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Relational Integration and Executive Function in Alzheimer's Disease

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Executive functions depend on the ability to represent relations between objects and events, and the prefrontal cortex provides the neural substrate for this capacity. Patients with probable Alzheimer's disease (AD) and control participants were administered measures of working memory and reasoning that varied systematically in their relational complexity. AD patients showed impairment on reasoning measures that required the online integration of relations but performed as well as control participants on nonrelational items and items requiring the processing of only single relations. When AD patients were divided into subgroups based on their performance on relational reasoning measures, the subgroup that showed significant impairment on relational integration measures exhibited a neuropsychological profile consistent with prefrontal cortical dysfunction.

Alzheimer's disease (AD) is the most common cause of dementia and is characterized by global cortical atrophy, resulting in deficits in declarative memory function and other cognitive domains. Dementia associated with AD is also characterized by a variety of impairments in higher level cognitive abilities. The extent to which these deficits result from domain-general executive dysfunction is not clear, given that many high-level cognitive tasks require multiple cognitive abilities. Thus, it is important to use tasks in which specific components of executive function can be examined. Furthermore, the neuropathological heterogeneity of patients with AD raises the possibility that executive deficits may be present in only a subset of those patients with mild or moderate AD.

An important question in the study of AD is whether qualitatively different subtypes exist that are the result of different etiological factors. It is difficult, however, to distinguish between qualitatively distinct subtypes, quantitative variability that leads to different impairment patterns, and differences in the time course of the appearance of symptoms (see Jorm, 1985, for a review). Although it is not clear if there are distinct etiological subtypes of AD, it is apparent that patients can be divided into subgroups, based on symptomatology, and that these subgroups are clinically relevant. For example, in a study of 181 patients with probable AD, a cluster analysis identified four subgroups of AD patients on the basis of different degrees of executive function impairment (Butters, Lopez, & Becker, 1996). All four groups exhibited severe memory impairment, while one of the groups showed intact executive function. This group was shown to have a slower disease progression than the other groups. The subgroup with normal executive abilities appeared to have a selective memory impairment, consistent with dysfunction limited to the temporal lobe.

When one examines memory deficits in AD more closely, furthermore, ample evidence indicates that, in many cases, short-term memory deficits, in particular, can often be attributed to failures of executive control rather than to impairments in short-term phonological memory (Morris & Baddeley, 1988). For example, although patients with AD demonstrate a relatively unimpaired recency effect in free recall and only a moderate impairment in memory span, they show significant impairment in short-term memory following distraction (Corkin, 1982; Dannenbaum, Parkinson, & Inman, 1988; Kopelman, 1985; Sullivan, Corkin, & Growdon, 1986). Cherry, Buckwalter, and Henderson (1996) found that the measure of cognitive control providing the best predictor of dementia severity in AD patients, as well as success rates on other neuropsychological measures, was a test of backward visual memory span. This finding is significant in that this measure represents a straightforward test of the ability to perform operations on information being held in short-term memory—the functions that define the concept of working memory. On the basis of analyses of the working memory impairments in AD, several authors (Becker, Boller, Saxton, McGonigle-Gibson, 1987; Morris & Kopelman, 1986) have argued for the existence of multiple, distinct patterns of cognitive impairment within AD: one centered around compromised declarative memory systems and one related to deficits in working memory and/or executive function.

Because of the wealth of evidence linking cognitive executive function to frontal cortical physiology, one might suspect that, if

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subgroups of patients with AD can be delineated on the basis of the results of psychological tests of executive function, they might also be distinguished through the identification of markers of frontal cortical pathology. In fact, evidence of AD-associated frontal cortical pathology comes from histological analyses. Arriagada, Growdon, Hedley-Whyte, and Hyman (1992), for example, described neurofibrillary tangles (NFTs) in frontal regions in AD patients with illness duration of more than 1 year. Furthermore, Johnson, Head, Kim, Starr, and Cotman (1999) established a correspondence between histological markers and the results of psychological testing, describing a subgroup of patients with AD who had exhibited disproportionate deficits in tests of executive functioning early in the course of the disease and who were found to show increased NFT pathology in the frontal lobes. Thus, there appears to be clear evidence for frontal pathology in AD, and it appears that this pathology may occur relatively early in the course of the disease in a subset of patients.

The purpose of the present study was to sort patients with AD into subgroups on the basis of their executive function performance using a formulation that quantifies the demands placed on executive capacities by different kinds of abstract problems by characterizing their relational complexity. Measures developed based on this system for quantification distinguished between problems that required the ability to integrate multiple cognitive relations, and thus placed high demands on executive capacities, and those that did not require the simultaneous consideration of multiple cognitive relations, and thus placed low demands on executive capacities. Once divided into subgroups on the basis of their performance on these measures, patients were then compared on standard neuropsychological tests in order to explore differences in the cognitive profile of these two subgroups.

Relational complexity has been proposed as a predictor of the reliance of problems on cognitive executive functions, as well as the degree of frontal involvement in a cognitive task (Halford, Wilson, & Phillips, 1998; Robin & Holyoak, 1995). This hypothesis is based on observations that stages in human cognitive development may be delineated by the ability to process relational representations of different complexities (Halford, 1984; Halford & Wilson, 1980). The present investigation follows our previous finding that the ability to integrate relations may be lost as a consequence of focal frontal degeneration (Waltz et al., 1999). That study examined relational processing abilities in two subgroups of frontotemporal dementia patients, those with focal anterior, temporal-lobe degeneration and those with evidence of frontal-lobe damage, using two sets of problems that varied in whether they required the integration of relations in the making of inferences. Patients with focal frontal brain damage showed selective impairment in the ability to integrate relations online, although they demonstrated relative preservation of static relational knowledge in semantic memory. In contrast, patients with anterior temporal damage were unimpaired on measures of relational integration.

In the present study, we examined relational processing abilities in AD patients by using the same two measures. By specifically manipulating relational complexity, we hoped to more precisely characterize executive impairments in AD patients than in previous work using standard neuropsychological tests. While several studies have revealed that AD patients show impairment on tests of reasoning and problem solving, no previous study has sought to systematically manipulate the complexity of abstract problems and to characterize the relations between relational reasoning performance and performance on standard tests of frontal lobe function. We hypothesized that AD patients would show impairment on measures dependent on the integration of relational representations. We also hypothesized that those patients with greater difficulty on problems requiring relational integration would perform more poorly on experimental and standard neuropsychological measures of working memory and executive function, but not necessarily on measures of episodic memory or domain-specific (e.g., language or visuospatial) processing.

Accordingly, participants were administered an experimental test of working memory function to determine if a dissociation similar to that predicted for relational reasoning would be observed in the performance of the groups on a working-memory task that requires participants to hold multiple relations in short-term memory and perform operations on them. In this measure, called the "*n*-back task" (Cohen et al., 1997; Jonides et al., 1993), participants are presented with series of items and are required to compare each item to the object *n* positions back and report whether the two items were the same or different. A larger *n* corresponds to an increased demand on working memory. For example, the 1-back condition requires the participant to hold in memory only the relation between the present letter and the previous letter, whereas the 2-back condition involves the maintenance of the temporal relations among three letters. Studies using functional magnetic resonance imaging with the *n*-back task have revealed dramatic increases in activation in mid-dorsolateral prefrontal cortex (Brodmann areas 9 and 46) between the 1- and 2-back conditions (Braver et al., 1997; Cohen et al., 1997). On the basis of the observation that the ability to dynamically integrate relations may be lost as a consequence of focal frontal degeneration (Waltz et al., 1999), we hypothesized that those AD patients with poor relational reasoning abilities would show impairment in the 2- and 3-back conditions of the *n*-back task relative to other AD patients, but that the two patient groups would exhibit similar performance in the 1-back condition.

Method

Participants

Study participants included 19 patients diagnosed with probable AD (9 men and 10 women) and a group of control participants consisting of 20 individuals recruited from among the spouses of patients and from senior recreation centers in the community (8 men and 12 women). Patients were assessed through extensive neurological examinations in dementia clinics at the University of California, Los Angeles, and were diagnosed with probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA; McKhann et al., 1984). Scores on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) ranged from 16 to 28. Assessment included a comprehensive neurological examination, laboratory studies, and neuropsychological testing as prescribed by the Technology Assessment Committee of the American Academy of Neurology (1994). The mean ages of the two participant groups were as follows: AD = 74.5 ± 1.5 years and controls = 75.3 ± 1.6 years. Educational attainment was also similar in the groups (AD = 14.8 ± 0.9 years and controls = 15.2 ± 0.4 years).

Materials and Procedure

All patients received a battery of standard neuropsychological tests, including either the Satz–Mogel version (Satz & Mogel, 1962) or the full version of the Wechsler Adult Intelligence Scale—Revised (WAIS–R;

Wechsler, 1981), the Wechsler Memory Scale—Revised (WMS–R; Wechsler, 1987), Rey–Osterrieth Figure Drawing (Osterrieth, 1944), the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), the Controlled Oral Word Association (COWA) Test (Bechtold, Benton, & Fogel, 1962), the Trail-Making Test (Reitan, 1955), and the Stroop test (Golden, 1978), all of which were administered in a separate 3-hr session.

Relational Integration Measure 1: Transitive inference problems. As a measure of deductive reasoning, participants were presented with transitive inference problems. Each item involved between two and four propositions. Each proposition was enclosed in a rectangle and stated a "taller than" relation between two individuals, which was presented as a card displaying a name on top, the words *taller than* in the middle, and a name below. The participants' task was to arrange cards corresponding to the individuals in descending order of their heights. In the one-relation version (Level 1 complexity), the pairs introduced the names in order of height (e.g., "Sam taller than Nate" and "Nate taller than Roy"). The correct ordering could therefore be achieved using a chaining strategy that proceeds one link at a time: to build a link, only one relation—that between the name currently at the end of the chain and its successor—need be considered. In the two-relation version of the task (Level 2 complexity), the pairs were introduced in a scrambled order (e.g., "Beth taller than Tina" and "Amy taller than Beth") so that the item currently at the end of the chain was not in the subsequent pair, making the chaining strategy inapplicable. The reasoner must therefore consider two relations simultaneously to determine the overall ordering of three names. Preschool children can solve one-relation transitive inference problems by chaining, but reliable success with two-relation problems is not observed prior to age 5 (Halford, 1984).

The ordered (Level 1) and scrambled (Level 2) problem sets each included three problems, which involved two propositions (three people), three propositions (four people), and four propositions (five people), respectively. A different set of names was used for each problem, and all propositions remained in view throughout the trial, eliminating any need for maintenance of information in memory.

Immediately following the transitive inference test, participants were administered a test of recognition memory for problem elements. The participant was presented with a list of nine pairs of first names, with each pair consisting of one name that had been used on the transitive inference test and one name that had not been presented during the experiment. The participant was asked to indicate which name from each pair had been on the test. This incidental recognition test provided a measure of participants' memory for recent episodes based on materials comparable to those used in the prior reasoning test.

Relational Integration Measure 2: Matrix problems. Inductive reasoning was assessed using problems adapted from the Raven Standard Progressive Matrices Test, which has long been used as a measure of cognitive skill (Carpenter, Just, & Shell, 1990; Raven, 1976). Nonrelational problems (Level 0 complexity) involved a visual pattern, with a blank space in the bottom right-hand corner (see Figure 1A). The participant completed the pattern by selecting from six possibilities, which could be done by simple pattern matching. Each one-relation problem (Level 1 complexity) involved a 2×2 matrix that required processing one relational change over either the horizontal or the vertical dimension; the other dimension was constant (Figure 1B). Two-relation problems (Level 2 complexity) required integrating two relational changes over the horizontal and vertical dimensions, respectively (Figure 1C). Thus, although the basic form of the task was constant across the three types of matrix problems, only the two-relation problems necessitated relational integration. A total of 20 problems were administered (7 at Level 0, 6 at Level 1, and 7 at Level 2).

Working memory measure: The n-back task. The *n*-back task has previously been used in human neuroimaging studies of working memory (Cohen et al., 1997; E. E. Smith et al., 1995). This task involved the presentation of a series of letters one at a time on a computer screen and required the participant to indicate whether each letter is the same as, or different from, the letter *n* positions back, where *n* was 1, 2, or 3 for a given block of trials (see Figure 2). We presented participants with five blocks of five test letters for each value of *n*. Each letter was displayed for 900 ms and was followed by the presentation of a blank screen for 3,600 ms for a total 4,500 ms between the onset of each letter. On seeing each letter, the participant indicated the response vocally, and the experimenter entered the response manually. Each letter was presented in its capital form and was the same as the letter *n* positions back on 50% of trials. Before each set of blocks at each value of *n*, instructions for the task were presented on the screen and read to the participant. Each participant then performed a practice block of letters before each set of five experimental blocks to confirm that the participant understood the instructions.

Testing was generally done in a single 2-hr session, with the transitive inference items presented first, immediately followed by tests of recognition memory, the set of matrix problems, and finally the *n*-back task. Of 19 AD patients, 3 were not administered the *n*-back task and 5 received only the 1- and 2-back versions because of time constraints. Otherwise, all AD patients completed all measures. All control participants received all tests, except for 1 who did not receive the *n*-back task and 1 who did not receive the matrix problems.

Results

Initial analyses compared performance of AD patients and control participants, using analyses of variance (ANOVAs). In a second phase of the analyses, AD patients were divided into subgroups on the basis of their performance of relational integration measures. Patients who scored more than two standard deviations below the control mean on at least one of the relational integration measures were assigned to the AD/relational integration (RI)− group, while the remaining patients were assigned to the AD/RI+ group. Because distributions of scores were nonnormal, nonparametric Mann–Whitney *U* tests were used for comparisons between patient groups on neuropsychological and characterizing measures.

Relational Integration Measures

Figure 3A depicts the performance of AD patients and control participants on transitive inference problems. An ANOVA comparing the patient and control groups revealed a significant main effect of participant group, $F(1, 37) = 9.69$, $p < .01$, a significant main effect of relational complexity, $F(1, 37) = 27.18$, $p < .01$, and a trend toward a significant interaction between the two variables, $F(1, 37) = 3.44$, $p = .07$, apparently resulting from a disproportionately larger difference for the two-relation problems than the one-relation problems for the AD patients versus the control participants. There was a significant difference between the scores of the AD patients (74.8 ± 2.7%) and those of control participants (86.1 ± 2.9%), $t(37) = 2.85$, $p < .01$, on the forced-choice recognition test of names used in the transitive inference task.

Figure 3B shows the performance of the AD patients and control participants on the matrix problems at each level of complexity. When the performance of AD patients was compared with that of control participants, an ANOVA revealed main effects of group, $F(1, 36) = 20.08$, $p < .01$, and complexity level, $F(2, 72) = 70.18$, $p < .01$, as well as a significant interaction between the two independent variables, $F(2, 72) = 5.41$, $p < .01$. The interaction apparently resulted from the fact that the group difference was much larger for the two-relation problems than for the other problems. If the groups are compared on only the nonrelational and two-relational matrix problems, the Group × Complexity interaction persists, $F(1, 36) = 4.93$, $p < .05$.

Working Memory Measure

Performance of AD and control groups on the *n*-back task was significantly different (see Figure 4). For participants who com-

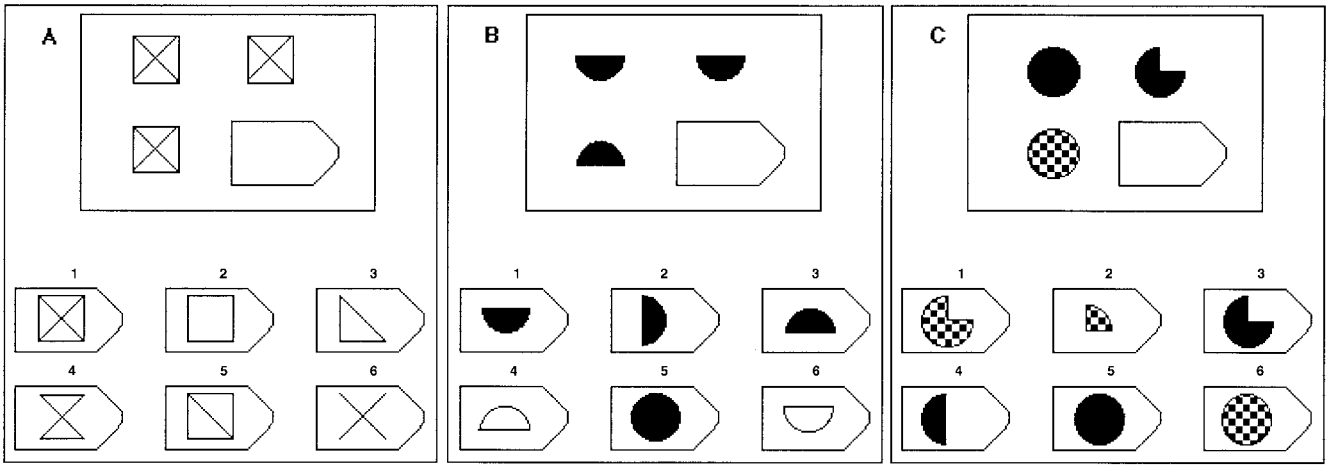

Figure 1. Examples of matrix problems. A: A nonrelational problem (Level 0) requiring only perceptual matching (correct response is Choice 1). B: A one-relation problem (Level 1). Participants need only to maintain the transformation along the vertical dimension (reflection across the *x*-axis) to choose the correct alternative (Choice 3). C: A two-relation problem (Level 2). Participants must integrate the relation along the vertical dimension (solid to checked pattern) and the relation across the horizontal dimension (removal of the upper right quadrant) to make the correct response (Choice 1).

pleted the 1- and 2-back tasks, an ANOVA revealed main effects of group, $F(1, 33) = 15.17$, $p < .01$, and load, $F(1, 33) = 36.38$, $p < .01$, as well as a significant interaction between the two independent variables, $F(1, 33) = 4.78$, $p < .05$. For participants who completed the 3-back version of the test as well, the results were similar, in that there was also a main effect of group and load, and an interaction between these variables. The interaction resulted from the fact that the AD patients performed worse than control

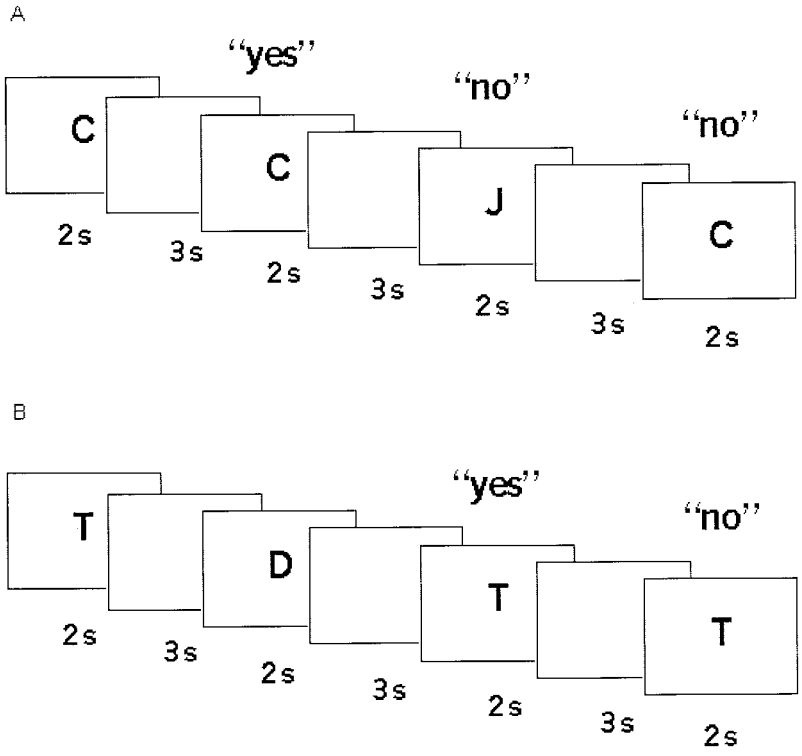

Figure 2. Illustration of the *n*-back task. A: A 1-back task, in which the participant must indicate whether each letter is the same or different as the letter just before it. B: A 2-back task, in which the participant must remember the exact positions of multiple letters to make a judgment.

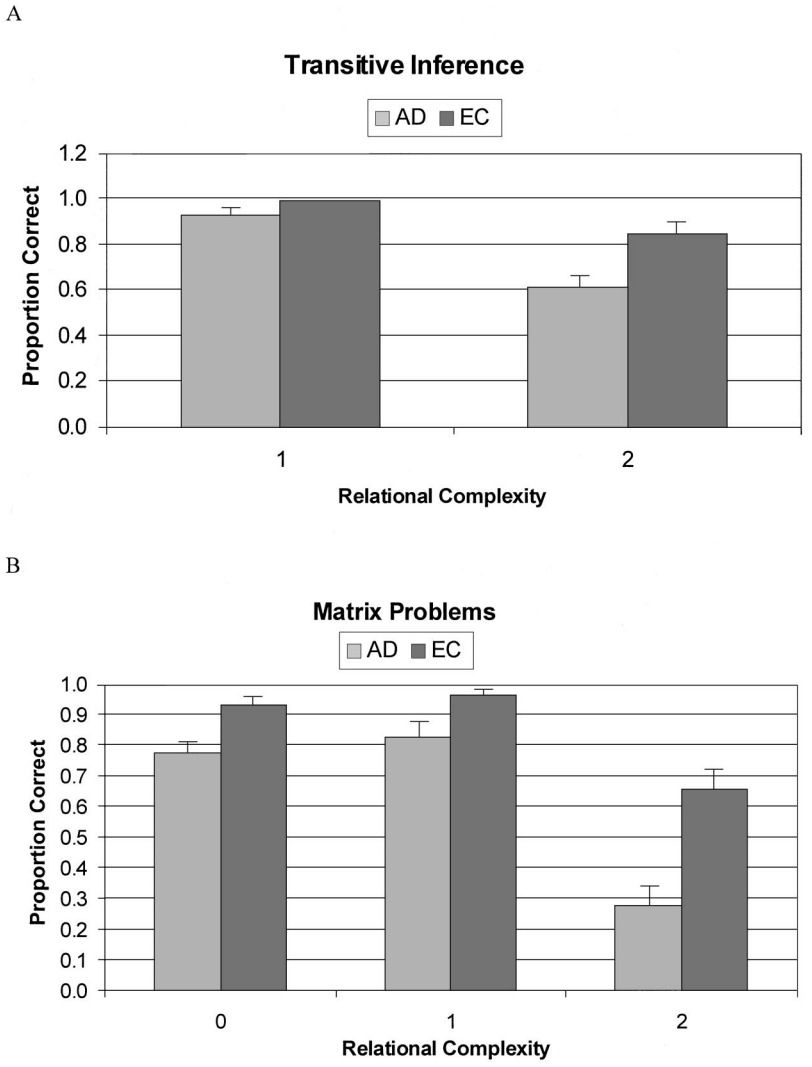

Figure 3. A: Performance of participant groups on transitive inference problems. All of the control participants performed at 100% on the one-relation problems. B: Performance of Alzheimer's disease (AD) and elderly control (EC) groups on visuospatial matrix problems. Error bars reflect one standard error of the mean in each direction.

participants on the higher load conditions, but performed similarly to control participants in the 1-back condition.

Comparisons Between Subgroups of AD Patients

When AD patients were divided into those who performed poorly on the relational integration tests (AD/RI−) and those who performed within the normal range (AD/RI+), several differences emerged between these groups (see Table 1). Three patients were classified as AD/RI− on the basis of their transitive inference performance, 4 patients were classified as AD/RI− according to their performance on the matrix problems, and 1 patient performed more than two standard deviations below the control mean on both tasks. Although 7 patients were classified on the basis of their low performance on one of the tasks, their performance on the other task was uniformly poor, although not quite two standard deviations below the control mean. The AD/RI− group was significantly worse on neuropsychological tests that measure executive function, such as the Similarities subtest of the WAIS–R, the ratio of Part B to Part A on the Trail-Making Test, and the interference condition of the Stroop Color–Word Test. Interestingly, the groups did not differ on the COWA test, suggesting that this verbal fluency measure taps into a somewhat different set of processing capacities (such as retrieval from long-term semantic memory), when compared with the other executive tasks used.

The AD/RI− subgroup was also impaired relative to the AD/RI+ group on the 3-back condition of the *n*-back, with a strong trend for an impairment on the 2-back condition as well ($p < .07$), suggesting that the patients who had difficulty with relational integration also had difficulty with increasing working memory load. Performance of the two groups was nearly identical on the 1-back version of the *n*-back task.

In contrast to the differences in executive function and working memory, the two groups of AD patients performed similarly on other measures (see Table 1). There were no differences in MMSE

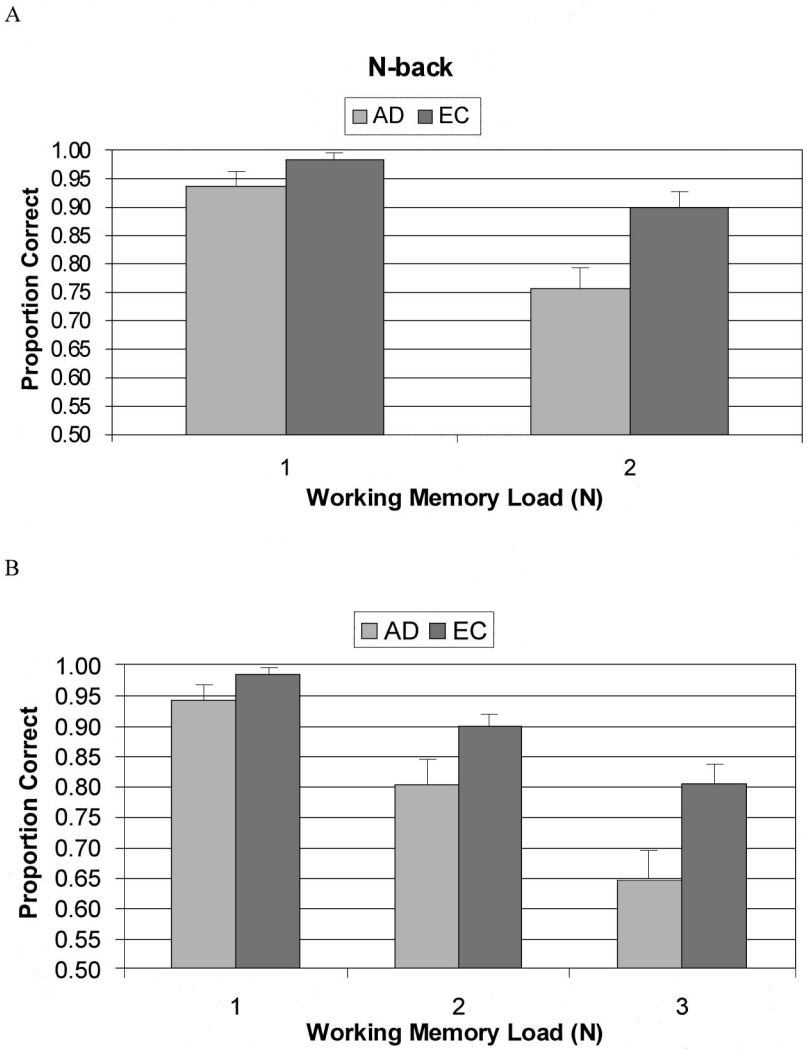

Figure 4. Performance of Alzheimer's disease (AD) and elderly control (EC) groups on the *n*-back task. A: Performance of the 16 AD patients and 19 EC participants on the 1-back and 2-back tasks. B: Performance of the subgroup of 11 AD patients who additionally completed the 3-back task as compared with the 19 EC participants. Error bars reflect one standard error of the mean in each direction.

($p > .4$), Full Scale IQ ($p > .5$), all subtests of the WMS–R ($ps > .15$), copying and recall of the Rey–Osterrieth figure ($ps > .5$), and the Boston Naming Test ($p > .65$). In addition, performance was nearly identical for the two patient groups on the recognition test for names used in the transitive inference task (74 ± 4% for the AD/RI− subgroup vs. 76 ± 4% for the AD/RI+ subgroup), although these groups differed substantially on the relationally complex inference generation part of the task (38% for the AD/RI− subgroup vs. 79% for the AD/RI+ subgroup). Thus, it appears that the AD/RI− subgroup did not show an overall cognitive impairment relative to the AD/RI+ group, but this group performed particularly poorly on tests of executive capacities sensitive to frontal-lobe function.

There was a trend for AD/RI− patients to be older than AD/RI+ patients ($p < .07$). Because executive functions decline with age, it is possible that this age difference could account for the differences in relational integration ability in the two groups. However, it is unlikely that age alone is responsible for these deficits because the mean age of control participants, who performed relatively well on relational integration, was not significantly different from the mean age for the AD/RI− group. It is possible that the patients in the AD/RI− group were at a more advanced stage of the disease than the patients in the AD/RI+ group. However, the similarity between MMSE scores and other cognitive measures for the two groups argues against this possibility. Finally, it is possible that deficits in relational integration and executive function may be more pronounced in patients who develop AD at an older age. Interestingly, the patients in the frontal-variant group described by Johnson et al. (1999) on the basis of neuropathological evidence had disease onset 7 years later than their standard AD group. Although this difference was not statistically significant in their study, it appears that the relation between age of AD onset and incidence of executive dysfunction deserves further investigation.

Table 1
Performance of Subgroups of AD Patients on Neuropsychological Measures

Measure	AD/RI−			AD/RI+				
	n	*M*	*SE*	*n*	*M*	*SE*	*U*	*p*
Characterizing								
Age	8	77.63	± 1.74	11	72.18	± 2.05	22.0	.068*
Education	8	13.75	± 1.16	11	15.55	± 1.26	29.5	.221
MMSE	7	22.43	± 1.62	11	24.18	± 0.76	30.0	.431
Working memory								
1-back proportion correct	8	0.95	± 0.03	8	0.93	± 0.04	28.5	.696
2-back proportion correct	8	0.69	± 0.05	8	0.83	± 0.04	14.5	.064*
3-back proportion correct	4	0.52	± 0.06	6	0.73	± 0.04	2.0	.031**
Declarative memory								
Forced-choice recognition	8	0.74	± 0.04	11	0.76	± 0.04	39.5	.692
WAIS–R								
Full Scale IQ	8	97.50	± 4.20	11	102.46	± 4.78	36.5	.535
Verbal IQ	8	96.00	± 4.61	11	103.00	± 4.45	31.0	.283
Performance IQ	8	100.63	± 6.58	11	101.09	± 5.23	43.0	.934
Information	8	17.50	± 1.88	11	18.55	± 2.15	39.0	.677
Vocabulary	8	36.00	± 6.49	11	40.73	± 6.99	36.0	.508
Similarities	8	9.00	± 2.30	11	15.27	± 1.27	17.0	.025**
Maximum Digit Span Forward	7	6.29	± 0.36	9	6.22	± 0.43	30.5	.911
Maximum Digit Span Backward	7	3.86	± 0.26	9	4.22	± 0.32	25.0	.457
WMS–R								
Logical Memory I	8	7.50	± 2.22	11	10.64	± 1.13	32.0	.319
Logical Memory II	8	1.25	± 1.00	11	2.55	± 1.05	28.5	.164
Spatial Processing and Memory								
Rey–Osterrieth Copy	8	25.31	± 3.30	11	26.05	± 3.43	37.0	.561
Rey–Osterrieth 3-min Delay	8	3.25	± 1.25	11	5.00	± 1.89	39.0	.672
Executive								
COWA	8	27.88	± 5.80	11	29.73	± 4.17	39.5	.710
Animals	8	9.88	± 1.34	11	12.82	± 1.02	27.0	.158
Trail-Making A (s)	8	74.25	± 13.01	11	64.73	± 9.03	35.0	.457
Trail-Making B (s)	4	159.25	± 18.87	9	135.67	± 15.47	24.0	.093*
Trail-Making B:A	4	3.71	± 0.64	9	2.32	± 0.21	17.0	.024**
Stroop Read (s)	8	72.88	± 8.42	11	61.09	± 6.00	28.0	.186
Stroop Color-Naming (s)	7	103.86	± 10.50	10	95.50	± 8.01	37.5	.591
Stroop Interference (s)	4	262.50	± 49.00	9	185.44	± 15.07	21.0	.054**
Stroop Interference: Color-Naming	4	2.62	± 0.16	9	2.10	± 0.24	23.0	.081*
Semantic knowledge								
Boston Naming (60 items)	7	45.14	± 3.38	11	46.27	± 2.65	33.5	.650

Note. Average times on the Trail-Making and Stroop tests are for patients who completed those parts of the tests. All patients were administered all parts of the Trail-Making and Stroop tests, but 6 patients were unable to complete Part B of the Trail-Making Test in the allotted time, and 6 patients were unable to complete the inconsistent part of the Stroop test. These patients were given the lowest rank on these measures for the purpose of analysis with Mann–Whitney tests. One asterisk indicates a trend for a difference at the $p < .10$ level. Two asterisks indicate a significant difference at the $p < .05$ level (two-tailed). AD/RI− = Alzheimer's disease patients who performed poorly on the relational integration tests; AD/RI+ = Alzheimer's disease patients who performed within the normal range on the relational integration tests; MMSE = Mini-Mental State Examination; WAIS–R = Wechsler Adult Intelligence Scale—Revised; WMS–R = Wechsler Memory Scale—Revised; COWA = Controlled Oral Word Association test.

Discussion

Impairment of Working Memory and Reasoning in AD

We found that AD patients showed a distinctive pattern of performance on measures of relational reasoning, relative to age- and education-matched control participants, in that they exhibited impairment on problems requiring the integration of multiple relations but not single relations. In contrast, performance of the AD group was relatively good on one-relation problems. When the sample of AD patients was divided into subgroups, on the basis of their relational integration ability, patients who performed poorly on relational integration measures exhibited a marked deficit in performance on three standard measures of executive function, relative to AD patients who showed little or no impairment on relational integration measures. Both patient subgroups performed as well as control participants on problems requiring only the manipulation of single relations in isolation.

It is of note that decrements in performance on multirelation reasoning problems appeared to occur independently of deficits in episodic memory in patient groups, paralleling the finding that medial temporal lobe and frontal lobe deficits are dissociated in normal aging (Winocur, Moscovitch, & Strauss, 1996), as well as observations that frontotemporal dementia patients and AD patients can be dissociated on the basis of differences in episodic memory (Hodges et al., 1999). The present results suggest that a subset of patients with AD may resemble frontal patients in terms of deficits in relational reasoning (Waltz et al., 1999). These data also indicate that relational integration tasks may be sensitive to prefrontal cortical dysfunction in AD and may be useful for detecting prefrontal dysfunction in a variety of neurological conditions.

The patients in the present study showed impairments in relational integration on both a deductive task and an inductive reasoning task. Because AD patients performed relatively well on one-relation and nonrelational versions of these tasks, it was not the case that AD patients were unable to understand the instructions or attend to the stimuli. However, the problems that did not require relational integration were quite easy for control participants, raising the possibility that ceiling effects masked a general reasoning impairment in AD patients. Although ceiling effects were present for the one-relation transitive inference problems and the one-relation matrix problems, performance of the control participants (93% $\pm$ 2.6) was significantly lower than 100% for the nonrelational matrix problems, possibly because some fairly difficult pattern matching items were included. As was shown, the Group $\times$ Complexity interaction persists if the groups are compared on only the nonrelational and two-relational matrix problems. Thus, it appears that patients with AD had particular difficulty when required to integrate multiple relations.

In general, the present findings provide support for the hypothesis that intact prefrontal cortex is necessary for the on-line integration of relational representations and that this capacity may constitute the essence of executive function. The need to represent and integrate relations may be a fundamental characteristic of tasks dependent on prefrontal cortical function, including standard neuropsychological assessment tools, such as the Wisconsin Card Sorting Test, the interference condition of the Stroop task, and Part B of the Trail-Making Test. The Stroop task, for example, requires participants to represent the written color name and the ink color as separate stimulus features, in order to respond to each independently. The Trail-Making Test (Part B) requires participants to integrate multiple independent series.

The present findings are consistent with those of a number of studies showing impairments in executive function fairly early in the course of AD (Perry & Hodges, 1999). The deficit in relational integration ability described in the present study is similar to the deficit seen by Lafleche and Albert (1995) in tasks requiring the concurrent manipulation of information. In this study, patients with mild AD were impaired on Part B of the Trail-Making Test and the Hukok Matrices Test (Daryn, 1977), which requires the synthesis of relations across more than one parameter. In addition, because abstract thought relies on the ability to integrate multiple relations, in that propositional elements need to be mapped across domains (Halford et al., 1998), the present findings are consistent with those of a number of studies showing impairments in abstract thought in mild-to-moderate AD. Studies have demonstrated difficulties in patients with AD in identifying similarities between objects or concepts (Huber, Shuttleworth, & Freidenberg, 1989; Martin & Fedio, 1983; Pillon, Dubois, Lhermitte, & Agid, 1986), in the comprehension of proverbs (Kempler, van Lancker, & Read, 1988), and in what have been termed *generational abilities*, an idea closely related to the capacity to perform inductive inference (Cronin-Golomb, Rho, Corkin, & Growdon, 1987). The results of additional studies suggest that individuals with AD experience particular difficulty in the performance of tasks of cognitive estimation, another form of inference (Goldstein, Green, Presley, & Green, 1992; Shallice & Evans, 1978; M. L. Smith & Milner, 1984). Quantifying the complexity of problems from neuropsychological tests in terms of relations, as we have done here, might provide a means for better understanding the types of problems that cause particular difficulty for individuals with impaired cognitive executive capacities that are due to frontal lobe dysfunction.

Integrating Behavioral and Neuroimaging Evidence for Subgroups of Patients With AD

We identified a subgroup of patients with AD who showed a pattern of performance relational reasoning measures similar to that of a group of patients with focal frontal lobe degeneration. Our findings are thus consistent with the results of studies showing evidence of a role for frontal cortical hypometabolism and deficits in executive function in AD. Using single photon emission computed tomography (SPECT), Eberling, Reed, Baker, and Jagust (1993) found, for example, that relative perfusion rates in orbitofrontal cortex correlated with performance on a cluster of neuropsychological measures of cognitive executive functions. Using SPECT, O'Brien, Eagger, Syed, Sahakian, and Levy (1992) observed reductions in left frontal perfusion rates in mild AD patients relative to control participants, with right frontal hypoperfusion also present in more severely affected patients. Brown et al. (1996) used SPECT to provide additional evidence for frontal cortical involvement in cognitive impairments observed in the progression from mild-or-moderate to moderate-or-severe AD. In particular, decrements in language, praxis, and abstract reasoning measures correlated with regional cerebral blood flow changes in bilateral inferior frontal regions. Brown et al. (1996) reported that the appearance of frontal lobe hypoperfusion and its progression were quite variable across the patients examined.

Grady et al. (1990) attempted to identify subgroups of AD patients by examining patterns of cerebral glucose metabolism using principal-components analysis of positron emission tomography data. These authors successfully identified four subgroups of AD patients: (a) a temporoparietal group, (b) a paralimbic group, (c) a left hemisphere group, and (d) a frontoparietal group. The authors found that differences among the groups were reflected in cognitive and behavioral measures. In particular, Grady and colleagues observed that AD patients in the frontoparietal group had the highest overall ratings of dementia severity according to both the MMSE (Folstein, Folstein, & McHugh, 1975) and the Dementia Rating Scale (Mattis, 1976). In addition, these patients showed the greatest impairment on practically all cognitive measures, including the WAIS (Full Scale), the WMS, measures of visuospatial abilities, and scores on tests of reasoning and problem solving (Raven Matrices, Porteus Mazes, and Trail-Making A). These patients also most frequently exhibited behavioral signs associated with frontal-lobe dysfunction, such as inappropriate behavior and psychosis. Patients in the temporoparietal group performed somewhat better than frontoparietal patients, but still showed considerable deficits, relative to control participants on all cognitive measures. Patients in the paralimbic group also showed impairment on all cognitive measures relative to control participants, but their deficits on tests of visuospatial reasoning were found to be less severe than groups with parietal involvement. Finally, patients in the left hemisphere group showed a relative absence of visuospatial deficits but were impaired on a measure of verbal fluency.

Several subsequent studies have provided additional evidence in support of the notion that subgroups of AD exist that are dissociable on the basis of the results of neuropsychological testing. Goldstein and coworkers (1992), for instance, have provided data suggesting that subgroups of AD can be delineated based on assessment of deficits in semantic processing. On the basis of the

results of neuropsychological testing, Binetti and colleagues (1993) identified two subgroups of AD patients: one showing an earlier age of onset and severe impairment on measures of language, abstract reasoning, and verbal fluency, and a second group showing more severe impairment on measures of declarative memory function. More recently, a subgroup of AD patients was described with relatively poor performance on Trail-Making A, the COWA fluency test, and the WAIS–R block design in the mild stages of dementia (Johnson et al., 1999). In postmortem analysis, these patients were shown to exhibit a significantly higher degree of NFT pathology in frontal lobes than did patients who had a more standard AD profile.

Our data appear to be consistent with the existence of a subgroup of mild–moderate AD patients with significant frontal involvement, in that deficits on measures of working memory and relational processing exhibited by AD patients in our sample occurred alongside deviant scores neuropsychological measures of frontal lobe function. Because there were no significant differences in other cognitive measures between the subgroups of AD patients with and without relational integration impairments, it does not appear that this group is more globally impaired. The fact that a trend exists toward a significant age difference between the AD/RI± and AD/RI− groups in our study suggests that deficits in executive function present in AD patients may be influenced by advanced age.

Using Behavioral Data to Identify Subtypes of AD

Evidence from neuropathological analyses (Bondareff et al., 1993; Johnson et al., 1999) suggests that it may be possible to speak of multiple *subtypes* of AD. Accordingly, considerable research and debate surround the question of whether heterogeneity in the *behavioral* presentation of AD warrants the specification of subtypes of the disorder. The identification of a subgroup of AD patients with cognitive deficits linked to prefrontal dysfunction raises the possibility that a separate or additional etiological factor may be involved. Prefrontal dysfunction may stem from a pathological process distinct from that responsible for the standard profile of AD, but it may also stem from the same pathological process (such as the death of cholinergic neurons). As Grady et al. (1988) noted, sequential involvement of cortical areas in the disease process could also be explained by progressive degeneration of acetylcholine-producing cells in the nucleus basalis of Meynert (nbM) because different cortical lobes are innervated by different sections of nbM (Grady et al., 1988). Degeneration of acetylcholine-producing cells in the nbM is one factor that has been frequently implicated in the cognitive deficits observed in AD (Whitehouse, Price, Clark, Coyle, & DeLong, 1981). Resolving the question of whether subtypes of AD stem from separate etiologies or heterogeneity within a standard etiology will require further integration of psychological observations with anatomical, physiological, and psychiatric data on a longitudinal basis.

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