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Transdermal nicotine administration enhances automatic auditory processing reflected by mismatch negativity

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Abstract

Mismatch negativity (MMN) is a component of event-related potentials (ERPs) with a wide-ranging applicability to the investigation of neuronal substrates of information processing in normal and psychopathological states. Nicotine has been shown to be implicated in the pathophysiology of psychiatric disorders as schizophrenia or Alzheimer's disease, and has also been proposed as a self-administered drug in schizophrenia. The goal of the present study is to elucidate the effect of nicotine on the auditory automatic processing reflected by MMN. Nicotine was administered transdermally under controlled dosage. Ten healthy volunteers attended the laboratory for one baseline session and two test sessions. The test sessions involved administration of a placebo patch and a nicotine skin patch, which were counter-balanced. The ERPs were recorded passively during an auditory oddball paradigm. Nicotine administration shortened the MMN latencies, and these effects were independent of the earlier ERP components, N100 and P200. In conclusion, nicotine enhances preattentive and automatic processing such as MMN system and these effects appear to be quite specific and independent of earlier cognitive stages than preattentive mismatch processing. The shortened MMN latency may be interpreted as a reduction of the amount of time required to complete a neuronal mismatch process through the ascending auditory pathway.

Keywords: MMN; Nicotine; Transdermal; ERP; N100; P200

1. Introduction

1.1. Cognitive-enhancing effects of nicotine

Cholinergic systems are well established as important components of the neural substrates of cognitive information processing, and nicotine acts on the cholinergic system as an agonist at one of the two principal classes of receptor for the endogenous transmitter, acetylcholine (Levin and Simon, 1998; Rezvani and Levin, 2001). Nicotine has been shown to have cognitive-enhancing effects, and its potency for selective activation of the active remaining central nicotinic cholinergic receptors has itself been advocated as a promising approach to the treatment of Alzheimer's disease (Sjoberg et al., 1998), in which pathology the selective loss of cholinergic receptors in the brains have been documented (Davies and Maloney, 1976). Functional MRI findings during a working memory ("n-back") task demonstrated that nicotine produces an increased blood oxygenation level-dependent (BOLD) signal response in the anterior cingulate, superior frontal cortex, and superior parietal cortex. This observation might point to mechanisms for nicotine-related enhancement of attention and working memory (Kumari et al., 2003).

1.2. Enhancing and speeding effects of nicotine on event-related potentials

P300, one of the most frequently reported components of event-related potentials (ERP), was described by Donchin (Donchin, 1981) as the physiological correlate of an

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updating of a cognitive hypothesis, or an updating of the working memory of what is expected in the environment. It has been suggested that P300 amplitudes are especially sensitive to the nicotine level (Houlihan et al., 1996). Nicotine/smoking decreases P300 latency in visual but not auditory tasks (Edwards et al., 1985; Houlihan et al., 1996), nonetheless, not all studies have obtained this result. The reported effects of smoking/nicotine on P300 amplitudes are discrepant and apparently subject to quite a variety of influences (Polich and Kok, 1995). The cognitive-enhancing effects of nicotine reflected by P300 amplitudes have not always been found with nicotine administration (Knott et al., 1999). For example, no effect of smoking on P300 amplitudes was found in a bimodal attention task (Lindgren et al., 1998) nor in a Stroop task (Ilan and Polich, 2001). The difficulty in controlling the experimental conditions might have attenuated the observable effects of nicotine on P300.

Houlihan et al. (2001) employed ERPs (N100, P200, N200, P300) during a short-term memory-scanning task, and reported the ERP-latency effects obtained for the probes were small relative to the effects of smoking/nicotine on RT (reaction time), suggesting that smoking shortened RT primarily by affecting response-related processes. Although the effect of smoking on N200 was small relative to its effects on RT, smoking decreased N200 latency for the memory-set stimuli and negative-probes.

1.3. Mismatch negativity

Another component of ERPs, Mismatch Negativity (MMN), is generated by a neuronal mismatch process between the sensory memory input from a deviant auditory stimulus (deviant) and a memory trace of frequent auditory stimuli (standard). Because the MMN is elicited even when the subjects are instructed to ignore the stimulation of the auditory channel, it has been suggested that the MMN is generated by an automatic process (Näätänen, 1990, 1992; Näätänen et al., 1993a,b; Näätänen and Alho, 1995a,b). Javitt et al. (1995a,b) suggested that MMN should be understood as an index of the functioning of an automatic alerting mechanism designed to stimulate individuals to explore unexpected environmental events. MMN generation is critically dependent upon the probability with which deviant stimuli are presented in that the MMN amplitudes increase as the deviant probability decreases (Näätänen and Picton, 1986). MMN amplitudes decrease as the interval is prolonged, demonstrating the weakening of the memory trace as a function of time (Mäntysalo and Näätänen, 1987). A stimulus change cannot elicit MMN if the memory trace has already decayed (Näätänen, 1992). MMN has a fronto-central scalp distribution pattern that can be modeled with generator sources in anterior regions of the supratemporal auditory cortex. An additional MMN generator in frontal cortex has been identified, indicating that frontal–temporal projection or a front-temporal feedback process may play a critical role in efficient MMN generation (Giard et al., 1990; Alho et al., 1994; Näätänen and Alho, 1995a,b).

Näätänen (1990) has proposed a model for the role of automaticity and attention in the processing of acoustic stimuli in which all auditory sensory information produced by preconscious processing is stored for a temporary period in the form of precise neuronal representations of sensory memory. In task-independent sensory analysis, the "transient–detector" systems are activated by the onset and offset of stimulus energy. The transient–detector systems bombard central executive processing such that when some momentary threshold is exceeded, there may be an attentional switch to the ongoing sensory processes and also to the results of previous sensory analysis stored in sensory memory. The "permanent feature–detector" system passes information extracted from the physical features of the acoustic stimuli to sensory memory. When a stimulus corresponding to the existing trace occurs, this trace receives sensory reinforcement and is consequently refreshed and strengthened. After a memory trace has been established for a specific stimulus, any stimulus that differs significantly from that memory trace will result in the generation of the MMN, thus providing an attention-switch signal to the executive mechanisms. This process, performed by the permanent feature–detector system, is automatic, parallel, preconscious, extremely rapid, and is not influenced by the direction of attention.

Näätänen and Escera (2000) argued that MMN can be measured in absence of attention and task requirements, which makes it particularly suitable for the testing of different clinical populations with levels of attention that have been ascertained and standardized. Because of such advantages over other criteria, MMN possesses utility in numerous existing as well as potential applications, particularly in the psychiatric field (Gené-Cos et al., 1999).

1.4. Memory trace in MMN system

Regarding the memory that is relevant to the MMN system, initially it was thought that sensory memory maintains representations of recent acoustic events against which subsequent stimuli can be compared (Näätänen et al., 1989). However, recent reports have indicated that the deviant is not compared to the representations of individual tones, but rather to the representations of invariance across tones (regularities in features or relationships between tones) (Cowan et al., 1993; Schroger, 1997; Ritter et al., 1998, 2002). Furthermore, during the tone pips which intervene in regular silent intervals, occasionally shorter, but not longer intervals elicited MMN, indicating that MMN generation seems to be due to something more than just new afferent elements activated by deviant but not-standard stimuli (Näätänen et al., 1993a,b).

Cowan et al. (1993) reported the process for memory formation, inactivation, and reactivation in the case of simple tonal stimuli. The trace developed by a single

stimulus presentation is not initially sufficient for MMN generation, until activated by a repetition of this stimulus (three or more times) and, further, the nonactivated trace lasts considerably longer (11–15 s) than its activated state (Näätänen and Alho, 1995a,b). Until the memory trace has decayed, even a single presentation of the standard is sufficient to reactivate the presentation of standard tone and MMN elicitation is possible (Cowan et al., 1993).

1.5. Relationships between NMDA, MMN, schizophrenia, and nicotine

A transient but significant improvement in auditory sensory gating after nicotine administration in schizophrenic patients has been reported (Adler et al., 1993). Nicotine receptor desensitization may be responsible for the sensory gating deficits in schizophrenia (Griffith et al., 1998). It has been well documented that nicotine modulates activity of midbrain dopamine neurons, as well as cortical glutamatergic inputs to the ascending dopamine systems (Imperato et al., 1986). Furthermore, stimulation of pre-synaptic nicotinic receptors on glutamaternergic neurons increases extracellular levels of glutamate in the prefrontal cortex (Vidal, 1996) and enhances excitatory glutamatergic inputs to the midbrain dopamine tracts (Toth et al., 1992). Deficits in *N*-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission may contribute to the clinical pathophysiology of schizophrenia (Javitt and Zukin, 1991; Krystal et al., 1994, 2000; Tsai et al., 1995). These findings have led to the speculation that the prevalence of smoking among schizophrenics, which is nearly three times higher than that of general population, is because nicotine partially remediates attentional and sensory processing deficits (Dalack and Meador-Woodruff, 1996). Smoking in schizophrenia may represent a self-medication effort to restore a deregulated cortical–mesolymbic system (Lohr and Flynn, 1992; Glassman, 1993; Glassman et al., 1993).

On the other hand, NMDA receptors may be critically involved in MMN generation (Javitt et al., 1995a,b, 1996). The combination of intracortical recording and pharmacological micromanipulations in awake monkeys demonstrated that both competitive and noncompetitive NMDA antagonists block the generation of MMN without affecting prior obligatory activity in primary auditory cortex (Javitt et al., 1996). Krystal et al. (2000) reviewed previous reports and suggested that NMDA antagonists preferentially disrupt a relatively early stage of memory encoding. It is likely that NMDA antagonists affect many facets of memory function, not only attention and working memory, but also an early stage of memory encoding.

Javitt et al. (1993, 1995a,b, 1998) and Shelley et al. (1991) reported attenuated MMN in schizophrenia, and indicated that impairment of memory underlying the MMN system might be related to the impaired working memory observed in schizophrenic patients.

1.6. Effects of nicotine on automatic processing and MMN

Ilan and Polich (2001) conducted a study of the effects of nicotine on automatic processing, although the Stroop (color-naming) task they employed was laborious and was not preconscious. The P300 amplitude during the Stroop task decreased after smoking, which implied that smoking might reduce the availability of the general attentional resources required to perform the Stroop task for incongruent words. In contrast, other reports suggested cognitive enhancing effects of nicotine reflected by the shortened P300 latencies. An alternative interpretation was that the decreased P300 amplitude seen after smoking reflects the increased automaticity of incongruent color naming, thus requiring less cognitive effort. One possible explanation for this phenomenon was that smoking helped subjects filter irrelevant stimuli, such that only relevant stimulus attributes were processed.

As cited in the above, MMN has a wide range of useful applicability. However, reports on the effects of nicotine on MMN have been noticeably lacking in the literature. Engeland et al. (2002) recorded the MMN of Alzheimer's disease patients receiving tacrine treatment and those receiving no treatment during pre- and post-oral nicotine administration. MMN amplitudes increased with nicotine administration in nontreated but not tacrine-treated patients, and MMN latencies were shortened by nicotine in both treatment groups. As MMN is a subcomponent of N200, which can be divided into MMN and N2b (Näätänen et al., 1993a,b), these findings might be compatible with the findings of shortened N200 (Houlihan et al., 2001). However, smoke-inhaled nicotine has not been shown to consistently alter MMN amplitudes in young adults (Knott et al., 1995).

1.7. Nicotine delivery system

The control of dosage of nicotine is complex and needs to be carefully monitored with smoking behavior, negative effects of abstinence, and many individual differences. Although the previous reports pertaining to cognition have generally agreed that smoking can improve performance on a variety of tasks, these so-called cognitive potentials have not always responded to acute smoking, or have responded in a less than robust fashion. Despite this inconsistency of smoking/nicotine effects, there is general agreement that further and better elucidation of effects of smoking/nicotine requires the use of a nicotine delivery system other than smoking to control dosage much more effectively. Transdermal administration of nicotine produces a nicotine blood level pattern distinct from other delivery methods such as smoking, chewing, or subcutaneous administration. Transdermal nicotine route is able to deliver a systemic dose over a 24 h period (Knott et al., 1999; Houlihan et al., 2001; Engeland et al., 2002; Kumari et al., 2003).

As already stated, MMN has a wide applicability. Furthermore, nicotine and MMN may be implicated in the neural substrates of cognitive dysfunction in psychiatric disorders such as Alzheimer's disease or schizophrenia. However, to the best of the authors' knowledge, MMN assessment during transdermal nicotine administration to healthy young adults has not yet been reported. The goal of the present study is to elucidate the effect of nicotine on the auditory automatic processing reflected by MMN. Nicotine was administered transdermally under a controlled dosage regimen.

2. Methods and materials

2.1. Subjects

Ten right-handed non-smoking volunteers (5 males) between the ages of 26 and 39 (29.9±4.9) were recruited. Seven of them never had a smoking habit, which was defined as regularly smoking more than a cigarette per week. The three who had formally smoked had abstained from smoking for over a year. All subjects reported that they had normal hearing, and were judged to be in good physical health on the basis of physical examination. After a complete description of the study was presented to the subjects, all subjects gave informed consent for this protocol, which was approved by the Institutional Review Board of the Juntendo Institute of Mental Health.

2.2. Study design

Subjects attended the laboratory for one baseline session and two test sessions. Study measurements were performed at the same time of day on three consecutive days. The first day is the baseline day with administration of neither Placebo nor Nicotine. On the 2nd and 3rd day for the test sessions, ERP recordings were scheduled in the evening, 8 h after nicotine or placebo administration via the skin patch applied in the morning. The test sessions involved administration of a placebo patch and a nicotine skin patch, which were counter-balanced.

2.3. Nicotine administration

Nicotine was administered by a transdermal nicotine skin patch (Nicotinell(r) TTS(r) 20) that delivers a systemic dose of 16.1±2.7 mg/day over 24 h ($AUC_{0\text{-}36}$: 474.9±86.7 ng h/ml). Nicotinell(r) TTS(r) 20 covers 20 cm^2, and has a total nicotine content of 35 mg. A maximum plasma nicotine concentration (^{c}max) of 21.9±3.0 ng/ml reaches 9 h (^{T}max) after a single application. The placebo patch was similar in size and color, and both the active and placebo patches were applied to an area on the upper back of the subjects. None of the subjects were able to distinguish the active and placebo patches on questioning at the end of the two test sessions.

2.4. Experimental tasks and procedure

The ERPs were recorded during an auditory oddball paradigm. A computer with custom-designed software generated acoustic stimuli and controlled both stimulus-timing and presentation. Tones were presented binaurally at a constant listening level (75 dB sound pressure level) through electrically shielded headphones held in place by the headset. The acoustic stimuli consisted of tones (sine waves) with a duration of 80 ms, including 10 ms rise and fall times. The frequency of the standard tones (probability=0.95) and the deviant tones (probability=0.05) were 1000 and 1050 Hz respectively, and the onset-to-onset interval was 600 ms. The experimental task consisted of a single block, which included 2000 tones. An ERP session for each subject on one condition took about 20 min.

2.5. ERP recording and analysis

ERPs were recorded under an entirely 'passive' condition, in which the subjects were asked to ignore the stimuli and to watch a silent movie projected on a video monitor. To standardize their level of attention, all subjects were told that they would have to give specific feedback about the movie at the end of the ERP session. They were instructed to avoid unnecessary eye movement and eye blinking during the session.

ERPs were recorded from Ag/AgCl disk electrodes placed at 13 scalp sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, O2, T5, T6) of the standard 10/20 system and recording electrodes were referenced to the nose. Additional electrodes were placed at the bilateral mastoids (LM: left mastoid, RM: right mastoid) under the ears. A bipolar electrode pair was placed above and over the outer canthus of the right eye to record the electrooculogram (EOG). Impedances of all electrodes were maintained below 5 KΩ.

EEG data was recorded and analyzed using a Brain Atlas 2® (Bio-Logic) system. During the task, the EEG and EOG were continuously digitized at 500 Hz per channel and stored on a computer disk using a 0.1–100 Hz on-line filter. EEG was filtered off-line with a bandpass of 0.1–35 Hz. At the conclusion of the experiment, EEG epochs of 512 ms duration (100 ms pre-stimulus, 412 ms post-stimulus) associated with each stimulus type were excised from the continuous record. The root mean square voltage of the EOG channel was computed to identify and discard epochs associated with eye movements and blink artifacts. All-single trial epochs were prestimulus-baseline corrected prior to the subsequent process. Epochs contaminated by EOGs, blinks, or muscle artifacts exceeding an artifact rejection threshold of +/−80 μV at any electrode were omitted from the analysis. Artifact-free epochs were segregated by stimulus codes and averaged for each subject. There was no significant difference

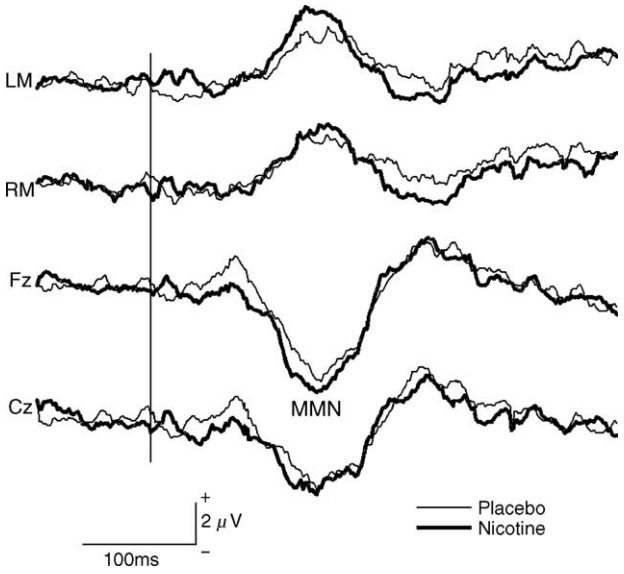

Fig. 1. Grand averaged difference waveforms (LM, RM, Fz, Pz). Negative deflection within the latency ranges of 120–185 ms was recognized as MMN. Polarity reversal of MMN waveforms between the mastoid and other electrodes was observed. The thin and bold lines indicate waveforms for placebo and nicotine, respectively. Positive values appear above baseline and negative values appear below. Waveforms for baseline were not presented, as they would overlap with placebo.

in the amount of accepted epochs between the conditions. A group-average across all ten subjects was also computed.

Difference waveforms were constructed by subtracting the waveform of the standards from that of the deviants. In every condition, topographic distributions were inspected to verify that MMN was maximum at the Fz or Cz electrodes, where the MMN is usually the largest. Peak amplitudes of MMN were detected within the latency ranges of 120–185 ms. For the purpose of this study, analyses were restricted to amplitudes and latencies of MMN at Fz and Cz. The amplitude of MMN was calculated for each subject as the mean amplitude in a 50 ms time window centered on each subject's peak latency, and then tabulated for the next procedures.

The N100 and P200 components at Fz and Cz for the standard and the deviant were also detected respectively within the latency ranges of 40–120 ms and 70–200 ms to determine the specificity of effects of nicotine on MMN compared to those on other ERP components.

The amplitudes of each ERP component were measured relative to the pre-stimulus baseline.

2.6. Statistical analysis

The data of MMN, N100, and P200, at Fz and Cz, was analyzed by means of an analysis of variance (ANOVA) with repeated measures. For MMN, ANOVAs with two repeated measures were performed. There were two factors, Drug (baseline, placebo, nicotine) and Electrode (Fz, Cz) as within-subject factors. For N100 and P200, Stimulus (standard, deviant) was added as a within-subject factor. Reduced degrees of freedom (Greenhouse–Geisser) were used when appropriate to counter violations of the sphericity assumption underlying ANOVA with repeated measures (epsilon values were provided). Alpha values of 0.05 were considered significant. Dunnett's post hoc procedures were performed at Fz. All statistics were performed using SPSS for Windows (SPSS, Chicago, Il).

3. Results

Polarity reversal of MMN waveforms between the mastoids and other electrodes was observed in all subjects, which indicated that the component defined as MMN in the present experiments was confirmed as that defined by Novak et al. (1990) (Fig. 1).

Table 1
Amplitude and latency of each ERP components (Fz, Cz) (Mean±S.D.)

	Baseline	Placebo	Nicotine
MMN			
Amplitudes (μV)			
Fz	−2.92±2.60	−2.85±2.32	−2.85±1.56
Cz	−2.35±2.21	−2.15±2.57	−2.04±1.54
Latencies (ms)			
Fz	159.6±19.3	157.8±21.8	140.0±10.8*
Cz	157.6±21.2	157.2±21.0	139.6±11.0
N100			
Standard			
Amplitudes			
Fz	0.26±1.34	0.62±1.44	0.51±1.39
Cz	0.81±1.50	1.29±1.73	1.19±1.75
Latencies			
Fz	81.2±22.3	82.0±21.2	77.2±21.1
Cz	79.4±20.5	79.4±18.5	76.4±17.3
Deviant			
Amplitudes			
Fz	1.51±2.19	0.69±1.93	1.27±2.30
Cz	2.06±2.39	1.32±2.43	1.73±2.37
Latencies			
Fz	74.2±34.3	78.2±26.4	62.6±26.5
Cz	72.2±30.4	76.8±25.7	59.6±26.4
P200			
Standard			
Amplitudes			
Fz	2.00±0.97	2.10±1.21	2.05±0.73
Cz	2.10±1.00	2.03±1.36	2.08±0.77
Latencies			
Fz	142.2±32.5	141.2±35.4	141.4±34.9
Cz	141.4±31.8	144.0±34.8	136.0±29.8
Deviant			
Amplitudes			
Fz	0.39±2.07	0.69±2.18	0.73±1.91
Cz	0.44±1.74	0.58±2.79	0.73±1.68
Latencies			
Fz	104.2±36.4	98.2±46.5	95.8±42.4
Cz	108.0±36.0	106.2±30.6	102.0±43.0

MMN latencies on nicotine administration were shorter than those on baseline and placebo and these effects are independent of N100 and P200.
* $P<0.05$.

3.1. MMN latency

ANOVA confirmed the effect of Drug [$F(2,18)=4.355$, $p=0.029$]. In Dunnett's post hoc procedures with MMN latencies at Fz on nicotine (140.0±10.8) as the control compared with those of placebo (157.8±21.8) and baseline (159.6±19.3), MMN latencies for nicotine were shorter than those for baseline [$p=0.027$] and placebo [$p=0.044$] (Tables 1 and 2). The electrode effect [$F(1,9)=0.707$, $p=0.422$] and the interaction of Drug × Electrode [$F(2,18)=0.208$, $p=0.681$, $\varepsilon=0.550$] were not significant.

3.2. MMN amplitude

ANOVA revealed a significant effect of the Electrode [$F(1,9)=17.888$, $p=0.002$], but not the Drug [$F(2,18)=0.052$, $p=0.949$]. The interaction of Drug × Electrode [$F(2,18)=0.442$, $p=0.649$] was not significant.

3.3. N100 latency

ANOVA did not reveal any significant effects: Drug [$F(2,18)=3.259$, $p=0.062$], Stimulus [$F(1,9)=1.263$, $p=0.290$], and Electrode [$F(1,9)=1.748$, $p=0.219$] effects, as well as the interactions of Drug × Stimulus [$F(2,18)=1.289$, $p=0.300$], Drug × Electrode [$F(2,18)=0.003$, $p=0.997$], Stimulus × Electrode [$F(1,9)=0.016$, $p=0.902$], and Drug × Stimulus × Electrode [$F(2,18)=0.272$, $p=0.765$] were not significant (Fig. 2).

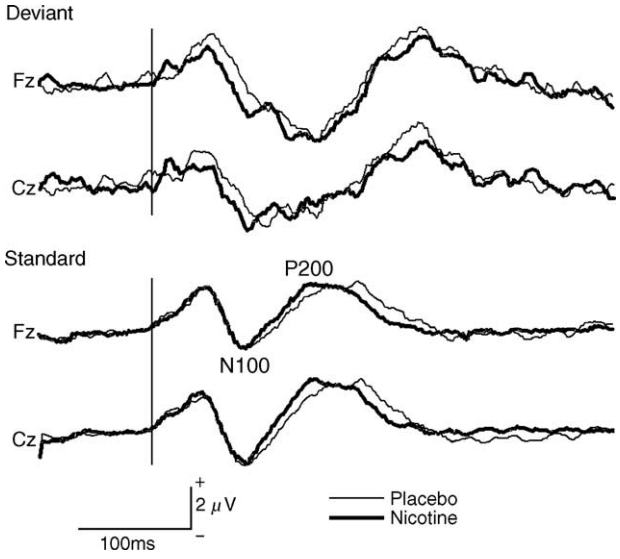

Fig. 2. Grand averaged waveforms to deviant and standard (Fz, Pz). N100 and P200 were observably recognized for both deviants and standards. The thin and bold lines indicate waveforms for placebo and nicotine, respectively. Positive values appear above baseline and negative values appear below. Waveforms for baseline were not presented, as they would overlap with placebo.

3.4. N100 amplitude

ANOVA revealed a significant effect of the Electrode [$F(1,9)=22.893$, $p=0.001$], but not the Drug [$F(2,18)=0.272$, $p=0.765$] and the Stimulus [$F(1,9)=1.425$, $p=0.263$]. The

Table 2
Summary of the statistical analyses for each ERP component

Source (df)	Latency			Amplitude		
	F	*p*	ε	*F*	*p*	ε
MMN						
Drug (2,18)	4.355	0.029	–	–	–	–
Electrode (1,9)	–	–	–	17.888	0.002	–
Drug × Electrode (2,18)	–	–	–	–	–	–
N100						
Drug (2,18)	–	–	–	–	–	–
Stimulus (1,9)	–	–	–	–	–	–
Electrode (1,9)	–	–	–	22.893	0.001	–
Drug × Stimulus (2,18)	–	–	–	–	–	–
Drug × Electrode (2,18)	–	–	–	–	–	–
Stimulus × Electrode (1,9)	–	–	–	–	–	–
Drug × Stimulus × Electrode (2,18)	–	–	–	–	–	–
P200						
Drug (2,18)	–	–	–	–	–	–
Stimulus (1,9)	–	–	–	–	–	–
Electrode (1,9)	11.121	0.009	–	7.287	0.024	–
Drug × Stimulus (2,18)	–	–	–	–	–	–
Drug × Electrode (2,18)	–	–	–	–	–	–
Stimulus × Electrode (1,9)	–	–	–	–	–	–
Drug × Stimulus × Electrode (2,18)	–	–	–	–	–	–

The non-significant effects were omitted. Significance was assumed for values of $p<0.05$.

interactions of Drug × Stimulus [$F(2,18)=2.478$, $p=0.112$], Drug × Electrode [$F(2,18)=0.296$, $p=0.747$], Stimulus × Electrode [$F(1,9)=0.235$, $p=0.640$], and Drug × Stimulus × Electrode [$F(2,18)=0.416$, $p=0.666$] were not significant.

3.5. P200 latency

ANOVA revealed a significant effect of the Electrode [$F(1,9)=11.121$, $p=0.009$], but not the Drug [$F(2,18)=0.493$, $p=0.619$] and the Stimulus [$F(1,9)=0.895$, $p=0.369$]. The interactions of Drug × Stimulus [$F(2,18)=0.540$, $p=0.491$, $\varepsilon=0.534$], Drug × Electrode [$F(2,18)=0.113$, $p=0.894$], Stimulus × Electrode [$F(1,9)=2.308$, $p=0.163$], and Drug × Stimulus × Electrode [$F(2,18)=0.299$, $p=0.745$] were not significant.

3.6. P200 amplitude

ANOVA revealed a significant effect of the Electrode [$F(1,9)=7.287$, $p=0.024$], but not the Drug [$F(2,18)=0.098$, $p=0.907$] and the Stimulus [$F(1,9)=0.000$, $p=0.988$]. The interactions of Drug × Stimulus [$F(2,18)=0.435$, $p=0.654$], Drug × Electrode [$F(2,18)=0.152$, $p=0.860$], Stimulus × Electrode [F (1,9)=0.023, $p=0.883$], and Drug × Stimulus × Electrode [$F(2,18)=0.002$, $p=0.998$] were not significant.

4. Discussion

In the results of this study, nicotine administration was found to shorten the MMN latencies, and these effects were independent of the earlier ERP components, N100 and P200.

4.1. What shortened MMN latency means

Accumulating evidence suggests a reduced MMN amplitude in psychiatric conditions, but, to our knowledge, only limited evidence for the altered MMN latency, as in the results presented here, have thus far been reported. Shortened MMN latency in socially withdrawn children has been reported, as well as their reduced MMN amplitudes (Bar-Haim et al., 2003), however, what the shortened MMN latency means has yet to be understood.

It has been proposed that there is an increase in frequency specific inhibition of populations of neurons that are responsive to the frequency of the repeated standard stimulus (Näätänen and Winkler, 1999). This inhibitory state that constitutes the memory trace is paralleled by an increase in excitability of neurons responsive to other frequencies. If the integrity of the signal is compromised in its transmission through the ascending auditory pathway, the development of neuronal inhibition to standard stimuli may be reduced. Then, the comparison of the standard and deviant stimuli may be impaired and smaller and delayed MMN will be elicited (Bullock and Gilliland, 1993; Woodward et al., 2001; Bar-Haim, 2002). Considering that NMDA receptors may be critically involved in MMN generation (Javitt et al., 1995a,b, 1996) and that nicotine increases glutamatergic inputs in the ascending dopamine systems in the midbrain (Imperato et al., 1986; Toth et al., 1992), the shortened MMN latency after nicotine administration in this study may be interpreted as a reduction of the amount of time required to complete a neuronal mismatch process at an earlier stage through the ascending auditory pathway. However, this is still a working hypothesis and we failed to find significant MMN amplitude change by nicotine in this study. The specific mechanism for shortened MMN latency still needs to be elucidated.

4.2. Specific effects of nicotine on MMN

In the case of attended stimuli, as the stimulus deviance increases, the MMN latency decreases and a parallel decrease is observed for reaction time (RT), suggesting that attention novelty detection is governed by preattentive sensory memory (Novak et al., 1992). Late ERP components might not be independent of MMN. When the discrimination difficulty of attention-independent and attention-dependent tasks was increased, the latencies of MMN and the late components such as P3b increased in parallel (Picton, 1992; Polich and Kok, 1995). As P3b latencies and RTs were also shortened following acute administration of nicotine, it is reasonable to suggest that previously reported psychomotor, vigilance and attentional benefits resulting from cholinergic treatment in Alzheimer's disease might be initially linked to the speed at which information was automatically processed in the preattentive, short-duration, sensory storage system as MMN processing (Engeland et al., 2002). In contrast, in the results of this study, MMN latencies were shortened by nicotine administration; nevertheless, N100 and P200 were not affected. Although these effects on MMN might affect later components such as P300, the effects of nicotine on MMN were independent of other ERP components reflecting an earlier stage than preattentive mismatch processing.

5. Conclusion

As discussed in the introduction, MMN has a wide applicability in investigating the neuronal substrates of information processing in both normal and psychopathological states (Gené-Cos et al., 1999; Näätänen and Escera, 2000). Nicotine has been shown to be involved in the pathophysiology or self-medication of patients with certain psychiatric disorders as schizophrenia or Alzheimer's disease. In the present study, the effects of nicotine, administered transdermally and delivered under controlled and effective dosage, shortened the MMN latencies, and

these effects were independent of the earlier ERP components, N100 and P200. In conclusion, nicotine enhances preattentive and automatic processing such as the MMN system, and the effects appear to be quite specific and independent of earlier cognitive stages than preattentive mismatch processing. The shortened MMN latency may be interpreted as a reduction of the amount of time required to complete a neuronal mismatch process through the ascending auditory pathway.

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