration compared to pre-nicotine administration ($F = 8.18$, $df = 1/5$, $P < .05$). No significant differences were observed between treatment groups when compared in either pre- or post-placebo/nicotine conditions or when using 1- or 3-s ISIs. In addition, no significant differences were observed between recordings elicited by the two ISIs.

Fig. 3 illustrates the mean ± S.E. MMN peak latencies (averaged across ISIs and groups) during pre- and post-placebo/nicotine conditions. Analysis of MMN latency values yielded a significant Drug × Trial interaction ($F = 5.57$, $df = 1/10$, $P < .05$). As shown in Fig. 3, post-placebo latencies were significantly slower than pre-placebo latencies ($F = 11.31$, $df = 1/11$, $P < .01$), and post-placebo latencies were also shown to be slower than post-nicotine latencies ($F = 7.15$, $df = 1/11$, $P < .05$), which were found to be significantly shortened compared to pre-nicotine latencies ($F = 5.48$, $df = 1/11$, $P < .05$). No differences were observed between pre-placebo and pre-nicotine latencies.

4. Discussion

Considerable attention has been paid to nicotine's dual role as a pharmacological tool for delineating neurochemical mechanisms underlying cognition and as a putative therapeutic agent in neuropsychiatric disorders (Durson and Kutcher, 1999; Le Houezec, 1998). The MMN, reflecting relatively automatic, nonsemantic sensory memory storage, has been promoted as a unique noninvasive CNS scalpel for probing the pathophysiology of preattentive processes and their modulation by psychopharmacological agents in cognitive disorders, including AD (Gené-Cos et al., 1999). In this current study, the presence of significant nicotine-induced amplitude and latency alterations strengthens the general utility of MMN indices as valuable neuroelectric measures suitable for indexing the acute neurocognitive impact of psychopharmacological challenges in AD. However, these exploratory results, achieved only with oral administration of a single, low dose in relatively small samples and in a THA-treated sample, which was clinically nonresponsive to the inhibitor treatment, must be treated cautiously, especially as they were captured in the absence of behavioral assessments, which may have provided useful insight into the relationship between nicotine-altered MMN measures of sensory memory and clinical/cognitive deficits in AD.

Larger peak amplitudes translate to more information in the echoic buffer. The diminished MMN amplitudes in medication-free DAT patients seen post-placebo (vs. pre-placebo) are of interest in their own right as they speak to the issue of short-term replicability, which is of importance when considering the clinical usefulness of MMN. As the observed placebo and nicotine MMN amplitude effects were shown only in the non-THA group and this group exhibited different, but not significant, baseline values across the two treatment session days, there will be a need to gauge and possibly improve the replicability of MMN waveforms in AD patients to simplify interpretation of treatment effects (Fig. 1). At the group level, good replicability has been observed at test intervals of 2 h (Escera and Grav, 1996) and 1 month (Pekkonen et al., 1995) in young adult subjects, but individual short (2 h)-term replicability has been somewhat poorer (Escera and Grav, 1996). As similar replicability studies have yet to be carried out in elderly populations, it is not possible to determine the role of normal aging processes in the time-related MMN alterations observed in the placebo session. Although the placebo-related MMN amplitude differences may reflect differential involvement of the subjects in the film viewing during the two recording sessions, they may result from reduced efficacy of the auditory sensory memory system and decreased sensitivity of the passive and automatic deviance detection mechanism or they may also be induced by arousal/vigilance deficits in AD. Cognitive (P3) potentials elicited in passive task paradigms are not noticeably affected in AD, but cortical hypoarousal patterns have been a characteristic feature of clinical and quantitative EEG profiles of these patients (Knott et al., 1999a,b). The fact that post-placebo dampening of MMN amplitudes were not observed in THA-treated patients suggests that continuous cholinesterase inhibition may act to stabilize, directly or indirectly (e.g., via arousal/vigilance changes), neuronal mechanisms subserving storage of physical stimulus features into sensory memory. Given that acute THA treatment in AD patients has been shown to reduce MMN amplitudes, sustained treatment may act to alter Chr sensitivity and its functional role in mnemonic processes. In AD subjects, elevation of tonic acetylcholine levels induced by THA treatment significantly increase cortical arousal/vigilance, as assessed by EEG measurements and by performance tasks requiring activation of basal forebrain cholinergic cells (Lawrenence and Sahakien, 1995). It should be pointed out as well that although the tacrine-treated patients entering this study had not exhibited MMSE improvements, their

stabilized MMSE scores over a 6-month treatment period may, if compared to deteriorating scores of placebo-treated patients over the same period, be considered as evidence of tacrine efficacy.

Nicotine augmentation of MMN amplitudes was observed only in nontreated patients and was evident with both 1- and 3-s ISIs. Enhanced amplitudes following nicotine treatment, effects opposite to those reported with CNS depressants, including alcohol (Gené-Cos et al., 1999; Jääskeläinen et al., 1995a,b), may have potential implications for episodic memory in AD as improvements in sensory memory could positively affect what is stored in working memory, with subsequent beneficial effects on longer-term memory in which newly learned information is stored (Gaeta et al., 1999). However, nicotine administered acutely has failed to improve short-term memory functioning in AD (Sahakian et al., 1989) but has improved behavioral performance on attentional tasks both in patients (Sahakian et al., 1989) and nonpatients (Pritchard and Robinson, 1998). Given the contention that attention is one of the first cognitive functions to deteriorate in AD and that the hallmark memory deficits in AD may in part be related to attentional deficiencies (Pekkonen et al., 1995), the modulation of MMN by nicotine is of theoretical and clinical interest in that the auditory MMN is one of the earliest of a sequence of electrophysiologically measurable brain responses involved in attentional switching to unusual stimuli in the acoustic environment. Involuntary attentional control or voluntary attentional focusing, by behaviorally relevant and unusual "real world" stimuli (e.g., machine-generated sounds, animal sounds and human voices) and by laboratory task stimuli, is neuroelectrically manifested not only by MMN elicitation but also by elicitation of two later ($\sim$250–600 ms) positive (P3a and P3b) potentials. As P3a is observed when infrequently presented stimuli interrupt attentional mechanisms engaged in active task performance and as P3b is elicited following detection of task-relevant target stimuli, these positive potentials are claimed to index the involuntary and voluntary capturing of attention, respectively (Escera et al., 1998). Although it should be cautioned that these potentials may reflect processes other than attention (Polich, 1998), some, but not all, studies (Anokhin et al., 2000) have shown them to be increased in amplitude by smoke-inhaled nicotine in smokers and by transdermal nicotine and subcutaneous nicotine administration in normal smoker and nonsmoker volunteers (Lehouezec et al., 1994; Knott et al., 1995, 1999a,b) as well as in AD patients (Katayama et al., 1995).

The failure to observe nicotine-induced MMN amplitude increments in THA-treated patients may be related to reduced nChr sensitivity resulting from chronic and/or acute superimposed morning doses of THA taken by these patients prior to their test session. As single-dose tacrine has been reported to disrupt MMN in AD (Riekkinen et al., 1997), additional studies, examining a battery of neuroelectrophysiological (EEG and ERPs) and performance test paradigms in response to variable dosing and repeated nicotine dosing in cholinesterase inhibitor-treated (e.g., donepezil, metrifonate and rivastigmine) patients, are required to more accurately evaluate the impact of these combined cholinergic interventions.

Nicotine shortened latencies of MMN elicited by 1- and 3-s ISIs in both treatment groups. Latency to peak MMN amplitude indicates the amount of time required to complete sensory discrimination processes. When the discrimination difficulty of attention-independent and -dependent is increased, the latencies of MMN and late cognitive ERP potentials, such P3b, increase in parallel. The P3b component of the ERP waveform has shown to be a reliable index of the detection, recognition and classification of target stimuli in cognitive tasks (Picton, 1992; Polich and Kok, 1995). P3b latencies, which have been consistently found to be delayed in AD relative to normal aged controls (Polich et al., 1990), index the speed of decision-making processes and more specifically the speed of stimulus evaluation and classification (Kutas et al., 1997; Magliero et al., 1984; Verleger, 1997). As P3b latencies and response/reaction times are also shortened following acute administration of nicotine (Pritchard and Robinson, 1998; Edwards et al., 1985; Houlihan et al., 1996a,b), it is reasonable to suggest that previously reported psychomotor, vigilance and attentional benefits resulting from cholinergic treatments in AD (Sahakian and Coull, 1994) may have been intimately linked to the speed at which information is automatically processed in the preattentive, short-duration, sensory storage system.

It is of interest to note that the analysis failed to yield differences in MMN amplitudes or latencies elicited by 1- and 3-s ISI conditions. It is possible that, in AD, abnormalities in sensory memory processes will have induced "floor effects" whereby progressive ISI increases may not have resulted in further memory trace decay. AD patients in one previous study exhibited smaller amplitudes at 3-s (and not at 1 s) ISIs compared to controls (Pekkonen et al., 1994). However, as 3-s MMN recordings were always acquired after 1-s MMN recordings, it is possible that the AD patients were simply more fatigued than elderly controls. Given the robust negative relationship between MMN amplitude and ISI in normal young adults and elderly controls (Pekkonen et al., 1993, 1996), the relative insensitivity to ISI manipulation may reflect a characteristic early processing deficit in AD, which is not necessarily modulated by cholinergic transmission. Regardless, given that the MMN, which is partly generated in the superior temporal gyrus (Gené-Cos et al., 1999) where nicotinic Chr loss in AD is well demonstrated, was altered by a single low dose of nicotine, it would be of interest to pursue these findings by examining the effects of day-long, intermittent low (2 mg) oral nicotine dosing on MMN and concurrently assessed cognitive functions in AD. These efforts would be particularly relevant if conducted in clinical responders to second -generation acetylcholinesterase inhibitors so as to

examine nicotine's possible synergistic actions on the remaining functional central nicotine Chrs already augmented by these treatments.

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