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Sensory cortical interactions in aging, mild cognitive impairment, and Alzheimer's disease

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Abstract

Progressive declines in memory function accompany normal aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD). Neuropathological studies suggest that damage to neurons providing connections between cortical areas may contribute to memory impairments in AD. Because AD develops slowly, similar neuropathological changes, to a lesser degree, may be present in MCI and some asymptomatic elderly subjects. In this study we tested the hypothesis that corticocortical interactions between sensory regions are impaired in aging, MCI, and AD, as compared with young subjects. When sensory cortical evoked potentials are elicited by pairs of stimuli the amplitudes of potentials to the second stimulus are attenuated. Corticocortical interactions were assessed by presenting stimulus pairs in different modalities (auditory/visual). There were significant group differences in the degree that a visual stimulus attenuated subsequent auditory potentials (young > healthy elderly > MCI > AD). Control experiments indicated equivalent amplitude reductions for all groups to the second stimulus for stimulus pairs having the same modality. These findings are compatible with progressive declines in corticocortical processing in aging, MCI, and AD. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Evoked potentials; Episodic memory; P50; N100; Habituation; Corticocortical

1. Introduction

The ability to retain information for short timeperiods in working memory, or longer timeperiods using episodic memory, involves numerous cortical regions [7,25]. Relative to young subjects, declines in working memory and episodic memory are observed in healthy aging [10], while profound impairments in working memory and episodic memory are found in Alzheimer's disease (AD) [21]. In addition to memory impairments, AD is also characterized by deficits in other cognitive domains including language, attention, and reasoning. Mild cognitive impairment (MCI) is a clinical diagnosis that characterizes elderly individuals with an isolated memory impairment that is more severe than in healthy aging, while other cognitive functions are normal [26,31,33]. Thus, memory changes in the elderly can be classified into three categories starting with mild alter-

ations in healthy aging, greater memory impairment in MCI, and severe memory and other cognitive deficiencies in AD.

The cognitive deficits in AD may be related to a possible disconnection between cortical areas due to pathology affecting neurons that provide long corticocortical connections [13,17,19,22,23]. MCI is considered a risk factor for the development of AD [26], which suggests that less extensive cortical disconnection, relative to AD, may contribute to the memory dysfunction in MCI.

The present experiment was designed to test the hypothesis of cortical disconnection in MCI and AD using physiological measures of auditory and visual cortical activity (evoked potentials) in response to specific sensory inputs (auditory tones and visual flashes). The experimental design capitalized on the anatomic segregation of ascending auditory and visual pathways from the periphery via the thalamus, which initially terminate, respectively, in the temporal and occipital lobes. Interactions between auditory and visual cortical regions were inferred by comparing evoked potentials to pairs of sensory stimuli having the same modality (intramodal pairs) with pairs of stimuli of two different modalities (crossmodal pairs).

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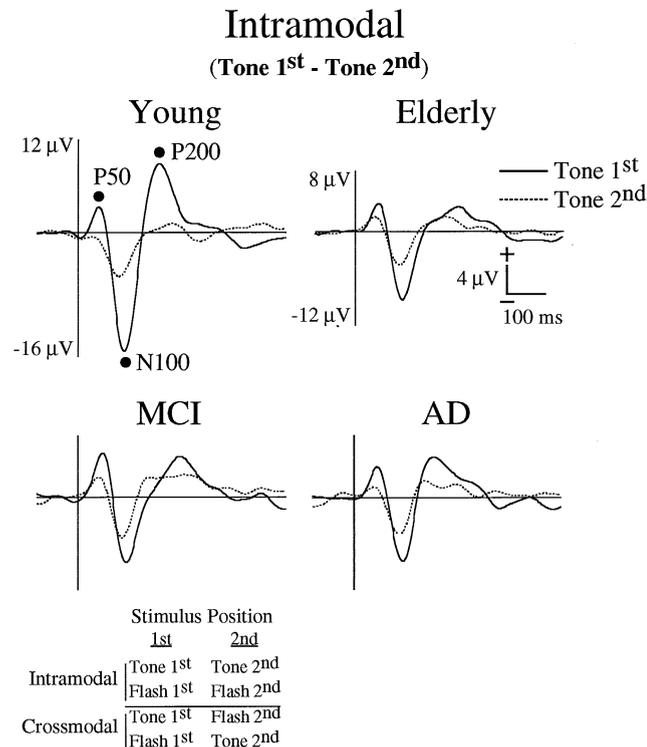


Fig. 1. Grand average intramodal auditory evoked potential tracings for young, elderly, MCI (mild cognitive impairment), and AD (Alzheimer's disease) groups. The first tone stimulus in each pair is indicated by "Tone 1st," while the second tone, presented 0.6 s later, is represented by "Tone 2nd." Vertical lines indicate stimulus onset. Inset depicts the experimental design showing the combinations of stimulus modality (auditory or visual) and stimulus position within a pair (1st or 2nd) that were tested.

The presentation of a stimulus elicits cortical potentials that can be measured in humans using scalp electrodes. These potentials vary in polarity (negative or positive) and approximate peak latency. Auditory stimuli elicit a waveform having three components: a positive peak ~ 50 ms poststimulus (P50), a negative peak at ~ 100 ms (N100), and a positive peak at ~ 200 ms (P200) (see Fig. 1). Visual stimuli elicit a series of low amplitude early components (N70, P100, N140) and a larger positive peak ~ 200 ms after stimulus presentation (vP200) at posterior electrode sites. Previous reports using stimulus pairs ($< \sim 10$ s inter-stimulus interval) show that the amplitudes of the N100 and P200 in response to a tone in the 2nd position of the pair are reduced when the 1st stimulus is either the same tone

(intramodal pair: auditory 1st stimulus - auditory 2nd stimulus) or a visual flash (crossmodal pair: visual 1st stimulus - auditory 2nd stimulus) [11,12]. Studies have also shown reductions in P50 amplitude to a tone in the 2nd position when the 1st stimulus is a tone (e.g. [8]). The amplitude of visual evoked potentials using intramodal pairs of flashes undergo similar effects, while the influence of auditory stimuli on visual evoked potential amplitudes is less well documented [12].

The reduction of a component's amplitude or latency due to previous stimuli is known as a refractory effect [24]. The neural mechanisms responsible for refractory effects in humans are currently unknown. Our hypotheses were that intramodal refractory effects involve synaptic interactions within the auditory pathway and auditory cortex, while crossmodal refractory effects may involve cortical connections between the visual and auditory cortices. Based on these hypotheses we predicted that refractory effects in MCI and AD patients would be impaired in the crossmodal, but not the intramodal, paradigm because AD pathology targets the intervening connections between primary sensory cortices while leaving primary auditory and visual cortex relatively intact until the later stages of the disease [2,5].

2. Methods

2.1. Subjects

There were 4 groups of subjects: young, elderly controls, MCI, and AD (Table 1). Young subjects were recruited from the UC Irvine student population and received course credit in exchange for their participation. Elderly controls, MCI, and AD subjects were recruited through the UC Irvine Alzheimer's Disease Research Center. Elderly subjects (elderly controls, MCI, AD) were given a battery of neuropsychological tests, including the Mini Mental State Examination, Trailmaking tests A and B, CERAD Word List Learning Task, WMS-R Logical Memory, Boston Naming Test, verbal fluency (FAS and Category), and CERAD Constructional Praxis. Not all subjects received the exact same battery of tests. Diagnosis of MCI was similar to the criteria of Petersen et al. [26]. MCI patients reported subjective memory complaints, and had scores > 1.5 SD below the mean age-adjusted normative score on the WMS-R Logical

Table 1
Demographic information

	Young	Elderly	MCI	AD
n	12	12	10	11
Male/Female	1/11	3/9	9/1	5/6
Age	19.8 \pm 1.4	73.8 \pm 5.2	76.9 \pm 2.8	77.4 \pm 7.9
Education (years)	14.0 \pm 0.4	15.8 \pm 2.6	16.1 \pm 3.0	15.1 \pm 2.8
MMSE Score (out of 30)	Not given	28.7 \pm 1.0	27.3 \pm 1.9	20.8 \pm 3.8

Memory test. Scores for individual MCI patients in other neuropsychological test categories, such as language, were generally within normal limits. AD diagnosis was based on the criteria of McKhann et al. [21], and all AD patients were diagnosed as probable AD. DSM III-R criteria were used for diagnosis of dementia. AD patients had scores >2.0 SD below the mean age-adjusted normative score on a memory test and at least one other cognitive domain assessed by neuropsychological testing. All AD subjects were in the mild stage of the disease (Mini Mental State: 19–25 out of 30), except for one subject that was severely impaired (Mini Mental State = 11/30). Four MCI and 9 AD subjects were taking the cholinesterase inhibitor donepezil for their memory complaints. Two additional MCI subjects were participating in a double blind study and may have been receiving donepezil. All subjects signed informed consent forms, and the experiments were performed in accordance with a protocol approved by the UC Irvine institutional review board.

2.2. Design

We employed a factorial design combining the factors of stimulus modality (auditory tone or visual flash) with stimulus position (1st or 2nd stimulus in the pair), resulting in 4 different sequences having every combination of stimulus modality and stimulus position (see Fig. 1 inset). For intramodal sequences (tone 1st – tone 2nd; flash 1st – flash 2nd) evoked potentials to both stimuli within the same sequence were analyzed. For the crossmodal conditions auditory stimuli were analyzed by comparing evoked potentials to the tone in the “tone 1st – flash 2nd” sequence with the tone in the “flash 1st – tone 2nd” sequence. The visual vP200 was analyzed similarly.

Each sequence contained 40 identical pairs of stimuli with a 0.6 s inter-stimulus interval and a 9.4 s inter-pair interval. Order of sequence presentation was counterbalanced across subjects within each group. Auditory stimuli were 1,000 Hz pure tones presented at ~ 70 dB SPL for 100 ms, including 5 ms rise/fall times, from 2 speakers ~ 0.75 m in front of the subject. White rectangular “flash” stimuli (14×28 cm; 48.7 cd/m²) were presented for 100 ms against a black background on a computer monitor ~ 0.75 m in front of the subject. All stimuli were clearly detectable by all subjects. For AD subjects an experimenter or caregiver was present with the subject to ensure they were watching the monitor screen and were attentive.

2.3. Electrophysiological recordings

Eight electrodes were placed at the Fz, Cz, Pz, Oz, T3, C3, C4, and T4 sites according to the 10/20 system [18]. Individual sweeps were corrected for eyeblink artifacts [16] and visually inspected for artifacts before being accepted into the evoked potential average. Average potentials for each individual were bandpass filtered between 1–16 Hz. Peaks of the P50, N100, and P200 were defined at the

maximum value between 35–70 ms, 80–140 ms, and 150–250 ms, respectively. Amplitude was calculated relative to a 100 ms baseline before stimulus presentation, and latency was determined relative to stimulus onset. All amplitudes and latencies were measured from the Cz electrode site. Potentials were maximal at Cz, but similar findings were observed at the other electrode sites. Amplitudes and latencies of the auditory evoked potential (P50, N100, P200), and a positive component having a latency of ~ 200 ms in the visual evoked potential (vP200) were separately analyzed. Earlier components of the visual evoked potential were not analyzed due to variability between groups and individual subjects. Component amplitudes were emphasized in this report because crossmodal latency effects were mostly limited to the N100 component.

2.4. Data analysis

Repeated measures ANOVA's were used for statistical testing. Separate ANOVA's were conducted for three group comparisons (young vs. elderly; elderly vs. MCI; MCI vs. AD) rather than for each group separately in order to test the effects of interest (aging, MCI diagnosis, AD diagnosis) while minimizing the total number of ANOVA tests. For the primary analysis each ANOVA was a 2 (Groups) \times 2 (stimulus position: 1st, 2nd) comparison. Statistical significance was set at $p < 0.05$, and Tukey tests were utilized for post-hoc comparisons.

3. Results

3.1. Intramodal stimulus pairs

Evoked potentials to the intramodal auditory stimulus pairs (P50, N100, P200) are shown in Fig. 1, and mean values are shown in Fig. 2. In all groups there was a significant reduction in the amplitudes of the P50, N100, and P200 components for the second tone relative to the first tone (stimulus position effect: Tone 1st $>$ Tone 2nd; all p values < 0.001). Overall N100 and P200 amplitudes were significantly larger for young vs. elderly subjects (p values < 0.03), and overall P50 amplitudes in MCI were significantly larger than in healthy elderly subjects ($p < 0.05$).

In response to pairs of visual stimuli the vP200 also demonstrated intramodal refractory effects. There was a significant effect for vP200 amplitude across stimulus position (Flash 1st $>$ Flash 2nd) in young vs. elderly, elderly vs. MCI, and MCI vs. AD (all p values < 0.01) (Fig. 2D).

Latencies of the auditory P50, N100, and P200 were significantly different across stimulus position for all 3 group comparisons (all p values < 0.01) (data not shown). Latencies of the visual vP200 were not significantly different across stimulus position for any group comparison (data not shown).

Intramodal

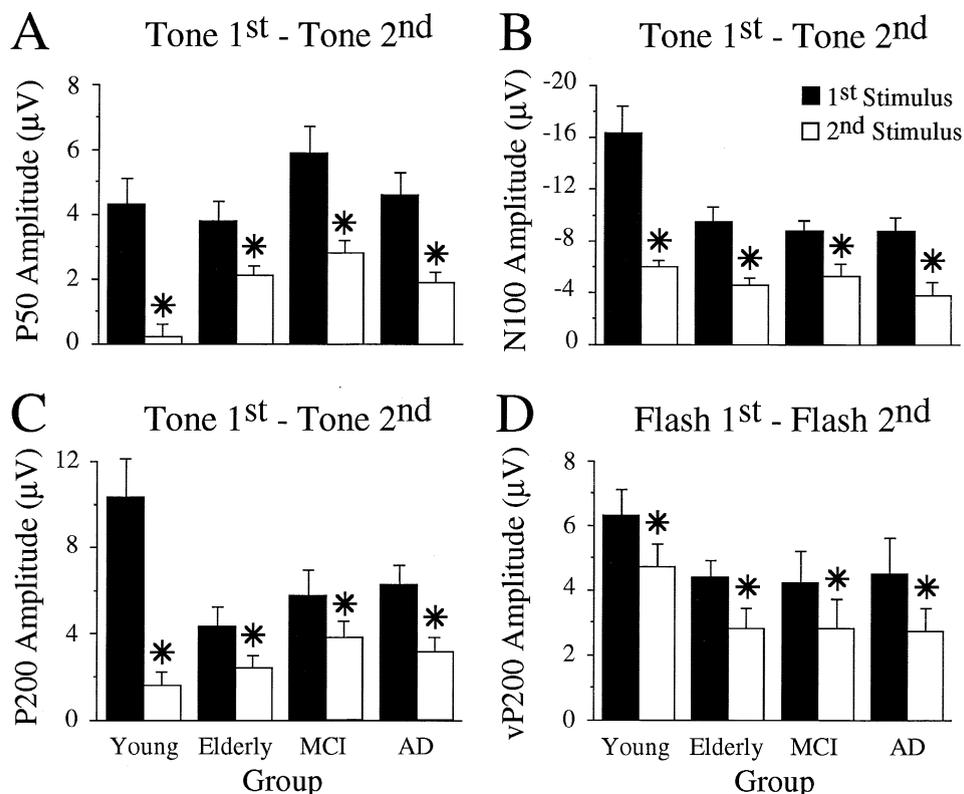


Fig. 2. Plots of component amplitudes for crossmodal condition. For all components in all groups there was a significant reduction in component amplitudes for the 2nd stimulus, relative to the 1st stimulus. Amplitudes of auditory P50 (A), N100 (B), and P200 (C) as a function of stimulus position. D) Visual vP200 component amplitude as a function of stimulus position.

3.2. Crossmodal stimulus pairs

The above findings using intramodal stimulus pairs indicate that the auditory P50, N100, and P200 components exhibit robust amplitude decreases from the 1st to 2nd tone in each tone pair. In the following section the effect of a visual stimulus presented before an auditory stimulus on evoked potential amplitudes to the tone will be examined.

Evoked potential tracings from auditory stimuli presented in crossmodal pairs are shown in Fig. 3, and mean P50 amplitudes are shown in Fig. 4A. P50 amplitudes in young vs. elderly and elderly vs. MCI had significant main effects for stimulus position (Tone 1st > Tone 2nd; $p < 0.02$). There were no significant group \times stimulus position interactions. Post hoc tests indicated significant differences between Tone 1st and Tone 2nd for the young and MCI groups. Although P50 amplitude for Tone 2nd was less than Tone 1st for most elderly subjects, there was not a significant difference across stimulus position due to 2 outliers that had much larger P50 amplitudes for Tone 2nd vs. Tone 1st. MCI subjects also had significantly larger overall P50 amplitudes than the healthy elderly ($p < 0.02$).

In contrast, P50 amplitude in the MCI vs. AD comparison was not significantly different across stimulus position,

but there was a significant group \times stimulus position interaction ($p < 0.04$). Post hoc tests indicated a significant difference across stimulus position for MCI (Tone 1st > Tone 2nd), but not AD. Thus, auditory P50 amplitudes were significantly reduced following the visual stimulus in the young, elderly, and MCI, but not AD, groups.

Mean N100 amplitudes in the crossmodal pairs are shown in Fig. 4B. For the young vs. elderly comparison there was a significant difference in N100 amplitude across stimulus position (Tone 1st > Tone 2nd; $p < 0.001$). In the elderly vs. MCI comparison there was not a significant difference in N100 amplitude across stimulus position, but there was a significant group \times stimulus position interaction ($p < 0.001$). Post hoc testing showed a significant difference across stimulus position for the young and elderly groups (Tone 1st > Tone 2nd), but not MCI. N100 amplitude in the MCI vs. AD comparison was not significantly different across stimulus position, and the group \times stimulus position interaction was also not significant. Thus, auditory N100 amplitudes were significantly reduced following the visual stimulus in the young and elderly groups, but not in MCI and AD.

P200 amplitudes to crossmodal pairs are plotted in Fig. 4C. For the young vs. elderly comparison there was not a

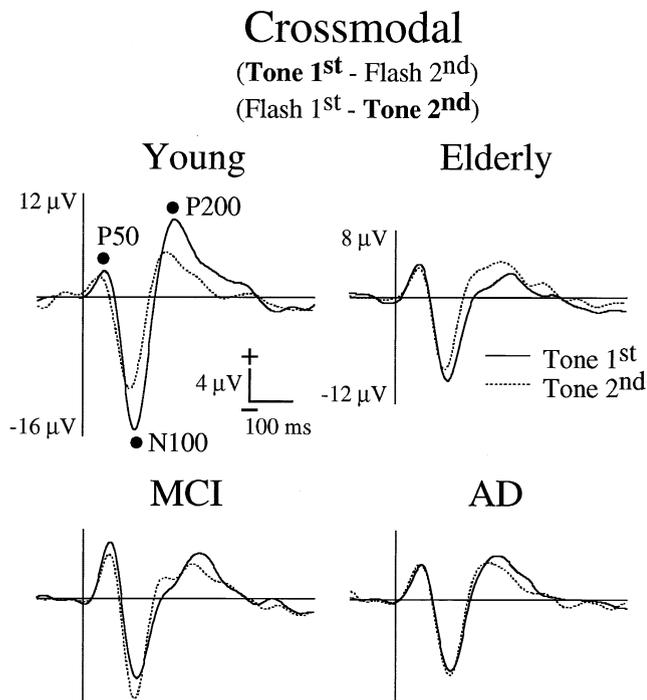


Fig. 3. Evoked potential amplitudes for crossmodal sequences. Grand average auditory evoked potentials from the crossmodal sequences in young, elderly, MCI (mild cognitive impairment), and AD (Alzheimer's disease) groups. Stimulus positions of the auditory stimuli from the two crossmodal sequences are shown in bold at top.

significant difference across stimulus position, but there was a significant group \times position interaction ($p < 0.04$). Post hoc testing showed a significant difference across stimulus position in young (Tone 1st $>$ Tone 2nd), but not elderly, subjects. There were no significant differences in P200 amplitude for the elderly vs. MCI comparison or the MCI vs. AD comparison. Thus, auditory P200 amplitudes were significantly reduced following the visual stimulus only in young subjects.

Latencies of the auditory components in crossmodal pairs displayed an inconsistent pattern of changes across groups and components. P50 latencies were significantly different across stimulus position for the young vs. elderly (Tone 1st $>$ Tone 2nd; $p < 0.01$), without a significant interaction. N100 latency was significantly different across stimulus position for all 3 group comparisons (Tone 1st $>$ Tone 2nd; all p values < 0.02). There were no significant P200 latency differences across stimulus position for any of the 3 group comparisons.

In all groups auditory stimuli had no significant effect on the amplitude of the subsequent visual vP200 potential (Fig. 4D).

3.3. Crossmodal refractory effects in individual subjects

Crossmodal refractory effects for P50 and N100 components from individual subjects in the elderly, MCI, and AD

groups as a function of mini-mental status exam score are shown in Fig. 5. To control for individual differences in the absolute amplitude of the components, P50 and N100 amplitudes are shown for Tone 2nd as a percent of Tone 1st amplitude. Values $< 100\%$ indicate a refractory effect (Tone 1st $>$ Tone 2nd).

Results show that most elderly (9/12) and MCI (9/10) subjects had P50 amplitudes $< 100\%$, while values in AD subjects were nearly evenly divided above (6/11) and below (5/11) the 100% line. In contrast, for the N100 component most elderly subjects (11/12) were $< 100\%$, while the majority of MCI subjects had larger N100 amplitudes for Tone 2nd ($> 100\%$; 8/10). As with the P50 component, AD subjects were divided above (6/11), below (4/11), and equal (1/11) to 100%. Importantly, there was substantial variability in the magnitude of crossmodal refractory effects within each group, which indicates that crossmodal refractory effects in the present study were not consistent enough to accurately distinguish between healthy elderly, MCI, or AD individuals.

3.4. Intramodal vs. crossmodal refractory effects

The event-related potential tracings in Figs. 1 and 3 suggest that the magnitudes of refractory effects for intramodal pairs were greater than crossmodal pairs. To test this impression, the difference in amplitude for each auditory component between Tone 1st and Tone 2nd was calculated by subtracting the amplitude of Tone 2nd from Tone 1st for each subject in the intramodal and crossmodal conditions. Groups having significant refractory effects in the intramodal and crossmodal conditions for the auditory P50 (young, elderly, MCI), N100 (young, elderly), and P200 (young) components were analyzed together.

For the P50 component there was a significant difference between intramodal and crossmodal conditions ($p < 0.0001$), but the group effect (young, elderly, MCI) and group \times condition interaction were not significant. For the N100 component there was a significant difference between conditions ($p < 0.0001$). There was also a significant group difference ($p < 0.02$), with young subjects having significantly larger N100 amplitude difference than the elderly group. The group \times condition interaction was not significant. In young subjects there was a significant difference for the P200 component between intramodal and crossmodal conditions ($F(1,11) = 16.4$; $p < 0.01$).

These results indicate that for each group having refractory effects in the intramodal and crossmodal conditions, the difference in amplitude between Tone 1st and Tone 2nd was greater in the intramodal condition, as compared with the crossmodal condition. The difference between intramodal and crossmodal refractory effects was equivalent among groups because there were no significant group \times condition interactions.

Crossmodal

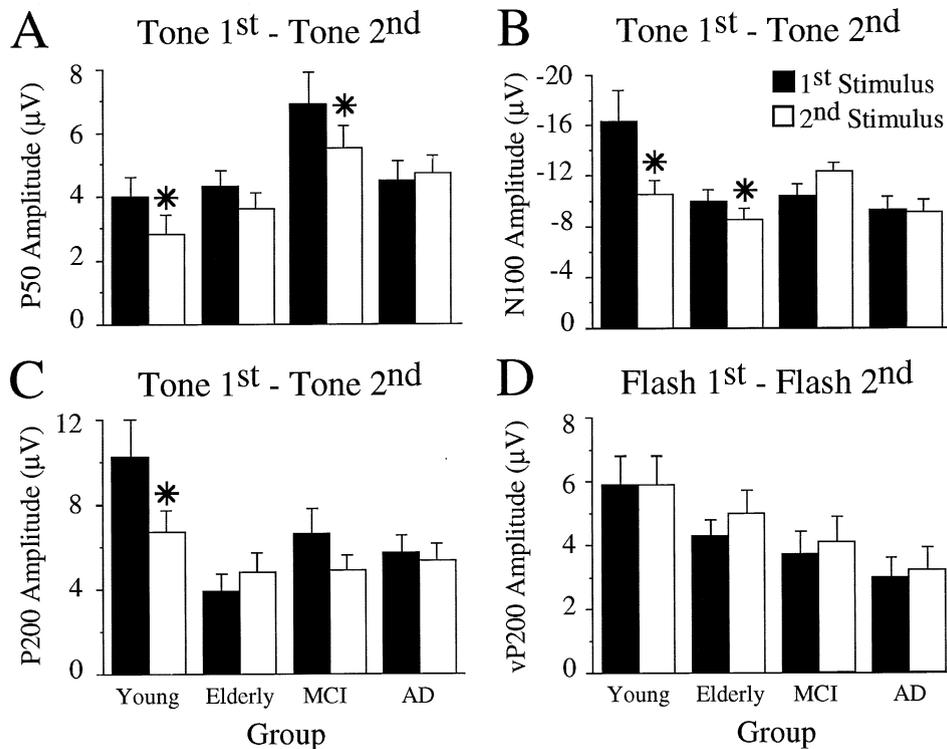


Fig. 4. Plots of component amplitudes for crossmodal condition. A) Auditory P50 amplitude as a function of stimulus position. For young and MCI subjects P50 amplitude was significantly ($p < 0.05$) larger for the 1st stimulus position. There was not a significant difference across stimulus position in the elderly due to 2 outliers who had substantially larger amplitudes for tones in the 2nd stimulus position. B) Auditory N100 as a function of stimulus position. Young and elderly subjects, but not MCI and AD subjects, exhibited significantly larger amplitudes in the 1st stimulus position. C) Auditory P200 amplitude as a function of stimulus position. Young subjects were the only group to demonstrate significantly larger amplitudes for the 1st stimulus position. D) Amplitude of the visual vP200 component as a function of stimulus position. There were no significant vP200 amplitude differences between stimulus positions. Asterisks indicate a significant difference between the 1st and 2nd stimulus position within a subject group.

4. Discussion

A summary of the statistical findings is shown in Table 2. Using intramodal stimulus pairs (Tone 1st – Tone 2nd, Flash 1st – Flash 2nd) refractory effects were observed for components of the auditory (P50, N100, P200) and visual (vP200) evoked potentials in all subject groups. In contrast, crossmodal refractory effects for pairs of different stimuli (Tone 1st – Flash 2nd, Flash 1st – Tone 2nd) demonstrated that the visual stimulus had varying degrees of effectiveness in reducing the evoked potential amplitudes to the upcoming auditory stimulus depending on the particular component and subject group.

There was a progressive decrease in the duration of time that a visual stimulus influenced the amplitude of subsequent auditory evoked potential components across study groups. In healthy young subjects all auditory components (P50, N100, P200) were attenuated by the preceding visual stimulus. In healthy aging the P50 and N100 were attenuated. In MCI only the P50 was attenuated, and in AD none of the components were affected by the previous visual stimulus. Note that although elderly controls and AD were

not directly compared, post hoc results within these groups indicate different patterns of crossmodal results. Taken together, these findings suggest a systematic reduction in the extent of interactions between cortical regions.

Parsimony would suggest that qualitatively similar changes in the brain are present in all older subjects, relative to the young, but with different degrees of severity across groups (elderly, MCI, AD). However, there is evidence that different neurobiological changes are present among groups, in particular the distinction between young and healthy aging [29], and healthy aging vs. MCI and AD [22]. For example, structural changes in prefrontal cortex, and the presence of neurofibrillary tangles in parts of the hippocampal formation are two of many differences at the cellular level between young and healthy elderly subjects [29]. When comparing healthy aging with MCI/AD, the amount of beta amyloid present in neocortical areas and the death of neurons in entorhinal cortex are two important differences between healthy aging and AD, and possibly MCI [22]. The variety of pathological differences between groups suggests that the orderly pattern of deficits in crossmodal refractory effects among groups may be attributable to different un-

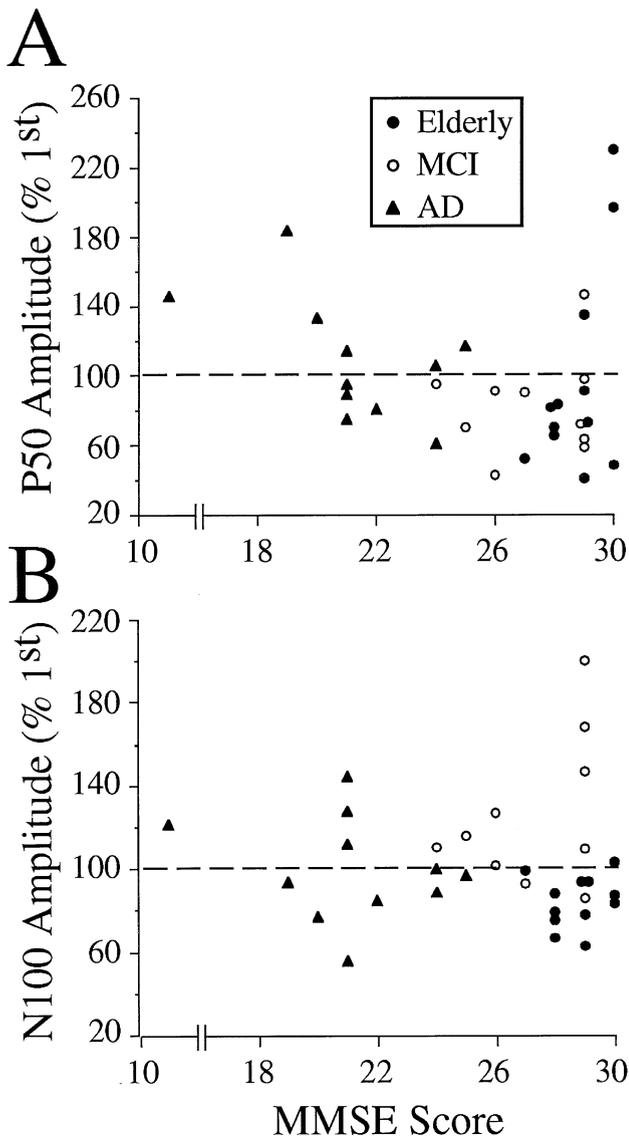


Fig. 5. Refractory effects for auditory evoked potentials (P50 and N100 amplitude) as a function of mini-mental status exam (MMSE) score in elderly, MCI, and AD groups. Component amplitudes elicited by tones in the 2nd position are plotted as a percentage of 1st position amplitudes. Dotted line indicates no difference between amplitudes for 1st and 2nd position (100%), and values <100% indicate a refractory effect (Tone 1st > Tone 2nd). P200 results are not shown because young subjects, who did not receive the MMSE, were the only group that had crossmodal refractory effects for the P200 component. A) Refractory effects for P50 component. Note that most elderly and MCI subjects showed reductions in P50 amplitudes (<100%) following the visual stimulus, while only 4/10 AD subjects were below 100%. B) Refractory effects for N100 component. Most healthy elderly subjects (11/12) demonstrated N100 refractory effects following the visual stimulus. Seven out of 11 MCI subjects had larger N100 amplitudes following the visual stimulus, while AD subjects were evenly divided between N100 amplitude increases/decreases following the visual stimulus.

derlying neurobiological changes. Therefore, the cross-modal results may not be due to similar neurobiological changes that are present to a varying degree among healthy elderly, MCI, and AD subjects.

In addition to the complex profile of neurobiological changes among the four groups in this study, the mechanisms responsible for crossmodal refractory effects are uncertain (see below). Thus, it would be premature to speculate about which neuropathological differences among groups are most relevant to group differences in event-related potentials. Because of this uncertainty, the event-related potential results should be interpreted as an indicator of functional differences between groups. That is, regardless of the particular neurobiological differences between groups, the data suggest that the deficits in crossmodal refractory effects are relevant to differences in cognitive ability between the subject groups. Performance on episodic memory tasks may be especially relevant to differences in the crossmodal paradigm because declines in episodic memory across groups parallel the changes in crossmodal refractory effects across groups. We speculate that, to the extent that crossmodal refractory effects index interactions between cortical regions, crossmodal refractory effects may reflect the ability of various cortical regions to form neural networks to mediate cognitive functions such as episodic memory.

Sensory thresholds were not measured, but all subjects were clearly able to detect the stimuli. The finding that intramodal refractory effects were seen to both auditory and visual stimuli in each group strongly suggests that the differences between groups seen in the crossmodal paradigm cannot be accounted for by possible differences in sensory thresholds between groups.

Generators of the P50, N100, and P200 components of the auditory evoked potential in humans have been localized within primary and secondary auditory cortex [1,20,30,32,34]. Accordingly, the amplitude changes seen in auditory evoked potentials in the intramodal and crossmodal tasks are likely due to changes in auditory cortical activity. Refractory effects in auditory cortex are probably not due to changes within a neuron following repeated discharges because refractory effects are seen even when the 1st tone has a different frequency than the 2nd tone [4,6]. Crossmodal refractory effects also demonstrate that the 1st stimulus does not have to elicit the same neural response as the 2nd stimulus in order to induce a refractory effect.

The mechanisms responsible for the crossmodal refractory effects initiated by a previous visual stimulus over the subsequent auditory evoked potential are unclear. The experimental rationale and predicted results were based on the working assumption that crossmodal refractory effects are accomplished via a corticocortical route, but we cannot rule out subcortical involvement. We favor the interpretation of corticocortical mediation of crossmodal refractory effects for three reasons. First, pathology of AD and MCI is mostly found in the neocortex and hippocampal formation, especially in the early stages of the disease [2,3,28]. Second, if crossmodal refractory effects were due to a nonspecific response to stimulus repetition we would expect crossmodal refractory effects when auditory stimuli preceded a visual

Table 2
Stimulus position effects (1st vs. 2nd) on the amplitude of evoked potential components

Comparison	Intramodal Pairs		Crossmodal Pairs		Reason for interaction
	Main effect	Interaction	Main effect	Interaction	
P50 (auditory)					
Young vs. Elderly	++++	ns	+	ns	
Elderly vs. MCI	++++	ns	+	ns	
MCI vs. AD	++++	ns	ns	+	MCI significant (1st position < 2nd position)
N100 (auditory)					
Young vs. Elderly	++++	ns	+++	+	1st stimulus young > 1st stimulus elderly
Elderly vs. MCI	++++	ns	ns	+++	Elderly significant (1st position > 2nd position)
MCI vs. AD	++++	ns	ns	ns	
P200 (auditory)					
Young vs. Elderly	++++	ns	ns	+	Young significant (1st position > 2nd position)
Elderly vs. MCI	++	ns	ns	ns	
MCI vs. AD	+++	ns	ns	ns	
vP200 (visual)					
Young vs. Elderly	++++	ns	ns	ns	
Elderly vs. MCI	+++	ns	ns	ns	
MCI vs. AD	++	ns	ns	ns	

Main Effect = stimulus position effect.

Interaction = group \times stimulus position interaction.

+ = $p < .05$.

++ = $p < .01$.

+++ = $p < .001$.

++++ = $p < .0001$.

ns = not significant.

stimulus, a result that was not observed. Third, the lack of crossmodal refractory effects in the elderly (P200) and MCI subjects (N100 and P200) are probably not due to a failure of the visual stimulus to influence the ascending auditory nuclei in the brainstem because earlier components in the elderly (N100) and MCI (P50) did exhibit crossmodal refractory effects. Pathological changes in the corticopetal noradrenergic and serotonergic systems in the brainstem are also seen in aging and AD [14], leaving the possibility that pathological changes in these subcortical nuclei may be relevant to the differences in crossmodal refractory effects seen in aging, MCI, and AD. However, if differences in noradrenergic and serotonergic systems were responsible for the crossmodal deficits in aging, MCI, and AD, a similar pattern of deficits should have been apparent in intramodal pairs, a result that was not observed.

In addition to group differences, there was an asymmetrical relationship between the ability of visual and auditory stimuli to induce refractory effects in the other modality. Visual stimuli could attenuate the amplitudes of subsequent auditory event-related potentials, but auditory stimuli did not affect the amplitude of subsequent visual event-related potentials in any group.

One caveat to consider is that the visual event-related potentials had a smaller signal to noise (S/N) ratio than the auditory potentials, which could have obscured a small crossmodal influence from auditory stimuli on subsequent visual event-related potentials. Intramodal refractory effects were observed for visual stimuli, which demonstrates that the S/N ratio did not preclude measurement of visual re-

fractory effects. Nonetheless, the finding that crossmodal refractory effects were smaller than intramodal refractory effects leaves open the possibility that a small S/N ratio prevented the measurement of crossmodal refractory effects in visual event-related potentials.

Differences in spatial attention may also be relevant to the difference in visual and auditory crossmodal effects. Because subjects fixated on the monitor screen visual stimuli may have been processed differently than auditory stimuli because spatial attention may have been directed toward the location of the visual stimuli, which was ~ 60 cm above the speakers. Recent studies suggest that spatial attention affects the processing of stimuli in different modalities, as long as the stimuli are presented from the same location [15]. A paradigm designed to assess the effects of spatial attention would be needed to resolve this issue.

Attention may also be more strongly associated with the visual modality by default [27]. Behavioral studies, for example, have shown a strong bias toward reporting the presence of only visual stimuli when visual and auditory stimuli are presented together [9]. Although an explanation at the psychological level need not constrain an explanation at the physiological level, a bias toward processing visual information relative to auditory information may account for the difference in the effectiveness of visual and auditory stimuli in inducing crossmodal refractory effects. Following this reasoning, we speculate that differences in attentional function among young, elderly controls, MCI, and AD patients may be relevant to the group differences in crossmodal refractory effects to visual-auditory stimulus pairs.

In summary, these findings provide convergent evidence with neuropathological data that suggest a cortical disconnection syndrome is present in AD. Moreover, the graded changes in crossmodal refractory effects observed in evoked potential components in aging, MCI, and AD may relate to the progressive changes in memory function in these groups.

Acknowledgments

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