Mechanisms Underlying Diminished Novelty-Seeking Behavior in Patients With Probable Alzheimer’s Disease

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Objective: To better understand apathy and disengagement in patients with Alzheimer’s disease (AD), the authors investigated possible behavioral mechanisms underlying diminished novelty-seeking activity in patients with probable AD. Background: Apathy and disengagement have been shown to be the most common behavioral changes associated with AD. Method: Patients and age-matched normal controls had their eye movements recorded while pairs of line drawings pitting an incongruous figure against a congruous figure were shown on a screen for 12 seconds. Characteristics of a subset of AD patients who were indifferent to novel visual stimuli as measured by exploratory eye movements were compared to those of a subset of AD patients who were attracted to novel stimuli to a degree similar to that of normal controls. Results: The indifferent patients were judged by informants, who completed a personality questionnaire, to exhibit a greater degree of apathy. The two AD groups did not differ in overall dementia severity or performance on a Saccade-to-Target Task that required shifts of attention and gaze. In a separate task, the indifferent patients were able to accurately identify the more novel stimuli in 97.5% of trials. Normal control subjects exhibited a strong bias toward processing novel stimuli, directing a higher proportion of their first fixations and dwell time to the incongruous stimuli whether the analysis was run for 3, 6, or 12 seconds of viewing. Indifferent patients did not direct their initial fixation toward novel stimuli and distributed their looking time evenly between incongruous and congruous stimuli throughout all measured intervals. Conclusions: The results suggest that the indifference to novelty observed in some patients with probable AD cannot simply be attributed to global cognitive decline, more elementary attentional deficits, or more rapid habituation of response to novel stimuli, or an inability to discriminate upon demand between stimuli of varying degrees of novelty. It is more likely that their behavior reflects a disruption, by AD pathology, of neural systems that modulate behavioral engagement and maintain attentional bias toward novel events in the environment. (NNBN 1999; 12:58-66)

Apathy and disengagement from the environment have been shown to be the most common behavioral changes associated with Alzheimer’s disease (AD) (1–9), and they often affect patients early in the course of the illness (2). Caregivers cite such changes in personality as one of the most distressing aspects of the disease (10). Most studies that have addressed apathy in AD have relied upon questionnaires, surveys, or structured interviews with caregivers. These studies have pointed to prevalence rates for apathy ranging between 46% and 92% (1,2,4–9).

Consistent with these observations about the behavioral indifference seen in AD, we have reported that as a group, patients are less engaged by and attracted to novel visual stimuli (11). When shown pairs of stimuli differing in the regularity of their elements or in their degree of incongruity (Curiosity Figures Task), as a group, AD patients
spent significantly less time than nondemented older control subjects visually exploring the novel stimuli as measured by eye movement recordings.

A closer examination of the data from our original report suggested that the differences between the AD group and normal controls may have been driven by a subset of AD patients who exhibited particularly aberrant responses to novel stimuli. We wondered what features, if any, distinguish this group of patients from others with AD. A richer characterization of the exploratory behavior of this subset of patients might allow us to better understand the factors that contribute to reduced novelty-seeking behavior in AD.

There are many candidate explanations for the diminished interest in novelty that we observed in patients with probable AD (PRAD). It could be due to (1) a global deterioration in cognitive status, (2) a general disruption of elementary systems for distributing and shifting attention and line of gaze, (3) an inability to discriminate which stimuli are more novel or incongruous, (4) an earlier habituation of response to novel stimuli, or (5) a diminished drive to explore novel/incongruous stimuli, despite being capable of identifying them. The first three hypotheses suggest that diminished curiosity and an apathetic response are mainly a reflection of a decline in cognitive abilities. The latter two hypotheses suggest that noncognitive processes such as reduced curiosity drive play an important role in diminished novelty-seeking behavior.

We tested these hypotheses using several approaches. Two groups of patients with probable AD who differed in terms of their responses to novel visual stimuli were identified. One group (PRAD-indifferent patients) reacted differently to novel stimuli and the other group (PRAD-curious patients) spent approximately the same proportion of time (over the 12-second viewing interval) as normal controls exploring novel stimuli. Comparing the performance of these two groups on tasks other than the Curiosity Figures Task provided an opportunity to examine the explanatory power of several proposed mechanisms to account for reduced novelty-seeking behavior in AD. If PRAD-indifferent patients were more severely demented or exhibited worse performance on attentional eye movement tasks compared to PRAD-curious patients, it would provide evidence in support of the first two hypotheses. We investigated the third hypothesis by testing whether PRAD-indifferent patients were capable of identifying which stimuli are incongruous or irregular, even if they do not prefer to spontaneously direct their attention and gaze to those stimuli. If they were incapable of identifying novel stimuli, one would predict that their performance would be at the level of chance. The fourth hypothesis was tested by a detailed analysis of the eye movement behavior of PRAD-indifferent, PRAD-curious, and nondemented age-matched controls in terms of first fixation (orienting response) (12) and percentage of dwell time spent on the novel stimuli during 3, 6, and 12 seconds of exposure to the pairs of visual stimuli. Based on the current literature examining apathy in AD (3,5,7,9,11), we predicted that the indifference some AD patients exhibit toward novelty would not be completely explained by an impairment of more general cognitive or elementary attentional abilities. Instead, we hypothesized a primary disruption of the natural tendency toward orienting to and exploring novel events in the environment (12–19) due to impairment in the neural systems that mediate these processes (20–30).

METHODS

Subjects

Seventeen patients (13 female, 4 male) with probable AD based on criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (31) participated in all protocols (PRAD-all). Patients were excluded if they (1) suffered from medical conditions such as hypothyroidism, vitamin B₁₂ deficiency, or neurosyphilis which could account for their dementing illness, (2) had evidence of infarction on computed tomography or T1-weighted images on magnetic resonance imaging, (3) had a Hachinski ischemic score (32) of greater than 4, or (4) had clinical evidence of major depression as defined by Diagnostic and Statistical Manual of Mental Disorders criteria (33). No subject was taking hypnotics, sedatives, or major tranquilizers. Thirteen age-matched normal controls (spouses of patients or community-dwelling volunteers, 10 female and 3 male) participated in the Curiosity Figures Task.

All subjects were given the Information-Memory-Concentration (IMC) subtest of the Blessed Dementia Scale (BDS) (34) to assess the overall severity of cognitive impairment. In addition, they were given a bedside neuroophthalmological examination (visual fields, pursuit movements, saccadic movements, and partial field optokinetic nystagmus) to test for elementary abnormalities of eye movement control which might influence performance on the experimental tasks. No subject exhibited significant impairment in ocular motility.

Informed consent was obtained from all subjects after the nature of the procedures had been fully explained. A family member of each patient cosigned the informed consent form.

Eye Movement Equipment

Eye movement data were collected using an Applied Science Group (Bedford, MA) Model 4000 video-based pupil center-to-corneal reflection system as described in detail in previous reports (11,13). No physical constraints or attachments were imposed on subjects while they viewed the stimulus presentation. Calibration was accomplished.
by having subjects fixate premapped locations on a computer monitor while eye position was recorded. All subjects were able to cooperate sufficiently to obtain an accurate calibration, which was checked before and after each task. The eye tracking system allows calibration accuracy to remain stable over the course of measurements.

Testing Procedures
At the start of an experimental session, demographic and medical information was elicited and the experiments were described. Informants completed a personality and behavioral questionnaire about the patient (see below). Each session consisted of the experimental tasks, the administration of the IMC subtest of the BDS, and a bedside neuro-ophthalmological examination, with ample time for rest periods throughout. For the eye movement experiment and the Novelty Identification Task, subjects were comfortably seated in the viewing room, which measured 1.5 × 1.4 m.

EXPERIMENTAL TASKS

Curiosity Figures Task
Ten pairs of stimuli were shown to subjects under two separate viewing conditions. These pairs of stimuli were a subset of the ones used by Berlyne (14) in his seminal studies on curiosity. One stimulus of each pair was a line drawing of an irregular or incongruous figure and the other was a regular or congruous counterpart to that figure (Fig. 1). Each stimulus subtended a visual angle of approximately 5° × 5° (vertical × horizontal), was well above threshold acuity and luminance levels, and was separated from the other stimulus (center to center) by approximately 18° of visual angle. Within the pairs presented, the incongruous figure appeared alternatively on the right or left side of the screen.

Condition 1 (Curiosity Figures Task) was relatively unstructured and spontaneous. Subjects were simply instructed to “look at the drawings however you like.” The pairs of figures were presented for 12 seconds each. A central cross at which the subjects were told to look was shown for 1 second between exposures. Under condition 2 (Novelty Identification Task), stimulus presentation was the same as for condition 1, but subjects were instructed to “point to the figure that is the more unusual or different one.”

Patients with probable AD first viewed the figures under the unstructured and spontaneous condition 1; later in the session, they viewed the figures under the more structured condition 2. The order of conditions was not randomized, as it was believed that the introduction of specific questions under the structured condition would influence subsequent viewing behavior. Condition 2 occurred approximately 15 minutes after condition 1. The intervening time included a rest period, the Saccade-to-Target Task (see below), and the administration of the bedside clinical neuro-ophthalmological examination. Normal controls were shown the pairs of figures under condition 1 only.

Eye movements were recorded under condition 1 while subjects viewed each pair of figures. For analysis, the display of each of the Curiosity Figures was divided into two main areas of interest (AOIs), consisting of boxes that were 10° × 11° (vertical × horizontal) of visual angle drawn around the incongruous and congruous stimuli. The final AOI represented the space on the screen not included in the AOIs surrounding the incongruous and congruous figures (called “neither” stimuli). The main dependent variable was the portion of dwell time, which was expressed as the percentage of total viewing time (i.e., the sum of all fixation times) that subjects spent fixating the AOIs surrounding the incongruous, congruous, or neither stimuli. These values were computed for the entire viewing duration (12 seconds per pair of figures) as well as for the 0 to 3-, 0 to 6-, 3 to 6-, and 6 to 12-second segments. The AOI within which a subject’s first fixation fell after stimulus onset was also determined. The relationships between visual dwell times during the first 3 seconds, second 3 seconds, and final 6 seconds of viewing were analyzed using regression analyses.

Under condition 2, the number of novel stimuli (of a total of 10) correctly identified was expressed as a percentage.

Saccade-to-Target Task
Patients also participated in a Saccade-to-Target Task. They were instructed to fixate on a 0.5° × 0.5° cross in the center of the screen until an empty box (5° × 5°) appeared 8° to the right or left of the cross for a duration of 200 milliseconds. They were told to look at the first box as soon

FIG. 1. Two examples from the Curiosity Figures Task. One stimulus differs from the other in terms of incongruity of parts (top) or irregularity of arrangement (bottom). (Reproduced from Berlyne (14), public domain.)

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as it appeared, to wait for the second box which would have an X or an O in it, and to look at it and silently note which letter appeared. The second box appeared on the screen for 450 milliseconds at 700 milliseconds after the erasure of the first box. All instructions were given while subjects were shown the sequence of events on the screen one step at a time. After subjects demonstrated that they understood the task, they were given 10 practice trials. Experimental trials ran continuously for 2 minutes, were evenly distributed to the right and left of screen center, and were presented in random order.

Dependent variables consisted of (1) percentage of correct trials (defined as any trial in which the initial saccade was in the direction of the target and the space subtended by $2^\circ \times 2^\circ$ of visual angle around the target position was subsequently fixated before target erasure) and (2) saccade latency (defined as the difference between the target onset time and the end of the previous fixation) for all correct trials.

**Personality and Behavioral Inventory**

Informants who knew the patients well completed a questionnaire developed in our laboratory on the current status of the patients’ personality and behavior. The inventory was modeled on the one used by Petry and associates (3). It consisted of 28 pairs of statements characterizing the extremes of a behavioral dimension. Informants were asked to judge where a patient fell on an 11-point scale (−5 to +5), where 0 represented the midpoint point between the extremes. Four of the items were developed to evaluate degree of apathy and included an assessment of (1) initiative, (2) participation, (3) interest, and (4) motivation. The paired statements were as follows: (1) extremely apathetic and content to do nothing/very energetic and often takes initiative, (2) never joins ongoing activities/enthusiastically participates in activities, (3) uninterested and insists on sticking to the same routine/curious and willing to try new things, and (4) needs constant supervision and direction/very independent and self-motivated. A score for each of the items was determined as was an Apathy Summary Score which averaged the results of all four items. 

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**Statistical Analysis**

Student’s $t$ tests were used to analyze intergroup data involving two groups (e.g., PRAD-indifferent vs PRAD-curious patients). ANOVAs were employed for intergroup data analysis involving the three groups (normal controls, PRAD-indifferent patients, and PRAD-curious patients) and were followed up by Duncan tests for multiple comparisons. If the variances were not normally distributed, nonparametric tests (e.g., Mann-Whitney $U$ statistic) were employed. Intragroup data were analyzed using paired $t$ tests or the Wilcoxon sign rank test. All $p$ values reported were two-tailed, except where indicated. Pearson correlation analysis was used to assess the relationship between BDS scores and performance on the Curiosity Figures Task. Regression analyses (SPSS, Chicago, IL) were performed to investigate how well visual dwell times on incongruous, congruous, and neither stimuli during early temporal intervals predicted visual dwell times during later different temporal intervals.

**RESULTS**

**Normal Controls Versus PRAD-All Patients**

There were no significant differences in mean age between the group of patients and normal controls; however, the normal controls had more years of education (Table 1). Patients were significantly more impaired on the IMC portion of the BDS (15.4 vs 0.72, $p < 0.01$). On the Curiosity Figures Task, normal controls spent significantly more time looking at the novel stimuli ($p < 0.05$) and significantly less time looking at neither stimuli ($p < 0.01$) than the patients with probable AD (see Table 1).

**PRAD-Indifferent Versus PRAD-Curious Patients**

PRAD-indifferent patients were defined as those patients whose percentage of dwell time on incongruous versus congruous stimuli differed by less than 6 percentage points. Eight of the 17 patients with probable AD fulfilled this criterion (7 female, 1 male). As a group, they spent 42.2% of their dwell time on incongruous stimuli compared to 42.1% on congruous stimuli ($p = 0.96$). Nine of the patients (6 female, 3 male) did not fit the criteria for PRAD-indifferent patients and were designated as PRAD-curious patients. As a group, they spent 51.1% of dwell time on the incongruous stimuli versus 35.8% of dwell time on the congruous stimuli ($p < 0.01$). The PRAD-curious patients were slightly older (74.9 ± 3.6 years) than the PRAD-indifferent patients (71.8 ± 6.7 years). There were no group differences in terms of years of education (Table 1).

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1 In an unpublished study from our laboratory involving 19 patients with probable AD (mean IMC score, 13.8) and 14 age- and education-matched controls (mean IMC score, 0.93), the mean score of the 28 personality variables as rated by the informants regarding the subjects’ current status was significantly more negative for AD patients than for normal controls ($p < 0.0002$). In contrast, there were no differences in the informants’ ratings for what subjects were like before the onset of clinical symptoms (for AD patients) or before retirement (for normal controls) ($p = 0.56$). In terms of the Apathy Summary Score, there were no differences between the AD group (2.72 ± 0.73) and the normal control group (3.5 ± 0.29) before the onset of the illness/retirement. In terms of current status, however, AD patients were much more apathetic (−0.51 ± 0.65) than normal controls (3.03 ± 0.77, $p < 0.0002$). The Apathy Summary Score correlated with a decline in the instrumental activities of daily living scale ($r = -0.41, p < 0.05$).

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1 The 6-percentage-point cutoff was chosen as it represented less than half of the average difference in percentage of dwell time on incongruous versus congruous stimuli observed in normal controls.
2). No patient in either group was clinically depressed or taking anti-depressant medication.

The performance of these two groups of AD patients was compared on the BDS, Personality and Behavioral Inventory, Saccade-to-Target Task, and Novelty Identification Task (see Table 2).

Dementia Severity

There were no statistically significant differences between PRAD-indifferent and PRAD-curious patients in terms of the IMC subtest of the BDS (17.4 ± 5.0 vs 13.7 ± 4.4, p = 0.16), although, on average, the PRAD-curious patients had slightly lower scores (see Table 2). Looking at all of the PRAD patients together, there was no significant correlation between dementia severity (IMC score) and percentage of dwell time on the incongruous stimuli (r = -0.27, p = 0.3).

Personality and Behavioral Inventory

PRAD-indifferent patients were judged by informants to be more apathetic than PRAD-curious patients on all four relevant items. The differences between the groups reached statistical significance (Mann-Whitney U statistic, one-tailed) for the Apathy Summary Score (−1.31 ± 1.29 vs 0.02 ± 1.08, p < 0.05) (see Table 2) and for the individual items evaluating lack of initiative (−2.00 ± 2.19 vs 0.38 ± 2.97, p < 0.05) and lack of motivation (−2.5 ± 1.76 vs −0.50 ± 1.51, p < 0.05). Group differences indicated a trend in the predicted direction for the items assessing lack of participation (−0.83 ± 2.40 vs 0.63 ± 2.13, p = 0.06) and lack of interest (−2.50 ± 2.17 vs −0.38 ± 2.97, p = 0.08).

Novelty Identification

PRAD-indifferent patients accurately identified the more novel stimulus 97.5% of the time. This performance was not significantly different from that of the PRAD-curious patients, which was 94.4%.

Attentional Eye Movement Task

On the Saccade-to-Target Task, there were no significant differences between PRAD-indifferent and PRAD-curious patients in terms of percentage of correct responses (47.9% ± 15.4 vs 47.9% ± 24.88, p = 0.81) or latency to initiate a correct saccade (232 ± 47 vs 223 ± 50 milliseconds, p = 0.85) (see Table 2). Although the normal controls in the current study did not participate in the Saccade-to-Target Task, prior work (35) has shown that compared to patients with PRAD, nondemented elderly patients have a much higher correct response rate (83%
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± 13%) but a similar latency (255 ± 78 milliseconds) of response.

Pattern of Eye Movements: Normal Controls Versus PRAD-Indifferent Patients Versus PRAD-Curious Patients

The pattern of eye movements for first fixations and across different temporal intervals (0–3, 0–6, and 0–12 seconds) is summarized in Table 3. The salient observations include the following. Only normal controls (not PRAD-curious or PRAD-indifferent patients) directed their first fixations significantly more often toward incongruous stimuli than toward congruous (p < 0.05) or neither stimuli (p < 0.01). In contrast to normal controls and PRAD-curious patients, PRAD-indifferent patients did not exhibit significant differences in percentage of dwell time on incongruous versus congruous stimuli during any of the temporal intervals. The viewing patterns of normal controls differed from those of PRAD-indifferent patients for first fixation (more on incongruous stimuli, less on neither stimuli, p < 0.03 by Mann-Whitney U statistic with Bonferroni corrections) and across all temporal intervals (larger percentage of dwell time on incongruous stimuli, smaller percentage of dwell time on neither stimuli, p < 0.05 by Duncan test). PRAD-curious patients did not differ from PRAD-indifferent patients in terms of their distribution of first fixations or percentage of dwell time on incongruous, congruous, or neither stimuli in the 0 to 3-second interval. In the 0 to 6- and 0 to 12-second intervals, however, PRAD-curious patients spent significantly more time on incongruous stimuli (p < 0.05 by Duncan test) and significantly less time on neither stimuli (p < 0.05 by Duncan test) than PRAD-indifferent patients.

Regression Analyses

The percentage of dwell time that each group spent on incongruous, congruous, and neither stimuli during the 0 to 3-, 3 to 6-, and 6 to 12-second intervals was examined using regression analysis. Normal controls exhibited an orderly and predictable pattern of eye movements and gaze preferences over the 12 seconds of viewing allotted. With only one exception, regression analysis revealed that the percentage of dwell time spent on incongruous, congruous, and neither stimuli during the first 3 seconds predicted the percentage of dwell time spent on each during the second 3 seconds and last 6 seconds (Table 4). Similarly, the percentage of dwell time spent during the second 3 seconds predicted the percentage of dwell time in the final 6 seconds.

In marked contrast, for PRAD-indifferent patients, the percentage of dwell time spent on incongruous, congruous, or neither stimuli during the first or second 3 seconds did not significantly correlate with the percentage of dwell time spent on each during subsequent periods. PRAD-

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<th>TABLE 3. First fixations and percentage of dwell time at 3-, 6-, and 12 seconds intragroup differences</th>
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<th>Dwell time of 6 seconds (%)</th>
<th>Dwell time of 12 seconds (%)</th>
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<tbody>
<tr>
<td>Group</td>
<td>Normal Controls</td>
<td>PRAD-Indifferent patients</td>
<td>PRAD-Curious patients</td>
<td>PRAD-curious patients</td>
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<td>Incongruous</td>
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APPLICATION signed rank test, p = 0.01.
curious patients also exhibited a much less predictable pattern of eye movement over time. Only the percentage of dwell time on neither stimuli during the first 3 seconds predicted the percentage of dwell time on neither stimuli during the second 3 seconds and the final 6 seconds (see Table 4).

**DISCUSSION**

Prior studies have demonstrated that apathy, disenagement, and indifference are the most common changes in behavior associated with AD (1–9). Apathy has been linked to a greater impairment in activities of daily living (7) and correlates strongly with degree of functional decline (36). To date, almost all of the studies on behavioral indifference in AD have been based on surveys, questionnaires, or interviews with reliable informants.

Our survey data revealed a greater degree of apathy and disenagement, as judged by informants, in patients who were indifferent to novel visual stimuli in the laboratory. This finding points to the real-world relevance of our laboratory-based study. A major advantage of our approach is that it allows for the exploration of the psychological mechanisms that may underlie these changes in behavior.

The study confirmed that as a group, patients with probable AD are less attracted to novel stimuli than age-matched nondemented controls. As with our original study (11), almost half (8/17) of the patients exhibited striking behavioral indifference to novel visual stimuli. Several mechanisms could account for this observation. The indifference seen in AD may be a direct consequence of cognitive deficits that lead to an inability to recognize which stimuli are unusual and thus to respond to all stimuli in a similar manner. If this were the case, one would predict that when such AD patients were explicitly asked to identify the more novel stimuli, they would perform close to chance (50%). In fact, on the Novelty Identification Task, the PRAD-indifferent patients successfully distinguished the more unusual or different stimuli on 97.5% of trials.

Clearly, these patients were able to attend to the task, discriminate between two figures, and cognitively identify the more unusual one.

The fact that overall cognitive decline cannot adequately explain indifference to novelty is also supported by the observation that there was no correlation between dementia severity (BDS) and performance on the Curiosity Figures Task. Furthermore, the difference in dementia severity between PRAD-indifferent and PRAD-curious patients was small and not statistically significant. Although the BDS does not provide a detailed survey of neuropsychological functions, it has been shown to yield a reliable measure of overall dementia severity closely correlating with decline in cognitive and functional status and with neuropathological markers of the illness (34,37–39). It is possible that with a larger sample, differences in overall severity between the groups of AD patients would have reached statistical significance, but the differences would probably remain relatively small and unlikely to explain a significant portion of the variance in novelty-seeking behavior. In keeping with these observations, Petry et al (3), Starkstein et al (7), and Bozzola et al (5) found no significant relationship between dementia severity and degree of apathy, and Craig et al (9) and Gilley et al (36) found only modest correlations between dementia severity (measured by the Mini-Mental State Examination) and personality changes.

Our data are not consistent with a related hypothesis that intellectual impairment causes AD patients to become overwhelmed by novel stimuli and thus to withdraw from or actively avoid them. If this were the case, we would have expected patients to have spent significantly more time looking at the congruous stimuli. In addition, PRAD-indifferent patients did not display behaviors to suggest that they were attracted to novel stimuli early in the course of viewing but then rapidly habituated their response. They did not orient their gaze to novel stimuli upon presentation of the pairs of figures, and they spent the same proportion of time looking at incongruous and congruous stim-
whether the analysis was run at the 3-, 6-, or 12-second point. Although more pervasive deficits in attention may be playing a role in the observed reduction in novelty-seeking behavior, this also does not appear to be an adequate explanation. PRAD-indifferent patients did not perform worse than PRAD-curious patients on the Saccade-to-Target Task, which required shifts of attention and gaze.

Although PRAD-curious patients exhibited a similar distribution of dwell times as normal controls for the 12-second interval, their eye movement behavior differed in several important ways. PRAD-curious patients were slower to orient to and focus on the novel stimuli, and their pattern of eye movements was much less consistent across temporal intervals. Normal controls were able to make a rapid assessment of which figure was more incongruous and to quickly orient their gaze in that direction. Their viewing preferences in the first and second 3-second intervals strongly predicted the subsequent pattern of gaze distribution, a finding not observed in PRAD-curious patients.

The current study as well as other recent reports in the literature (3,5,7,9) suggest that the brain systems mediating engagement, curiosity, and orientation to novelty can be markedly impaired in AD. PRAD-indifferent patients exhibited a reduction in the natural bias toward attending to novel stimuli in the environment which also characterizes the behavior of nondemented elderly controls and is one of the defining features of curiosity (11,13–20). Under the structured condition, the questions posed by the examiners to the PRAD-indifferent patients may have increased the engagement and attentional focus that was lacking under the spontaneous viewing condition. Without external prompting, these patients do not appear to spontaneously initiate or activate the attentional resources shown to be available under the structured condition, and they fail to direct these resources appropriately toward objects in their environment.

It is likely that AD disrupts the neural systems that have been shown to modulate behavioral engagement, including those of the basal forebrain, temporoparietal junction, limbic regions, and ascending monoaminergic pathways (21–24,40–48). Most importantly, the prefrontal cortex plays a central role in the control of novelty-seeking behavior and engagement with one’s surroundings (20,25,46,49–53). Recently, Craig and colleagues (9) found that in patients with probable AD, apathy was associated with more severe hypoperfusion in prefrontal and anterior temporal regions on single photon emission computed tomography. In AD, the extent of pathology in the frontal cortex is more variable than in posterior association cortices, especially in the early and middle stages of the illness (26–30,54–56). This may provide an explanation for the difference in novelty-seeking behavior exhibited by PRAD-curious and PRAD-indifferent patients. The latter group may be suffering from a greater degree of pathology within the frontal lobes or their connections. Future research on novelty-seeking behavior in patients with probable AD would be enhanced by including functional imaging studies and neuropsychological tests particularly sensitive to frontal lobe functions.

We conclude that in some AD patients, the diminished drive toward novelty can be dissociated from the sustained ability to recognize novel visual stimuli. The indifference to novelty exhibited by these patients cannot be solely attributed to global cognitive decline, more elementary attentional deficits, or an inability to discriminate upon demand between stimuli of varying degrees of novelty. It remains to be determined whether these neural systems can respond to pharmacological manipulations to improve performance on novelty-seeking tasks in the laboratory and more importantly to augment engagement in the activities of daily life.

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