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Effects of stimulus sequence on event-related potentials and reaction time during target detection in Alzheimer's disease

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Abstract

Objectives: To examine evoked potentials and behavior as a function of stimulus sequence in an auditory target detection paradigm in Alzheimer's disease (AD).

Methods: Evoked potentials and reaction times were collected from 12 healthy elderly controls and 10 patients with mild AD. Subjects pressed a response button to high-pitched target tones ($P = 0.20$) that were randomly intermixed with low-pitched frequent tones. We measured pre-stimulus readiness potential (RP), event-related potentials (P50, N100, P200, N200 and P300), and reaction time as a function of the stimulus sequence.

Results: AD subjects performed at comparable levels of accuracy as controls, but had significantly increased reaction times. Grand averaged potentials in AD showed a significant reduction of the amplitude of the RP, and an increase of P300 latency. Both controls and AD showed speeding of reaction time, increases in RP amplitude, and decreases in P300 latency as a function of the number of frequent tones preceding the target. Sequential changes of other components (P200 and N200) were found in controls but not AD.

Conclusions: AD patients have systematic changes of both RT and certain of the evoked potential components as a function of stimulus sequence. Moment-by-moment changes in target expectancy are largely preserved in AD, even though overall performance and evoked potential measures of expectancy (RP) and stimulus classification (P300 latency) are abnormal. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Oddball; Evoked potentials; Dementia; Expectancy

1. Introduction

In auditory target detection subjects are required to identify infrequent target stimuli embedded within a sequence of standard tones by either counting the number of targets or pressing a button when a target is presented (Sutton et al., 1965). Target tones typically differ from the frequent tones along a physical dimension, such as tone frequency or intensity. Frequent tones and targets elicit 3 event-related potential waves, the P50, N100, and P200. In addition, targets also elicit an N200/P300 complex and a late slow wave (see Donchin and Coles, 1988 for a review). An early slow wave, termed the readiness potential (RP), also develops before the presentation of both targets and frequent tones (Deecke et al., 1969; Starr et al., 1995).

Previous reports using auditory target detection have

shown that the properties of several components of the evoked potential change in healthy normals as a function of age (Goodin et al., 1978a; Pfefferbaum et al., 1980; Picton et al., 1984; Iragui et al., 1993; Anderer et al., 1996). N100 amplitude and latency are typically unaffected by aging (Picton et al., 1984; Iragui et al., 1993). P200 amplitude and latency usually increase with age, while the N200 increases in latency and decreases in amplitude (Iragui et al., 1993; Anderer et al., 1996). P300 latency consistently increases by ~1–2 ms/year (Goodin et al., 1978a; Picton et al., 1984; Iragui et al., 1993; Anderer et al., 1996) and amplitudes typically decrease with age (Picton et al., 1984; Iragui et al., 1993; Anderer et al., 1996). The effects of aging and dementia on the RP have not yet been described.

Dementia, including Alzheimer's disease (AD), is accompanied by abnormal evoked potentials in target detection (Goodin et al., 1978b). AD patients typically have longer P300 latencies (~2 SD) and smaller P300 amplitudes relative to healthy age-matched controls (e.g. Goodin et al., 1978b; Polich et al., 1990).

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Most evoked potential studies of target detection have constructed grand averages of frequent and target tones drawn from the entire tone sequence. However, Squires et al. (1976) reported that P300 amplitude to targets varies depending on the specific sequence of recently presented stimuli (see Gonsalvez et al., 1999 for a review). Similarly, N100 amplitudes to frequent tones change across the stimulus sequence, with larger amplitudes associated with longer trains of frequent stimuli (Hermanutz et al., 1981; Hirata and Lehmann, 1990). Starr et al. (1997) described changes of evoked potentials across a series of frequent and target tones in young healthy subjects. After a target, RP and N100 amplitudes to the subsequent frequent tone were reduced compared to frequents occurring just before the target, and these components then increased linearly with repeated presentation of frequents. The P50 exhibited the opposite pattern of changes, with a maximum amplitude following a target and linear decreases in amplitude to later frequents. Reaction time (RT) to targets decreased with increases in the number of frequent tones occurring in a row before the target. Thus, in the target detection paradigm both auditory evoked potentials and the ensuing behavioral response exhibit systematic changes depending on the pattern of recently presented stimuli. These changes that accompany stimulus sequence may be related to implicit expectancies concerning the likelihood that a target will be presented.

The main objectives of this exploratory study were to define the parameters of the RP in AD and aging, and to determine whether evoked potentials and behavioral measures change as a function of stimulus sequence in AD.

2. Methods

2.1. Subjects

Two groups of subjects were tested. The first group was composed of 12 healthy elderly subjects recruited from a control population at the UC Irvine Alzheimer's Disease Research Center. Ten out of 12 subjects in the elderly control group were right-handed, and there were 8 females and 4 males. With one exception the subjects were not currently taking any psychotropic medications. One control subject was taking amitriptyline for the treatment of peripheral neuropathy. Two of the subjects wore hearing aids, and all were able to clearly distinguish the frequent and target stimuli.

The Alzheimer's disease (AD) group was composed of 10 patients (6 females, 4 males) diagnosed with possible or probable AD according to current NINCDS-ADRDA criteria (McKhann et al., 1984). Eight of the subjects were taking donepezil at the time of testing. One AD subject was prescribed a hearing aid, but did not require it for the experiment. The AD subjects were recruited from the UC Irvine Alzheimer's Disease Research Center. All subjects signed informed consent forms, and the experiments were

performed in accordance with a protocol approved by the UC Irvine Institutional Review Board. All AD subjects and controls were administered the mini-mental status exam (Folstein et al., 1975) to screen for cognitive impairment on the day of the experiment, or within 9 months of testing.

The mean ages of the control and AD groups were 66.3 ± 1.6 and 72.0 ± 3.1 years, respectively, and were not significantly different. The education level was also not significantly different between groups (16.7 ± 0.7 and 15.5 ± 0.8 years for control and AD groups, respectively). Mini-mental status scores were significantly different between groups ($t(20) = 6.1$, $P < 0.0001$), with the control and AD subjects scoring a mean of 29.1 ± 0.3 and 23.0 ± 0.9 points, respectively.

2.2. Target detection task

The target detection task was a two-tone discrimination, or 'oddball', paradigm containing a sequence of 300 tones with a constant ISI of 2.5 s. Tones were presented from two speakers placed ~ 0.75 m in front of the subject at ~ 70 db peak SPL, as measured from where the subject sat. The stimuli were 100 ms in duration, with 10 ms rise and fall time. Each sequence contained 300 tone stimuli, and was 12.5 min in duration. Frequent stimuli were 1000 Hz pure tones delivered with a probability of 0.80 (240 tones/sequence). Target tones were 2000 Hz pure tones presented with a probability of 0.20 (60 tones/sequence). Subjects were instructed to quickly press a response button with the thumb of their dominant hand in response to the target tones. Two AD subjects needed to be reminded at the beginning of the test session to push the button *only* to the target tones.

The sequence of tones was randomly determined with the following constraints: (1) each target tone was followed by at least one, but no more than 9, frequent tones; (2) in only two instances was a target followed by one frequent, and in one instance followed by 9 frequents. Frequent tones were classified and sorted according to their serial position after the last target ($T + n$) (see Fig. 1). Thus, the frequents presented immediately after a target were labeled ' $T + 1$ ', the second frequent after the target was ' $T + 2$ ', and so on

Fig. 1. Example of stimuli in the target detection sequence. Frequent tones (1000 Hz) are labeled 'Lo'. $T + n$ indicates the sequential position of frequent tones *after* the last target was presented. Target tones (2000 Hz) are labeled 'Hi', and n_T indicates the number of frequent tones in a row after the previous target. The interstimulus interval was a constant 2.5 s, and the frequent and target probabilities were 0.80 and 0.20, respectively.

up to 'T + 9'. Target tones were classified and sorted according to the number of preceding frequent tones since the last target (n_T). Thus, target tones preceded by one frequent tone were denoted '1_T', two frequent tones before the target was '2_T', and so on up to '9_T'.

2.3. Electrophysiological recordings

During the recording session subjects were seated inside a sound attenuating, electrically shielded chamber. Seven Ag/AgCl recording electrodes at sites Fz, Cz, Pz, C3, C4, T3 and T4 were placed on the scalp according to the 10–20 system (Jasper, 1958). In addition, two electrodes were placed above and below the left eye to monitor eye movements, and an electrode placed on the forehead served as ground. Electrodes on the left and right mastoid served as references in a linked mastoid configuration. For all recordings electrode impedances were $\leq 5 \text{ k}\Omega$ and they were checked occasionally during the recording session. The EEG and EOG were digitally amplified with a bandpass of DC–100 Hz and a digitization rate of 500 Hz. EEG, EOG, and stimulus trigger pulses were collected continuously. All data were further processed and analyzed off-line. An eyeblink correction algorithm was used to correct for artifacts (Gratton et al., 1983). Individual sweeps were sorted and averaged according to stimulus type. Sweeps were automatically rejected if activity on a scalp site exceeded $100 \mu\text{V}$. The sweeps were then visually inspected for artifacts before being accepted in the evoked potential average. Sweeps were rejected if the subject failed to press the button to target tones or incorrectly pressed the button in response to frequent tones.

Fig. 2. Reaction times in the control and AD groups. Dots indicate the mean RT of a subject within a given group. Horizontal lines indicate the mean for each column. The broken line indicates the RT (523 ms) that is 2.5 SD from the control mean.

2.4. Data analysis

Latencies of behavioral responses were calculated relative to stimulus onset. Accuracy was measured as the percentage of correct responses to target tones (out of 60), and the number of button presses (false alarms) in response to frequent tones. Reaction times were also sorted according to the number of preceding frequent tones, as in the target evoked potentials (1&2_T, 3&4_T and $\geq 5_T$). Reaction times less than 100 ms or $> 3 \text{ SD}$ from a given subject's mean RT were rejected from the analysis.

The EEG was digitally filtered using FFT and inverse FFT procedures, and filter settings were adjusted depending on the component of interest. The pre-stimulus slow potential, RP, was low pass filtered (DC–3 Hz, 12 db/octave). For P50, N100, P200, N200 and P300 components the EEG was bandpass filtered at 1–16 Hz, 12 db/octave to attenuate slow shifts. The high pass filter effectively attenuated the RP from the post-stimulus components (P50, N100, P200, N200 and P300).

RP amplitude was quantified using a window measure-

Fig. 3. Grand average of control and AD potential tracings to frequent (A) and target (B) tones (DC–100 Hz). The data are from -1 to $+1$ s relative to stimulus onset, which is indicated by the middle vertical line. In both averages the RP, P50, N100 and P200 are present. In response to target tones the N200, P300 and SW are also evident.

ment of the mean potential between -600 and 0 ms relative to stimulus presentation. The baseline period for RP amplitude measures was -1000 to -900 ms.

The amplitudes of all stimulus evoked potentials were defined relative to a 200 ms pre-stimulus baseline period. For frequent and target tones the P50, N100, P200 and RP were measured. In addition, for target tones the N200 and P300 potentials were also measured. Amplitude and latency of the P50 were defined as the point of maximum positivity between 40 and 80 ms post-stimulus. N100 amplitude and latency was defined as the maximum negativity between 80 and 160 ms, while P200 amplitude and latency was the maximum positivity between 150 and 250 ms. The N200 was defined as the maximum negativity between 175 and 250 ms that immediately preceded the large P300 wave. P300 amplitudes and latencies were defined as the maximum positivity between 250 and 600 ms. In subjects with distinct P3a and P3b waves, P300 measures were taken from P3b. Peak latencies of components were calculated relative to stimulus onset.

Previous results indicate that the P200 elicited by frequent tones increases in duration as the number of frequent occurring in a row increases. The prolonged P200 can extend into the latency range of the P300 (Starr et al., 1997). The duration of P200 was defined as the latency at the minimum point on the descending curve of the P200. This point corresponded to either a return to baseline or the point where the evoked potential waveform became level after the P200. Identical results were found by defining P200 duration relative to N100 latency (latency of minimum point after P200 minus N100 latency) or P200 latency (data not shown).

For analysis of sequential evoked potential changes frequent stimuli were grouped into 5 averages: $T + 1$ ($n = 60$), $T + 2$ ($n = 58$), $T + 3$ ($n = 43$), $T + 4$ ($n = 30$) and $T + 5-9$ ($n = 48$). The $T + 5-9$ group consisted of $T + 5$ through $T + 9$, which were combined in order to have enough sweeps for a reliable average. For the same reason average evoked potential waveforms to targets were combined into 3 groups: $1&2_T$ ($n = 17$), $3&4_T$ ($n = 22$) and $5-9_T$ ($n = 21$).

2.5. Statistical analysis

Evoked potentials and behavioral data were analyzed using repeated measures analysis of variance (ANOVA). The Greenhouse–Geisser correction was applied to control type I error. When the Greenhouse–Geisser was utilized the adjusted P values were reported. Two-tailed differences of $P < 0.05$ were considered significant. Significance for post-hoc testing was set at $P < 0.05$. Post-hoc testing employed Tukey tests or trend analysis when appropriate.

Behavioral analysis included the factors Group and Sequence position (n_T). Factors used to evaluate the amplitude and latency of components included Group (elderly controls and AD), Stimulus type (frequent and

target), Sequence position ($T + n$ for frequent and n_T for targets), and electrode Site (Fz, Cz, Pz, C3, C4, T3 and T4).

3. Results

3.1. Grand averages

3.1.1. Performance

All subjects responded to target tones with an accuracy of $>90\%$. There were no significant differences in accuracy between groups, with all group means $>97\%$ correct. The mean percentage of false alarms to frequent tones (1.1 and 1.6% for control and AD groups, respectively) was also not significantly different between groups.

Mean RTs were significantly slower in AD compared to healthy controls ($F(1, 20) = 8.4$, $P < 0.01$) (Fig. 2). Reaction times in $5/10$ AD subjects were >2.5 SD above the mean RT of controls.

3.1.2. Grand averages of evoked potentials to frequent and target stimuli

The grand averages from the Cz electrode to frequent and target tones for AD and controls are shown in Fig. 3. The potentials consist of a slow pre-stimulus RP followed by the P50, N100 and P200 components after stimulus presenta-

Table 1
Mean grand average components from Cz

Component	Amplitude (μV)		Latency (ms)	
	Frequents	Targets	Frequents	Targets
RP ^a				
Control	-2.0	-3.1	N/A ^f	N/A
AD	0.1	0.0	N/A	N/A
P50 ^b				
Control	2.7	2.2	48.9	51.6
AD	4.4	4.2	51.0	50.1
N100				
Control	-8.5	-8.1	110.1	111.1
AD	-8.8	-7.9	109.2	107.4
P200 ^c				
Control	4.8	4.2	197.6	179.6
AD	4.4	5.9	197.7	184.8
P200 duration (ms) ^d				
Control	N/A	N/A	325.2	N/A
AD	N/A	N/A	268.4	N/A
N200				
Control	–	-2.7	–	229.8
AD	–	-1.7	–	257.2
P300 ^e				
Control	–	6.4	–	333.9
AD	–	3.7	–	383.4

^a Amplitude – group effect: $P < 0.01$.

^b Amplitude – group effect: $P < 0.05$.

^c Latency – stimulus effect: $P < 0.05$.

^d Latency – group effect: $P < 0.05$.

^e Latency – group effect: $P < 0.01$.

^f Not applicable.

tion. In response to targets an N200, P300 and late slow wave (SW) were also elicited. Comparison of the grand averaged potentials in AD and controls in Fig. 3 shows several differences in the components (e.g. RP, P50, P200 and P300).

In the following analysis we examined amplitude and latency differences as a function of group (controls versus AD) and stimulus type (frequent versus target). The mean amplitude and latency data are shown in Table 1. Grand average tracings are presented in Fig. 4.

3.1.2.1. Group differences (AD/controls). The amplitudes of two of the components differed significantly between AD and controls. The RP was larger in controls than AD, whereas P50 had the reverse relation being larger in AD than in controls. The RP was absent in the grand average

in AD (0.0 μV) compared to the mean value of $-1.6 \mu\text{V}$ in controls (Fig. 4A,B) ($F(1,20) = 11.1$, $P < 0.01$). The P50 was significantly larger in AD (4.3 μV) as compared to controls (2.4 μV) ($F(1,20) = 5.0$, $P < 0.04$). Although P300 amplitude in AD (3.6 μV) was reduced to nearly 50% of the mean value found in controls, this difference failed to attain significance.

Controls had a significantly longer P200 duration than AD ($F(1,20) = 5.9$, $P < 0.03$). The mean P300 latency was significantly slower in AD (379.2 ms) compared to controls (336.3 ms) ($F(1,20) = 8.0$, $P < 0.01$). There were no other significant latency differences between AD and controls.

3.1.2.2. Stimulus type (target/frequent). Three components were elicited in the grand averages to both frequent and

Fig. 4. Filtered grand average tracings divided according to group and stimulus type. Stimulus onset is shown by the vertical line through each tracing. (A,B) RPs preceding frequent tones in controls and AD. Potentials were low pass filtered (DC–3 Hz). (C,D) Evoked potentials to frequent tones in controls (C) and AD (D). Potentials were bandpass filtered (1–16 Hz) to attenuate slow shifts. (E,F) Evoked potentials to target tones in controls (E) and AD (F). As in (C,D) tracings were bandpass filtered (1–16 Hz).

targets: the P50, N100 and P200. N100 amplitude was marginally larger to frequent ($-8.6 \mu\text{V}$) than to targets ($-8.0 \mu\text{V}$) ($F(1, 20) = 4.4$, $P = 0.05$). P200 latency was significantly reduced by 15.7 ms for frequent tones ($F(1, 20) = 7.9$, $P < 0.01$).

3.1.2.3. Interactions. There were no significant interactions between group and stimulus type.

3.1.2.4. Topography. There were no significant interactions

between the control and AD groups in topography across either the 3 midline electrodes or between hemispheres on the 4 lateral sites for any measure. The topographic patterns observed here were similar to previously published data.

3.2. Sequence position averages

3.2.1. Performance

Reaction time as a function of the target's sequence position is shown in Fig. 5A. A repeated measures ANOVA showed a significant difference in RT across sequence position (positions 1&2_T, 3&4_T and 5–9_T) ($F(2, 40) = 8.6$, $P < 0.001$). The group $\times$ sequence position interaction was also significant ($F(2, 40) = 4.0$, $P < 0.03$). Post-hoc testing in the control group showed significant pairwise differences in RT between position 1&2_T versus positions 3&4_T and 5–9_T. Position 3&4_T was not significantly different from 5–9_T. In AD a different pattern was observed. The mean RTs between positions 1&2_T and 3&4_T were not significantly different from each other. However, RTs at position 5–9_T were significantly less than 1&2_T and 3&4_T. Fig. 5B illustrates these findings by expressing RT as a percentage of position 1&2 for each position. In both groups RT decreased by $\sim 10\%$. The elderly controls exhibited shorter RTs after ~ 3 frequent in a row, while in the AD group RT decreases were delayed until at least 5 tones had occurred in succession.

Table 2

Potentials to target tones versus sequence position

	Sequence position		
	1&2_T	3&4_T	5–9_T
Amplitude (μV)			
RP^a			
Control ^b	–1.6	–3.3	–3.6
AD ^b	0.9	–0.3	–0.5
Latency (ms)			
P50			
Control	50.4	52.4	53.8
AD	49.4	53.2	49.7
N100			
Control	111.0	110.3	113.2
AD	106.6	109.8	105.8
P200^c			
Control ^d	185.7	174.2	174.8
AD	182.6	187.9	185.4
N200^a			
Control ^d	253.2	235.2	230.5
AD	257.3	249.1	251.8
P300^c			
Control ^b	367.5	346.4	341.9
AD ^b	390.3	375.1	360.9

^a Significant main effect of sequence position.

^b Significant linear trend.

^c Significant group $\times$ sequence position interaction.

^d 1&2_T > 3&4_T = 5–9_T.

Fig. 5. (A) RT as a function of sequence position. The 3 averages consist of RTs to targets with one or two preceding frequent (1&2_T), 3 or 4 preceding frequent (3&4_T), or 5 through 9 frequent (5–9_T). (B) In order to illustrate the sequence effects for each group independent of the overall RT differences, the RTs were normalized to 1&2_T for each group. RT savings are evident in controls starting at 3&4_T, while RTs in AD do not decrease until 5–9_T.

3.2.2. Averaged potentials to target tones

We examined pre- and post-stimulus brain potentials for targets as a function of sequence position (n_T) (see Table 2). RP amplitude was significantly different across sequence position in both controls and AD ($F(2, 38) = 4.7$, $P < 0.02$). RP amplitudes increased with the number of frequents before the target (Fig. 6A). In contrast, the P50, N100, P200, N200 and P300 components in controls and AD did not exhibit significant changes in amplitude across sequence position.

Latencies of the P50 and N100 components were not

significantly different across sequence position. Latency changes as a function of sequence position were evident for the P200, N200 and P300 waves (see Fig. 6B–D). A significant group $\times$ sequence position interaction was found for P200 latency ($F(2, 40) = 4.2$, $P < 0.03$) (Fig. 6B). Post-hoc testing showed that 3&4_T and 5–9_T values in the control group were significantly faster than 1&2_T. In the AD group no significant differences were found between positions.

N200 latency exhibited a main effect for sequence position ($F(2, 40) = 8.4$, $P < 0.001$) (see Fig. 6C). Although

Fig. 6. Components in the control and AD groups to target stimuli as a function of sequence position. In order to have enough sweeps for reliable averages the data were compiled into 3 subaverages: 1&2_T, 3&4_T, and 5–9_T. (A) RP amplitudes preceding targets across sequence positions. In both groups RP amplitude increased significantly with sequence position. The dotted line indicates 0 μV . (B) P200 latency across sequence position. The graph illustrates the significant interaction between controls and AD, with P200 latencies decreasing over sequence position in controls, but not in the AD group. (C) N200 latency across sequence position. The group $\times$ sequence position interaction did not attain significance, although the control group exhibited more marked latency reductions across sequence position. Latencies in the AD group were not significantly different across sequence positions. (D) P300 latency across sequence position. In both groups P300 latency showed a significant linear trend across sequence position.

sequential latency reductions were more pronounced in controls, the group $\times$ sequence interaction did not attain significance ($P = 0.09$). However, differences in latency reductions between groups were pronounced (e.g. 22.7 ms in controls versus 5.5 ms in AD for 5–9_T) and therefore additional testing was performed. In controls there were significant differences in N200 latency across sequence positions ($F(2, 11) = 10.7$, $P < 0.001$). Post-hoc testing showed that latencies for 3&4_T and 5–9_T were significantly less than 1&2_T. No significant differences were found across sequence position in the AD group.

P300 latency was significantly different across sequence position ($F(2, 40) = 6.9$, $P < 0.01$), without an interaction with group (see Fig. 6D). Post-hoc testing indicated significant P300 latency differences between 1&2_T and 5–9_T for controls and AD.

3.2.3. Averaged potentials to frequent tones

The amplitudes of the components as a function of sequence position are presented in Table 3. Group average RP tracings for the T + 1, T + 3 and T + 5–9 positions are illustrated in Fig. 7A,B. Note that in AD the RP was positive to T + 1, only becoming negative after several frequent tones in sequence were presented. Fig. 8A depicts RP amplitudes as a function of sequence position for both groups. RP amplitude was significantly different across sequence position ($F(4, 80) = 4.9$, $P < 0.01$), with increasing negativity for greater numbers of frequent tones in a row. The group $\times$ sequence position interaction was not significant. Trend analysis showed a significant linear trend for increasing negativity across position in controls ($P < 0.02$) and in the AD group ($P < 0.03$). Both groups had the same slope ($-0.5 \mu\text{V}/\text{sequence position}$), but the Y intercepts were markedly different between groups (-0.5 versus 1.5 for controls and AD, respectively). In the AD group single sample t tests showed that T + 1 and T + 2 were not significantly different from 0, indicating that although their valences are positive (1.2 and $0.7 \mu\text{V}$, respectively), these results cannot be considered to be an abnormal positive pre-stimulus shift.

The group average evoked potentials are shown in Fig. 7C,D. P50 amplitude did not significantly change as a function of sequence position. N100 amplitude was also not significantly different across position. There was a group $\times$ sequence interaction for N100 amplitude ($F(4, 80) = 2.9$, $P < 0.03$). Separate analysis of the control and AD groups showed that the controls failed to demonstrate a significant difference across position. N100 amplitudes were significantly different across sequence position in the AD group ($F(4, 36) = 3.5$, $P < 0.02$), although post-hoc testing showed no significant differences between any of the means. P200 amplitudes did not significantly change as a function of sequence position.

P50, N100 and P200 latencies did not significantly change across stimulus positions, and there were no significant group $\times$ sequence interactions. P200 duration was

significantly different across stimulus positions ($F(4, 80) = 5.7$, $P < 0.001$) (see Fig. 8C). Trend analysis showed a significant linear increase in duration across sequence position in controls ($P < 0.05$), but not in the AD group.

3.2.4. Averaged potentials to frequent tones immediately before ($T - 1$) and after ($T + 1$) targets

Because sequential changes were not seen in the P50, N100 and P200 in either group we wanted to cross-validate this finding using a different measure. Consequently, we divided all of the individual sweeps to frequent tones into two subaverages, one before target presentation ($T - 1$) and one immediately after target presentation ($T + 1$). This technique has the advantage of an enhanced S/N ratio (up to 60 sweeps/average), as compared to the subgroup averages presented in the sequential analysis.

P50, N100 and P200 amplitudes were not significantly different between $T - 1$ and $T + 1$ for either group. A previous study using young subjects has shown that P50, N100 and P200 amplitudes are significantly different between $T - 1$ and $T + 1$ (Starr et al., 1997).

4. Discussion

4.1. Grand averaged behavior and brain potentials

The RT results in our study are consistent with previous findings of slowed RTs in AD on a variety of tasks (Ferris et al., 1976; Pirozzolo and Hansch, 1981; Goldman et al., 1999). Our findings are also compatible with reports show-

Table 3
Potentials to frequent tones as a function of sequence position

	Sequence position				
	T + 1	T + 2	T + 3	T + 4	T + 5–9
<i>Amplitude (μV)</i>					
RP ^a					
Controls ^b	-0.8	-1.5	-2.4	-2.1	-3.0
AD ^c	1.2	0.7	-0.7	-1.4	-0.2
P50					
Control	3.2	2.7	2.6	3.1	2.6
AD	4.3	4.5	4.5	4.9	4.4
N100					
Control	-8.4	-8.3	-8.9	-9.2	-8.6
AD	-8.8	-9.0	-7.9	-9.0	-9.3
P200					
Control	4.9	4.8	5.3	5.3	5.1
AD	4.5	4.3	4.6	4.6	5.1
<i>P200 duration (ms)^a</i>					
Control ^b	313.2	327.3	350.2	361.9	393.5
AD	275.2	281.9	278.5	285.9	300.4

^a Significant main effect of sequence position.

^b Significant linear trend.

^c Significant linear trend for T + 1 through T + 4.

Fig. 7. Grand average tracings in the control and AD groups for frequent tones (T + 1, T + 3 and T + 5–9 sequence positions). (A,B) RPs in controls (A) and AD (B). In both groups there was a significant increase in RP amplitude across sequence position. This was most apparent in controls who exhibited linear increases with sequence position. The AD group also exhibited linear increases in RP amplitude from T + 1 to T + 4 (see Fig. 8), but had a reduced value for T + 5–9. (C,D) P200 duration in controls (C) and AD (D). In controls P200 duration increased substantially with sequence position, which suggested the development of positive potentials in the P300 latency range. The 3 dots labeled P200 duration indicate the approximate durations (read from left to right) for T + 1, T + 3 and T + 5–9, respectively. For the AD group there were no significant changes in P200 duration across sequence position. In comparison with controls there were fewer indications of the development of a positive waveform in the P300 latency range.

ing increased P300 latency and reduced amplitude in AD (Goodin et al., 1978b; Pfefferbaum et al., 1984; Polich et al., 1990). Although group differences between controls and AD for P300 amplitude did not attain significance, the effect was in the expected direction (i.e. P300 amplitudes were smaller in the AD group). Eight out of 10 AD subjects were taking donepezil at the time of testing, a compound that has been shown to slightly reduce auditory P300 latency (~9 ms) but not affect ERP amplitudes (Reeves et al., 1999). Thus, the absence of a significant P300 amplitude difference in AD was probably not due to the use of donepezil.

We have shown in this study that a negative slow potential shift that develops before stimulus presentation, the RP,

is reduced in AD. The RP is related to motor responding because the amplitude of the RP is nearly absent when subjects are instructed to keep a mental count of the target tones (Starr et al., 1995). The RP may reflect cognitive factors related to the expectancy to make a motor response, such as motor programming (Goodin et al., 1993; Starr et al., 1995). The reduced RP amplitudes seen in AD might indicate deficits in brain activity underlying the expectancy for responding, which may contribute to the prolongation of RTs in AD.

Studies of AD subjects using a paired click paradigm have shown that the P50 is attenuated or absent in many AD patients (Buchwald et al., 1989; Green et al., 1997), a result that appears to depend on rapid interstimulus intervals

(Fein et al., 1994). Our findings of a robust P50 in AD using slow stimulus rates are also consistent with a previous MEG study of a magnetic component having 50 ms latency in AD (Pekkonen et al., 1994).

4.2. Behavior and brain potentials as a function of stimulus sequence

The current study revealed dynamic changes in both RT

and brain potentials in controls and AD. Changes in RP amplitude, P300 latency to targets, and to a lesser degree RT, were similar across groups. However, controls also had reductions in P200 and N200 latency to targets and increases in P200 duration to frequent tones, none of which were observed in AD.

Previous studies using choice RT paradigms have also documented sequential changes of RT in normals (Remington, 1969; Kornblum, 1973) and Parkinson's disease (Goodin et al., 1999). In the present study, both controls and AD exhibited RT reductions as a function of the number of frequent tones before targets. However, AD subjects required a greater number of frequent tones to precede the target before significant reductions in RT were evident. This suggests that the threshold for motor response expectancy for an uncertain event is elevated in AD.

Sequential changes in P50, N100 and P200 amplitude to frequent tones were absent in both groups. This finding appears to be age-related because these components are affected by sequence position in young subjects (Starr et al., 1997).

P200 duration to frequent tones increased across sequence position in elderly and young controls, but not AD. P200 generation has been localized to auditory association cortex (Scherg and Von Cramon, 1986; Rif et al., 1991; Siedenberg et al., 1996), and the absence of sequential P200 duration changes in AD may reflect the involvement of auditory association cortex in mild AD.

There were additional group differences in component latencies to targets as a function of stimulus sequence. In controls, P200 and N200 latency were reduced with sequence position, as was RT. Unlike controls, the AD group did not demonstrate significant reductions of P200 and N200 latency, even for long sequences of frequent tones that were associated with decreases in RT. As with the P200 duration results, the lack of sequential latency changes in P200 may indicate an impairment of auditory association cortex in AD.

P300 latency in AD did change with sequence position in a linear manner similar to controls. In young normals P300 latencies are strongly correlated with N200 latency (Michalewski et al., 1986). Results from the present study demonstrate that the timing of P300 can be decoupled from the occurrence of N200.

Sequential effects in RT and brain potentials appear to reflect a sensitivity to the structure, or pattern, of recently presented stimuli. The stimulus pattern includes stimulus type (frequent or target), as well as the number of tones and/or the time that has elapsed since the last target was presented. We suggest that sequential changes of brain potentials and reaction time can be considered to reflect implicit short-term memory, similar to perceptual priming (Schacter, 1995). If such a linkage were established, our findings showing sequential changes in AD (i.e. RT, RP and P300 latency) would be consistent with previous reports of intact perceptual priming in mild AD (Gabrielli, 1998).

Fig. 8. RP and P200 duration as a function of sequence position. (A) RP amplitude versus sequence. Both groups exhibited a linear increase in RP amplitude (i.e. greater negativity) with increases in sequence position. (B) P200 duration versus sequence position. Controls exhibited a significant linear increase in P200 duration across sequence position. The AD group failed to demonstrate significant increases across sequence position.

4.3. Brain potentials and aging

The grand average and sequential RP changes observed in elderly controls were comparable to results in young subjects (Starr et al., 1995, 1997). These findings imply that the elderly controls were comparable to young subjects in terms of motor programming, a notion that may be relevant to the absence of age-related RT differences in target detection (Picton et al., 1984; Iragui et al., 1993).

Results from the sequential analysis of evoked potentials to frequent tones in elderly controls differ from previous findings using young subjects (Hermanutz et al., 1981; Hirata and Lehmann, 1990; Starr et al., 1997). In young subjects P50 amplitude decreases across sequence position, N100 increases across sequence position, and the P200 increases for T + 1 (Starr et al., 1997). We showed in elderly controls that the P50, N100 and P200 failed to exhibit sequential changes. It appears that the amplitudes of P50, N100 and P200 in healthy elderly subjects are less sensitive to the specific pattern of recently presented stimuli, as compared with young subjects. The goals of the present experiment concerned changes due to AD rather than healthy aging. Consequently, future study would be required to directly compare the sequential evoked potential changes in young and healthy elderly subjects.

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