

Research Article

A SYSTEM FOR RELATIONAL REASONING IN HUMAN PREFRONTAL CORTEX

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Abstract—*The integration of multiple relations between mental representations is critical for higher level cognition. For both deductive- and inductive-reasoning tasks, patients with prefrontal damage exhibited a selective and catastrophic deficit in the integration of relations, whereas patients with anterior temporal lobe damage, matched for overall IQ but with intact prefrontal cortex, exhibited normal relational integration. In contrast, prefrontal patients performed more accurately than temporal patients on tests of both episodic memory and semantic knowledge. These double dissociations suggest that integration of relations is a specific source of cognitive complexity for which intact prefrontal cortex is essential. The integration of relations may be the fundamental common factor linking the diverse abilities that depend on prefrontal function, such as planning, problem solving, and fluid intelligence.*

Reasoning depends on the ability to form and manipulate mental representations of relations between objects and events. For example, transitive inference (a type of deductive reasoning, in which the truth of the premises ensures the truth of the conclusion) requires the ability to integrate two relations that share an element (e.g., given that Bill is taller than Charles and Abe is taller than Bill, it follows that Abe is taller than Charles). Similarly, in drawing analogies (a type of inductive reasoning, in which the initial premises determine the plausibility of the conclusion), relational reasoning is also essential (e.g., in the problem “person is to house as bear is to what?” the shared roles, dweller and dwelling, constrain the inferred answer, “cave”). Problem solving and planning also necessarily depend on relational integration. For example, using the elementary problem-solving strategy of difference reduction (Newell & Simon, 1972) requires integration of a difference between the present state and the goal state (a relation, such as “this wall lacks a coat of paint”) with the expected change that would be produced by an operator applied to the present state (a second relation, such as “painting the wall will add a coat of paint”). Forming subgoals by means-ends analysis also requires integration of multiple relations (e.g., “a paintbrush can be used to apply paint”; “I lack a brush”) to derive relevant subgoals (“I must find a brush”).

There is a critical gap between the capacity to comprehend single relations and the capacity to integrate multiple relations (Halford & Wilson, 1980; Halford, Wilson, & Phillips, 1998; Maybery, Bain, & Halford, 1986). For example, understanding the single relation “Bill is taller than Charles” can be accomplished using perception (given a visual scene) or language (given a sentence); in contrast, integrating two relations, such as “Bill is taller than Charles” and “Abe is taller than Bill,” to draw the transitive inference requires more than percep-

tual or linguistic processing alone. Although there is evidence that nonhuman primates have some capacity to process relations (Premack & Woodruff, 1978; Thompson, Oden, & Boysen, 1997; for a review, see Tomasello & Call, 1997), humans display far greater sophistication in relational reasoning across a wide range of content domains.¹ Given the large increases in the size of prefrontal cortex in human evolution (Benson, 1993), prefrontal cortex may be the locus of a system for relational reasoning in humans (Holyoak & Kroger, 1995; Robin & Holyoak, 1995).

This hypothesis is broadly consistent with evidence that prefrontal cortical dysfunction leads to selective decrements in performance on tasks involving hypothesis testing, categorization, planning, and problem solving, all of which involve relational reasoning (e.g., Delis, Squire, Bihle, & Massman, 1992; Milner & Petrides, 1984; Owens, Downes, Sahakian, Polkey, & Robbins, 1990; Shallice & Burgess, 1991). However, these complex tasks could be failed for many reasons and were not designed to test the specific hypothesis that the prefrontal cortex is critical for relational integration.

In the present study, we examined performance on simple tasks requiring deductive or inductive reasoning, using closely matched variants that differed specifically in whether or not success required integration of multiple relations. We hypothesized that patients with prefrontal cortical dysfunction would exhibit impaired performance when asked to integrate multiple relations, yet would perform normally when only one relation needed to be considered. In order to rule out the possibility that any performance deficits in relational reasoning observed in prefrontal patients could be attributable to some general cognitive impairment, we compared their performance on several tasks with the performance of patients with anterior temporal lobe damage, as well as that of normal control subjects. It has long been established that patients with lesions of medial temporal lobe structures show impairments in acquisition of new declarative memories, despite the preservation of other cognitive abilities (Scoville & Milner, 1957; Squire, Knowlton, & Musen, 1993). Recent results indicate that patients with lateral anterior temporal lobe lesions exhibit deficits in semantic knowledge (Graham & Hodges, 1997; Hodges, Patterson, Oxbury, & Funnell, 1992). We predicted that prefrontal patients would be impaired on tasks requiring relational integration, but would perform more accurately than patients with anterior temporal lobe lesions on tests of semantic memory and episodic recognition.

1. Chimpanzees (Gillan, 1981), monkeys (Harris & McGonigle, 1994), rats (W.A. Roberts & Phelps, 1994), and pigeons (Terrace, 1991) are capable of learning serial orderings when the items are introduced in sequential order and multiple trials are provided so that adjacent pairs are overlearned. However, these various types of associative transitivity observed in nonhuman animals can be distinguished from inferential transitivity (D’Amato, 1991). Only humans over 5 years of age appear to be able to make transitive inferences reliably in one trial by integrating multiple premises (Halford, 1984).

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METHOD

Participants

The participants were 6 patients with focal damage to prefrontal cortex, 5 patients with focal damage to anterior temporal cortex, and 7 neurologically intact individuals. Patients in the study had been diagnosed with fronto-temporal dementia (FTD), a common dementia subtype distinct from dementia of Alzheimer's type (Brun, 1993; Snowden, Neary, & Mann, 1996). In the early stages of FTD, the degenerative process tends to be localized to either prefrontal or anterior temporal cortical areas; there is involvement throughout anterior cortical regions in advanced stages. In the frontal variant of FTD, damage is initially localized in prefrontal cortex. Figure 1a depicts an example of metabolic activity in a normal brain; this image can be contrasted with Figure 1b, which depicts the abnormal metabolic activity of a representative prefrontal patient in the present study. In the temporal variant (Edwards-Lee et al., 1997), an example of which is depicted in Figure 1c, the anterior temporal lobes initially degenerate while dorsolateral prefrontal regions remain structurally and physiologically intact. Patients with the temporal variant of FTD have been found to exhibit semantic dementia, characterized by impairments in semantic knowledge (Hodges et al., 1992).

Patients were divided into subgroups based on the inspection of functional brain images produced by the single positron emission computer tomography (SPECT) technique using ^{99m}Tc hexamethyl propylenamine oxime (HMPAO). Foci of hypoperfusion were identified by a medical professional not associated with the study, and each patient was assigned to either the prefrontal or the temporal group based on these determinations. When blood flow measurements in prefrontal cortex were compared with those in other regions using xenon 133 (^{133}Xe), patients in the prefrontal group showed significantly reduced blood flow in prefrontal cortex (an average prefrontal:global cortical perfusion ratio of 0.58 ± 0.08), relative to patients in the anterior temporal group (an average prefrontal:global cortical perfusion

ratio of 0.88 ± 0.09), $t(6) = 2.61$, $p < .05$. The perfusion ratios of the two patient groups did not overlap.

All patients received a set of standard neuropsychological tests, including the Wisconsin Card Sorting Test (WCST; Heaton, 1995), Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), and Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981). These tests were administered in a separate 3-hr session. The two patient groups were matched for mean age, education, and severity of dementia, as measured by the Mini-Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975) and WAIS-R. The 6 patients with prefrontal degeneration (4 men) averaged 65.4 ± 4.0 years of age and 16.0 ± 1.1 years of education; they had an average score of 23.8 ± 2.0 on the MMSE and a full-scale IQ of 96.0 ± 6.4 on the WAIS-R (the mean in the general population is 100). The 5 patients with anterior temporal degeneration (3 men) averaged 63.2 ± 4.8 years of age, 17.8 ± 0.8 years of education, an MMSE score of 23.0 ± 1.8 , and a full-scale IQ of 94.8 ± 8.0 . The 7 normal control subjects (2 men) had an average age of 64.9 ± 2.5 years and an average educational attainment of 16.4 ± 1.1 years. Relative to the anterior temporal group, the prefrontal group was significantly impaired on several traditional tests of prefrontal function, including a shortened form of the WCST (0.6 ± 0.4 categories achieved from a maximum of 4, with $60.3 \pm 8.7\%$ of errors being perseverative, vs. 2.8 ± 0.4 categories achieved, with $19.3 \pm 3.7\%$ of errors being perseverative, $p < .005$ for both measures).

Materials and Procedure

The measure of deductive reasoning was performance on a set of 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, presented as a card displaying a name on top, the words "taller than" in the middle, and a name below. The task was to arrange cards corresponding to the

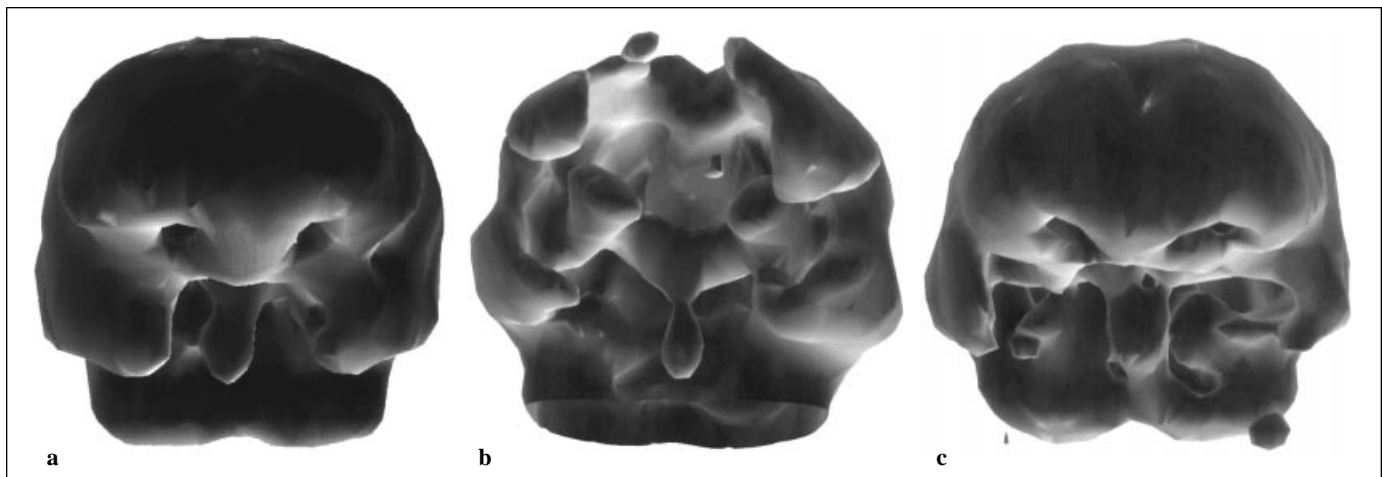


Fig. 1. Anterior views of brain images illustrating the extent of cortical damage in patients tested in the present study. Areas in gray exhibit normal perfusion rates as measured by single positron emission computer tomography; white areas exhibit significant hypoperfusion. The image of an individual with normal perfusion rates in all cortical areas is shown in (a). The image of a patient with focal prefrontal cortical damage (b) shows severe hypoperfusion in prefrontal cortical areas, with relative sparing of temporal cortical areas. The image of a patient with focal anterior temporal cortical damage (c) shows subnormal blood flow in anterior temporal cortical areas, with near-complete sparing of prefrontal cortical areas.

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; Nate taller than Roy). The correct ordering could therefore be achieved using a chaining strategy that proceeded one link at a time: To build a link, only one relation—that between the name at the end of one chain and its successor—had to 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; Amy taller than Beth) so that the item at the end of one chain was not in the subsequent pair, making the chaining strategy inapplicable. The reasoner therefore had to 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, 1993).

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

Immediately following the transitive-inference test, participants were administered a test of recognition memory for problem elements. Each 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 used in the prior reasoning test.

Inductive reasoning was assessed using matrix 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, 1941). Nonrelational problems (Level 0 complexity) involved a visual pattern, with a blank space in the bottom right-hand corner (see Fig. 2a). The participant completed the pattern by selecting from six possibilities; the solution required 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 vertical dimension; the other dimension was constant (Fig. 2b). Two-relation problems (Level 2 complexity) required integrating two relational changes over the horizontal and vertical dimensions, respectively (Fig. 2c). 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 was administered (7 at Level 0, 6 at Level 1, and 7 at Level 2).

Testing was generally done in a single 1-hr session, with the transitive-inference items presented first, immediately followed by the test of recognition memory and then the set of matrix problems. Of the 6 prefrontal patients, 1 was not tested on the transitive-inference items and 1 was not tested on the matrix problems. Recognition memory for transitive-inference items was tested in 3 of the prefrontal patients. All 5 anterior temporal patients participated in all tests. All control subjects received all tests, except for 1 whose recognition memory was not tested.

RESULTS

We hypothesized that patients with prefrontal cortical damage would show selective impairment on problems requiring integration of multiple relations, relative both to patients with anterior temporal lobe damage and to control subjects. The results obtained for the deductive transitive-inference problems provided strong support for our hypothesis, as shown in Figure 3a. An analysis of variance comparing the two patient groups and control group revealed an interaction between locus

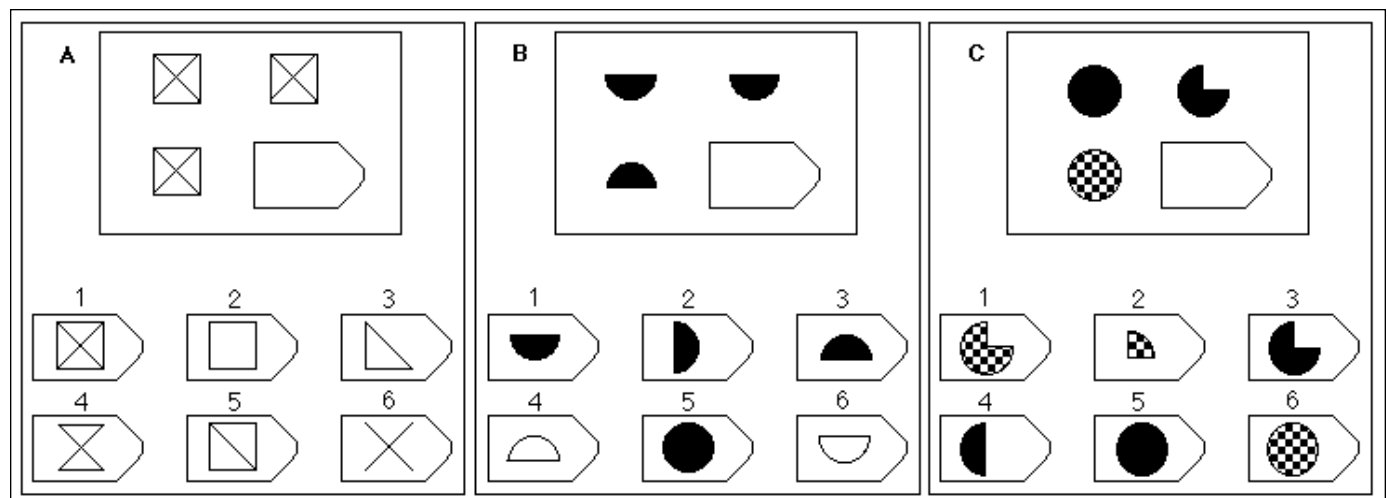


Fig. 2. Examples of problems adapted from the Raven Standard Progressive Matrices Test. This task required participants to choose the item from the bottom of the figure that would complete the pattern at the top. An example of a nonrelational problem (Level 0) is shown in (a). Solution requires only perceptual matching (correct response is Choice 1). An example of a one-relation problem (Level 1) is shown in (b). Participants need only to maintain the transformation along the vertical dimension (reflection across the x -axis) in order to choose the correct alternative (Choice 3). An example of a two-relation problem (Level 2) is shown in (c). 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) in order to make the correct response (Choice 1).

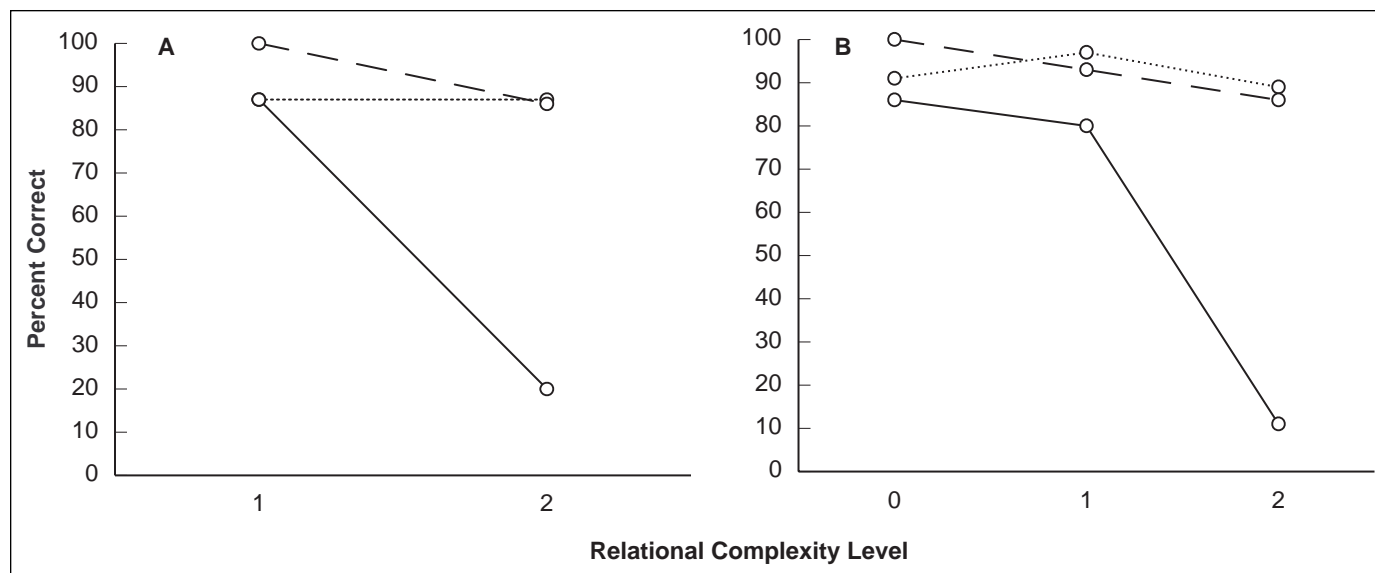


Fig. 3. Accuracy on the test of transitive inference (a) and matrices test (b) for each group of participants. Results are shown for patients with prefrontal damage (solid lines), patients with anterior temporal damage (dotted lines), and normal control subjects (dashed lines). Standard errors ranged from 8% to 20%.

of damage and relational complexity, $F(2, 14) = 5.79, p < .02$. When presented with problems for which names could be ordered correctly by chaining, processing only one relation at a time (e.g., Dave taller than Gary; Gary taller than Bart), patients with prefrontal cortical damage ordered the elements correctly in $87 \pm 8\%$ of cases. Their performance was quantitatively similar to that of patients with anterior temporal lobe damage ($87 \pm 13\%$ correct) and control subjects (100% correct). None of these differences were significant by a Newman-Keuls test. However, for problems in which the order of propositions was scrambled (e.g., Mona taller than Kim; Stef taller than Mona), so that premise integration required processing two relations at once, patients with prefrontal cortical damage showed a complete inability to order problem elements, producing a correct ordering in only $20 \pm 20\%$ of problems, a rate not significantly different from chance (7%). Newman-Keuls tests indicated that the performance of the prefrontal patients on Level 2 problems was significantly worse than that of patients with anterior temporal lobe damage ($87 \pm 13\%$ correct, $p < .01$) and also control subjects ($86 \pm 14\%$ correct, $p < .001$).

Performance on the inductive matrix problems also showed striking differences between patients with damage to prefrontal cortex and those with damage to anterior temporal cortex, as well as normal control subjects, in the ability to integrate multiple relational premises, as shown in Figure 3b. An analysis of variance revealed an interaction between group and complexity level, $F(4, 28) = 14.53, p < .00001$. Newman-Keuls tests indicated that the two patient groups did not differ either from each other or from normal control subjects in the average proportion of correct responses given to either Level 0 or Level 1 problems, with performance above 80% correct in all cases. For the Level 2 problems, however, Newman-Keuls tests revealed a significant difference ($p < .001$ for both comparisons) between the mean percentage of correct responses given by patients with prefrontal cortical damage ($11 \pm 5\%$, chance = 17%) and the performance of both patients with anterior temporal lobe damage ($89 \pm 5\%$) and normal control subjects ($86 \pm 6\%$).

Additional analyses revealed double dissociations between relational reasoning and both episodic memory and semantic knowledge (see Fig. 4). Relative to prefrontal patients, temporal patients were impaired on the two-item forced-choice test of declarative recognition memory for names presented on the transitive-inference test ($56 \pm 10\%$ correct vs. $96 \pm 4\%$ correct for prefrontal patients; normal control subjects responded correctly to $86 \pm 5\%$ of items), $t(6) = 3.01, p < .05$. For those patients tested on both Level 2 transitive-inference problems and the matched forced-choice recognition problems, an analysis of variance revealed a significant crossover interaction for the prefrontal versus temporal patients, $F(1, 6) = 6.53, p < .05$. Temporal patients showed a decrement, relative to prefrontal patients, on the Boston Naming Test (16.6 ± 9.3 for anterior temporal patients vs. 52.2 ± 1.9 for prefrontal patients; maximum = 60), $t(8) = 3.75, p < .01$, and also on the Information subtest of the WAIS-R (9.0 ± 3.4 for anterior temporal patients vs. 22.0 ± 2.8 for prefrontal patients; maximum = 30), $t(8) = 2.91, p < .02$. Both of these tests assess semantic knowledge.

DISCUSSION

Our findings indicate that the human prefrontal cortex plays an essential role in relational reasoning—specifically, in the integration of multiple relations. For both a deductive task (transitive inference) and an inductive task (matrix completion), the performance of prefrontal patients dramatically deteriorated when the task required simultaneous integration of two binary relations, rather than being solvable by processing one relation at a time. Developmental evidence indicates that the capacity to integrate multiple relations is acquired at about age 5 (Halford, 1984, 1993), paralleling increases in performance on tests diagnostic of prefrontal dysfunction and in the coordination of electrical activity in prefrontal cortex with that in posterior cortical systems (Case, 1992; Levin et al., 1991). Although the overall IQs of the

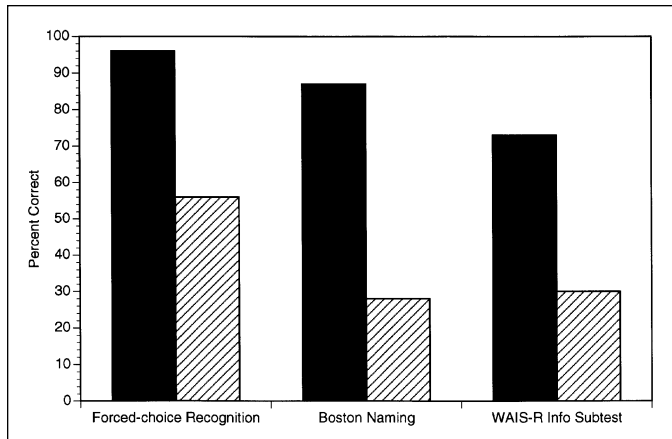


Fig. 4. Accuracy on tests of declarative memory (forced-choice recognition) and semantic knowledge (Boston Naming Test and Information subtest of the Wechsler Adult Intelligence Scale–Revised). Results are shown for patients with prefrontal damage (solid bars) and patients with anterior temporal damage (slashed bars). Standard errors ranged from 3% to 15%.

prefrontal patients were in the normal range, their complete inability to solve two-relation transitive-inference problems placed them at a preschool level on this task. The fact that the prefrontal patients also failed two-relation matrix problems indicates a general impairment of relational reasoning, spanning both deduction and induction.

The relative success of the prefrontal patients on no-relation and one-relation variants of the same tasks rules out explanations based on motivation, inability to follow instructions, or tendency to perseverate. The success of the anterior temporal patients on two-relation problems establishes a dissociation between the reasoning ability of the prefrontal and anterior temporal groups, which were closely matched in disease process, age, IQ, and education. At the same time, the performance of prefrontal patients was superior to that of the temporal patients on a test of recognition memory and on tests dependent on semantic knowledge. The resulting double dissociation between relational reasoning versus both episodic memory and semantic knowledge rules out a general “difficulty” factor as the source of the prefrontal group’s impairment.

Prefrontal cortex has been implicated in the performance of a large number of higher level cognitive tasks, such as memory monitoring, management of dual tasks, rule application, and planning sequences of moves in problem solving (D’Esposito et al., 1996; Duncan, Burgess, & Emslie, 1995; Smith, Patalano, & Jonides, 1998). It has not been established, however, whether a common factor links these diverse tasks. It has often been suggested that prefrontal cortex is particularly important for difficult tasks, but the theoretical basis for what factors are relevant in making some tasks more difficult than others has not been established. We propose that the integration of relations is a specific source of cognitive complexity for which an intact prefrontal cortex is essential. Double dissociations of the sort observed in the present study rule out any simple relationship between prefrontal performance and overall task difficulty.

The present hypothesis can be extended to explain frontal impairments in the domain of action planning. Complexity increases with the depth of embedding in a subgoal hierarchy (Carpenter et al., 1990; Shallice & Burgess, 1991), as subgoal embedding is a special

case of relational interaction (see Halford et al., 1998, for an analysis of the relational complexity of versions of the Tower of Hanoi puzzle). The management of dual tasks necessarily increases relational complexity, as the reasoner must integrate the temporal relations between two action sequences. In fact, relational reasoning appears critical for all tasks identified with executive processing and fluid intelligence.

We propose that a deficit in relational integration in patients with prefrontal lesions may account for impairments in the inhibition of prepotent responses, as demonstrated by deficits in prefrontal patients on tasks such as the WCST (Milner, 1963), Stroop test (Perret, 1974), and antisaccade task (Guitton, Buchtel, & Douglas, 1985). Loss of the ability to inhibit prepotent responses can be brought on by decrements in working memory capacity (Dunbar & Sussman, 1995; R.J. Roberts, Hager, & Heron, 1994). We contend that in order to override a prepotent response, an individual must simultaneously consider multiple response-outcome relations. For example, in the WCST, a reasoner must consider both the current sorting relationship (e.g., color) and a different sorting relationship (e.g., shape), and must explicitly represent that one is no longer correct and thus the other might be. Without the capacity to integrate these two relations, the reasoner would act on the basis of the single, dominant response-outcome association. Thus, the deficits in response inhibition demonstrated by prefrontal patients can be seen to follow directly from a deficit in relational integration. The hypothesis that prefrontal cortex is required for the simultaneous processing of multiple relations also fits well with data for prefrontal patients showing deficits in declarative memory tasks such as memory for spatiotemporal context (Schacter, 1987; Shimamura, 1995). These deficits may arise out of an impaired ability to represent, as well as to make inferences based on, variable temporal relations.

The present study obtained a sharp break in performance for prefrontal patients when a reasoning task required integration of two binary relations. Further work, using neuroimaging as well as neuropsychological techniques, will be required to determine the role of prefrontal cortex across a wider range of complexity variations. For example, Halford (1993; Halford et al., 1998) has proposed that processing two binary relations is equivalent in complexity to processing one trinary relation (i.e., a predicate that takes three semantically confusable arguments, as in “John introduced Tom to Bill”). If so, prefrontal patients should show impairment in processing single relations that are more complex than the binary relations used in the present study. In addition, normal adults are clearly capable of processing more complex relational structures than any of those used in the present study.

Neuropsychological and functional imaging studies indicate that different regions in prefrontal cortex subservise distinct functions. The ventromedial region has been implicated in the relationship between emotion and decision making (Bechara, Damasio, Tranel, & Damasio, 1997), and the dorsolateral prefrontal cortex (DLPFC) has been implicated in working memory and executive functions (Baddeley, 1992). (For electrophysiological studies of working memory in nonhuman primates, see Fuster, 1995; Goldman-Rakic, 1988; for neuroimaging of working memory in humans, see Cohen et al., 1997; Jonides et al., 1993). The operations that support relational reasoning may form the core of an executive component of working memory, which implies both the active maintenance of information and its processing (Halford et al., 1998). In other words, relational integration may be the “work” done by working memory. We thus view our results as being consistent with the idea that DLPFC, which was severely damaged in all our prefrontal patients, is critical for working memory.

Relational reasoning requires a capacity to bind elements dynamically into roles (perhaps by synchronizing neural activity; see Hummel & Holyoak, 1997; Shastri & Ajanagadde, 1993), and to maintain these bindings as inferences are made. These operations underlying relational integration may distinguish working memory from a passive short-term memory buffer. Working memory tasks often require participants to integrate relations, such as the relative temporal order of multiple stimuli. Indeed, the sharp performance decrement shown by our prefrontal patients on multiple-relation problems parallels a step function observed in parametric neuroimaging studies of working memory. Functional magnetic resonance imaging (fMRI) studies using the n -back task have revealed a step function in the activation increase associated with DLPFC (Cohen et al., 1997). The quantal step occurs at $n = 2$ (which requires participants to decide whether the present stimulus in a continual sequence is identical to the one presented "two back," i.e., the stimulus immediately preceding the one immediately preceding the present stimulus). Identifying the item that is "two back" requires integration of two temporal relations (stimulus $n - 1$ preceded present stimulus n ; stimulus $n - 2$ preceded stimulus $n - 1$), and hence is comparable in complexity to the two-relation tasks used in the present study.

Our neuropsychological findings complement imaging studies of reasoning, which have shown involvement of the same areas as are activated in working memory tasks. An fMRI study of Raven problems revealed activation in multiple brain regions, including DLPFC (Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997). A study of performance on a transitive-inference task using positron emission tomography found increased activation in both DLPFC and areas of parietal cortex (Baker, Dolan, & Frith, 1996). Neuropsychological evidence such as that provided by the present study makes a unique contribution by establishing that the prefrontal region is necessary for relational integration (rather than simply being active during reasoning tasks, perhaps performing some secondary function such as task monitoring). Postulating a neural system for integrating multiple relations provides an explanation of why a wide range of tasks, all of which depend on processing multiple relations simultaneously, are sensitive to prefrontal damage and activate DLPFC.

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