Visual Motion Processing in Aging and Alzheimer's Disease

Neuronal Mechanisms and Behavior from Monkeys to Man

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Aging and Alzheimer's disease (AD) are accompanied by impairments of autonomous navigation and spatial orientation that commonly demand the abandonment of driving and independent living. We have studied the neuronal mechanisms of navigation using single neurons in monkey cerebral cortex, finding a specific population of cells that processes the visual motion patterns of optic flow that provide important cues about self-movement. We have found that AD patients show pronounced deficits in the perceptual processing of optic flow, with different patterns of less severe impairment in mild cognitive impairment and cognitive aging. These perceptual deficits occur in subjects who show difficulties in real-world navigation that can be linked to visual associative processing impairments. Human neurophysiological recordings reveal a robust link between navigational capacity and cortical information processing in aging and AD. We conclude that visual information processing is progressively impaired in aging and AD. We speculate that these behavioral impairments reflect the progress of mechanistically linked cortical pathophysiologies that are manifestations of the fateful transition from cognitive aging to AD.

Key words: **vision; aging; Alzheimer's disease**

Introduction

We are guided in our daily exploration of the world by the radial patterns of visual motion in optic flow.[1,2] The optic flow field provides moving observers with a rich source of information that supports navigation and spatial orientation (Fig. 1). Experimental analyses show that the heading of self-movement[3–6] and 3-D environmental layout cues in optic flow are used by species, from insects[7] to rats[8] to humans,[9,10] to support orientation and guide navigation. In humans, optic flow contributes to controlling ambulatory and vehicular self-movement.[11–13]

The importance of optic flow in daily activities is consistent with the analysis of its radial patterns in specialized extrastriate cortical dorsal pathway processing centers[14,15] that contain neurons devoted to optic flow responsiveness.[16–21] Functional imaging has extended these findings to humans by demonstrating dorsal extrastriate visual cortical activation[22–25] by optic flow stimuli.

Neurophysiology of Optic Flow Analysis

Single-neuron recordings in behaving monkeys have characterized optic flow responses in the medial superior temporal area (MST).[16,18,26] The dorsal segment of MST

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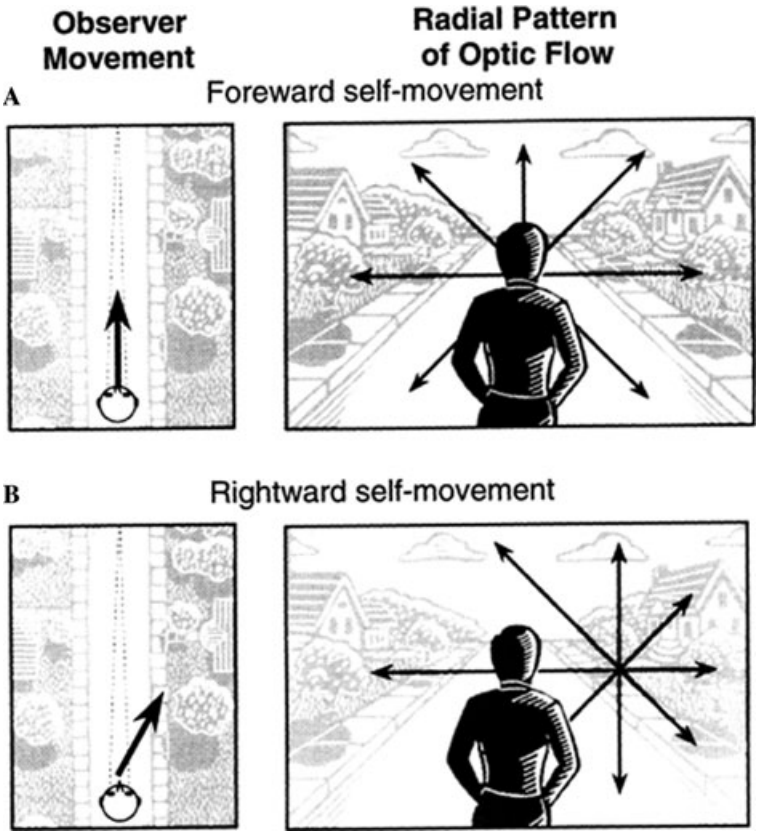

Figure 1. Observer movement through the environment (left, top down view) creates a radial pattern of visual motion called the optic flow field (right, experiential view) that surrounds the observer and indicates the direction of self-movement. (**A**) Forward self-movement results in a symmetrical pattern of radial motion with the focus of expansion (FOE) indicating the observer's heading direction. (**B**) Forward and to the right self-movement results in a shift of the radial FOE to the right, indicating the observer's shifted heading direction.

(MSTd) contains neurons that respond to optic flow stimuli that simulate self-movement in a variety of different directions.[18–20,27,28] We have recently used such stimuli to test the hypothesis that individual MSTd neurons respond best to optic flow simulating a coherent range of self-movement directions in 3-D space and that the MSTd neuronal population net vector provides a veridical representation of 3-D heading.

To test this hypothesis, we studied MSTd neuronal responses to optic flow stimuli simulating observer movement along 14 headings in 3-D space. The monkey was trained to maintain fixation at the center of the 90° × 90° display screen. Neuronal responses to optic flow patterns simulating different self-movement heading directions show selectivity that can encode movement in 3-D space. These 3-D heading direction response profiles are well fit by 3-D Gaussians with a wide range of selectivity for their preferred heading direction and for a plane of heading preference (Fig. 2). Preferred headings were evenly distributed in 3-D self-movement space, suggesting that MSTd neurons support the visual analysis of self-movement for navigation and orientation, possibly mediated by neuronal population response encoding of heading direction.

We have extended these studies to better understand the impact of ongoing behavioral

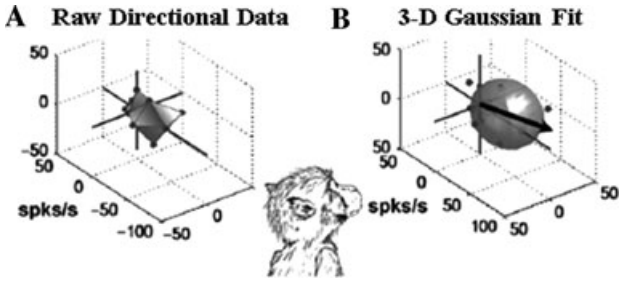

Figure 2. Responses of a single MSTd neuron recorded from behaving monkey cerebral cortex during the presentation of 14 optic flow stimuli simulating different directions of observer self-movement. The responses are shown as a 3-D plot of response amplitude for each of the directions. (**A**) Raw firing rate responses to optic flow show preference for movement up, back, and to the right. (**B**) The 3-D Gaussian fit to those data yielding a 3-D net vector that characterizes the direction and strength of the neuron's heading selectivity.

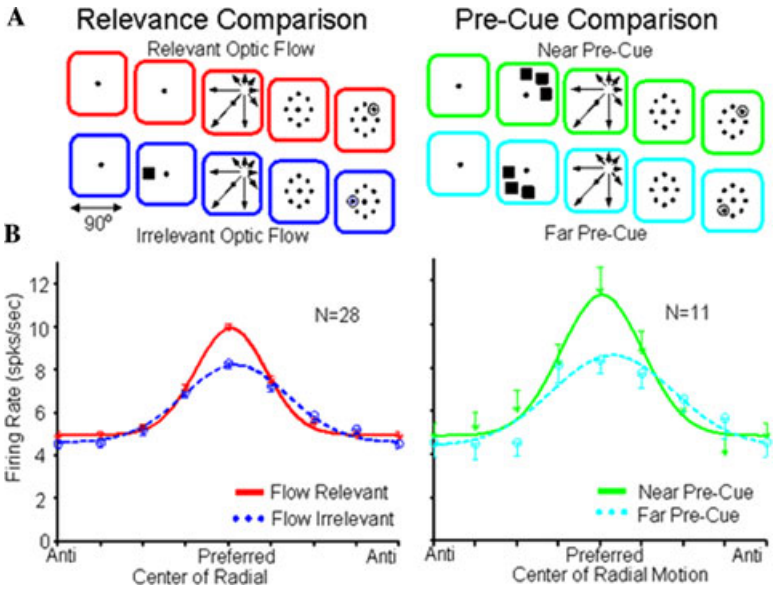

Figure 3. Spatial cueing effects on MST neuronal responses to optic flow. Responses of an MSTd neuron to eight directions of outward radial optic flow plotted as response amplitude (ordinate) versus simulated heading direction (abscissa) graphs. (**A**) Non-cue trials (left, top) in which the monkey had to indicate the radial center of motion were interleaved with spatial pre-cue trials (right top) in which the flow was behaviorally irrelevant. In pre-cue trials, the pre-cues could occur either near to or far from the center of motion in the subsequent optic flow stimulus. (**B**) MSTd neurons showed stronger responses to task relevant (left) optic flow, over task irrelevant optic flow. Among responses to task irrelevant optic flow responses (right), MSTd neurons showed greater response when the radial center of motion in the optic flow was near the pre-cue location. (In color in *Annals* online.)

tasks on the optic flow responses of MSTd cortical neurons. To do so, we trained monkeys in interleaved trials in which identical optic flow stimuli were either directly specifying the target location of a subsequent saccade, or were an irrelevant distracter independent of the previously specified saccade target (Fig. 3A). There is a great deal of diversity in the responses of MST neurons, but in general, responses to relevant optic flow are of larger amplitude and greater direction selectivity than responses to irrelevant optic flow (Fig. 3B, left). In addition, responses

to irrelevant optic flow show an influence of the relative distance between the pre-cued saccade target location and the radial center of motion in the subsequent, irrelevant optic flow stimulus: trials in which the pre-cue location happens to be closer to the radial center evoke stronger and more selective responses than trials in which the pre-cue happens to be far from the radial center (Fig. 3B, right).

Together, these studies suggest that MST neurons are specialized for analyzing the visual motion in optic flow and for representing self-movement heading direction in those responses. Further, we find that the amplitude and heading direction selectivity of these responses are modulated by the details of the monkey's ongoing behavioral tasks.

Psychophysics of Alzheimer's Disease

Our findings in monkey cortical neurophysiology led us to consider the potential role of disordered optic flow analysis in human visuospatial disorientation. The visuospatial disorientation of Alzheimer's disease (AD) has several relevant features: patients get lost despite their recognizing landmarks, describing the route, recognizing familiar landmarks, and showing relative preservation of other capacities. In addition, AD is a common illness in which visuospatial impairments have life-changing consequences. Finally, there is the substantial predisposition of AD pathology in poster extrastriate cortical areas, including those specialized for higher-order visual motion processing.

A variety of basic visual deficits have been described in AD[29,30] that may reflect more anterior visual mechanisms than those responsible for visual motion processing impairments.[31–33] Many AD patients suffer from higher-order visual motion processing deficits[34] including selective impairments in perceiving the patterned visual motion of optic flow[35] that provides moving observers with information about their heading direction.[36]

In our early studies we characterized memory capacity and visual motion processing in young normal (YN) and older normal (ON) adult subjects and in patients with mild cognitive impairment (MCI) and patients with AD to see if deficits in these realms occur as isolated impairments. Each subject underwent neuropsychological testing and gave push-button responses to indicate perception of panoramic visual motion stimuli. In a series of two-alternative, forced-choice tasks, we determined psychophysical motion coherence thresholds in young adults, older adults (OA), patients with MCI, and patients in the early stages of AD. We presented three stimulus sets to determine thresholds for left or right directed horizontal motion, left or right heading direction outward radial optic flow, and left or right heading direction inward or outward radial optic flow (Fig. 4). In all three stimulus sets the subjects responded with a left or right button push.

Subjects from all groups did well on horizontal motion perception, attesting to their ability to see the stimuli and respond reliably in the task. Some MCI and many AD patients showed elevated perceptual thresholds for outward radial optic flow. Some OA, many with MCI, and almost all AD patients showed elevated thresholds for in/out radial optic flow (Fig. 5).[37]

These perceptual impairments were associated with poorer performance on the Money Road Map test of spatial navigation but not with verbal or visual memory deficits. These findings led us to conclude that impaired visual motion processing can accompany memory deficits in MCI or AD, or may occur separately in otherwise intact ONs. This suggests that visuospatial impairment may develop as an independent sign of neurodegenerative disease, possibly preceding conditions that satisfy diagnostic criteria for MCI or AD.

Navigational Impairments in Alzheimer's Disease

We have now linked these psychophysical studies with the naturalistic assessment of navigational performance in aging and AD by

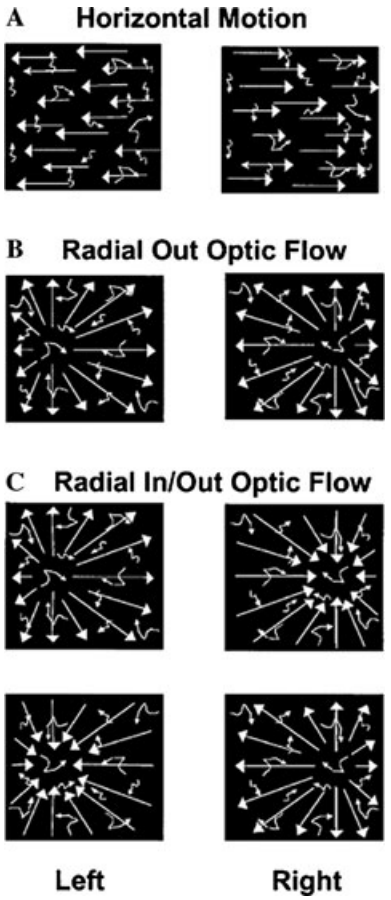

Figure 4. Examples of stimuli used to determine horizontal motion (**A**), radial outward optic flow (**B**), and radial in/out optic flow (**C**) coherence thresholds. Over numerous trials, the ratio of coherently moving dots to incoherently moving dots was manipulated by parameter estimation by sequential testing algorithm to determine the minimum percentage of coherent motion needed by each individual to make accurate left/right discriminations regarding the direction of motion. Subjects responded by pressing one of two buttons to indicate left or right motion as shown in the figure.

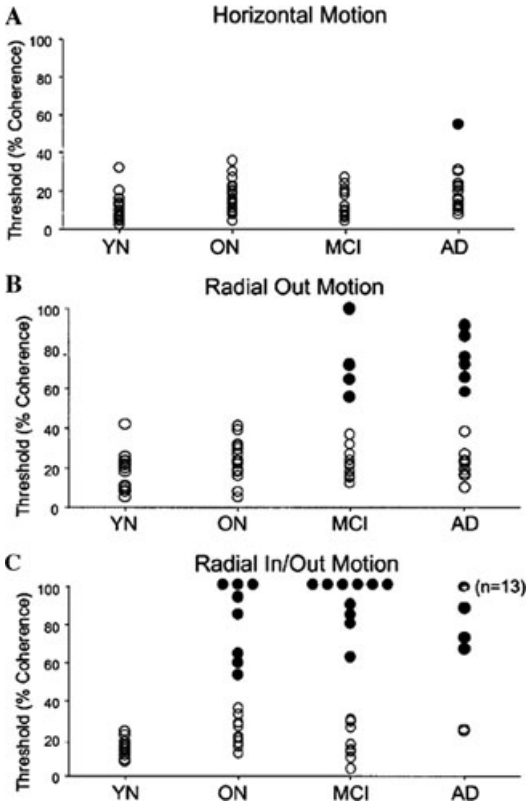

Figure 5. Visual motion coherence thresholds (ordinate) for the three motion patterns tested and four subject groups. Black circles identify individuals with coherence thresholds >50%. (**A**) All groups attained low thresholds in left/right horizontal motion discrimination without between-group differences. (**B**) Outward radial optic flow revealed higher thresholds in the AD group ($F_{3,72} = 4.86$, $P < 0.01$) and a trend toward increasing mean thresholds across groups. (**C**) Interleaved inward and outward radial motion showed much higher thresholds in the ON, MCI, and AD groups compared with the YN group. The AD group was also different from the ON and MCI groups.

developing a real-world navigational test battery.[38] We studied the navigational performance of YN, middle-aged (MA), OA, and AD by using the lobby of Strong Memorial Hospital as the testing environment. Subjects were seated in a wheel chair and taken on a route through the lobby. After the excursion subjects were asked questions from a battery of eight subtests designed to evaluate a wide variety of aspects of information about the test route and the test environment (Fig. 6).

There was decreasing performance (lower scores on all tests) in the OA and early AD subject groups. In particular, these groups showed more pronounced impairment in the video clip location and photograph location subtests that probed the ability to link a scene from the route with a location within the environment (Fig. 7). Viewed another way, we found that the

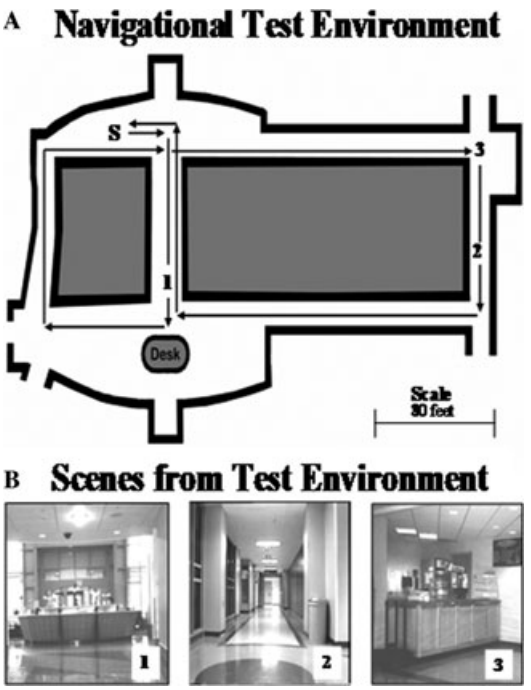

Figure 6. The real-world navigational test environment was the lobby of the Strong Memorial Hospital. This figure shows a top-down view of the test route and illustrates several scenes encountered along that route (numbered). Subjects sat in a wheelchair as they were moved along the route over a period of 4 min. After the route demonstration, a battery of eight tests was administered to measure the subjects' access to information about the route and the environment.

tendency to become lost is shared by almost all AD patients (93%) and some OA subjects (38%). A battery of seven neuropsychological studies did not reveal any significant links between becoming lost and either memory, fluency, or other test scores. We conclude that navigational impairment in aging and AD is not related to memory deficits but instead reflects an inability to link recognized scenes with information regarding their relative location that was obtained when moving through the environment.

The combination of perceptual and navigational deficits led us to seek an objective approach to quantifying visual motion processing in aging and AD. We based our efforts on established methods for eliciting and recording visual motion evoked responses.[39] Human visual motion processing has long been investigated using scalp-recorded visual motion evoked potentials.[40] A negative wave peaking over parietal areas about 200 ms after stimulus onset (N200)[39] is sensitive to the direction and timecourse of visual motion stimuli.[41]

Linking Mechanism and Function

We developed an approach to using radial optic flow stimuli to elicit visual motion evoked potentials. We first have subjects fixate the center of the projection screen and then we present a random pattern of stationary dots. After a few hundred milliseconds, the dots move to create a radial pattern of optic flow. We record the responses to optic flow onset and compare the N200 response amplitudes across subject groups. We reasoned that optic flow response mechanisms identified in monkeys[20] and humans[42] might generate specific cortical evoked potentials.

Even though radial optic flow contains a mixture of all motion directions that might complicate the elicitation of a coherent neural response, we found robust N200 responses evoked by optic flow. Comparing the N200 optic flow responses in OA and AD patients, we found greatly diminished N200 response amplitudes in AD, suggesting a cortical neurophysiological homolog of increased optic flow perceptual thresholds in early AD (Fig. 8A).

Further study revealed robust links between N200 amplitude, selective impairments of optic flow perception, and navigational impairment in AD patients. Multiple linear regression analysis revealed that performance on real-world navigational tests can be predicted by the combination results from three tests, in decreasing order of relative influence: (1) optic flow evoked N200 response amplitudes, (2) radial optic flow motion coherence thresholds, and (3) contrast sensitivity profiles (Fig. 8B).

We conclude that navigational impairment in AD is linked to a disorder of extrastriate

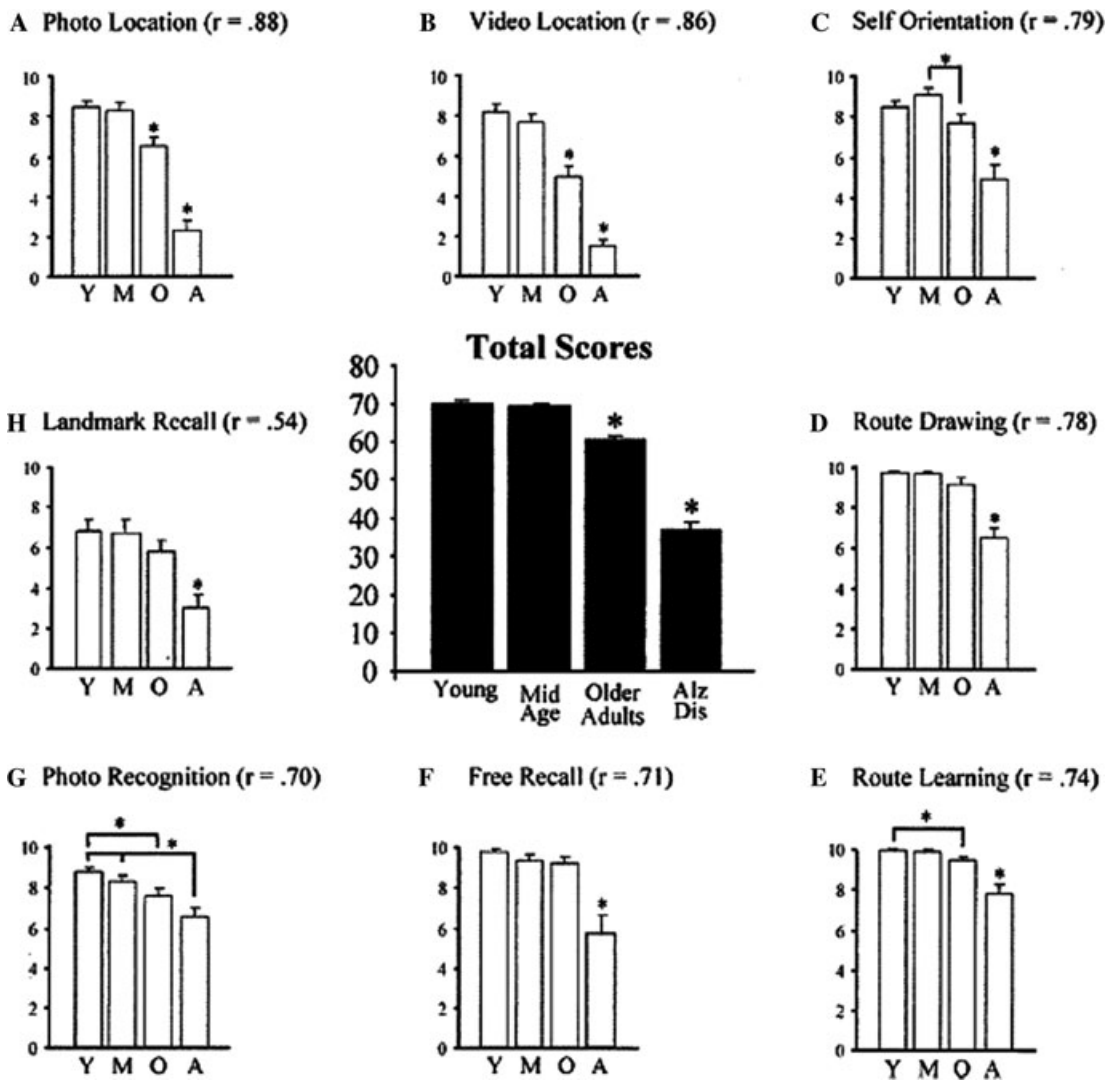

Figure 7. Group performance on the navigation test for each subject group. The OA group showed significantly poorer performance than the YN or MA groups. The AD group showed significantly poorer performance than all other groups. The tests of photo and video location most powerfully distinguished the AD group from the others. Asterisks mark significant ($P < 0.05$) group differences between indicated group and all others or group indicated by bracket.

visual cortical motion processing reflected in measures of specific perceptual capacities, daily functional competencies, and cortical neurophysiological responsiveness. We believe that these effects reflect links between optic flow processing in dorsal stream extrastriate cortex and the established predisposition for the accumulation of AD pathology in those areas.[43] In cases where these functional and pathological changes are relatively isolated, they may be related to visual association cortical symptomatology in the recognized AD variant syndrome of posterior cortical atrophy.[44,45] The impairments observed in our studies are consistent with the progressive decline of cortical information processing for navigation and spatial orientation, likely representing the spread of pathology across extrastriate cortical areas for perceptive and associative visual processing.

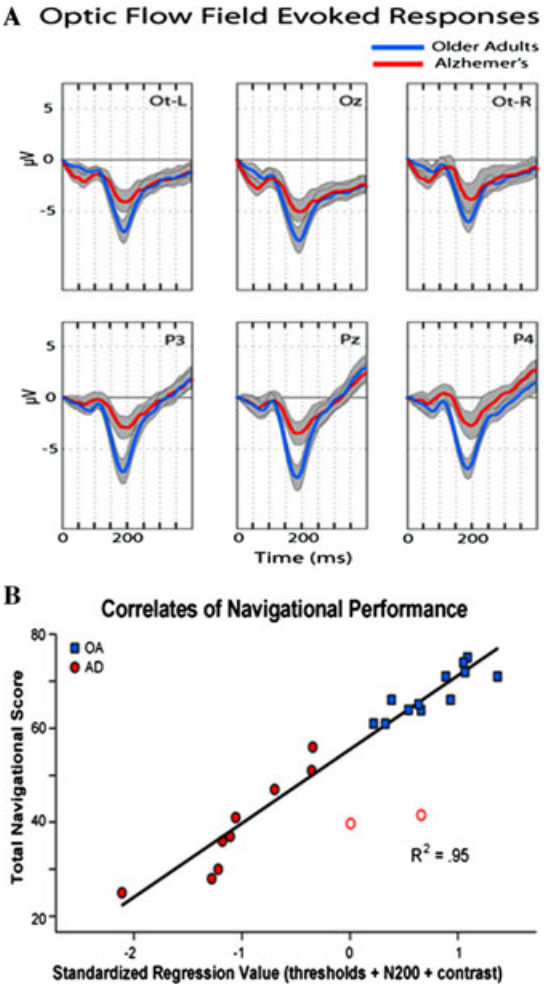

Figure 8. (**A**) Visual motion evoked potentials tracings from six posterior scalp electrodes showing greatly diminished optic flow evoked N200s in AD patients (red) compared with OA (blue). (**B**) Relationship between navigational performance (ordinate) and combined psychophysical and visual motion evoked potentials in OA and AD subjects. (In color in *Annals* online.)

Conflicts of Interest

The author declares no conflicts of interest.

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