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Pathophysiology underlying diminished attention to novel events in patients with early AD

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Article abstract—*Background:* Patients with mild to moderate AD often are apathetic and fail to attend to novel aspects of their environment. *Objective:* To investigate the mechanisms underlying these changes by studying the novelty P3 response that measures shifts of attention toward novel events. *Methods:* While event-related potentials were recorded, mildly impaired AD patients and matched normal controls (NC) viewed line drawings that included a repetitive background stimulus, an infrequent target stimulus, and infrequent novel stimuli. Subjects controlled how long they viewed each stimulus by pressing a button. This served as a measure of their allocation of attention. They also responded to targets by depressing a foot pedal. Patients did not differ from NC in age, education, estimated IQ, or mood but were judged by informants to be more apathetic. *Results:* P3 amplitude to novel stimuli was significantly smaller for AD patients than NC. However, P3 amplitude to target stimuli did not differ between groups. For NC, P3 response to novel stimuli was much larger than to background stimuli. In contrast, for patients with AD, there was no difference in P3 response to novel vs background stimuli. Although NC spent more time looking at novel than background stimuli, patients with AD distributed their viewing time evenly. Remarkably, for patients with AD, the amplitude of the novelty P3 response powerfully predicted how long they would spend looking at novel stimuli ($R^2 = 0.52$) and inversely correlated with apathy severity. *Conclusions:* The decreased attention to novel events exhibited by patients with AD cannot be explained by a nonspecific reduction in their attentional abilities. The novelty P3 response is markedly diminished in mild AD, at a time when the target P3 response is preserved. The disruption of the novelty P3 response predicts diminished attention to novel stimuli and is associated with the apathy exhibited by patients with AD.

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Patients with AD at mild to moderate stages of the disease frequently are apathetic and fail to direct attention to novel or interesting aspects of their environment.^{1–3} Previous research in our laboratory has suggested that reduced attention to novelty by patients with AD cannot be explained solely as a reflection of overall dementia severity, the inability to identify which stimuli are novel, or a reaction to becoming overwhelmed by environmental stimulation.^{4,5} What additional processing deficits may be contributing to this observed decline in behavior? For example, unlike normal controls (NC), do the

brains of patients with AD fail to generate an early signal that indicates the presence of a novel or potentially significant event that requires additional attentional resources and exploratory activity? Or, do patients with AD generate such a neural signal but then fail to act appropriately on it?

The novelty P3 event-related potential (ERP) can serve as an index of the neural processes involved in allocating attention to novel events.^{6–12} Lesion studies and investigations employing intracranial recordings, electrical source analysis, or functional imaging indicate that the novelty P3 response is subserved by

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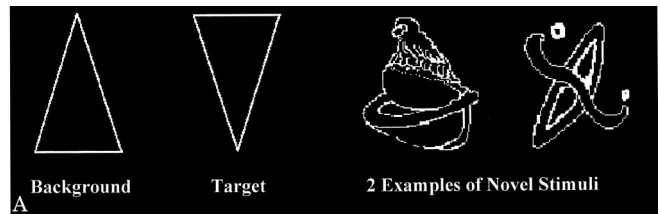
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a distributed cerebral network with major components in frontal and temporolimbic regions.^{10,12-19} We hypothesized that Alzheimer's pathology would lead to impairment of the frontal and temporolimbic structures involved in the novelty processing system²⁰⁻²⁴ and that this would contribute to the diminished attention patients with AD pay to novel aspects of their environment, a core feature of the apathy syndrome.²⁵⁻²⁷ Thus, we expected patients with AD to have an extremely diminished novelty P3 response that would strongly predict their degree of reduced viewing duration of novel stimuli. Moreover, we hypothesized that even very mildly demented AD patients would show a marked disruption of the novelty P3 at a time when their target P3 was still relatively well preserved. This finding would confirm the presence of abnormalities in the novelty processing system very early in the course of the illness and indicate that it was not simply attributable to a non-specific decrement in attentional capacity.

Methods. *Subjects.* Ten patients with probable AD showing only mild cognitive and functional impairment and 20 well-matched NC subjects participated in this study. Patients with probable AD were diagnosed according to the National Institute of Neurological Disorders and Stroke/AD and Related Disorders Association criteria.²⁸ They were excluded if they had medical conditions that could account for their dementing illness; had evidence of infarction on CT or T1-weighted images on MRI; had a Hachinski ischemic score²⁹ of greater than 4; or had clinical evidence of major depression as defined by *Diagnostic and Statistical Manual, 4th rev.* criteria.³⁰ Only patients who scored ≥ 18 on the Mini-Mental State Examination (MMSE)³¹ were included. Normal control subjects were recruited from the Boston area. They were excluded if they had a history of dementia, cerebrovascular disease, alcohol abuse, or a focal neurologic examination. Informed consent was obtained from all subjects. A family member of each patient with AD cosigned the informed consent. The study was approved by the Human Research Committee at Brigham and Women's Hospital.

Subjects were characterized by demographic information and scores on the 1) MMSE,³¹ a measure of dementia severity; 2) the American version of the National Adult Reading Test (AmNART),³² an estimate of premorbid intellectual capacity; 3) informants' responses to the Apathy Scale³³ and the Personality and Behavioral Inventory-Apathy subscale,^{5,12} both measures of apathy; and 4) the Zung Depression Scale,³⁴ a measure of mood state. Informants also completed a structured interview to derive a Clinical Dementia Rating (CDR) score³⁵ for each patient. All subjects also underwent a formal neurologic examination.

Stimuli. Event-related potentials were recorded while subjects viewed a series of line drawings, white on black background, presented at the center of a high-resolution computer monitor. Three categories of visual stimuli were used: 1) a frequent, repetitive background stimulus (70%); 2) an infrequent target stimulus (15%); and 3) infrequent novel stimuli (e.g., fragmented or "impossible" objects) shown only once each (15%) (figure 1A). Stimuli subtended



Normal Controls

AD Patients

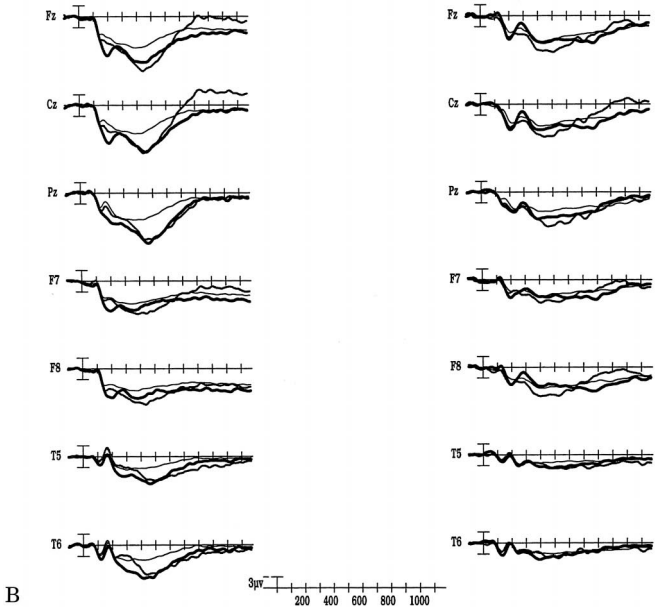


Figure 1. (A) Repetitive background stimulus (70% frequency), target stimulus (15% frequency), and two examples of the novel stimuli (15% frequency). (B) Grand average event-related potential plots for midline and lateral sites in response to background stimuli (thin lines), target stimuli (thick lines), and novel stimuli (bold lines) for normal control subjects and patients with AD.

a visual angle of $\sim 2.75^\circ$ and appeared within a fixation box subtending a visual angle of $\sim 3.5 \times 3.5^\circ$ that remained on the screen at all times. Stimuli were presented in pseudorandom order in six blocks of 50 stimuli each.

Procedure. Subjects were informed that the experiment involved the study of brain wave responses as they looked at different kinds of drawings. They were told that they would be viewing a set of drawings and that they could look at each picture as long as they liked. They controlled the viewing duration by a button press that triggered the onset of the next stimulus. Subjects were explicitly told that they would not be asked questions about the pictures at the conclusion of the experiment. Subjects also were told to respond to the designated target stimulus by pressing a foot pedal (ipsilateral to the button press). We called the targets "sequence markers" and indicated to subjects that they were included in the task to help the experimenters keep track of where they were in the sequence of drawings. The response hand/foot used by subjects was randomly assigned. Although viewing durations were calculated by subtracting the stimulus onset time from the button press time, all stimuli were displayed

Table Subject characteristics and experimental data

Characteristics and data	NC subjects, mean (SEM), n = 20	Patients with AD, mean (SEM), n = 10	p Value
Subject characteristics			
Sex, F:M	12:8	5:5	NS
Age, y	68 (2)	72 (3)	NS
Education, y	16 (1)	15 (1)	NS
AmNART	121 (1)	113 (4)	NS
MMSE	29 (0.2)	24 (1)	<0.0005
Zung	30 (1)	33 (1)	NS
Apathy (0–42)	6 (1)	15 (2)	<0.005
Apathy (0–40)	6 (1)	19 (3)	<0.005
Experimental data			
P3 amplitude at midline sites, μ V			
Novels	15 (1)	9 (1)	<0.0005
Backgrounds	9.2 (0.4)	7.1 (0.8)	<0.05
Targets	15 (1)	11 (2)	NS
P3 latency at Pz, ms			
Novels	456 (15)	462 (31)	NS
Backgrounds	393 (14)	455 (27)	<0.05
Targets	475 (15)	508 (26)	NS
Duration novels/duration backgrounds	2.8 (0.4)	1.7 (0.4)	<0.007
Percent target hits	97 (1)	71 (8)	<0.05
Percent false alarms	0.14 (0.05)	2.8 (1.3)	<0.005
Median reaction time to targets, ms	1,276 (184)	1,918 (416)	<0.05

NC = normal control; AmNART = American Version of the National Adult Reading Test³⁹; MMSE = Mini-Mental State Examination³⁸; Zung = Zung Depression Scale⁴⁰; Apathy (0–42) = Apathy Scale⁷; Apathy (0–40) = Apathy Subscale, Personality and Behavioral Inventory.¹⁰

for a minimum duration of 600 ms. The interval between the offset of one stimulus and the onset of the next stimulus ranged between 800 and 1,300 ms. The experimental trial did not commence until after subjects completed a series of practice runs and demonstrated their understanding of the task procedures.

ERP recordings. An electrode cap (Electro-Cap International, Eaton, OH) was used to hold the seven active electrodes to the scalp; their locations were based on the international 10–20 system. They included three midline sites (Pz, Cz, Fz) and four lateral sites (F7/8, T5/6). All sites were referenced to the left mastoid, and the impedance between each recording site and the reference was reduced to less than 5K Ω . An electrode was placed beneath the left eye (left mastoid reference) to check for eye blinks and vertical eye movements and another electrode to the right of the subject's right eye (referenced to an electrode to the left of the left eye) to check for lateral eye movements. A final electrode was placed over the right mastoid (referenced to the left) to monitor asymmetric mastoid activity. (None was found.)

The EEG was amplified by an SA Instrumentation (San Diego, CA) acquisition system (model H & W 32BA), using a band filter with negative 3db cutoffs of 0.01 and 40 Hz, and continuously digitized (200 Hz) by a computer yielding 1,280 ms data from each electrode site, beginning 100 ms before stimulus onset.

A continuous record of the raw EEG was stored on hard disk. Off-line, EEG epochs for the three stimulus types (background, target, novel) were averaged separately. Trials with eye movements or amplifier blocking were excluded from data analysis. In cases with excessive eye blinks, a blink correction program was employed³⁶ that computed the impact of the blink on the waveforms in each channel. The P3 was defined as the peak positive wave between 325 and 600 ms, measured with respect to the average of the 100 ms prestimulus baseline.

Data analysis. Data were analyzed by using repeated measures analysis of variance (ANOVA). There were two levels of group (AD patients, NC subjects), and for ERP and duration data, three levels of stimulus type (background, target, novel). For ERP measures, there were three midline electrode sites and four lateral electrode sites with two levels, one for each hemisphere. Between-group analyses that yielded significant interactions between group, stimulus type, electrode site, or hemisphere were further analyzed by using planned comparisons between the levels of the variable. In looking at scalp site interactions with other variables, the data were normalized using a *z* score technique³⁷ similar to the method recommended by McCarthy and Wood³⁸ to avoid problems associated with interpreting site by factor interactions by using ANOVA. The Geisser–Greenhouse correction was applied for all repeated measures with greater than 1 *df*.

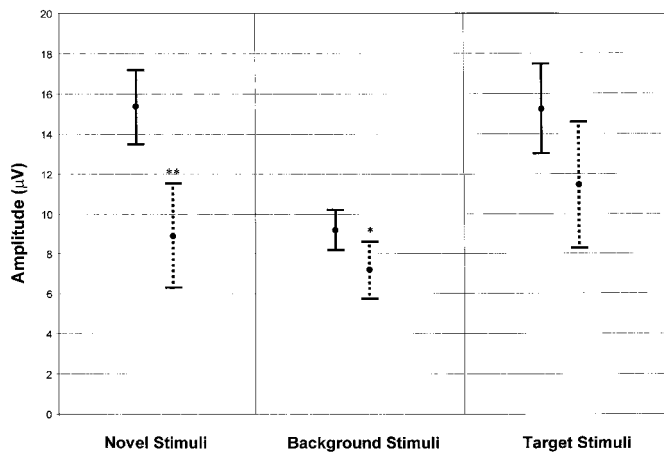


Figure 2. P3 amplitude (in μV) at midline sites (pooled across Fz, Cz, and Pz) (mean \pm 95% CI) for normal control (NC) subjects (solid lines) and patients with AD (dashed lines). P3 to novel stimuli was smaller for patients with AD (midline, $p < 0.000005$; lateral, $p < 0.002$). P3 to background stimuli was slightly smaller for patients with AD at midline sites ($p < 0.05$), but not at lateral sites. P3 to target stimuli was not different between groups at midline sites but was slightly smaller for patients with AD at lateral sites ($p < 0.05$). For NC, P3 response to novel and target stimuli did not differ and were both larger than background stimuli ($p < 0.000005$). For patients with AD, P3 to novel and background stimuli was not significantly different. However, P3 to target stimuli was larger than to background stimuli (midline, $p < 0.02$, lateral, $p < 0.01$) (* $p < 0.05$, ** $p < 0.0005$).

Data sets involving the behavioral results (e.g., viewing durations, reaction times) or demographic variables that were not normally distributed were transformed (e.g., inverse function) before statistical analyses. If assumptions for parametric analyses were still violated, nonparametric statistics (e.g., Mann–Whitney U tests) were employed. Regression analysis was employed to determine the relationship between novelty P3 amplitude and viewing durations. Pearson Correlation analyses were used to assess the degree of association between novelty P3 amplitude and severity of apathy in patients with AD. All p values reported are two-tailed, except for the correlation analyses, which are one-tailed.

Results. *Subject characteristics.* The table summarizes the characteristics of each subject group. Patients with AD were in an early stage of the illness (mean MMSE, 24), but were significantly more impaired than NC subjects (mean MMSE, 29). Consistent with the mild severity of their illness, CDR scores for AD patients ranged from 0.5 to 1, with a mean of 0.85. The groups did not differ in terms of age, years of education, estimated premorbid IQ, or affective symptoms. Patients with AD showed a mild degree of apathy; however, they were significantly more apathetic than the NC subjects.

P3 data. Figure 1B presents the grand average ERP plots for NC subjects and patients with AD. Figure 2 illustrates the mean P3 amplitude data at midline sites for both groups and reports the statistical results at midline and lateral sites. P3 amplitude to novel stimuli was much

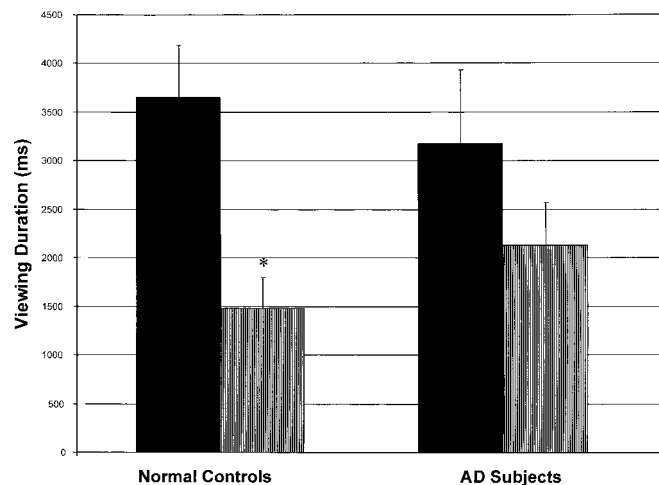


Figure 3. Viewing duration (mean \pm SEM) of novel stimuli (black columns) and background stimuli (striped columns) for normal controls and patients with AD (* $p < 0.0005$).

smaller for AD patients than NC subjects at midline ($p < 0.0005$) and lateral sites ($p < 0.002$). P3 amplitude to target stimuli did not differ between groups at midline locations but was slightly smaller for AD patients at lateral locations ($p < 0.05$). Patients with AD did not differ from NC subjects in terms of P3 amplitude to background stimuli at lateral sites, but generated slightly smaller responses at midline locations ($p < 0.05$). Within-group analyses indicated that, for NC subjects, P3 response to novel stimuli was equal to that of target stimuli, both of which were much larger than to background stimuli (midline: $p < 0.000005$; lateral: $p < 0.000005$). In contrast, for patients with AD, P3 response to novel stimuli was not larger than to background stimuli. However, their P3 response to target stimuli was larger than to background stimuli (midline: $p < 0.02$; lateral: $p < 0.01$).

Midline scalp distribution in response to the various stimulus types did not differ between groups after normalizing the data.³⁷ For both groups, P3 response to background stimuli was more anteriorly distributed than to novel or target stimuli ($p < 0.01$). For NC, the novelty P3 response was larger at right than left hemisphere sites ($p < 0.005$), whereas for AD patients there was no difference in response across hemispheres. P3 latency at midline electrode sites did not differ between groups in terms of response to novel or target stimuli (see the table). Patients with AD had a longer P3 latency to background stimuli than did NC ($p < 0.006$). For NC, the P3 latency to novel stimuli was longer than to background stimuli ($p < 0.000005$). However, for patients with AD, there was no difference in P3 latency response to novel and background stimuli.

Viewing duration. NC subjects and patients with AD spent very different amounts of time looking at various stimulus types ($p < 0.02$). Within-group analyses showed that NC subjects devoted much more time to exploring novel than background stimuli ($p < 0.0005$). In contrast, patients with AD distributed their viewing duration much more evenly between novel and background stimuli ($p > 0.1$), as a result of their spending more time on background and less on novel stimuli than NC subjects (figure 3). Response times in patients with AD may have been affected

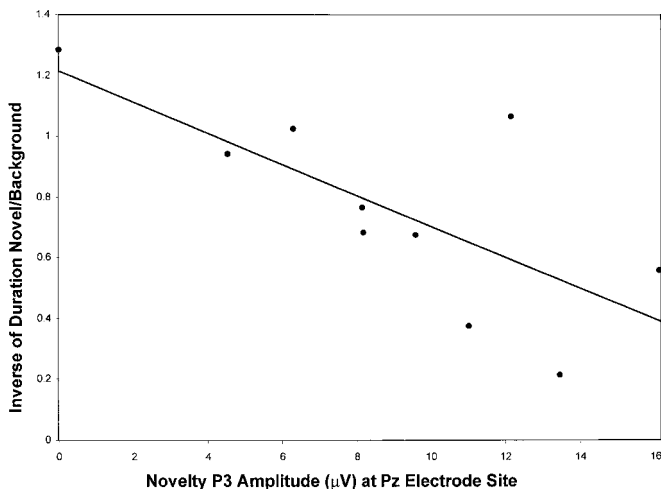


Figure 4. Plot of the relationship between novelty P3 response and viewing duration. $R = 0.72$; $R^2 = 0.52$; $p < 0.02$.

by nonspecific changes in speed of motor or cognitive processing. To help control for these factors, we constructed a measure of proportionality. Compared with AD patients, NC subjects spent more time looking at novel relative to background stimuli (i.e., ratio of viewing duration of novel stimuli to viewing duration of background stimuli) (see the table).

Relationship between novelty P3 response and viewing duration in patients with AD. For patients with AD, the amplitude of the novelty P3 response strongly predicted how long they spent looking at novel stimuli. Fifty-two percent of the variance associated with the viewing duration novels/viewing duration backgrounds was accounted for by the novelty P3 amplitude at Pz, as shown by regression analysis ($R = 0.72$, $R^2 = 0.52$, $p < 0.02$) (figure 4).

A 10- μ V increase in the novelty P3 amplitude was associated with an approximately 62% increase in the duration of viewing directed to novel relative to background stimuli. In patients with AD, the relationship between viewing duration of novel stimuli and the P3 wave was specific to the novelty P3 response. No correlation was found between viewing duration novels/viewing duration backgrounds and P3 response to target stimuli or background stimuli. Also, the relationship between the amplitude of the novelty P3 and viewing duration was much stronger for patients with AD ($R^2 = 0.52$) than NC subjects ($R^2 = 0.32$, $p < 0.01$). Finally, correlation analyses between novelty P3 amplitude and degree of apathy level in patients with AD indicated a strong trend toward an inverse relationship. The amplitude of the novelty P3 at midline sites inversely correlated with degree of apathy as rated by informants on the Apathy Scale³³ ($R = -0.56$, $p = 0.05$) and the Personality and Behavioral Inventory⁵ ($R = -0.53$, $p = 0.07$), after excluding an outlier from these analyses (who fell noticeably outside the computed regression line).

Behavioral responses to targets. Both NC and AD patients looked at target stimuli longer than background stimuli (AD, $p < 0.01$; NC, $p < 0.00005$). The two groups did not differ significantly in terms of the ratio of time spent looking at target relative to background stimuli (NC: 2.2 [0.2]; AD: 2.3 [0.3], mean [SEM]). Compared with NC, patients with AD had a lower mean percent target hit rate (see the table). In addition they had a slower median reac-

tion time to target stimuli and a higher mean false alarm rate than NC.

Relationship between behavioral responses to targets and the processing of novel stimuli. The impaired behavioral response of patients with AD to targets raises the possibility that their diminished response to novel stimuli is merely a reflection of reduced attentional abilities in general. To explore this possibility, we compared the responses to novelty of NC subjects to a subset of AD patients ($n = 5$) who performed as well as NC subjects in identifying targets (i.e., percent hit rate). This group of patients with AD did not differ from NC subjects in terms of age, education, Zung Depression Scale, or AmNART score. However, like the AD sample as a whole, they scored worse on the MMSE (AD: 26 [2]; NC subjects: 29 [0.2], $p < 0.05$) and were more apathetic than NC subjects according to the two questionnaires completed by informants ($p < 0.05$). There were no significant group differences in percent hit rate for target stimuli, P3 latency to novel, background, or target stimuli, and P3 amplitude to background or target stimuli. In striking contrast, these patients with AD had a smaller mean P3 amplitude to novel stimuli (AD: 8[3] μ V; NC: 15[1] μ V, $p < 0.005$) and a smaller ratio of viewing duration novel stimuli to viewing duration background stimuli (AD: 1.8 [0.7]; NC: 2.8 [0.4], $p < 0.01$).

Discussion. The purpose of investigating the P3 response in the current study was to search for a marker of neural activity whose disruption could help explain important behavioral changes seen in AD, and contrasts with many reports in the literature that have focused on the potential diagnostic utility of the target P3 wave.³⁹⁻⁴² Both clinical and experimental observations note that even in the early stages of the illness, patients with AD show a reduced tendency to direct attention to the novel or interesting aspects of their surroundings^{4,5} and are often described as apathetic.¹⁻³ Previous work has suggested that such changes could not be explained simply by loss of cognitive capacity (dementia severity) or an inability to identify which stimuli are novel.³⁻⁵ The current study investigated other possible processing deficits that could contribute to these changes.

A major finding of this study is that, as predicted, the novelty P3 response is extremely disrupted in AD. The novelty P3 amplitude was much smaller for patients with AD than for NC subjects. Unlike NC subjects, patients with AD did not generate a larger P3 response to novel than background stimuli. This result is consistent with the very limited data about the novelty ERP responses that are found in the literature. Yamaguchi and colleagues⁴³ reported that patients with AD showed a reduced novelty P3 response to stimuli presented in the visual modality. In contrast, using an analogous task in the auditory modality, they did not find group differences.⁴⁴ However, reports of other ERP studies in the auditory modality have shown that, relative to NC subjects, patients with AD show more impaired electrophysiologic responses to novel stimuli under conditions in which subjects must attend to stimuli (i.e., to determine whether to respond to a target stimulus) than

under conditions in which they are told to ignore the auditory stimuli.^{45,46} In keeping with this observation, it is not surprising to have found robust differences in the novelty P3 between patients with AD and NC subjects under a condition in which subjects had to actively attend to novel stimuli.

A second major finding is that the markedly reduced novelty P3 response is observed very early in the clinical course of AD. It was seen across the whole group of patients with AD, whose mean MMSE score was 24, as well as in the least impaired AD subset, whose MMSE score was only 26. During the same stage of the disease in which patients with AD showed a very abnormal novelty P3 response, their target P3 response was relatively well preserved. As illustrated in figure 2, although there was no overlap between patients with AD and NC subjects in the mean \pm 95% CI of the novelty P3 amplitude, there was considerable overlap between groups for the target P3. Also of note, target P3 latency was not prolonged in patients with AD relative to NC subjects, a result that contrasts with much of the literature on target P3 response in patients with AD.⁴⁰⁻⁴² The overlap in P3 latency between the groups may be another indication of how early the patients with AD were in the course of their illness. It makes the finding of diminished novelty P3 amplitude in these AD patients even more remarkable.

The results of this study strongly support the hypothesis that, in contrast to NC subjects, patients with AD fail to generate an appropriate neural signal (i.e., the novelty P3) in response to the onset of a novel event. Extending the results of our prior work¹² to AD, the current study shows the powerful link between disruption of the novelty P3 response in patients with AD and their abnormal visual exploration of novel stimuli in their environment. Thus, another salient finding of this study is that, in patients with AD, the amplitude of the novelty P3 response accounted for more than half of the variance (52%) associated with viewing duration of novel relative to background stimuli.

What are the potential sources of these abnormal responses to novelty? One possibility is that they are completely explained by a nonspecific decline in attentional resources available to patients with AD. Alternatively, they may be linked more specifically to impairment of the neural system for attending to and processing novel stimuli. Patients with AD, especially late in the course in the disease, show diminished attentional abilities, especially in terms of the voluntary deployment of resources.^{20,47} The current study suggests that this cannot be the complete explanation for their reduced exploration of novel stimuli. Patients with AD were selected in a very mild stage of the illness. They did not show significant impairments in the P3 response to target stimuli, which argues against a nonspecific decrease in attentional capacity. Moreover, even the subset of AD patients who performed as well as NC subjects in identifying targets, suggesting relatively well-preserved attentional abilities, showed a

significant reduction of P3 amplitude and viewing duration of novel stimuli.

Results of this study powerfully suggest that disruption of the neural system that mediates the orienting to and processing of novel events contributes to the decline in the response of patients with AD to novelty. Converging evidence from studies employing depth electrodes, electrical source analysis, functional imaging, and patients with focal lesions suggests that the novelty P3 response is subserved by a distributed cerebral network with major components in frontal and temporolimbic areas.^{10,13-19} The distribution of pathology in early AD would be expected to impair the functioning of these crucial regions within the novelty processing system.

We strongly suspect that disruption of this novelty processing system also contributes to the disengagement and apathy that is commonly observed in patients with AD, even early in the disease. The novelty P3 response can provide an important window into the underlying physiologic changes that are associated with behavioral disengagement. The current study indicated a correlation between the degree of a patient's diminished novelty P3 response and his or her apathy severity. The link between impairment in novelty P3 response and behavioral changes in AD may increase understanding of improvements in neuropsychiatric symptoms (such as apathy) after treatment with cholinesterase inhibitors^{48,49} and serve as a marker to be followed in response to newer medications with potential disease altering properties. Our current work needs to be expanded, using a larger sample of patients with AD, who exhibit a wider range of dementia severity and a greater variation in their level of apathy.

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