NAVAL AEROSPACE MEDICAL RESEARCH LABORATORY
NAVAL AIR STATION, PENSACOLA, FL 32508-5700

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EFFECTS OF TRANSDERMAL SCOPOLAMINE ON AUDITORY-MONITORING PERFORMANCE AND EVENT-RELATED POTENTIALS

R. R. Stanny and R. N. Shull

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A. J. MATECZUN, CAPT, MC USN
Commanding Officer

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ABSTRACT

Motion sickness is a persistent problem in aviation, particularly for trainees who have not yet acclimated to the flight environment. Patch-administered, transdermal scopolamine treatments are sometimes used to reduce the symptoms of motion sickness in aviators. However, scopolamine's side effects on attentional and memory processes have raised concerns that the drug may compromise the abilities of those it was meant to help. The study described here was a neural and behavioral examination of the effects of transdermal scopolamine on vigilance and attention in an auditory-monitoring paradigm. Subjects were asked to detect acoustic target stimuli randomly distributed in a sequence of tones presented to the right ear. Event-related potentials (ERPS) were recorded as subjects performed the task. In one condition, subjects wore a transdermal scopolamine patch; in a second condition, subjects wore a placebo patch. The transdermal scopolamine treatment yielded a small reduction in the discriminabilities of target stimuli. Correct-response reaction times were not significantly affected. An early negative ERP resembling a processing negativity (PN) was extended in duration in the scopolamine condition. This result, in the context of PN theory, suggests that scopolamine rendered the discrimination more difficult but does not suggest that scopolamine affected selective-attention mechanisms. Another early negative ERP resembling a mismatch negativity (MMN) was delayed in the scopolamine condition. This result, in the context of MMN theory, tends to confirm the idea that scopolamine rendered the stimuli less discriminable. Although the data do not rule out the possibility that scopolamine may have directly affected cholinergic mechanisms responsible for the attentional processing of auditory information, the simplest explanation of the results appears to be that scopolamine affected discriminability by altering the responses of sensory-system neurons at a relatively early point in the course of perceptual processing (at or below the levels of processing at the PN and MMN are generated). The effects of transdermally administered scopolamine observed in this study were fairly small. Nevertheless, the data were consistent with previous studies indicating that scopolamine affects attentional performance. However, the data also suggest that scopolamine's effects on attention, in this task, might be secondary to an influence of the drug on auditory-sensory processing. The drug should be prescribed with some caution, particularly in conditions of high workload in which small degrees of inattention might produce substantial probabilities of operator error.

INTRODUCTION

Motion sickness is a persistent problem in aviation that can be especially serious for individuals training to become pilots who have not yet acclimated to the flight environment. Scopolamine has been used to avoid the symptoms of motion sickness in both aviation and nonaviation environments, but its side-effects have led to concerns that its use might possibly compromise the abilities of those it was meant to help. Scopolamine's side effects include drowsiness, fatigue, slowing, difficulties in performing concurrent tasks, and a form of amnesia (e.g., Caine, Weingartner, Ludlow, Cudahy, & Wehry, 1981; Drachman & Leavitt, 1974; Frumin, Herekar & Jarvik, 1976; Nissen, Knopman & Schacter, 1987; Rasmusson & Dudar, 1979; Rusted, 1988; Sitram, Weingartner & Gillin, 1978).

The study described here was an examination of the effects of transdermally administered scopolamine on human performance and event-related potentials (ERPs). Transdermal administration, by means of a patch applied to the skin behind an ear, is a particularly convenient way to give a long-lasting dose of the drug. Scopolamine is a competitive antagonist of acetylcholine that acts at muscarinic receptor sites. The drug is thought to relieve motion sickness by blocking cholinergic transmission in pathways connecting the vestibular system with central nuclei that control vomiting (Weiner, 1985). Scopolamine, however, also blocks cholinergic transmission elsewhere in the nervous system. This presumably gives rise to the drug's well-known psychological side effects.

Among these effects is an impairment of memory. Several groups have concluded that scopolamine affects memory by impairing the ability to acquire new memories (Drachman & Leavitt, 1974; Nissen et al., 1987). Some data suggest that a retrieval deficit may occur as well (Caine et al., 1981). Results from studies in nonhumans appear to be consistent with the existence of at least an acquisition deficit (Caine et al., 1981). The scopolamine memory deficit may be limited to declarative memories, inasmuch as some evidence suggests that scopolamine does not affect the creation of procedural memories (Nissen et al., 1987).[1]

These results suggest that scopolamine's effects on memory might be similar to the amnesic syndrome produced by damage to the temporal lobes. Classical temporal lobe amnesia appears to be characterized by a selective loss of the ability to create declarative memories despite a spared ability to create procedural memories (Zola-Morgan, Squire & Mishkin, 1982), an effect also reported to occur following scopolamine administration (Nissen et al., 1987). The temporal lobe syndrome is usually observed in association with damage to the temporal cortex and anatomically related structures of the hippocampus and amygdala. The normal functioning of the memory system implicated in temporal lobe amnesia may depend partly on cholinergic neurons. Support for this idea comes from observations that Alzheimer's dementia, which is characterized by a similar pattern of memory deficits, is accompanied by large reductions in cholinergic neurons, especially in structures traditionally associated with temporal lobe amnesia (Bowen, Smith, White & Davidson, 1976).

Some data, however, suggest that the effects of scopolamine and Alzheimer's dementia may not be entirely parallel. Some investigators have reported that the pattern of memory deficits in Alzheimer's patients differs from that observed in scopolamine-treated normals; for example, scopolamine administration may not produce the increased false-positive and intrusion errors observed in individuals with Alzheimer's dementia (Beatty, Butters & Janowsky, 1986). Furthermore, Alzheimer's patients may be less impaired in vigilance performance than scopolamine treated normals (Lines et al., 1991). Indeed, the results of several studies suggest that the effects of scopolamine on memory could be secondary to the drug's effects on attentional processes (Grober, Leipzig, Lipton & Wisniewski, 1989; Wesnes, Simpson & Kidd, 1988). A tendency for

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[1]Declarative memories are memories for facts and events, whereas procedural memories are memories that support well-learned motor skills, cognitive routines, or "habits" (Squire, 1986; Mishkin, Malamut & Bachevalier, 1984).

scopolamine to produce inattentiveness could produce an acquisition deficit by reducing the initial strengths of memory traces. A similar interpretation of the effects of sleep deprivation on memory has been made by Polzella (1975), who suggested that the effects of sleep deprivation on memory may be attributable to reductions in initial trace strengths caused by lapses of attention that interfere with perceiving or rehearsing to-be-remembered stimuli.

Studies of ERPs have indicated that P300 ERPs are affected by scopolamine. Increased P300 latencies have been reported in visual reaction time (RT) tasks following scopolamine treatment (Callaway, Halliday, Naylor & Schechter, 1985). Increased P300 latencies and decreased amplitudes have also been observed in an auditory monitoring task (Meador, Loring, Adams & Davis, 1987). Some results, furthermore, suggest that P300 might be associated with a cholinergic, temporal lobe memory system. For example, P300 ERPs have been reported to be affected by drugs with anticholinergic effects, but not by drugs with adrenergic or serotonergic effects (Callaway, 1984; Meador et al., 1989). Evidence for the idea that at least a portion of the P300 activity that can be recorded with surface electrodes is generated in the temporal lobes comes from observations of P300-like waves in depth recordings from temporal lobe structures in humans (Altafullah, Halgren, Stapelton & Crandall, 1986; Halgren et al., 1980; Wood et al., 1984). Evidence consistent with an association between P300 and memory processes has been found in studies showing that individuals with disorders of recent memory produce abnormal P300 responses (Meador et al., 1987).

The study described here was designed to replicate and extend observations of the effects of scopolamine on ERPs. The design of the experiment also allowed us to examine two other attention-related ERP components, the processing negativity (PN) and the mismatch negativity (MMN). Processing negativities, also referred to as "Nd" waves, are observed in recordings from subjects who are selectively attending to a particular physical feature of an information source (such as acoustic frequency; Hansen & Hillyard, 1980). These ERP components are slow, negative-going waveforms elicited by stimuli that possess a feature of a type to which a subject is attending. At least two different auditory processing negativities may exist. One is a comparatively short-latency wave that tends to peak between 100 and 200 ms poststimulus. The second is a longer-latency wave that may extend to 500 ms poststimulus or later. The earlier PN segment has been attributed to the selective processing of events in attended information channels, whereas the later segment has been attributed to processes associated with "maintaining" or "updating" the selective attention system based on newly acquired information from the attended channel. Some evidence suggests that the later PN segment may be observed only when the monitoring task is fairly difficult (Hansen & Hillyard, 1983, 1984; Näätänen, 1982).

Mismatch negativities (MMNs) are elicited by deviant stimuli--stimuli that differ from those presented during the preceding several seconds. The latencies of MMN waves tend to decrease as a function of the magnitudes of physical differences between their eliciting stimuli (Näätänen, Paavilainen, Alho, Reinikainen & Sams, 1987). On the other hand, the amplitudes of MMN waves tend to be relatively constant, depending little, if at all, on the magnitudes of the differences between eliciting stimuli--provided those differences exceed a minimum value (Sams, Paavilainen, Alho & Näätänen, 1985). Näätänen, Gaillard & Mäntysalo (1978) have suggested that the MMN reflects the operation of a preperceptual mechanism that detects stimulus change. The MMN appears to be elicited automatically; that is, MMNs are elicited by deviant stimuli regardless of the direction of an individual's attention (Näätänen, et al., 1978). Näätänen (1985) has proposed that the MMN reflects the operation of an auditory short-term memory system that functions to alert individuals to changes in their acoustic environments. Thus, the MMN behaves in some respects like an orienting reflex.

METHODS

SUBJECTS

Twelve male volunteers participated in this experiment. Their ages ranged from 21 to 24 yrs and averaged 21.9 yrs; their weights ranged from 68 to 86 kg and averaged 78 kg. All were right handed. One subject was eliminated from the analysis because his scopolamine patch fell off during the night preceding an experimental session. A second subject's ERPs were not analyzed due to electroencephalogram (EEG) recording difficulties.

DRUG TREATMENT

The experiment was a double-blind, counterbalanced, crossover design. Each subject participated in two separate sessions held at the same time on the same day of two consecutive weeks. In session 1, scopolamine was administered to half of the subjects using a transdermal scopolamine patch applied to the left mastoid process. The remaining subjects were administered an identical placebo patch containing no scopolamine. The patches were applied 12 h prior to testing, and the scopolamine-treated patches released the drug into circulation at a nominal rate of about 0.5 mg/day. Patches were removed within 2 h of the end of session 1, allowing a 6-day washout period before session 2. In session 2, the drug conditions were reversed between the two subgroups.

STIMULI

Stimuli comprised two, randomly ordered sequences of 1.0- and 1.2-kHz tone bursts. One sequence was presented to the left ear, and the other sequence was presented to the right ear. The tones were presented one at a time at 2.0-s intervals. A randomly selected 50% of the tones were delivered to the left ear. The remaining 50% were delivered to the right ear. Twenty percent of the tones delivered to each ear were 1.0 kHz; the remaining 80% of the tones delivered to each ear were 1.2 kHz.

The tones were constructed by multiplying sine waves by trapezoids so as to produce 50-ms bursts with 9-ms onset and offset ramps. They were synthesized by a computer, converted to analog electrical waveforms with 16-bit resolution at 50 kHz, attenuated to yield intensities of 65 dBA, and delivered dichotically to the subjects over TDH-49 headphones.

ERP RECORDING

Event-related potentials were recorded from frontal, central, and parietal midline recording sites (International 10-20 system Fz, Cz, and Pz). The reference electrode was placed on the nose; a forehead electrode was used as the ground. Eye movements were monitored using vertical and horizontal bipolar electro-oculogram (EOG) recordings. The EOG and EEG were amplified by 2000 and 20,000, respectively, filtered between 0.1 Hz and 0.1 kHz, and digitized at 0.25 kHz for 1.2 s beginning 200 ms before the onset of each stimulus. Amplifiers were calibrated before and after each subject's run.

PROCEDURE

The subject was asked to press a response key with his dominant hand whenever a 1.0-kHz tone (a "target" stimulus) was delivered to his right ear. He was asked to ignore all stimuli presented to his left ear, including 1.0-kHz tones. The subject was asked to respond as quickly as possible while maintaining accuracy near 100% correct. The target and nontarget stimuli were presented in four, 9-min blocks of 272 stimuli each. The first 12 stimuli in each block consisted of tones presented in a systematically repeating order, to help fix the

frequencies in memory. The data from these trials were ignored. The next 10 stimulus presentations were treated as warm-up trials; the data from these trials were also ignored.

DATA ANALYSIS

A correct detection was defined as a keypress with an onset not earlier than 72 ms after the onset of a target stimulus and not later than 1800 ms after the onset of a target stimulus. A miss was scored when no keypress occurred during a similar period relative to the onset of a target. A correct rejection was scored when no keypress occurred during a similar interval relative to the onset of a nontarget. A false alarm was scored when a keypress was made during a similar interval relative to the onset of a nontarget.

The ERP data from individual trials were examined offline for electrical artifacts using a computerized artifact detection and compensation protocol (Stanny & LaCour, 1990). The routines checked each epoch and channel of EEG for motion artifacts, eye blinks and movements, electrode pops, amplifier saturation, and dead amplifiers. Ocular artifacts were compensated, when possible, using a computerized, ocular artifact filter derived from that of Gratton, Coles, and Donchin (1983). All summary ERP measurements were scored by machine. Thirty-two signal averages were formed for each subject, corresponding to the factorial combination of two recording sessions, four blocks of trials per session, and four stimulus types per block. Data from trials on which errors were made were not used in the analysis. A preliminary analysis failed to detect an effect of blocks on the ERP measurements, so the averaged ERPs were collapsed across blocks. New summary measurements taken on these larger averages were used in the remainder of the analysis.

Significance tests were performed using repeated-measures analyses of variance (ANOVAs) and repeated measures and mixed-model multivariate analyses of variance (MANOVAs). Calculations were performed with the BMDP 4V *General Univariate and Multivariate Analysis of Variance* program (Dixon, Brown, Engelman, Hill & Jennrich, 1988).

RESULTS AND DISCUSSION

TARGET-DETECTION PERFORMANCE

Overall performance was high: The mean hit rate was 94.24%, and the mean false-alarm rate was 0.45% (pooled across the three classes of nontarget stimuli). Hits were less frequent in the scopolamine condition than in the placebo condition, averaging 91.32% following scopolamine administration and 97.58% in the placebo condition. The false-alarm rate was slightly higher in the scopolamine condition than in the placebo condition, averaging 0.59% under scopolamine and only 0.29% in the placebo condition. The MANOVA performed to test the significance of the effects of the scopolamine treatment on hit and false alarm rates yielded a $T^2 = 10.43$, for which the equivalent $F(2,8) = 4.63$, $p < .05$. The overall mean of the RT distribution was 435 ms; RTs associated with correct target detections were not significantly longer in the scopolamine condition than in the placebo condition, averaging 469.6 versus 458.7 ms.

EVENT-RELATED POTENTIALS

Figure 1 shows grand average ERPs elicited by stimuli delivered to the unattended (left) ear. The grand averages shown in Fig. 1 were constructed by averaging ERPs across blocks of trials and across subjects. The waveforms drawn with solid lines are responses from the scopolamine condition; those drawn with broken lines are responses from the placebo condition. Responses to the low-probability, 1.0-kHz tones are displayed in the column of panels on the left; responses to the high-probability, 1.2-kHz tones are displayed in the column

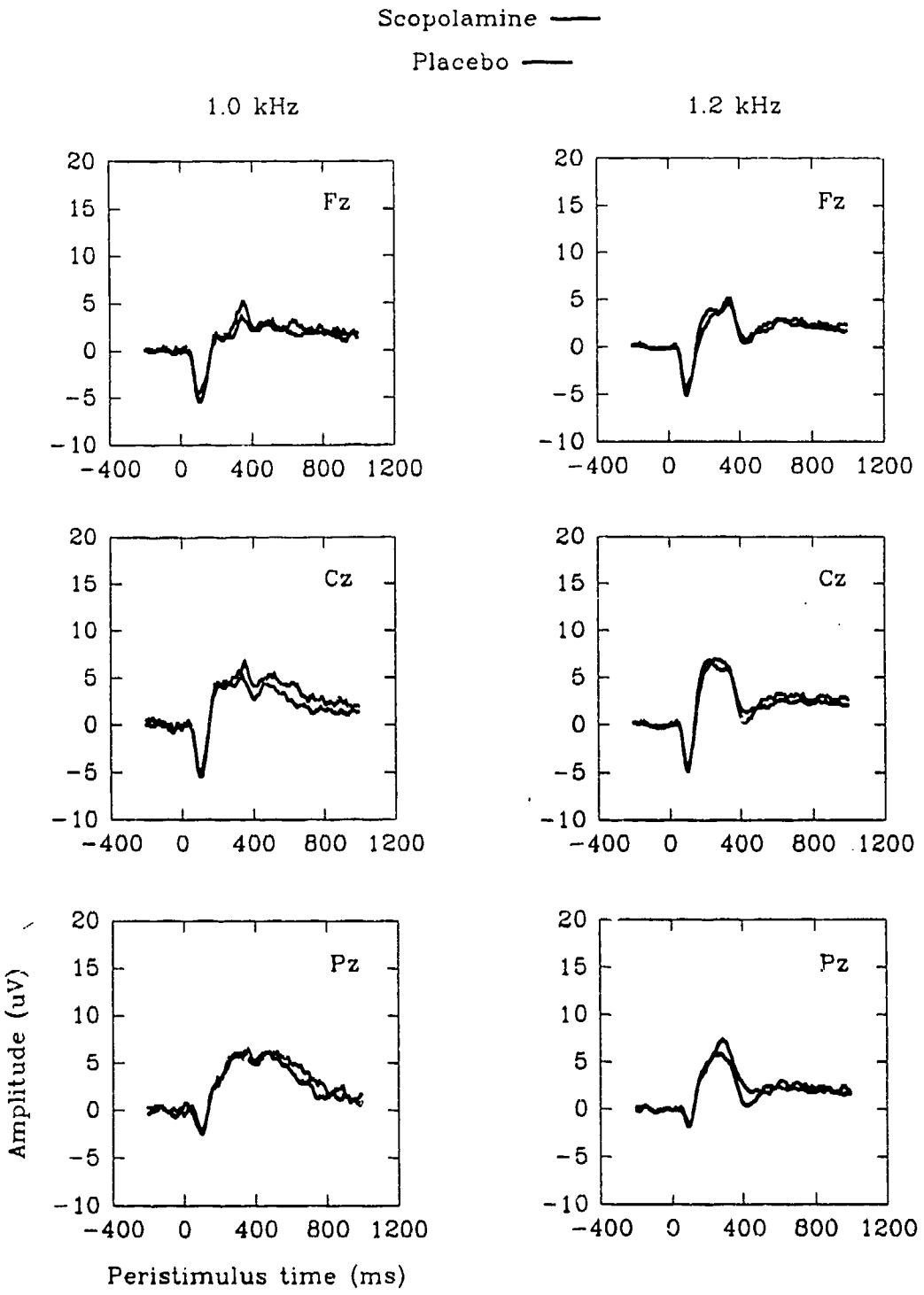

Figure 1. *Event-related potentials elicited by nontargets delivered to the unattended (left) ear. Panels on the left contain responses to 1.0-kHz stimuli. Panels on the right contain responses to 1.2-kHz stimuli.*

on the right. Responses from anterior (Fz), central (Cz), and posterior (Pz) recording sites are shown in the upper, middle, and lower rows of panels, respectively.

A salient feature of the ERPs in Fig. 1 is a negative-going peak near 100 ms poststimulus, N100, which is most prominent in the central and frontal recordings. A positive-going complex of more variable form can be seen in the vicinity of 300-400 ms poststimulus. In the 1.0-kHz responses from Pz, this positive complex appears to extend to nearly 800 ms poststimulus. Overall, responses to a given stimulus differed very little between scopolamine and placebo conditions (Fig. 1). An inspection of the figure suggests that the differences between the responses to low- and high-probability stimuli are somewhat more pronounced.

Figure 2 shows grand average ERPs elicited by stimuli delivered to the attended (right) ear. As in Fig. 1, the waveforms drawn with solid lines are responses from the scopolamine condition; those drawn with broken lines are responses from the placebo condition. Responses to the low-probability, 1.0-kHz tones (the target stimuli) are displayed in the left-hand column of panels. Responses to the high-probability, 1.2-kHz tones are displayed in the right-hand panels. As in Fig. 1, responses from Fz, Cz, and Pz are shown in the upper, middle, and lower rows of panels, respectively.

The ERPs elicited by target stimuli (the responses shown in the left column of Fig. 2) are characterized by large, positive-going P300 waveforms with peaks near 400 ms poststimulus. The average latency of the individual subjects' P300 ERPs was, in fact, slightly shorter in the scopolamine condition than in the placebo condition (408.7 ms vs. 433.7 ms). This difference, however, was not significant. In an initial analysis of the effect of scopolamine on P300 amplitudes, we compared the amplitudes of P300 responses measured relative to machine zero (i.e., measured relative to 0.0 μV at the computer's analog-to-digital converter). In this analysis, scopolamine reduced peak P300 amplitudes by 5.7 μV, from 13.8 μV to 8.1 μV, averaged across the three recording sites. A within-subjects MANOVA yielded a significant F-ratio for this effect, $F(1,9) = 98.36$, $p < .00005$. The magnitude of the effect did not vary significantly between recording sites. However, a second analysis performed on P300 amplitudes measured relative to the mean voltage during the 200 ms immediately preceding stimulus onset yielded no significant effect of scopolamine. This result suggested that the apparent reduction in P300 amplitude noted in the first analysis might have been caused by negative shift of the EEG baseline (in the scopolamine condition) during the final few hundred ms prior to stimulus onset. However, an analysis of mean EEG amplitudes, calculated across the 200 ms immediately prior to stimulus onset, yielded no significant difference between drug conditions. Given the lability of the effect in the present data, it may be prudent to conclude that we observed no effect of scopolamine on P300 amplitude.

Processing negativities were derived by subtracting ERPs elicited by nontargets delivered to the nominally unattended input channel (the left ear) from ERPs elicited by nontargets delivered to an attended input channel (the right ear). The resulting difference waves contain negative deflections with peaks near 160 ms (Fig. 3). The amplitudes of the early segments of the PNs were measured as the mean voltages between 100 and 200 ms poststimulus. The obtained values were -1.44 μV in the no-drug condition and -1.21 μV in the drug condition, averaged across the 3 recording sites. The difference was not significant. Examination of the traces in Fig. 3 suggests, however, that the PN may have been prolonged in the scopolamine condition, an effect that has been observed by others in association with increases in task difficulty (Hansen & Hillyard, 1980, 1983, 1984). Measurements of average PN amplitudes during a time window extending from 200 to 350 msec poststimulus yielded an average difference between scopolamine and placebo conditions of 1.29 μV. This amplitude difference was significant, $F(1,9) = 17.24$, $p = .0025$.

Grand average mismatch negativity waveforms are also shown in Fig. 3. The MMN waves were derived from ERPs elicited by tones delivered to the unattended ear. The derivation was performed by subtracting ERPs elicited by the higher probability tones from those elicited by the lower probability tones. The solid curves are responses from the placebo condition, and the broken curves are responses from the scopolamine condition. The difference waves contain negative peaks with average latencies of about 255 ms

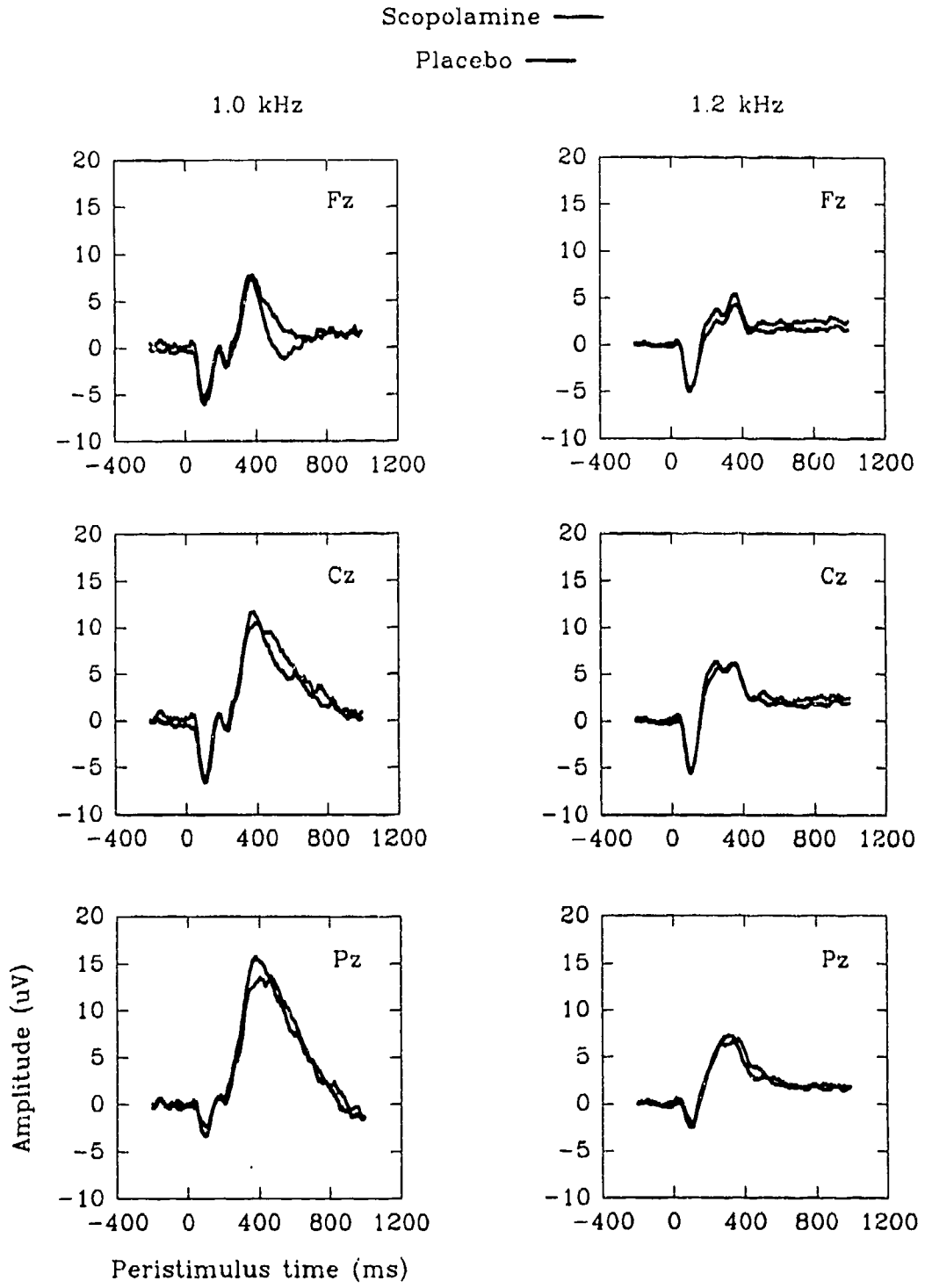

Figure 2. *Responses to stimuli delivered to the attended (right) ear. Panels on the left contain responses to 1.0-kHz targets. Panels on the right contain responses to 1.2-kHz nontargets.*

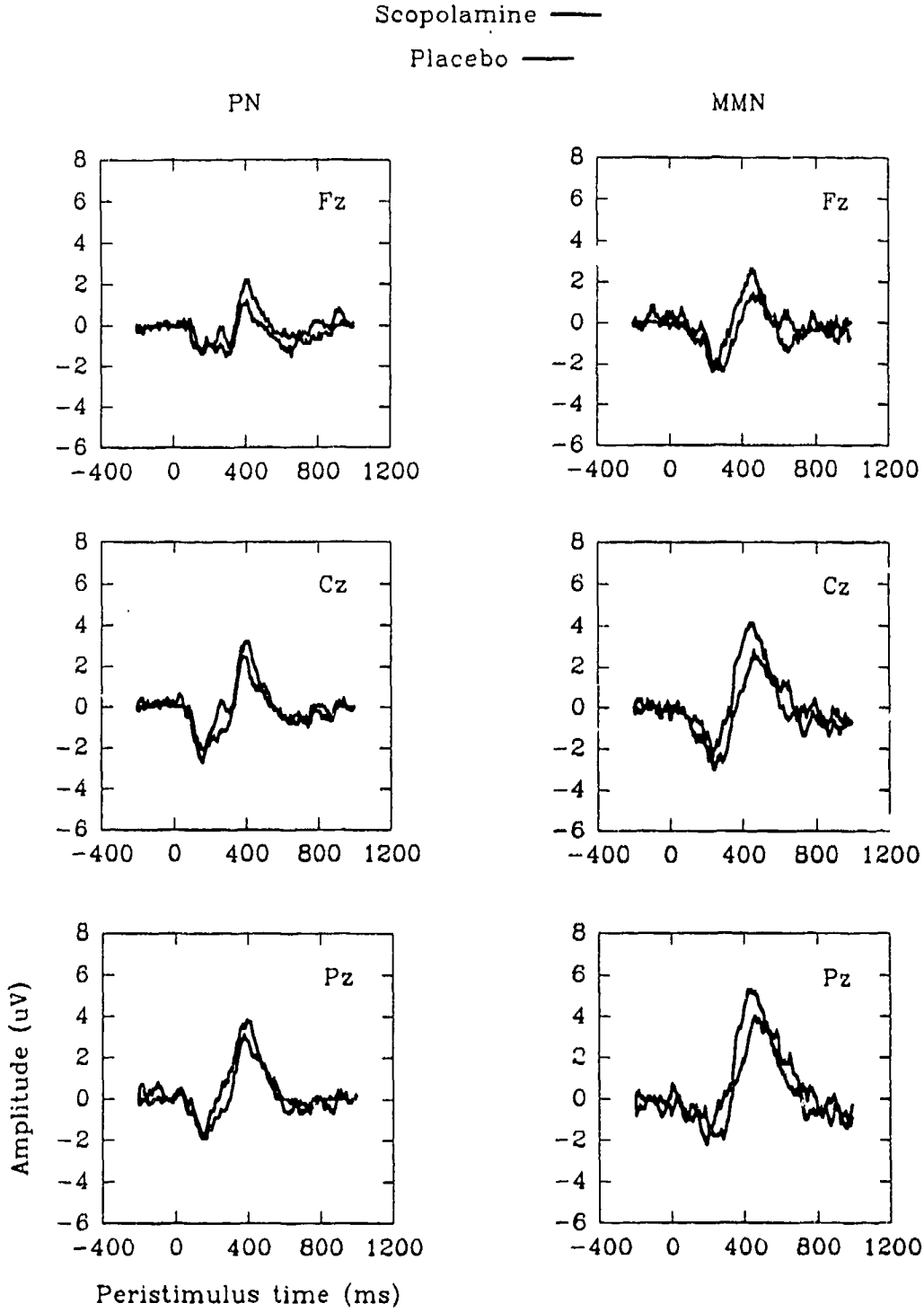

Figure 3. *Processing negativities (PNs) and mismatch negativities (MMNs) elicited by stimuli in the experiment. Panels on the left contain PNs; panels on the right contain MMNs.*

and amplitudes of about -4.0 μV that resemble the MMN waves described by Näätänen, Gaillard and Mäntysalo (1978).

The peak latency of the mismatch negativity was increased in the scopolamine condition, relative to placebo, by an average of 61.7 ms. There was no effect of scopolamine on the peak amplitude of the MMN, which averaged 4.0 μV in the drug condition and 4.1 μV in the placebo condition. This result, an increase in MMN latency with no increase in MMN amplitude, seems to be a typical consequence of factors that render stimuli physically less discriminable (Näätänen et al., 1987; Sams et al., 1985). A MANOVA performed on variates comprising MMN peak amplitudes and latencies at the three recording sites yielded a significant effect of scopolamine on MMN latencies, $F(1,9) = 8.39$, $p < .02$. The effect of scopolamine on MMN amplitudes was not significant.

CONCLUSIONS AND RECOMMENDATIONS

The effects of transdermally administered scopolamine observed in this study were small. A higher dose of scopolamine might have yielded larger effects; however, the study was motivated primarily by interest in the side effects of the transdermal scopolamine patches. The results were, in fact, qualitatively consistent with previous reports of scopolamine-related attention deficits (which were discussed in the Introduction). Interestingly, however, the results seem to be as well explained by the hypothesis that scopolamine affected auditory-perceptual processing as by the hypothesis that scopolamine affected attentional mechanisms. The main observations of the experiment can be summarized as follows:

(1) The increase in false-alarm rates that occurred without a compensating increase in hit rates suggests that scopolamine administration was associated with a reduction in subjects' abilities to discriminate the stimuli.

(2) Assuming that the amplitudes of late-PN segments increase as discriminations become more difficult (Hansen & Hillyard, 1983, 1984; Näätänen, 1982), the evidence for an increase in late-PN amplitudes in the scopolamine condition is consistent with the behavioral data, which suggest that scopolamine reduced stimulus discriminability.

(3) Assuming that reductions in stimulus discriminability delay the MMN (Näätänen, et al., 1987), the increased MMN latencies observed in scopolamine condition are also consistent with the idea that scopolamine reduced stimulus discriminability.

(4) Given the correctness of assuming that the amplitudes of early PN segments reflect attentional selection (Hansen & Hillyard, 1983, 1984; Näätänen, 1982), the absence of a scopolamine-related change in the early PN segment is consistent with the hypothesis that the scopolamine treatment might have reduced discriminability *without* affecting selective attention processes.

(5) Assuming that the MMN reflects the operation of an orienting-like mechanism (Näätänen, 1985), the results are consistent with the idea that orienting to stimuli in unattended information channels might be impaired under scopolamine. The evidence that stimuli were less discriminable under scopolamine, however, suggests that this effect could be an indirect consequence of a reduction in discriminability, rather than a direct effect of scopolamine on a mechanism subserving orienting.

Our results clearly support the idea that transdermal scopolamine should be prescribed cautiously for individuals who will engage in activities in which failures of attention might lead to significant operator errors.

Scopolamine combined with dextroamphetamine has been reported to not significantly affect performance on a set of laboratory tests when administered in low doses (Schmedtje, Oman, Letz & Baker 1988). These investigators have concluded that this combination of drugs may be a safe prophylactic therapy for motion sickness in space settings. However, the possibility that anticholinergic drug effects may vary substantially with environmental conditions, task type, and level of training (Fibiger, 1991), suggests that the generality of this conclusion might warrant investigation.

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R.R. Stanny and R.N. Shull

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
NAVAEROMEDRSCHLAB
51 HOVEY ROAD
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13. ABSTRACT *(Maximum 200 words)*

Patch-administered, transdermal scopolamine is sometimes used to reduce the symptoms of motion sickness in aviators. The drug's side effects on attention and memory, however, have led to concern that the drug might compromise the abilities of those it was meant to help. The study described here examined the effects of transdermal scopolamine on performance and event-related potentials (ERPs) in an auditory-monitoring task. The scopolamine treatment yielded a small reduction in the discriminability of acoustic targets. Reaction times did not change significantly. Effects of the treatment were noticeable in concurrently recorded ERPs within 300 ms of the onsets of acoustic stimuli. The data were consistent with previous studies indicating that scopolamine affects attentional processes. The present results suggest that scopolamine's effects may be expressed quite early in the course of perceptual processing. Although the effects observed here were small, the drug nonetheless should be prescribed with caution, particularly in high-workload situations in which minor failures of attention could substantially increase probabilities of operator error.

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