

## 69. Preparation Deficits in Parkinson's Disease

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Twelve patients with Parkinson's disease and 12 age-matched controls completed a visual reaction time task in which preparatory interval delays were randomly presented. The preparatory intervals (1, 3, and 5 s) began with an auditory warning signal that preceded the presentation of the visual target. Simple and choice RT tasks were used in separate blocks. The results indicated that there was a preparatory effect for both groups. However, PD patients produced a larger preparatory effect than normal controls in simple RT. This effect was due to a larger RT difference between groups on the shortest PI. Because this finding is specific to simple RT, it may indicate the presence of an attentional control deficit in the PD group.

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Parkinson's disease (PD) is characterized by slowness in movement initiation (akinesia), tremors, and reduced movement execution (bradykinesia). In the cognitive domain, impairments of memory, visuomotor functions, and attention have been reported in persons with PD. Preparation is an attentional process that allows individuals to get ready to perform actions, which involves energizing the appropriate action schemas prior to stimulus occurrence (Stuss, Shallice, Alexander, & Picton, 1995). One way to measure specific preparation is to compare performance on simple RT tasks with that on choice RT tasks. Specific preparation is more involved in simple RT than in choice RT tasks because in the former, the response is predictable and the appropriate schema can be prepared prior to stimulus occurrence. The intentional preparation of a specific motor response is thought to be impaired in PD. Goodrich, Henderson, and Kennard (1989) found a smaller advantage in performance on simple over choice RT in PD patients. They also reported that the simple RT of PD patients was less impaired by a secondary task than it was for control participants. Significant correlations observed between performance on simple RT and executive tasks (Jordan, Sagar, & Cooper, 1992) in persons with PD support the contention that the simple RT deficit in PD arises from impairments in controlled attentional processes. However, not all findings are compatible with the preparation impairment hypothesis, since persons with PD are in some cases slower in choice than in simple RT tasks relative to control participants (see Jahanshahi, Brown, & Marsden, 1992). This may be related to differences in the temporal parameters of the experiments.

Although preparing a response necessitates knowledge about what should be done, knowing when to react is also a crucial aspect of preparation. The temporal aspect of preparation has rarely been directly explored in Parkinson's disease. In RT tasks, preparatory processes take place during the interval that separates the warning signal and the imperative signal. The characteristics of this preparatory interval (PI) (i.e., their range and distribution) affect response latency considerably, and manipulation of the PI provides information about the mechanisms involved in temporal prepara-

tion. The goal of this study is to investigate further the preparation deficit in PD by manipulating the different parameters involved in temporal preparation. This can be achieved through the use of variable PI values in the same block of trials. A feature of such a design is that response preparation necessitates the use of both temporal and probability information: because PIs vary from trial to trial and because participants cannot maintain preparation for the entire range of PI values, they usually prepare for the most probable moment of stimulus occurrence. RT normally decreases as PI increases because the probability of stimulus occurrence increases with time. Optimal performance involves modulating preparation as a function of the moment at which stimulus occurrence is most probable. Thus, analyzing the pattern of performance across PI values provides informative data regarding PD patients' capacity to modulate their level of preparation.

### *Method*

*Participants.* Participants in the experiment were 12 patients (mean age 64.9 years, school level 12.3 years) who received a diagnosis of Parkinson's disease and 12 healthy matched controls (mean age 64.1 years, school level 13.3 years). All control participants were in good health and none of them had undergone surgery or suffered from psychiatric disorders in the few years prior to testing. They had no history of neurological disease and did not take any medications known to affect cognitive functions. To exclude persons with mild cognitive decline, control participants completed a short mental examination (MMSE = 29, Mattis Dementia Scale = 140). PD patients were all on stable antiparkinsonian medications at the time of evaluation. There was no apparent cognitive decline in the patient group (MMSE = 29.3, Mattis Dementia Scale = 138.7).

*Materials and procedure.* Participants completed simple and choice reaction time tasks. Each trial was initiated by pushing down the central button of a three-button response box after a warning signal (a 1000-Hz tone). Participants were required to push the button until the occurrence of the imperative signal (a black circle 4 in. in diameter). In the simple RT condition, the black circle appeared in the center of the screen. Participants reacted by quitting the home key and pushing down the right response key as quickly as possible. Halfway through the block, they were instructed to respond to the left button. In the choice RT condition, the target occurred to the right or left of the center of the screen and the participant reacted by quitting the home key and pushing down the corresponding response key to the right or left of the home key. In both the simple and the choice RT conditions, PIs were 1, 3, and 5 s in duration. The proportions of each PI value were equated in each block of trials. After 5 practice trials on both tasks, 30 trials were completed in simple RT and 60 in choice RT for each duration condition. Both simple and choice RT conditions were completed twice within a single experimental session. Testing times were separated by a 30- to 40-min delay.

### *Results*

Initiation time (IT) was measured from the occurrence of the imperative signal to the moment that the participant quit the central button. Since there was no significance difference between times 1 and 2 for both simple,  $t(22) = 0.29$ , and choice RT,  $t(22) = 1.87$ , results were pooled over sessions for further analysis. An ANOVA was performed on these data with Group as between subject factor and Condition (simple vs choice) and Direction (left or right button) and PI (1, 3, 5 s) as within

subject factors. Results indicated that persons with PD were slower than the control participants,  $F(1, 22) = 14.6, p < .001$ , and that IT decreased with PI,  $F(2, 44) = 25.78, p < .001$ . Moreover, IT was longer overall in the choice than in simple RT,  $F(1, 22) = 59.73, p < .001$ . Importantly, the Group by Condition by PI interaction reached significance,  $F(2, 44) = 3.39, p < .05$ . This was due to a larger IT decrease for the PD group from the first to the second PI in the simple RT condition ( $p < .05$ ), resulting from a larger group difference on the first PI.

An ANOVA involving the same factors was performed on motor time (time taken to execute the movement from the home key to the response button). The findings indicated that participants with PD took longer to execute their responses than the control participants,  $F(1, 22) = 18.1, p < .001$ , and that for both groups, motor time was longer in the choice than simple RT condition,  $F(1, 22) = 16.8, p < .001$ . Motor time also increased slightly with PI; however, this finding did not reach significance,  $F(2, 44) = 3.5, p = .06$ . No interaction with group was observed for motor time.

### Conclusion

The findings reported in the present study support the hypothesis of an attentional control deficit in PD that affects the preparation of voluntary actions. Furthermore, the results suggest that this preparation deficit is influenced by the temporal aspects of the task. The results indicate that PD patients were more influenced than controls by PI in a simple RT task. As a result, simple RT impairment is larger for the first PI values than for latter ones. This pattern of results was not obtained in choice RT, where PD patients were slower than controls at all PI values and where the PI effect was similar in both groups. These findings suggest that although specific preparation takes place in PD patients, it requires longer preparatory intervals. A delay in initiating action preparation is possible (Jahanshahi et al., 1992). This pattern may also be due to the strategic control of action preparation in highly probable events, specifically, the one occurring after the longest PIs in a variable PI design. This would be an appropriate strategy if attending to the whole range of PI values is too difficult for PD patients. It is also possible that PD affects the flexibility to modulate the level of activation of a given schema. By modulating the activation level, one could prepare the response for the first PI and increase preparedness when probability increases. This ability to modulate preparation may be impaired in Parkinson's disease.

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## 70. Neuropsychological Correlates of Performance on Subject-Ordered Pointing Tasks with Words and Designs as Stimuli in a Sample of Patients with Parkinson's Disease

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The subject-ordered pointing (SOP) task requires subjects to plan and monitor a complex response and is thought to place demands on executive functioning. Patients with Parkinson's disease were administered SOP tasks with words and abstract designs and verbal and nonverbal clinical measures with varying sensitivity to executive dysfunction. Performance on SOP with words was significantly correlated only with performance on verbal clinical tests sensitive to executive dysfunction. In contrast, performance of SOP with designs was only significantly correlated with performance on nonverbal clinical tests sensitive to executive dysfunction. These results support SOP's sensitivity to executive dysfunction and are consistent with a previous study of unilateral prefrontal and hippocampal lesions, which suggests that SOP with words and designs draw upon dissociable neurocognitive systems. © 2001 Academic Press

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In the subject-ordered pointing (SOP) task subjects are presented with a stack of cards. The same stimuli are printed on each card, but the spatial configuration of the stimuli varies across the cards. Subjects are asked to work through the stack and select a different stimulus on each card. To avoid selecting a stimulus more than once subjects must continually monitor their responses and use this (typically supraspan) information to organize their sequence of responses. Consequently SOP is thought to place sizable demands on executive functioning, principally the ability to internally develop an appropriate working memory strategy, and to use the resultant information to guide stimulus selection.

Petrides and Milner (1982) compared SOP performance by healthy controls and patients bearing unilateral surgical lesions of the prefrontal cortex or the hippocampus to treat medically refractory epilepsy. Subjects with prefrontal damage were the least likely to report consistent use of a well-defined strategy to perform the SOP task. Additionally, the effect of prefrontal and hippocampal damage depended on the stimuli used. Subjects with lesions of left prefrontal cortex were impaired on SOP with words and designs, while patients with right prefrontal lesions were only impaired on SOP with designs. A material-dependent dissociation was also present in subjects' performance after unilateral hippocampal damage: Lesions to the left hippocampus impaired SOP with words but not designs, while lesions to the right hippocampus impaired SOP with designs, but not words.

This pattern of results suggests that SOP performance with words and designs is sensitive to dysfunction within dissociable neural systems. Performance with words may be sensitive to dominant hemisphere dysfunction, while performance with designs may be sensitive to dominant and nondominant hemisphere dysfunction. The sensitivity of the SOP task with designs to nondominant and dominant hemisphere dysfunction may reflect the important role played by verbally based executive strategies in the coordination of both verbal and nonverbal information processing (Chow & Cummings, 1999) and/or the role played by the left hemisphere in the production of the voluntary movements required to perform all SOP tasks (Kimura & Archibald, 1974).

Given Petrides and Milner's results, the SOP task may be a useful clinical measure of executive functioning within the verbal and nonverbal domains. To examine this

notion we investigated the psychometric relationships between SOP performance with words and abstract designs and performance on verbal and nonverbal neuropsychological measures thought to have varying sensitivity to executive dysfunction in a sample of patients with Parkinson's disease. Of interest was whether a double dissociation would be manifest in the relationships between SOP performance with words and abstract designs and performance on the verbal and nonverbal clinical measures sensitive to executive dysfunction.

## Methods

### *Subjects*

Twenty-nine patients with advanced Parkinson's disease served as subjects [mean age 64 years (SD = 12.8), mean time since PD diagnosis 12.8 years, mean education 12 years (SD = 3.2), mean Dementia Rating Scale total score = 130.7 (SD = 11.1), 27 right-handed]. All the subjects were undergoing neuropsychological evaluation prior to unilateral pallidotomy, thalamotomy, or pallidal stimulation. All subjects were tested while medicated during a self-described 'on' state. University and Hospital ethics approval was obtained and informed consent was obtained from all subjects.

### *Measures*

*Subject-ordered pointing.* SOP tasks with words and abstract designs as stimuli were administered. Each task contained 12 different stimuli randomly arranged on 12 different cards. The order of administration of the two tasks was counterbalanced across the subjects. The total number of errors made with each type of stimulus served as the dependent variable.

### *Verbal Measures*

*Rey Auditory Verbal Learning Test (RAVLT): Delayed Recall.* The number of words recalled after a 30-min delay served as the dependent variable. The ability to encode, retain, and retrieve supraspan verbal information necessary for delayed recall performance is thought to be impaired by verbal executive dysfunction.

*Rey Auditory Verbal Learning Test (RAVLT): Delayed Recognition.* The total number of true positives minus the number of false positives obtained on delayed recognition testing served as the dependent variable. In comparison to delayed recall, delayed recognition performance is thought to be relatively less effected by executive dysfunction and served as a verbal control task.

*Verbal fluency: CFL.* The total number of words provided during three 60-s trials served as the dependent variable. Verbal fluency is thought to be adversely affected by executive dysfunction via failure to develop an effective self-directed search of one's lexicon and/or difficulty inhibiting previous responses.

### *Nonverbal Measures*

*Corsi blocks: Total score forward and backward.* Subjects' ability to repeat demonstrated spatiotemporal sequences forward and backward was assessed. For all subjects performance was assessed first in the forward condition and then in the backwards condition. Compared to Corsi blocks backward, performance of Corsi blocks forward is thought to be relatively less sensitive to executive dysfunction and served as a nonverbal control task. Two trials were administered of each span length, larger spans were progressively tested, and testing was terminated when a subject failed

TABLE 1

Clinical measures	Subject-ordered pointing errors	
	Words	Abstract designs
Verbal		
RAVLT delayed recall	-.41*	-.28
Verbal fluency (sum trials 1-3)	-.47*	-.33
RAVLT delayed recognition	-.30	-.09
Nonverbal		
BVRT (errors)	.33	.55**
Corsi blocks (total backward)	-.29	-.52**
Corsi blocks (total forward)	.07	-.25

\*  $p < .05$  (two tailed).

\*\*  $p < .01$  (two tailed).

both trials of a given span length. The total number of correct trials for the forward and backward conditions served as dependent variables.

*Benton Visual Retention Test (BVRT): Administration A.* A measure of the ability to reproduce increasingly complex abstract designs after a brief exposure. The ability to encode, retain, and retrieve the information necessary for reproduction is thought to be impaired by executive dysfunction. The total number of errors made reproducing the 10 designs served as the dependent variable.

### Results

The correlations between errors on the SOP tasks with words and abstract designs and performance on the clinical measures are presented in Table 1. Overall, the expected statistical dissociation is present. Only the verbal clinical measures most sensitive to executive dysfunction (delayed recall performance on the RAVLT and verbal fluency) were significantly correlated with SOP performance with words. In contrast, the verbal clinical measure less sensitive to executive dysfunction (delayed recognition on the RAVLT), and performance on all the nonverbal clinical measures, did not correlate with SOP performance with words. The nonverbal clinical measures most sensitive to executive dysfunction (BVRT and Corsi block—backward) were significantly correlated with SOP performance with designs. In contrast, the nonverbal clinical measure less sensitive to executive dysfunction (Corsi blocks—forward), and performance on all the verbal clinical measures, did not correlate with SOP performance with designs.

### Conclusions

A double dissociation was obtained in the correlates of SOP performance with words and abstract designs. Patients' performance of SOP with words was significantly correlated only with their performance on the verbal clinical tests thought to be sensitive to executive dysfunction. In contrast, patient's performance of SOP with designs was only significantly correlated with their performance on the nonverbal clinical tests thought to be sensitive to executive dysfunction.

These results lend support to the notion that the SOP task is sensitive to executive dysfunction: SOP performance was found to correlate only with those clinical measures thought to be sensitive to executive dysfunction. The present results also pro-

vide support for the notion that SOP tasks with words and abstract designs draw upon dissociable neurocognitive systems: SOP performance with words and designs correlated only with the clinical measures most sensitive to executive dysfunction in the verbal and nonverbal domains, respectively. Taken together, the present results begin to characterize the system of empirical relationships between SOP performance and performance on other measures of cognitive functioning, a process which is important to both confirm the validity of the SOP as a measure of executive dysfunction and facilitate the integration of this potentially very useful test into clinical practice.

These results likely primarily reflect prefrontal, and not hippocampal, dysfunction in our subjects. Patients with Parkinson's disease are known to have dysfunctional dorsolateral prefrontal–basal ganglia circuitry (Taylor & Saint-Cyr, 1995). Additionally, the absence of a relationship between SOP performance and AVLT recognition performance, and the presence of a relationship between SOP performance and verbal fluency and Corsi blocks backward performance is consistent with prefrontal, and not hippocampal, dysfunction.

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## 71. Self-Report on Memory Abilities and Prospective Memory in Parkinson's Disease

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Memory dysfunction is a frequent deficit occurring with Parkinson's disease (PD). This study examined prospective memory in medicated patients with Parkinson's disease using a self-report Prospective Memory Questionnaire developed by Hannon et al. (1990). Four subscales were assessed: Long-Term Episodic, Short-Term Habitual, Internally Cued, and Techniques to Remember. The performance of 22 nondemented PD patients was compared with that of healthy controls (NC) matched for age, IQ, and education. PD patients did not differ from NC on Long-Term Episodic and Internally Cued Scales, but showed significant differences on Short-Term Habitual and Techniques to Remember Scales. There was no correlation between declarative memory tasks and any of the prospective memory scales. The results suggest that PD might provide a useful model to investigate the relationship between prospective and declarative memory. © 2001 Academic Press

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### Introduction

Prospective memory (the ability to remember to perform future actions) is one of the least investigated types of memory in normal (Harris, 1984), elderly (Dobbs & Rule, 1987), and brain-injured adults (Mateer, Sohlberg, & Crinean, 1987). All three

of these groups, however, describe prospective memory as one of their most significant areas of memory deficit. Self-rating instruments and clinical measures of prospective memory are poorly developed. The relationship between self-rating of prospective memory abilities and actual performance may help us understand memory function since individuals' beliefs about their own memory abilities, whether accurate or inaccurate, influence their behavior. One might expect frontal cognitive functions to play a central role in prospective memory. Prospective memory has a strong temporal component, and the sensitivity of temporal memory to frontal dysfunction is well documented. In addition, prospective memory requires coupling of an action with an intended goal. The role of controlling actions by their intended results has been shown consistently (Duncan, 1986). Everyday life is largely organized in routine-based, well-learned activities which do not require structured planning or a continuous control of action. Planning and control of action are required only when a new problem arises that cannot be solved by any existing schema.

Cognitive studies in PD patients have indicated that they tend to be impaired on some tasks which are sensitive to frontal lobe damage such as problem solving, planning, and temporal ordering (Taylor et al., 1986; Partiot et al., 1996). Patients with PD have also revealed working and long-term memory deficits (Marie et al., 1995; Taylor et al., 1990). Shimamura et al.'s (1991) review of studies indicates that individuals with frontal lobe lesions have impaired prospective memory, despite performing normally on declarative memory tasks (i.e., tests of new learning). In contrast, amnesic patients perform well on numerous prospective memory tasks, but fail many declarative memory tasks. Several studies suggest that dissociations between prospective and declarative memory impairments, which are similar to those on the Shimamura et al. study (1991) with amnesic and frontal lesion patients might be obtained in PD patients. Mohr et al. (1990) have shown impaired declarative memory but preserved prospective memory, whereas the opposite pattern of performance was observed by Owen et al. (1992) in the early-stage PD groups. These findings point to the possibility that declarative and prospective memory may be within separable or linked (Troster et al., 1995).

In the present study, prospective memory has been examined using a self-report questionnaire.

### *Participants*

Parkinson's disease (PD) patients ( $N = 22$ ) attending the Movement Disorders Clinic at the Toronto Western Hospital and nonneurologically impaired controls ( $N = 22$ ) were recruited for this study. Mean age of subjects was 60.0 years (range 37–80 years). All subjects were matched for age, IQ, and education. Subjects whose current estimated IQ fell more than 1.5 SD below the premorbid intellectual level estimated with the AMNART were excluded on the basis of possible dementia. Subjects having hallucinations, and 'on and off' fluctuations were also excluded. PD patients were taking standard antiparkinsonian medications but those taking anticholinergic drugs were also excluded. PD patients were in the early stages (1 to 3; Hoehn & Yahr, 1967) of the disease.

### *Procedure*

All subjects received a standard battery of tests measuring verbal IQ, verbal memory, confrontation naming, motor speed and dexterity, verbal reasoning, semantic and phonemic verbal fluency, working memory and depression. Two questionnaires were administered: the Frontal Lobe Personality Scale (FLOPS) and the Prospective

TABLE 1  
Scores of Groups on Neuropsychological Tests: Means (SD)

Group	VCAT	Motor (Purdue)	GDI	Fluency fruits	FLOPS		Prospective memory	
					Apathy	Exec.Dys.	Tech to remem	Short-term habits
Control	19.6 (2.6)	49.8 (5.9)	1.8 (2.4)	16.8* (3.4)	21.8 (6.0)	25.6 (6.1)	46.7 (19.5)	1.2 (1.7)
PD	16.5 (5.7)	37.1 (8.1)	5.6 (5.0)	13.5 (3.3)	31.0 (8.8)	35.6 (9.4)	26.6 (19.8)	3.3 (3.3)

\*  $p < .01$ , two tailed.

Memory Questionnaire (PMQ). The Prospective Memory Questionnaire consists of four subscales: Long-Term Habitual, Internally Cued, Short-Term Habitual, and Techniques to Remember. Internal consistency of the PMQ is .92 and test-retest reliability is .88 (Hannon et al., 1994).

### Results

Individual  $t$  tests between PD patients and NC participants indicated no differences for age, VIQ, and education. PD and NC groups differed on verbal reasoning, Verbal Concept Attainment Test (VCAT), motor function, semantic fluency (Fruits), and level of depression Geriatric Depression Inventory (GDI), with PD patients reporting more depressive symptomatology. There were differences between the two groups on frontal behaviors (Apathy and Executive Dysfunction) using the FLOPS (see Table 1).

*Prospective memory questionnaire.* A one-way ANOVA with repeated measures was conducted which revealed an overall group main effect, i.e., PD differed significantly compared to NC,  $F(3, 40) = 75.9, p < .001$ . There was an interaction between the two groups on the two subscales: Short-Term Habitual and Techniques to Remember,  $F(3, 40) = 4.44, p < .01$ .

*Correlations.* In PD patients there was a positive correlation between GDI scores and the Prospective internally cued subscale ( $r = .43, df 20, p < .05$ ), but not with measures of Long-Term Habitual, Short-Term Habitual, and Techniques to Remember. Post hoc univariate analysis indicated a homogeneity of slopes,  $F(1, 40) = 0.12, p \geq .05$ . Analysis of covariance was conducted to correct for GDI only on one dependent scale (Internally Cued) and the results revealed there was no significant difference between two groups on this variable. Post hoc tests revealed that the two groups differed significantly on two subscales: Short-Term Habitual and Techniques to Remember,  $F(1, 42) = 6.8, p < .01$ ;  $F(1, 42) = 11.6, p < .001$ .

Scores were not significantly correlated with declarative tasks for either group. PD patients' scores on the Techniques to Remember subscale were positively correlated with scores on the verbal reasoning task (VCAT) ( $r = .49, df 20, p < .02$ ). Age was not significantly correlated with PMQ subscales for PD as well as NC groups.

### Conclusions

These results indicate that PD patients performed more poorly than NC on short-term memory tasks and on the use of many techniques to help one remember to perform prospective memory tasks. PD patients and NC did not differ on tasks requiring internal cues, nor on tasks which are to be performed in the future on an irregular schedule (e.g., sending a birthday card). In everyday life we rely on our ability to

recall our planned intention as well as the content of that intention at the appropriate time. Most of the actions in everyday life are spontaneously accomplished without the need to formulate a prior intention. Our daily activities are routine based and are automatic, implicit, and easily activated. In the PMQ, Short-Term Habitual scale taps into routine activities which involve procedural memory. The basal ganglia have been proposed as an anatomical component of the procedural system involved in routine activities (Mishkin et al., 1984). Therefore, the deficit displayed by PD patients in this study may be attributed to impairment of the procedural system resulting from basal ganglia pathology. On the other hand, results from the Techniques to Remember scale suggest that, compared to NC, PD patients do not use external cues to help them remember to perform the prospective memory tasks. Several studies indicate that PD patients benefit from external cues in set shifting, for both verbal and nonverbal tasks (Robertson & Flowers, 1990; Taylor et al., 1986; Brown & Marsden, 1988). If PD patients were to use external cues to perform future actions, this might enhance their performance in daily life and as a result, could improve their quality of life.

One limitation of this study is that it is self-report in nature. Subjects' responses may be validated by asking the caregivers to complete the questionnaire as well. Future studies will investigate the use of external cues in prospective memory tasks.

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## 72. Behavioral Changes in Subtypes of Primary Progressive Aphasia and Other Frontotemporal Dementias

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We compared the frequency of apathy, disinhibition, and dysphoric depression among 12 patients with nonfluent (frontal) primary progressive aphasia (PPA), 11 with semantic dementia (temporal variant of PPA), and 27 with non-PPA frontotemporal dementia (FTD). Nonfluent PPA patients were less likely to manifest neuropsychiatric symptoms at onset than the other groups ( $p < .05$ ), while semantic dementia patients differed in featuring early depression to accompany onset of language impairment ( $p < .01$ ). Significantly more FTD patients (96.3%) than PPA (45.5–75%,  $p < .05$ ) manifested apathy. Frequencies of disinhibition and depression converged for all three patient groups over the course of illness. PPA subtypes demonstrate behavioral disturbances similar to cases of non-PPA FTD. The differences between groups may reflect sparing of insight in nonfluent PPA and semantic dementia patients.

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The syndrome of primary progressive aphasia (PPA) is characterized by acquired progressive language deficits that dominate other cognitive deficits in severity, at least at the onset of impairment. PPA has four manifestations: nonfluent, semantic dementia, a mixed syndrome featuring both nonfluent and semantic dementia features, and an anarthric type. We consider all types of PPA to be frontotemporal dementias, based on regional neurodegenerative changes affecting frontal and/or temporal lobes in the dominant hemisphere. Nonfluent PPA patients have functional neuroimaging abnormalities in the dominant frontal lobe; semantic dementia in dominant temporal lobe; and mixed aphasia patients in the perisylvian region. Patients with these diagnoses may eventually experience spread of abnormalities posteriorly and/or to the contralateral hemisphere.

Changes in behavior and personality have been reported in PPA patients, but these disturbances usually develop late in the course of illness. In contrast, neuropsychiatric symptoms such as apathy, disinhibition, and depression are required for the diagnosis of non-PPA frontotemporal dementia (FTD). We wanted to test the null hypothesis that PPA patients do eventually develop these particular behavioral changes as frequently as non-PPA FTD patients do. To our knowledge, our study is the first to compare neuropsychiatric characteristics among patients with (1) nonfluent PPA, (2) semantic dementia, (3) mixed nonfluent and semantic dementia, and (4) non-PPA FTD.

### *Methods*

The UCLA Frontotemporal Dementia Clinic and the UCSF Memory Disorders Clinic collected complete histories, physical examinations, and Neuropsychiatric Inventories (Cummings, 1994) on 25 cases with PPA from 1989 to 1999. Patients had non-fluent PPA if they manifested progressive worsening of nonfluent, effortful speech in the relative absence of other cognitive deficits, and SPECT scan of brain showed bilateral or unilateral frontal hypoperfusion. Patients had semantic dementia if they manifested progressive worsening of fluent speech with paraphasic errors, poor comprehension, and poor repetition in the relative absence of other cognitive deficits, and brain SPECT showed bilateral or unilateral temporal hypoperfusion. Angular gyrus syndrome patients were excluded, since their functional neuroimaging shows a left parietal abnormality, instead of temporal. Mixed aphasia patients showed nonfluent speech and poor comprehension, with close onset of the two features, and no other cognitive deficit to indicate Alzheimer's disease as the underlying diagnosis.

The UCLA Memory Disorders and Alzheimer’s Disease Clinic and the Harbor–UCLA Neurobehavior Clinic collected complete histories, physical examinations, and NPIs on 27 cases with FTD from 1989 to 1999. Patients had FTD if they manifested: (1) early loss of personal awareness, (2) loss of executive skills, (3) hyperorality, (4) relative sparing of visuospatial skills and praxis, (5) progressive dementia, and (6) SPECT scan of brain showing bilateral or unilateral anterior frontal or temporal hypoperfusion more severe in the frontal or temporal areas than in the posterior temporal–parietal regions (Miller, 1997; The Lund and Manchester Groups, 1994). Geschwind (1998) reported the autopsy-confirmed diagnostic accuracy of FTD patients identified through the UCLA Alzheimer’s Disease Center at over 90%.

We defined onset age as the earliest age at which the presenting symptoms were reported. Histories of present illness provided data on behavioral changes at onset of illness, while the NPI supplied data on presence or absence of apathy, dysphoric depression, and disinhibition at presentation or during continuing care at a dementia care center. MANOVA and  $\chi^2$  testing were used to compare mean age at onset, time to diagnosis, and frequency of neuropsychiatric symptoms among the four diagnostic groups. The sample of two mixed aphasia patients was very small.

*Results*

Among our sample of 27 FTD, 12 nonfluent PPA, 11 semantic dementia, and 2 mixed PPA patients, the four groups shared similar mean onset ages, gender distributions, and mean levels of education (see Table 1). Length of illness before diagnosis varied widely and did not differ significantly among the diagnostic groups.

Table 1 summarizes the prevalence of neuropsychiatric symptoms. As expected from the diagnostic criteria, more FTD patients began their illness with neuropsychiatric symptoms than did PPA patients, but only the nonfluent PPA and FTD group comparison achieved a statistically significant difference ( $p < .05$ ). All of the FTD patients developed behavioral disturbances within 2 years of developing frontal dys-executive syndromes.

TABLE 1  
Demographics and Neuropsychiatric Symptoms in Patients with Frontotemporal Dementia (FTD) or Primary Progressive Aphasia (PPA)

	Non-PPA FTD (n = 27)	Nonfluent PPA (n = 12)	Semantic dementia (n = 11)	Mixed aphasia (n = 2)
% Female	63	50	36.3	50
Mean years of education	14.9	14.3	14	16
Mean onset age (years)	58.3	62	65.5	68.5
Mean delay to diagnosis in years (range)	4.5 (1–33)	3.3 (1–7)	3.8 (0.5–10)	3.5 (1–6)
% with behavioral disturbance at presentation	66.7	25 <sup>†</sup>	46.2	0
% with apathy	96.3	75 <sup>†</sup>	45.5**	0
% with disinhibition	63	41.7	54.5	0
% with symptoms of dysphoric depression at onset	14.8	25	54.5*	0
% developed depression over course of illness	37	41.7	54.5	0

\*  $p \leq .01$ .  
 \*\*  $p < .001$ .  
 †  $p < .05$ .

Nonfluent PPA patients were followed up to 6 years after onset of illness, semantic dementia to 9 years, and mixed aphasia to 6 years. Apathy has occurred much more frequently among all groups than depression or disinhibition. Significantly fewer nonfluent PPA patients ( $p < .05$ ) and semantic dementia patients ( $p < .001$ ) than FTD patients had apathy. Early symptoms of depression occurred significantly more frequently in semantic dementia than in FTD ( $p \leq .01$ ), but similar proportions of the nonfluent, semantic dementia, and FTD groups developed depressive symptoms and disinhibition over the course of illness.

### Discussion

Nonfluent, semantic dementia, and mixed subtypes of PPA belong to the spectrum of frontotemporal dementias, not only because of focal involvement of frontal and temporal lobes but also due to a shared constellation of neuropsychiatric symptoms. Behavioral changes developed most consistently in the non-PPA FTD group, but the proportions of patients with depression and disinhibition were fairly similar among the PPA and FTD groups. Over time, the nonfluent PPA, semantic dementia, and non-PPA FTD groups' neuropsychiatric profiles converged.

The diagnostic criteria for PPA account for differences in onsets of behavioral disturbance (Mesulam & Weintraub, 1992), but it is interesting to note that when PPA patients develop neuropsychiatric symptoms, lower proportions of PPA patients develop apathy, while dysphoric depression is relatively common and has earlier onset in some PPA patients. These differences may reflect a sparing of insight in nonfluent PPA and semantic dementia patients. Further investigation may reveal how PPA patients may be immune to loss of insight relative to their non-PPA FTD counterparts despite pathological changes in dominant frontal and temporal lobes.

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## 73. The Relationships between Executive Dysfunction and Frontal Hypometabolism in Alzheimer's Disease

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A series of tasks assessing executive functions was administered to patients with Alzheimer's disease and control subjects. Two groups of Alzheimer patients were examined: patients with hypometabolism restricted to the posterior (temporal and parietal) cerebral areas and

patients with hypometabolism in both posterior and anterior (frontal) cerebral areas. The performance of the Alzheimer patients was inferior to control subjects on all executive tasks. However, the two groups of Alzheimer patients did not differ from each other on all tasks except one. These data indicate that frontal lobe hypometabolism is not necessary to produce executive impairment in Alzheimer's disease. Consequently, executive dysfunction could be the consequence of a disconnection process between posterior and anterior cerebral areas.

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## Introduction

The presence of executive dysfunction relatively early in Alzheimer's disease is now well established (e.g., Collette et al., 1999a). However, there exists at present some debate concerning the neurobiological substrates of these deficits. Indeed, for some authors, executive impairment is specifically related to frontal lobe impairment (e.g., Shallice, 1988) but frontal lobe dysfunction does not seem to be a prominent feature in the earlier stages of the disease (Kennedy & Frackowiak, 1994). In addition, other authors suggest that executive control requires the integration of information coming from different cerebral areas (e.g., Collette et al., 1999b). Consistent with that interpretation, recent studies described Alzheimer's disease as a disconnection process between different cerebral areas (Morris, 1994). Consequently, the aim of this study was to explore the executive functioning of Alzheimer patients with hypometabolism restricted to posterior (temporal and parietal) cerebral areas or hypometabolism in both posterior and anterior (frontal) cerebral areas. Indeed, the existence of a larger executive impairment in Alzheimer patients with posterior and frontal hypometabolism than in patients with only posterior hypometabolism would be consistent with the main involvement of frontal areas in executive processes. On the contrary, the existence of similar performances in the two groups of patients would be more consistent with the hypothesis of executive functioning depending on more diffuse cerebral areas.

## Method

Fourteen subjects meeting the NINCDS-ADRDA criteria for probable Alzheimer's disease (AD) and 12 elderly control subjects (CS) were evaluated on different tasks assessing executive functions. The patients included in this study were selected from a pool of AD patients who underwent PET scan at rest. The brain metabolism distribution of these patients was visually analyzed and rated by three clinicians in order to isolate (a) patients with hypometabolism restricted to posterior (parietal and temporal) cerebral areas and (b) patients with both frontal and posterior hypometabolism. With this procedure, 7 patients showing isolated posterior hypometabolism (NF AD) and 7 patients with posterior and anterior hypometabolism (F AD) were selected. The two groups of AD patients did not differ from CS with regard to their age [ $F(2, 26) = 0.18, p > .5$ ] and their schooling level [ $F(2, 26) = 0.24, p > .5$ ].

Five executive tasks were administered: (1) the *go/no-go task* requiring to respond as quickly as possible following the presentation of a stimulus "A" but to inhibit the response when a stimulus "B" is presented; (2) the *Stroop interference task* in which subjects are confronted with words written in different colors and are asked to name the colors as quickly as possible while ignoring the words themselves: the performance of the subjects in that condition was compared to a condition in which subjects have to name colored squares; (3) a *selective attention task* ("D2") in which subjects have to detect letters *d* surrounded by two lines in a page filled with *d*'s and *p*'s (also surrounded by one, two, three, or four lines); (4) a *verbal phonemic fluency task* requiring to generate a list of words beginning with the letter *p*; and (5) a *verbal*

TABLE 1  
Performance [Mean (SD)] of the Control Subjects (CS) and Alzheimer Patients  
with (F AD) and without (NF AD) Frontal Hypometabolism

	CS	F AD	NF AD
Mattis (total score)	140.5 (3.90)	118.33 (9.83)	124.20 (9.52)
Semantic fluency (number of words)	25.33 (6.37)	14 (4.57)	17 (4.86)
Phonemic fluency (number of words)	21.33 (6.02)	8.67 (4.50)	15.5 (7.50)
Go/no go (response time)	482.33 (74)	464.14 (93)	589.14 (126.90)
D2 (number of correct items)	283.25 (73.49)	194.33 (132.21)	208.6 (54.97)
Stroop (interference score)	0.29 (0.09)	0.47 (0.21)	0.37 (0.51)

*semantic fluency task* requiring to generate as many as possible exemplars of the animal category.

### Results (see Table 1)

Overall performance on the *Mattis Dementia Rating Scale* was significantly lower for the two groups of AD patients than for control subjects [AD F vs CS,  $U = 2$ ,  $p < .0005$ ; AD NF vs CS,  $U = 2.5$ ,  $p < .0005$ ], but that performance was not different in the two groups of patients [ $U = 8.5$ ,  $p > .1$ ]. On the *go/no-go task*, the response time of the NF AD was significantly slower than that of the F AD [ $U = 6$ ,  $p > .05$ ] and (marginally) CS [ $U = 19$ ,  $p = 0.05$ ], while the response time of the F AD and CS did not differ [ $U = 40$ ,  $p > .5$ ]. With regard to the *Stroop interference task*, the interference score (measured as the difference in response time when subjects have to name the colored squares and to name the color of words of color) was not different in the two groups of patients [ $U = 11$ ,  $p > .5$ ] and that measure was different between the control subjects and NF AD patients [ $U = 2$ ,  $p < .005$ ] and (marginally) F AD patients [ $U = 13$ ,  $p = .07$ ]. The two groups of AD patients had a similar performance on the *selective attention task* [ $U = 11$ ,  $p > .1$ ] and that performance was lower than that of CS [F AD vs CS,  $U = 13$ ,  $p < .05$ ; NF AD vs CS,  $U = 11$ ,  $p < .05$ ]. The number of words generated on *semantic fluency* was similar in the two AD groups [ $U = 11$ ,  $p > .1$ ] but was inferior to that given by CS [F AD vs CS,  $U = 6$ ,  $p < .005$ ; NF AD vs CS  $U = 11.5$ ,  $p < .05$ ]. With regard to *phonemic fluency*, both AD groups generated a similar number of words [ $U = 7$ ,  $p > .05$ ]. Moreover, the fluency score of the CS was superior to that of F AD but similar to NF AD [F AD vs CS,  $U = 3$ ,  $p < .005$ ; NF AD vs CS,  $U = 17$ ,  $p > .08$ ].

### Discussion

Taken as a whole, these results confirm the existence of executive deficits in Alzheimer's disease. Moreover, these executive deficits were found both in the group with only posterior hypometabolism and in the group with posterior and frontal hypometabolism. These data suggest that executive dysfunction in Alzheimer disease is not related to the presence of frontal lobe impairment but rather to the existence of a disconnection process between anterior and posterior cerebral areas. More generally, these data are in agreement with the hypothesis that executive processes are not dependent only on frontal cerebral areas.

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74. Semantic Knowledge for Verbs, Nouns, and Abstract Concepts in Frontotemporal Dementia and Alzheimer's Disease

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Studies of picture naming in Alzheimer's disease have demonstrated the presence of category-specific anomia and semantic impairment. We tested demented subjects' naming of concrete nouns presented as line drawings and naming of action verbs presented as still line drawings and as computer animations. A semantic association judgment test for the same items presented as words, and also for abstract concepts, was also administered. Seventeen Alzheimer's disease subjects were found to be more impaired in naming and semantic knowledge for biological nouns and abstract concepts compared to nonbiological nouns and verbs. In contrast, seven equally impaired frontal lobe dementia subjects lacked category specificity. These findings are compatible with recent neuroimaging studies suggesting that verbs and nonbiological nouns may be represented in frontal lobe regions. © 2001 Academic Press

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Introduction

Alzheimer's disease (AD) patients are known to have difficulty in tasks such as picture naming (Hodges, Salmon, & Butters, 1991) and semantic judgment (Grossman, Robinson, Biassou, White-Devine, & D'Esposito, 1998). Detailed studies have also demonstrated the presence of category effects in their naming performance. For example, Silveri et al. (1991) showed that AD subjects had a category-specific naming impairment for living things compared to nonliving things. Robinson et al. (1996) demonstrated that AD patients were more impaired in action naming than in object naming. At the same time, Cappa et al. (1998) found that frontal lobe dementia (FLD) patients, to a greater extent than AD patients, were also more severely impaired in action naming than in object naming. These findings may have important implications for theories concerning the underlying mechanisms and anatomical substrates of semantic memory.

However, the above-mentioned naming studies suffer from some methodological shortcomings. First, they did not take into full account confounding factors including visual complexity and familiarity between categories of stimuli (Funnell & Sheridan, 1992; Stewart, Parkin, & Hunkin, 1992). Second, their control subjects performed

at ceiling on all stimulus sets, and it was uncertain whether one category set is more difficult than the other even for normal subjects. Third, studies of “verb knowledge” or “action naming” using static pictures were also problematic. Actions, by definition, refer to the “process of doing.” The static pictures in the standard Action Naming Test (Obler & Albert, 1982), however, represent a frozen moment of action across time which cannot simply be depicted by a snapshot. It is almost analogous to supplying incomplete stimuli in an object naming test by omitting components of the objects. Hence, still line drawings seem to be an unnatural way of depicting action concepts.

The first objective of the present study was therefore to determine if AD and FLD subjects in fact showed differences in naming performance when given category stimulus sets that were controlled for confounding factors, difficulty level, and ceiling effects. We also created computer animations, which resembled more closely actions, to test for action naming. If category effects could be confirmed in the pattern of the subjects’ naming performance, our second objective was to determine if the same pattern could also be reflected in a completely different semantic task which probed the same categories presented for naming. If the same pattern of deficit was found on both tasks, we would have converging evidence pointing to a *semantic memory* deficit underlying the selective naming impairment observed in the subjects.

### *Methods*

*Subjects.* Sixteen AD and 5 FLD patients, diagnosed according to standard clinical criteria (McKhann et al., 1984; Neary, Snowden, Gustafson, et al., 1998), were studied. All met the following requirements: Hachinski scores less than 4 (Hachinski, et al., 1975), no evidence of focal brain disease, adequate vision, and consenting. They were mildly or moderately demented according to their Mini-Mental State Examination scores (Folstein, Folstein, & McHugh, 1975) (AD mean  $22.5 \pm 3.9$ ; FLD mean  $21.1 \pm 4.5$ ). Sixty elderly normal controls were also recruited. The three groups were matched for age and education.

*Naming task.* Black-and-white line drawings were taken from published sources (Kaplan, Goodglass, & Weintraub, 1983; Obler & Albert, 1982; Snodgrass & Vanderwort, 1980). Animations, in the form moving line drawings demonstrating different human action sequences, were also constructed using the Life Forms software (Credo Interactive Inc., Canada). Control subjects also gave ratings for familiarity and complexity for the test items. The four naming tests were (1) 45 biological entities; (2) 45 nonbiological objects; (3) 17 static drawings of actions; and (4) 17 animations. The tests were all matched for accuracy [ $F(3, 120) = 0.05$ ; NS], word frequency [ $F(3, 120) = 0.49$ , NS (Francis & Kuçera, 1986)], familiarity [ $F(3, 120) = 1.70$ ; NS], and complexity [ $F(3, 120) = 2.47$ ; NS]. The controls’ average accuracy score was about 80% in each test, thereby avoiding any ceiling effects.

*Semantic association judgment task.* This test was based on the Pyramids and Palm Trees Test of semantic association (Howard & Patterson, 1992). In each question, subjects were asked to indicate which of the two words was more like a target word (e.g., lamb: goat, sheep). A laptop computer displayed on the screen the target word to the top and the two choices (the answer and the semantic distracter) to the left and right bottom corners. Subjects entered their responses by pressing labeled keys corresponding to the left or right words. Accuracy and reaction time were emphasized and recorded.

The words were drawn from the same semantic categories used in the naming task. We also included abstract nouns which could not be properly tested in a naming test. We selected 18 questions in each of the four semantic categories such that the stimu-

lus sets were matched for accuracy [ $F(5, 195) = 0.20, p > .05$ ] and reaction time [ $F(5, 195) = 1.82, p > .05$ ] according to controls' performance. Again, controls averaged at 90% correct (no ceiling effect) in all categories.

### Results

*Naming task.* Because different control subjects participated in different naming tests, separate *t* tests between the three groups were performed on the percentage (%) correct scores on each of the tests. AD and FLD subjects were significantly less accurate than control subjects in all four naming tests ( $p < .001$ , Bonferroni corrected).

Within-group analyses in AD subjects revealed that their scores on naming tests were also significantly different [ $F(3, 45) = 27.2, p < .001$ ]. Post hoc Tukey's test demonstrated that they performed worse on naming biological (mean  $33 \pm 15\%$ ) than on naming nonbiological objects (mean  $42 \pm 14\%$ ;  $p < .05$ ). They were also significantly worse on naming actions depicted by line drawings (mean  $39 \pm 19\%$ ) compared to animations (mean  $59 \pm 15\%$ ;  $p < .01$ ). Their performance on naming animations was significantly better than on the other three tests ( $p < .01$ ). FLD subjects, however, did not show any differences across categories (overall mean  $54 \pm 27\%$ ).

*Semantic association judgment task.* On examining the percentage of correct response, a group (control, AD, FLD)  $\times$  category (abstract nouns, biological nouns, nonbiological nouns, verbs) MANOVA demonstrated significant main effects for group ( $p < .001$ ) and for category ( $p < .001$ ). The group  $\times$  category interaction was also significant ( $p < .01$ ). Simple effects tests revealed that AD and FLD subjects were significantly more impaired than control subjects at the semantic association judgement in all four categories ( $p < .01$ ).

Within-group analyses in AD subjects revealed that their scores in these categories were significantly different [ $F(3, 171) = 8.98; p < .01$ ]. Post hoc Tukey's test demonstrated that they were less accurate with biological nouns (mean  $67 \pm 12\%$ ) than with nonbiological nouns (mean  $79 \pm 13\%$   $p < .01$ ) and with action verbs (mean  $81 \pm 13\%$ ,  $p < .05$ ). They were also less accurate with abstract nouns (mean  $68 \pm 14\%$ ) than with nonbiological nouns ( $p < .01$ ) and with action verbs ( $p < .05$ ). Again, FLD subjects did not demonstrate category effects in this task (overall mean  $76 \pm 6\%$ ).

*Overall analysis.* We also examined the relative accuracy in individual subjects on both the naming task and the semantic association judgment task. A consistent biological–nonbiological difference in favor of the biological category on both tasks was noted in 81% of AD subjects. Also, 94% of AD subjects performed better with the verb than with the biological category on both tasks. In contrast, FLD subjects showed no consistency in performance between the two tasks.

### Discussion

Several findings emerged from this study. First, we confirmed the presence of category effects in the naming performance of AD subjects. They showed a disproportionate deficit for biological entities compared to nonbiological objects. Moreover, when presented with animations, their naming performance was significantly better than the other semantic categories we tested. This was not unexpected, as our hypothesis was that the apparent deficit in action naming reported in previous studies (Cappa et al., 1998; Robinson, Grossman, White-Devine, & D'Esposito, 1996) was due largely to poor testing stimuli which disregarded the time dimension of action con-

cepts. Second, our results in the semantic association judgment test revealed a pattern of semantic deficit in AD subjects consistent with that found in the naming task. Hence, converging evidence from the two semantic memory tasks implicates an impairment of processing at the semantic memory level. Third, AD subjects were impaired in the semantic association judgment task for abstract nouns to a degree equivalent to biological objects. Similarly, FLD subjects also performed poorly on abstract nouns, but not significantly worse than other categories. This is the first such report in AD and FLD to our knowledge.

FLD subjects lacked category specificity and consistency in both semantic tasks. In particular, they did not show a relative advantage for verbs and nonbiological nouns over biological nouns, as observed in AD subjects. The contrasting results from the two groups are consistent with lesion (McCarthy & Warrington, 1985) and neuroimaging (Grossman et al., 1997; Herholz et al., 1996) studies suggesting that verbs and nonbiological concepts are preferentially instantiated in frontal regions, whereas biological concepts are mainly instantiated in posterior temporal regions.

In summary, our study clarifies the relationship between deficits in different categories of knowledge in AD and FLD. We found solid evidence for the presence of category differences in the naming performance of AD subjects that were due not to visuoperceptual or lexical–phonologic deficits but rather to the underlying semantic memory impairment. FLD subjects, however, did not demonstrate any category-specific effects and were equally impaired in all tested categories. These findings support the hypothesis that verbs and nonbiological nouns may be preferentially represented in frontal lobe regions.

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## 75. Behavioral, Neuropsychological, and SPECT Correlates of Frontal Lobe Functioning in Dementia

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The relationship of behavioral changes to other diagnostic information regarding dementia (SPECT, neuropsychological performance, depressive symptomatology) was examined. Our results revealed that in a mild dementia group (Alzheimer's disease and frontotemporal dementia patients; CDR = 0.7 + 0.4) frontal personality changes as measured by the Frontal Lobe Personality Scale (FLOPS), depression (Cornell), and IADLs were strongly related to neurologist's global impression (CDR). Both SPECT and neurocognitive performance were not related to CDR. Further, we demonstrated that behavioral changes associated with dementia were associated with frontal and temporal ROIs on SPECT as opposed to posterior ROIs on SPECT. Thus, behavioral change as measured by the FLOPS was related to frontal lobe and limbic functioning as measured by SPECT and overall clinical impression (CDR).

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Diagnostic evaluation of dementia typically involves multiple data sources such as clinical impression, neuropsychological testing, structural imaging, and functional imaging. It would be helpful to add behavioral data in a quantifiable manner to the diagnostic formulation, particularly in mixed dementia presentations. In the case of some dementias such as frontotemporal dementia, behavioral changes in fact may be the earliest symptoms. Early detection of dementia becomes more critical as treatment options to arrest or delay progression are developed. In this study, we sought to examine the relationships among behavioral manifestations of dementia, neuropsychological test performance, and SPECT imaging. In this study, we examined the relationship between frontal and posterior brain functioning as measured by single-photon emission computed tomography (SPECT), neuropsychological test performance, and behavior change as measured by the Frontal Lobe Personality Scale (FLOPS). It was hypothesized that a coherent picture utilizing multiple data sources would emerge of frontal behavioral syndromes in a dementia population.

Since frontal behavioral syndromes may precede measurable cognitive decline, we sought to measure behavioral changes associated with the frontal lobes. The Frontal Lobe Personality Scale (FLOPS—Family version) is a brief, psychometrically sound instrument that has been shown to measure frontal behavioral syndromes (Grace, Stout, & Malloy, 1999). Family members record their impressions of the dementia patient's behavior prior to onset of dementia and at the present time. In this manner, the FLOPS controls for variations in baseline personality and quantifies the extent of behavior change with dementia. Previous studies with the FLOPS have demonstrated that family ratings of frontal lesion patients show significantly greater elevations on the FLOPS compared to non-frontal lesion patients and to healthy controls. The FLOPS has been shown to relate to other neuropsychiatric instruments such as the Neuropsychiatric Inventory and to instrumental activities of daily living.

Our specific aim for this study was to examine the relationship of behavioral changes (i.e., measured by the FLOPS) to other diagnostic information employed in the diagnosis of dementia as follows: (1) SPECT, (2) cognitive performance on neuropsychological testing, and (3) emotional functioning/depressive symptomatology. Our respective hypotheses were as follows:

1. Behavioral changes associated with dementia would be associated with Frontal and Temporal ROIs on SPECT as opposed to posterior ROIs on SPECT.
2. Behavioral changes would be distinct from the cognitive profile of these patients due to the mild level of dementia evidenced in our sample.
3. Behavioral changes (apathy subscale in particular) would be associated with family member's endorsement of patient's depressive symptoms.

### *Methods*

*Participants.* Forty patients (mean age 73 years; SD = 7.2), mean education 12 years; SD = 3.1) were evaluated for degenerative dementia in an outpatient neurology clinic. As part of their diagnostic work up, they underwent SPECT imaging, brief neuropsychological evaluation, neurobehavioral evaluation, and a neurological exam. Brain CT or MRI was obtained if not already available to rule out structural lesions. In addition, 30 of these patients underwent an extended neuropsychological evaluation. Overall, the patients were in the early stages of dementia with Clinical Dementia Rating (CDR) mean 0.7 (SD = 0.4) and mean Folstein Mini-Mental Status Exam (MMSE) of 23/30 (SD = 3.2). The sample included probable Alzheimer's disease (AD) and probable frontotemporal dementia (FTD) since these would be expected to produce different imaging, neuropsychological, and behavioral profiles.

*Procedure.* Twelve regions of interest (ROIs) in frontal and posterior brain areas were defined and measured using a quantitative imaging analysis program. SPECT scans were performed using DSI Cersaspect Camera with an intravenous injection of 20 mCi (740 mBq) of Tc-99m bicisate. Sixty four-slices were obtained 1.67 mm in thickness. The slice which best displayed the cerebellum was chosen as baseline and cerebellar ROIs were placed on this slice. For cortical ROIs slices were chosen approximately 6, 9, 11, and 13 slices cephalad to the cerebellar slice. A series of dartboard ROIs were generated on each of these slices. Using standard templates (Damasio & Damasio, 1989), cortical regions were divided into 12 smaller ROIs and average counts per minute/pixel were generated for each of these smaller ROIs. Averages were taken for 4 frontal ROIs, 2 medial temporal ROI's, and 6 posterior ROIs.

Brief neuropsychological evaluation consisted of the MMSE, Category Fluency, and the Clock Drawing Test. The extended neuropsychological evaluation included

Controlled Oral Word Association Test, Trail Making Test, Boston Naming Test, Wechsler Adult Intelligence Scale subtests (Block Design, Similarities, Matrix Reasoning), Wechsler Memory Scale (Logical Memory I and II), and word list learning. Behavioral measures included the FLOPS and the Cornell Scale for Depression in Dementia (Cornell). Family members completed the FLOPS, recording their impressions of their family members' behavior before the onset of dementia (pre) and at the present time (post). FLOPS pre–post change scores were calculated as an estimate of overall behavior change following the onset of dementia symptoms. Change scores ranged 107 points with mean change of 39 points. The greater change score reflected the emergence of more pronounced frontal behavior.

### *Results*

Consistent with our first hypothesis, a trend was found between frontal and FLOPS change scores ( $r = -.30$ ,  $p = .06$ ), a significant correlation was found between temporal ROIs and FLOPS change scores ( $r = -.32$ ,  $p = .05$ ) and no significant correlation was found between posterior ROIs and FLOPS change scores. Frontal ROIs were significantly correlated with the Apathy subscale of the FLOPS ( $r = -.32$ ,  $p = .05$ ) but not with the Disinhibition or Executive subscales.

Consistent with our second hypothesis, behavioral changes were distinct from performance on cognitive tasks. More specifically, the FLOPS was not significantly correlated with MMSE, Verbal Fluency, Block Design, Clock Drawing, Trail Making Test, or Boston Naming Test. Of interest, COWA was significantly correlated with both frontal and temporal ROIs (frontal  $r = .52$ ,  $p = .01$ ; temporal  $r = .51$ ,  $p = .01$ ).

Although we did not find significant relationship between the FLOPS total change score and the Cornell, behavioral changes on the FLOPS Apathy subscale were significantly associated with family member's endorsement of patient's depressive symptoms on the Cornell ( $r = .44$ ,  $p = .01$ ).

Overall, ratings of dementia based on neurologist's clinical impression as quantified by the Clinical Dementia Rating Scale (CDR) were significantly correlated with FLOPS Apathy subscale ( $r = .41$ ,  $p = .02$ ), Cornell ( $r = .41$ ,  $p = .01$ ), and instrumental activities of daily living (IADL,  $r = -.45$ ,  $p = .02$ ), but not with neuropsychological measures or SPECT ROIs.

### *Conclusions*

This study demonstrates that the quantification of behavioral changes evidenced in the early stages of dementia are critical to the diagnosis of dementia. Our results revealed that in a mild dementia group including patients with either AD or FTD, frontal personality changes, depressive symptomatology, and IADLs were strongly related to neurologist's global impression as rated on the CDR. This is important in mild dementia because in our sample both SPECT and neurocognitive performance was not sensitive to CDR. Further, we demonstrated that behavioral changes associated with dementia were associated with frontal and temporal ROIs on SPECT as opposed to posterior ROIs on SPECT. Thus, behavioral change as measured by the FLOPS were related to frontal lobe and limbic functioning as measured by SPECT.

Behavioral changes were found to be distinct from the cognitive profiles of these patients most likely due to the early stage of dementia evidenced in our sample. Further, with the exception of verbal fluency, which is known to be a sensitive measure in early dementia, cognitive performance did not relate to SPECT.

Behavioral changes (FLOPS apathy subscale in particular) were associated with

family member's endorsement of patient's depressive symptoms. Quantification of family impressions of changes in personality and emotional functioning is a critical component in early detection of dementia. Thus, measures such as the FLOPS and Cornell that quantify family impressions should be routinely included in dementia evaluations. Likewise, these measures may be helpful additions to dementia research in their ability to quantify and describe early behavioral change in mild dementia samples.

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### 76. Theory of Mind in Patients with Frontal Variant Frontotemporal Dementia (fv) FTD

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#### Background

Normal humans have complex abilities in the areas of interpersonal skills, social cognition, and reasoning. One key component of these skills relates to the ability to make inferences about the mental states of others, referred to as 'theory of mind' (ToM). ToM develops in complexity over the first 10 years of life through first-order false beliefs (the ability to understand that others may not know what you know) and second-order false beliefs (i.e., beliefs about beliefs) to the understanding of faux pas (i.e., when something has been said when it should not have been said). Finally, the ability to recognize complex emotions and mental state from facial expression, and particularly solely from the eyes, has been postulated as an advanced/adult aspect of ToM (Baron-Cohen et al., 1997; Stone et al., 1998). Individuals with Asperger's and autism fail ToM tasks while in Down's syndrome intellectual function is impaired but individuals perform well on ToM tests. Studies of patients with focal cerebral lesions imply a role for the orbital (ventromedial) region of the frontal lobes (Stone et al., 1998).

Patients with the frontal variant of frontotemporal dementia (fv-FTD) present with insidious changes in personality, including lack of empathy or unconcern for others, disinhibition, and other socially inappropriate behavior and loss of insight (Gregory et al., 1999; Levy et al., 1996). Patients are typically unconcerned by the emotional state of others and tend to develop odd stereotypic behaviors. These reports are reminiscent of the abnormal interpersonal interactions and behaviors found in autism. Despite these gross alterations, patients with fv-FTD often perform normally on traditional frontal executive tasks which may reflect the orbitofrontal locus of pathology (Rahman et al., 1999; Gregory et al., 1999). We hypothesized that impaired ToM may underlie some of the behaviors observed in this patient population.

## Methods

### *Participants*

Patients with fv-FTD ( $n = 13$ ; aged 44 to 67 years) fulfilled consensus criteria for FTD. Cases presenting with semantic or language deficits were excluded. Structural (CT or MRI) and functional neuroimaging (HMPAO-SPECT) was performed in all cases. Controls consisted of education and age-matched volunteers from the Medical Research Council–Cognition and Brain Sciences Unit subject panel.

### *General Tests*

Patients scored highly on the caretaker-based Neuropsychiatric Inventory (NPI) (Levy et al., 1996). All underwent an extensive general neuropsychological test battery. Working and episodic memory, immediate and delayed story recall, and recall of a Rey figure, perceptual, and spatial abilities were normal in all cases. A number of patients showed mild impairment on stringent tests of semantic memory such as the graded Naming Test, abstract, and concrete synonymy judgment. Performance on frontal executive tasks (verbal fluency for words beginning with F, A, and S, Wisconsin card sort test etc.) was variable but over half scored within the normal range. On the Mini-Mental State Examination 11 of the 13 scored above 24 (mean 27.3).

### *Theory of Mind Tests (Stone et al., 1998; Baron-Cohen et al., 1997)*

*First-order false belief tests.* Four stories based on the classic Sally-Ann scenario with false belief and control comprehension questions were used.

*Second-order false belief tasks.* Four more complex stories involved person 1 putting an object somewhere and leaving the room. Person 2 moves the object. While person 1 is out of the room he peeks back in and sees person 2 moving the object, but person 2 does not know that person 1 has seen this. The subject is then asked “when person 1 enters the room where will person 2 think that person 1 thinks the object is.”

*Recognition of social faux pas.* Ten stories containing a social faux pas and 10 control scenarios without a faux pas were presented. Subjects were asked if something was said which should not have been and if so what was said inappropriately and why. Comprehension of story content was also tested.

*The mind in the eyes test.* Twenty-four photographs of the eye region of faces were presented. Subjects were asked to make a choice between two words which best describe what the individual in the photograph is thinking or feeling.

## Results

### *First-Order False Belief Task*

On this task 5 of the 13 patients (38%) showed deficits, which were usually mild. Patients achieved a mean score of 0.79 (SD 0.32), while controls performed perfectly  $-1.0$  ( $t = 2.38$ ,  $p = .02$ ).

### *Second-Order False Belief Task*

Two patients were completely unable to grasp the concepts entailed in the second-order false belief test and of the 11 able to complete the task, 4 (38%) were impaired.

Patients had a mean score of 0.79 (SD 0.35); controls were again at ceiling with a mean score of 1.0 ( $t = 2.17, p = 0.04$ ).

### *Faux Pas Task*

The greatest deficits were seen on the social faux pas test. Only 3/11 (27%) patients performed within the normal range taken as the control mean  $\pm$  2SD. The mean score of the fv-FTD patients (0.62, SD 0.24) was significantly lower than that of controls (0.95, SD 0.06),  $t = 4.83, p = .0001$ . On control questions, which assessed comprehension, the patients performed well although 4 of the 13 made some errors.

### *Mind in the Eyes Test*

Normal controls found the mind in the eyes test relatively difficult (mean 0.77, chance 0.5) but the fv-FTD group were significantly impaired (mean 0.67),  $t = 1.8, p = .04$ .

There was good intercorrelation between the various ToM tests (except the mind in the eyes), but no significant correlation between performance on any of the ToM tests and traditional measures of frontal executive dysfunction (verbal fluency/FAS and WCST). MMSE was significantly correlated with performance on the mind in the eyes only ( $r = .79, p = .001$ ). It is notable that one of the most behaviorally disturbed cases (NPI score = 74) failed disastrously on the faux pas test (0/40 on the target stories and 10/10 on the control stories) but obtained a perfect score on the MMSE (30/30) and sorted 6/6 categories on the WCST. There was, however, a positive correlation between scores on the social faux pas test and the NPI, indicating that these measures may be related to a common factor.

## Conclusions

We have shown that patients with fairly mild fv-FTD—as indicated by their performance on a range of neuropsychological measures including traditional frontal executive tasks and generally normal scores on the MMSE—fail on tests of ToM. Deficits on the first and second-order false belief questions were less frequent and tended to be found in the patients with longer standing disease, but the majority of patients failed on the social faux pas test and had difficulty with the mind in the eyes test. These findings have both practical and theoretical implications.

From a practical clinical perspective there is a need for objective measures of the social dysfunction shown by patients with fv-FTD. At present, clinicians rely on caretaker reports which may be biased or even unavailable. Standard measures of frontal function are insensitive to the orbitofrontal pathology of fv-FTD and even sophisticated structural and functional imaging methods may not detect changes for a number of years (Gregory et al., 1999). With the advent of behavioral modifying therapies the need for methods of assessment is even more pressing.

Theoretically these data confirm that ability to perform ToM tasks may be lost in adult life (Stone et al., 1998) and breakdown in this putative module may underlie many of the changes in personality and behavior reported by relatives in such cases. The level of impairment in the mildest cases was similar to that observed in patients with Asperger's syndrome and equates to the development stage of children aged 7 to 8 years who can pass first- and second-order belief tests but makes errors on the more difficult faux pas (Stone et al., 1998; Baron-Cohen et al., 1997). The more impaired fv-FTD resembled patients with autism who regularly fail even the first-order false belief tasks. Our finding support the notion that ToM depends upon a distributed circuit in which the orbitofrontal cortex plays a key role.

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### 77. Relationship between Patterns of Glucose Metabolism and Memory, Visuospatial Function, and Depression in Nondemented Parkinson's Disease Patients: A Positron Emission Tomography Study

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Nondemented Parkinson's disease (PD) patients have a "dysexecutive" cognitive deficit that is thought to result from frontal lobe dysfunction. Depression is common and may be etiologically unrelated to cognitive or motor symptoms. Fifteen PD patients and 14 age-matched controls underwent FDG/PET and neuropsychological tests. The data were analyzed using *t* tests and partial least squares (PLS). Depression in the PD group was associated with decreased frontal metabolism bilaterally and not with parietooccipitotemporal dysfunction. Impaired cognitive performance in the PD group was associated with abnormal metabolism in bilateral medial temporal and parietooccipital cortex, but not with abnormal frontal metabolism. This suggests dysfunction in nonfrontal brain regions is important in the cognitive deficit of PD and that depression is not a reaction to abnormal cognition. © 2001 Academic Press

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### Introduction

It has long been known that specific cognitive deficits are present in clinically *nondemented* PD patients, even at the earliest stages of disease. In addition to difficulties with classical "frontal lobe" tasks, impairments in visuospatial processing and memory have also been noted. While a unifying hypothesis accounting for all clinical findings remains elusive, it is widely hypothesized that the essential cognitive abnormality is dysexecutive. That is, the extent to which a subject has problems with a visuospatial, memory, or other cognitive task is equal to the extent to which frontal lobe/executive function is involved in that task. Anatomically, the lesion is hypothesized in frontal or frontosubcortical regions (Dubois, 1997; Brown, 1990).

Depression is an affective disorder that occurs frequently in PD. As depression may precede or occur with an intensity not correlated with motor or cognitive impairment, many believe it is an expression of primary PD pathology in the brain and not a "reaction" to motor or cognitive impairment (Ring, 1994).

The primary cause of PD is a loss of dopamine-containing cells in the substantia

nigra with a concomitant reduction in striatal dopamine concentrations. In many PD patients, levodopa administration can improve the signs and symptoms of their illness presumably by replenishing presymptomatic nigrostriatal dopamine stores. However, while dopaminergic pharmacotherapy is very effective in the relief of rigidity and bradykinesia, other symptoms such as cognitive disability and depression are less amenable to this form of treatment. Thus nigrostriatal dopaminergic depletion cannot account for all aspects of the clinical phenomenology of PD.

A useful model for understanding the motor abnormalities in PD involves abnormal dopamine modulation of the motor corticostriatopallidal–thalamocortical (CSPTC) loop. The existence of cognitive (prefrontal) and emotive (limbic) CSPTC loops has been proposed (Wichmann, 1996). However, their effect upon cognition and affect, as well as the extent to which they may be dysfunctional in PD, is less well understood than the motor CSPTC loop. Nonetheless, dysfunction involving prefrontal and limbic CSPTC loops remains a strong hypotheses for cognitive and affective dysfunction in PD.

Partial least squares (PLS) (McIntosh, 1996) is an analytic technique that can be used to relate a group of behavioral measures with brain function. The central procedure of PLS is a singular-value decomposition (SVD) of a covariance matrix that consists of brain-behavior covariance maps. The output of the SVD is paired “singular vectors” or “latent variables.” That is, a set of scores for each behavior that is paired with a pattern of brain function.

Thus, using PLS we can evaluate the relationship between glucose metabolic patterns and memory, visuospatial function, and depression. The input consists of behavioral measures of tasks representing these cognitive domains in a group of PD patients and their FDG/PET scans. The output consists of images of relative changes in glucose metabolism that is correlated with these behaviors. We hypothesize: (1) Depression results from a specific functional pathology and is not a reaction to severity of cognitive impairment. Thus, we expect depression ratings and cognitive ratings to correlate with different brain activation patterns. (2) Cognitive impairment is exclusively “dysexecutive”; thus, we expect memory and visuospatial behavioral ratings to correlate highly with an activation pattern involving frontal lobe and/or subcortical structures connected to the frontal lobe.

### *Methods*

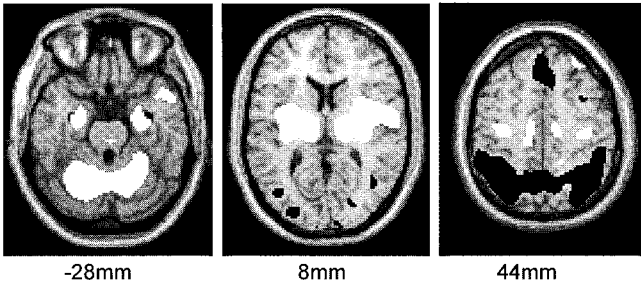
We used FDG/PET to study 15 nondemented (MMS  $28.4 \pm 1.8$ ) PD patients [age  $59.2 \pm 9.2$  years, 12M 3F, Hoehn and Yahr (H&Y)  $3.3 \pm 0.9$ , Unified Parkinson’s Disease Rating Scale (UPDRS)  $35.6 \pm 16.1$ ]. Fifteen age-matched normal subjects ( $57.1 \pm 10.6$ , 7M 8F) served as controls. All PD patients underwent neuropsychological evaluation within 2 weeks of PET. We analyzed the PET data in the following ways: (1) Using Statistical Parametric Mapping software (SPM99b Wellcome Institute of Cognitive Neurology, London, UK), we performed a voxel-by-voxel *t* test on the PD and control groups to identify brain regions where resting glucose metabolism in the PD group differed from controls. This information was used to better interpret the relative changes in brain activity identified by a subsequent PLS analysis of the PD group. The PLS analysis was performed on the PD group alone. Using PLS we generated patterns of regional activity (singular images) representing pixel by pixel covariances with three behavioral measures: the California Verbal Learning Test summary score (CVLT), the Hooper Visual Organization Test raw score (VOT), and the Beck Depression Inventory (BDI).

*Results*

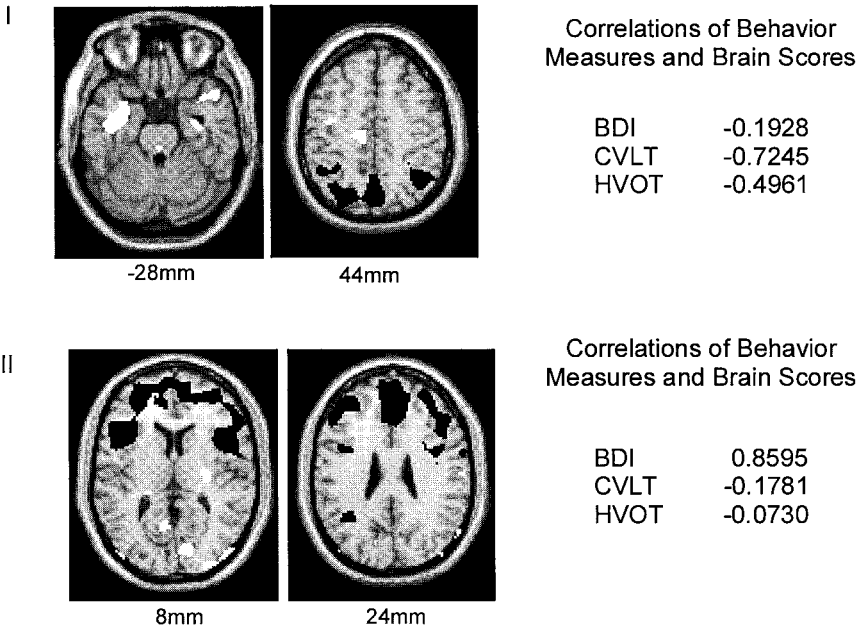
The PD and control groups were matched for age. By MMS criteria, the PD group was nondemented (MMS 28.4 + 1.8). However, neuropsychological tests of the PD patients showed impairment in CVLT (32.1 + 14) and VOT (19.7 + 4.3), with mild depression (BDI 11.4 + 6.6). In addition, compared to normative values, PD group mean scores were impaired (>1 standard deviation) on Trails B and several measures within the Wisconsin Card Sorting Test. However, mean values were no different from age-adjusted normative values on The Stroop Test, Boston Naming, Controlled Oral Word Association Tests, and Trails A.

The SPM analysis (see Fig. 1A) showed that compared to controls, the PD group had higher glucose metabolism bilaterally in basal ganglia, medial and anterior temporal lobes, and cerebellum. Glucose metabolism was lower in the PD group in parie-

**A. Glucose Metabolism in Parkinson's Disease Compared to Controls (SPM t test)**  
 Parkinson's Disease > Controls (white), Parkinson's Disease < Controls (black)



**B. Singular images from first (I) and second (II) latent variables (PLS analysis).**  
 Glucose metabolism relatively decreased (black) and increased (white)



**FIGURE 1**

tooccipital lobes and medial frontal cortex. Dorsolateral prefrontal lobes were no different between the groups.

The first singular image (see Fig. 1B, I) was composed of relatively increased glucose metabolism in medial and anterior temporal lobes bilaterally and relatively decreased metabolism in parietooccipital lobes bilaterally. Correlations between the three behavior measures and brain scores for this singular image were CVLT  $-0.7$ , VOT  $-0.5$ , and BDI  $-0.2$ . Both cognitive measures but not depression correlated with this pattern of brain metabolism. Thus, brain regions identified as abnormal in PD by SPM were correlated with impaired memory and visuospatial performance.

Glucose metabolism in the second singular image (see Fig. 1B, II) was relatively decreased in the frontal cortex bilaterally and increased in the cerebellum bilaterally. Behavior-to-brain score correlations for the second singular image were BDI  $0.9$ , CVLT  $-0.2$ , VOT  $-0.1$ . That is, a pattern of brain metabolism that correlated essentially with depression.

### Conclusion

Behavior ratings for depression (BDI) and cognitive abnormalities (CVLT, VOT) correlated with different patterns of brain function. This supports the hypothesis that depression in PD is not simply an affective response to increasing cognitive difficulties. Further, increased severity of depression was associated with lower bilateral frontal brain metabolism supporting the hypothesis that depressive symptoms in PD are specifically associated with frontal lobe dysfunction.

In the PD group, memory and visuospatial function is associated with abnormal metabolism in medial temporal and parietooccipital lobes but not with abnormal metabolism in frontal/subcortical regions. That is, in some but not all areas identified as having abnormal metabolism by SPM.

At rest, patterns of glucose metabolism are associated with cognitive performance. These patterns include nonfrontal brain regions expected to be involved in these tasks. Demonstration of frontal lobe dysfunction in PD may require PET imaging during task performance. Moreover, frontal lobe dysfunction may be more evident in patients with more severe disease.

Understanding the mechanisms by which abnormal metabolism occurs in brain regions distant from the nigrostriatal pathology of PD is crucial to developing rational treatment for the cognitive dysfunction.

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## 78. Serial Neuropsychological Assessment in a Patient with Sleep Apnea: Anoxic Brain Damage or Frontotemporal Dementia

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Serial neuropsychological assessment can increase understanding of etiology in dementia, particularly in cases where multiple disorders may contribute to the clinical picture. The patient presented in this case study was assessed on three occasions over 36 months. When first assessed, S.B. was a 62-year-old man with a history of sleep apnea treated with CPAP. He was referred for assessment because of memory difficulties and behavioral change characterized by apathy, reduced spontaneous speech, and neglect of self-care. Across the three assessments, he demonstrated intact memory and visuospatial skills but impaired abstraction and verbal fluency. His neuropsychological profile and behavioral changes are most likely due to frontotemporal dementia. His progressive behavioral disturbance cannot be explained by sleep apnea alone. © 2001 Academic Press

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### *Introduction*

In many patients with dementia, the differential diagnosis is complicated by coexisting conditions or risk factors. For example, a patient may present with symptoms suggestive of Alzheimer's disease but also have a history of stroke and depression. Serial neuropsychological assessment can help illuminate the disease processes that contribute to cognitive impairment in these patients.

### *Method*

The present case report describes a patient, S.B., who was assessed on three occasions over 39 months. S.B.'s neuropsychological assessment results, behavioral symptoms, and neuroimaging findings will be compared to the profiles characteristic of sleep apnea, frontotemporal dementia, and Alzheimer's disease.

### *History*

S.B., a 63-year-old right-handed retired man with a university education, was referred for neuropsychological assessment from a Memory Disorders Clinic. When first seen, S.B. acknowledged memory problems, but he was very passive and much of his history was obtained from his wife. She reported that S.B.'s memory problems became noticeable approximately 2 years previously and had gradually worsened. For example, he would forget information he had read. His wife also reported a number of behavioral changes, including loss of sense of humor; apathy; loss of sensitivity to social cues in conversation; difficulty planning, organizing, and making decisions; and a tendency to speak as if "programmed to tell a story." He had become less dependable, had lost interest in former hobbies, and required prompting to change clothes and care for his appearance. At visit 2, his wife reported that there had been no change in his memory. However, he had developed urinary incontinence. At visit 3, his wife reported that he continued to be incontinent and to show no concern about this. He had episodes of repetitive shouting and his desire for junk food had increased.

S.B.'s medical history is significant for moderate obstructive sleep apnea syndrome and mild periodic limb movement disorder (restless leg syndrome). These conditions

were diagnosed in May 1994. According to his wife, S.B. had snored loudly for approximately 1.5 years before being diagnosed with sleep apnea. A few months after diagnosis, S.B. began treatment with CPAP (continuous positive airway pressure). S.B. reported that, approximately 1 year prior to the first assessment, he was involved in a motor vehicle accident in which his car was rear-ended by a garbage truck. He denied loss of consciousness. S.B. has no history of hypertension, heart disease, diabetes, thyroid dysfunction, or stroke. There is no family history of dementia. In 1998, S.B. fell in the bathroom and remained on the floor until his wife returned from work. On interview, S.B. reported that he lost consciousness from the fall, but his wife could not confirm this.

### *Neuropsychological Assessment Results*

Across all three assessments, S.B.'s behavior in the test session was characterized by flat affect, passivity, little or no spontaneous verbal response, and mild impulsivity (a tendency to start tests before being told to do so). At visit 1, he demonstrated constant movement of his left leg. He related two anecdotes that were spoken without preamble and were unrelated to context. At visit 2, leg movement was observed after the test session. He demonstrated episodes of somnolence and made no efforts to maintain alertness. At the third visit, he showed repetitive motion of both his left leg and left arm. After the session, he began shouting while in the washroom.

Table 1 summarizes the results of his test performance across the three assessments. Overall, he gave concrete responses on measures of verbal abstraction, particularly at visit 1 and 2. Variable impairment was noted on tests of verbal fluency. Delayed recall and recognition were within normal limits. Verbal recall improved when he was given semantic cues. At visit 2, he performed in the impaired range on immediate and delayed memory for paragraphs and designs (WMS-R). However, he appeared very drowsy during that part of the assessment. Throughout testing, he performed in the average range on measures of naming and visual construction. In addition, he performed well (average range) at visits 1 and 2 on the Wisconsin Card Sorting Test (WCST), a measure of problem solving that is sensitive to frontal lobe dysfunction.

### *Neuroimaging*

CT scanning (January 1996, January 1998) revealed cortical atrophy and enlargement of the ventricular system and bilateral frontal lobe atrophy (June 1998). EEG (June 1998) was normal. SPECT scanning (December 1995, May 1996) demonstrated moderately severe bilateral hypoperfusion in the frontal and temporal lobes. In March 1999, SPECT showed stable hypoperfusion in frontotemporal regions (mild in temporal lobes) and some decreased perfusion in the basal ganglia bilaterally. A CSF flow study (January 1998) showed abnormal flow over the cerebral convexity but was not typical of normal pressure hydrocephalus.

### *Discussion*

The behavioral symptoms, neuropsychological assessment results, and neuroimaging data in this case are all consistent with frontal lobe dysfunction. The most striking features of S.B.'s behavior are apathy and stereotypic speech. Possible causes of frontal lobe dysfunction in this patient include sleep apnea, traumatic brain injury, frontotemporal dementia, and Alzheimer's disease.

Patients with sleep apnea have been found to show impairment on neuropsycholog-

TABLE 1  
Summary of Neuropsychological Assessment Results

Test/domain	December 1995	December 1996	March 1999
Dementia Rating Scale (DRS)	Within normal limits—impaired on verbal abstraction (conceptualization)	Within normal limits—impaired on verbal abstraction (conceptualization)	Borderline impaired on initiation and preservation
Naming of pictured objects	Average	Average <sup>1</sup>	Average
Verbal fluency—first letter (CFL/FAS)	Borderline impaired	Average	Impaired
Verbal fluency—category	Average	Borderline impaired	Impaired
Verbal learning (California Verbal Learning Test)	Impaired (better with cues)	Low average	Low average (better recall with category cues)
Delayed verbal recall (CVLT)	Low average	Average	Average
Delayed verbal recognition (CVLT)	Average	Average	Average
Primary auditory memory span (Digit Span)	Low average	Low average forward, average backward	Average
Psychomotor speed/attention (Trails A/B, Digit Symbol)	Average	Trails A: borderline Trails B: low average Digit Symbol: average	Trails A/B: borderline Digit Symbol: average
Visual Construction (Key–Osterrieth Complex Figure, Block Design)	ROCF: Average, Block Design: high-average to superior	ROCF: average <sup>a</sup> Block Design: superior	ROCF: low average Block Design: very superior
Delayed visual reproduction (ROCF)	Average	Average to high average <sup>a</sup>	Average
Verbal abstract reasoning (WAIS-R similarities)	Impaired	Low average	Low average

<sup>a</sup> Tests administered for a research study in September 1996.

ical testing. Deficits in memory span (Naegele et al., 1998) and problem solving (Bedard et al., 1993) have been found to persist even after treatment with CPAP. In S.B.'s case, CPAP treatment was effective in reducing the number of apneas and hypopneas from 20 per hour to 14 per hour. Despite persistent apnea, S.B. did not show deficits in problem solving and his verbal memory span was within normal limits. Patients who experience frequent episodes of cerebral hypoxia due to sleep apnea have been found to show cognitive impairment (Rourke & Adams, 1996), but such patients are not described as demonstrating personality changes, apathy, or incontinence.

It is possible that S.B. sustained damage to the frontal lobes in the motor vehicle accident he reported in the initial interview. However, we do not have information about the specifics of the accident or about the temporal relationship between the accident and symptom onset. Also, a traumatic brain injury would not explain a progressive dementia syndrome.

Conversely, S.B.'s behavioral and neuropsychological profile fits very well with the Lund and Manchester Groups' clinical description of frontotemporal dementia (Brun et al., 1994). S.B.'s behavior is characterized by stereotyped speech, mental rigidity and inflexibility, and loss of social awareness. His behavioral disturbance

has gradually progressed, in that he has become more neglectful of his self-care and has developed a habit of repetitive shouting. His penchant for junk food has increased. In terms of mood, he is not depressed, but he does demonstrate apathy, inertia, and asponaneity. Spatial orientation and praxis are intact. Other hallmarks of frontotemporal dementia illustrated by the case of S.B. include onset prior to age 65 years, early incontinence, normal EEG, frontotemporal atrophy and hypoperfusion on neuroimaging, and impaired frontal lobe functions (e.g., verbal fluency) with intact memory and visuospatial abilities.

It is possible that prolonged hypoxia due to sleep apnea contributed to the initial development of frontal lobe dysfunction in this patient. Sleep apnea may also affect the severity of his current symptoms. However, his clinical profile does not appear to differ from that of patients with frontotemporal dementia who do not have sleep apnea.

Overall, it appears likely that S.B. suffers from frontotemporal dementia. However, Alzheimer's disease may affect the frontal lobes preferentially in some cases. Nonetheless, S.B. does not present the typical pattern seen in Alzheimer's disease. Specifically, he does not demonstrate aphasia, apraxia, or agnosia (McKhann et al., 1984). His memory is inefficient, but he does not show the amnesia typical of AD. If he does have frontotemporal dementia, it is likely that S.B. will eventually become mute. He may also develop compulsive behaviors.

This case illustrates how serial neuropsychological assessment can assist with differential diagnosis in dementia. This is particularly important when treatable conditions, such as sleep apnea, may be contributing to the clinical picture.

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## 79. Relational Reasoning and Semantic Inhibition in Human Prefrontal Cortex

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Reasoning relies on the ability to detect and manipulate relations among objects or events, while inhibiting semantically related, but irrelevant information. It has been suggested that the prefrontal cortex plays a central role in these abilities. We present preliminary findings from two experiments comparing the reasoning performance of patients with frontal-variant frontotemporal dementia (FTD) with that of normal controls. A verbal analogy task revealed

that patients' analogy performance was lower than that of controls. Additionally, the results suggested that patients have difficulty inhibiting highly related semantic information. A picture analogy task revealed that patients tend to make fewer relational responses than controls and instead tend to respond based on perceptual or semantic similarity. These results support the hypothesis that prefrontal cortex is important in relational reasoning. © 2001 Academic Press

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Central to the ability to reason is the ability to form and manipulate mental representations of relations between objects and events. For instance, in a verbal analogy such as PRINCE:KING::PRINCESS:? the reasoner needs to form mental representations of the relation between PRINCE and KING (prince is lesser than king) and map it to the second pair in order to select the correct answer, QUEEN. Thus, PRINCE:KING is mapped to PRINCESS:QUEEN and the analogy is successfully solved. Several studies have shown that the human prefrontal cortex is critical for relational integration (e.g., Waltz et al., 1999). A second proposed capacity that may be important for relational reasoning is the ability to inhibit other semantically related responses. For example, a reasoner may be asked to solve the verbal analogy BLACK:WHITE::NOISY:? by choosing between the possible solutions: QUIET and NOISIER. In order to choose the relationally correct answer (QUIET), the reasoner must ignore the high semantic similarity between NOISY and NOISIER. It has been proposed that this type of semantic filtering is a critical function of the human prefrontal cortex (Shimamura, 1995).

In this study we report two preliminary experiments with patients diagnosed with frontal-variant frontotemporal dementia (FTD), which investigate this possible dual role of the human prefrontal cortex. In our first study participants solved verbal analogy problems in which the degree of semantic association was varied between the first term of the second pair and the target and distractor items. In the second study, participants studied pairs of semantically and relationally rich picture analogies and were asked to choose an item in the second picture to go with an item in the first picture. Pairings could be based on either perceptual/semantic or relational information. We hypothesized in both studies that patients with frontal-variant FTD would have difficulty using relational information and that they would show particular difficulty when semantic/perceptual information favored non-relational responses.

### *Method*

*Participants.* The participants were two patients with focal damage to prefrontal cortex (one woman, one man) and two neurologically intact individuals (one woman and one man). Patients in the study had been diagnosed with FTD, a common dementia subtype distinct from dementia of Alzheimer's type (Snowden, Neary, & Mann, 1996). Inclusion criteria for patients in the study were Mini-Mental Status Examination scores over 20 and functional neuroimaging abnormality (SPECT, PET) in the frontal lobes. Patients were matched to normal control participants with respect to age (M P = 48, M C = 46) and educational attainment (M P = 17, M C = 13).

### *Verbal Analogies*

*Materials and procedure.* The analogies were selected from a set of 200 forced-choice verbal analogy problems provided by R. J. Sternberg (Sternberg & Nigro, 1980). The problems were of the type A:B::C:? where subjects select between choices D and D' based on the relationship between A:B. These problems were normed for difficulty on 54 undergraduate students at the University of California, Los Angeles. Fifty problems were chosen from this set and divided into easy and

hard groups based on student error rate. Word association values for the C–D and C–D' pairs were collected from 150 undergraduates. From these values a semantic facilitation index (SFI) was calculated for each problem. The SFI was defined as the difference between the word association for the correct pair (C–D) minus the incorrect pair (C–D'). Thus, when the SFI is positive for a problem, semantic associations favor the correct response. When the SFI is negative, semantic associations between C and D' hinder selecting the relationally correct response and thus must be inhibited. Easy and hard problems, as determined by error rates in undergraduate students, were not significantly different with respect to mean SFI values,  $t(24) = 0.52$ , ns.

Problems were presented one at a time using a notebook computer. An instruction screen containing one example was read to each participant and they had the opportunity to ask questions. After completion of a practice session, the experimenter began the task. After the participant indicated their choice the experimenter would press the corresponding key on the keyboard. Correct answers were randomized with respect to whether they were listed first or second.

### *Picture Analogies*

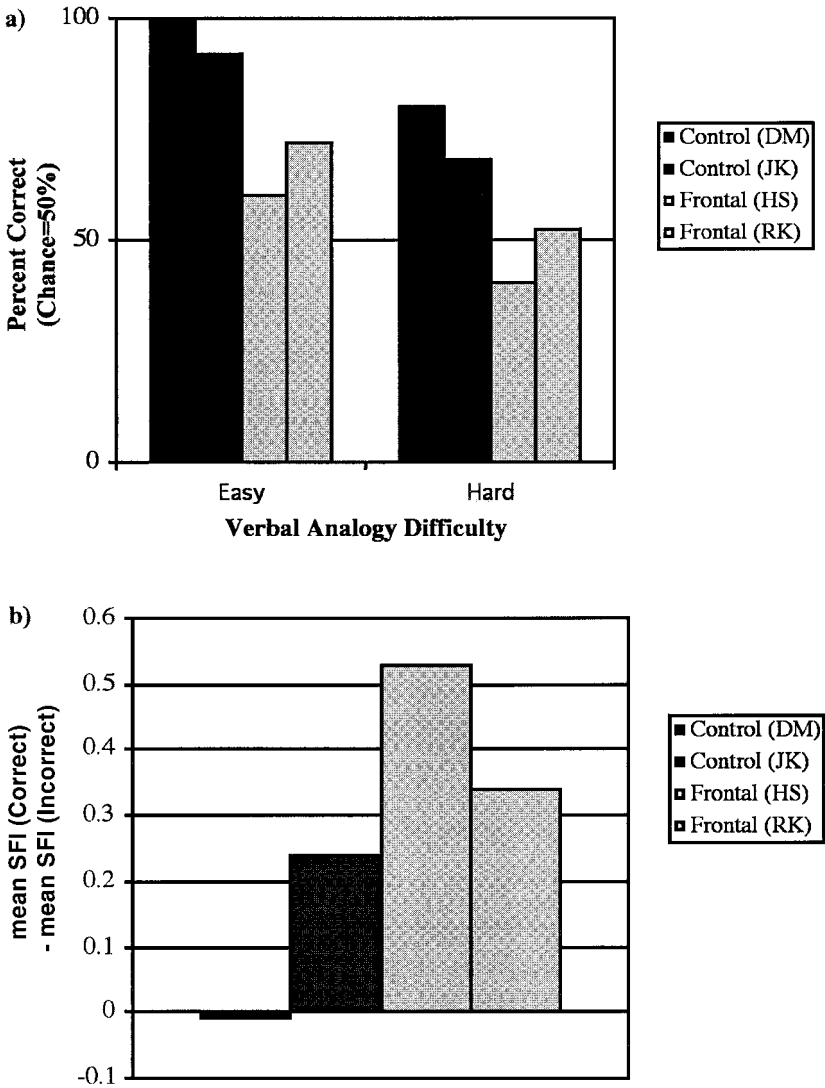
*Materials and procedure.* The stimuli consisted of 10 pairs of pictures, 8 of which were used by Markman and Gentner (1993) and the other 2 from J. Tohill and K. J. Holyoak. Each of the pictures showed a visual scene with three or more objects. One of these objects could be cross-mapped; that is, it could be judged as corresponding to one object on the basis of perceptual/semantic attributes, but to a different object on the basis of the role it plays in a system of relations. In one example, a woman in the top picture uses an umbrella to shield herself from rain, while in the bottom picture the same woman standing next to a cart with an umbrella shield herself from rain using a newspaper. The umbrella in the top picture could be paired with the umbrella on the cart based on physical attributes or mapped to the newspaper based on the system of relations. Three objects in the top picture were marked with numbers. Participants were told that they could be asked to decide which object in the bottom picture "goes with" any of the three numbered objects in the top picture.

Pictures were presented vertically on sheets of paper. After the participant studied the picture for 10 s, he or she was asked to identify one object in the second picture which "goes with" the potentially cross-mapped object in the top picture. After the participant answered they were asked to describe what was happening in the two pictures.

### *Results*

*Verbal analogies.* Patients were significantly worse than normal control participants at solving the verbal analogies,  $F(1, 3) = 28$ ,  $p < .001$ . Hard problems were more difficult for both groups than easy problems,  $F(1, 3) = 14$ ,  $p < .05$ . There was no significant interaction between participant type and difficulty in this small sample.

In order to assess the importance of semantic inhibition on verbal analogy performance, the mean SFI was calculated for the correct and incorrect responses for each participant. The difference between the mean SFI for correct and incorrect responses reflects the degree to which participants were able to inhibit semantically related distracters (D'). Patients showed consistently lower difference scores (see Fig. 1b) than normal controls, suggesting that they experienced more difficulty inhibiting semantically related distracters; however, this difference was not significant with the current number of participants (M P = 0.44, M C = 0.13;  $F(1, 3) = 4.3$ ,  $p < .17$ ).



**FIG. 1.** Verbal analogy performance in normal controls and frontal-variant FTD patients. (a) Accuracy results. (b) Difference in semantic facilitation index for correct and incorrect verbal analogy responses.

*Picture analogies.* Patients produced significantly fewer relational responses than normal controls in the picture mapping task ( $M P = 1.5$ ,  $M C = 9$ ;  $F(1, 3) = 98$ ,  $p < .01$ ).

*Discussion*

In this study we examined two relational reasoning tasks in which frontal-variant FTD patients show a preference for semantic over relational information. Performance in a verbal analogy task appeared to be impaired by an inability to inhibit semantically related distractor items. In the picture-analogy task patients showed a strong preference for semantic or perceptual associates, as opposed to the relational mappings that were preferred by normal controls. An alternative possibility is that perceptual and semantic associations are simply the default process that remains when

the capacity to bind and manipulate relations is disabled. In a study involving performance on a variant of the Raven's Progressive Matrices, Waltz et al. (1999) found that frontal-variant FTD patients showed a significant decline in performance when they were required to integrate more than one relation. In the current study we report poor patient performance relative to normal controls when patients are asked to map a single relation across a verbal analogy problem. Performance on a verbal analogy may require simultaneous consideration of the relation between the A and B terms and that between the A and C terms, in order to choose the appropriate D response. The results of the present study are consistent with the basic finding that the prefrontal cortex is necessary for the integration of relations; and furthermore, it suggests that the prefrontal cortex contributes to the inhibition of competing semantic information.

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## 80. A Reversed Temporal Gradient for Episodic Memory Is Seen in Semantic Dementia but Not “Frontal Variant” Frontotemporal Dementia

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Studies of autobiographical memory in semantic dementia (SD, temporal variant of fronto-temporal dementia) have revealed a “reversed” temporal gradient of impaired recollection; SD subjects show impaired recall of memories from distant relative to recent past. It has been proposed that this may be explained by impaired strategic retrieval secondary to concomitant frontal lobe damage. To test this hypothesis, a group of frontal variant Frontotemporal dementia (fvFTD) subjects ( $n = 6$  to  $8$ ) underwent two experiments using (i) the Autobiographical Memory Interview and (ii) a 20-item “free” Crovitz. In contrast to SD, fvFTD subjects showed no memory gradient although their absolute memory score on the Crovitz was significantly worse than controls. Implications for strategic retrieval, and temporal and frontal lobe contributions to memory, are discussed. © 2001 Academic Press

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### Introduction

Studies of autobiographical memory in semantic dementia (SD) have revealed relative impairment of recall of memories from distant as compared to recent past (Graham & Hodges, 1997). In other words there is a reversal of the temporal gradient of memory loss typically seen in subjects with amnesic syndromes (such as due to mesial temporal lobe damage.)

SD is a clinical variant of frontotemporal dementia [see Neary et al., 1998, for review]; it manifests as a progressive loss of semantic knowledge (e.g., word meanings, facts) and is associated with atrophy of the left polar and inferolateral temporal lobe. There is also a predominantly 'frontal variant' of frontotemporal dementia (fvFTD) which manifests with the behavioral disturbances recognized to be associated with frontal lobe dysfunction. With time, the clinical profiles of SD and fvFTD tend to blur as pathology becomes widespread through the frontal and temporal lobes.

Successful memory retrieval has been divided into two types: 'cue-dependent' in which the cue itself is sufficient to trigger a successful retrieval (thought to be dependent on posterior brain regions) and 'strategic' in which the cue alone is not sufficient and a 'search strategy' needs to be implemented to effect a successful retrieval, the latter thought to be frontal lobe dependent (Moscovitch, 1992).

Given that SD subjects may develop concomitant frontal involvement, it has been proposed by Nadel and Moscovitch that the reversed memory gradient may actually be a consequence this frontal pathology (Nadel & Moscovitch, 1997). They argue that the strategy required to retrieve a memory from the distant past may be more demanding than that for recent events and therefore more likely to be impaired in cases with frontal pathology.

The purpose of this study was to test the hypothesis that the reversed temporal gradient seen in SD may be a consequence of frontal lobe damage. If this were the case, then one would expect to observe the same phenomenon in a group of subjects with fvFTD. To this end, two techniques to probe remote episodic memory were employed: the Autobiographical Memory Interview (AMI) (Kopelman et al., 1990) and a 20-item version of the Crovitz cue-word test.

*Subject groups.* Three subject populations were compared to controls: SD, fvFTD, and Alzheimer's disease (AD). Those with SD and fvFTD fulfilled local and consensus criteria (Neary et al., 1998) for diagnosis of these conditions. The SD group was all impaired on our semantic battery (e.g., graded naming test, pyramids and palm trees test, category fluency) and showed prominent atrophy of left temporal lobe on imaging studies. All of the fvFTD group presented with the characteristic 'frontal' behavioral syndrome (e.g., disinhibition, impulsivity, stereotypic, or ritualistic behaviors), assessed both on clinical history and quantitatively using the Neuropsychiatric Inventory. They were relatively impaired on tests of frontal/executive function, though no single test in this domain was universally impaired in all subjects. To exclude cases with temporal lobe involvement from the fvFTD group, those who were impaired on the semantic battery were not included.

The AD group was defined by NINCDS-ARDRA criteria. Patients with AD reach floor levels on memory tests early in the disease course; to ensure that all patients could perform the tasks only mild cases were included, some of whom had MMSE scores  $>24/30$ . All patients underwent a full neuropsychological test battery and brain imaging.

Known confabulators were excluded from these experiments. Subject groups were matched for years of education and duration of illness. In experiment 2, there was a significant age difference between fvFTD (mean  $\pm$  SEM:  $55.8 \pm 3.1$ ) and controls ( $65.4 \pm 1.4$ ) though not between fvFTD and SD ( $60.6 \pm 1.9$ ) or SD and controls. The AD group ( $73.7 \pm 2.1$ ) were significantly older the controls [ $F(3, 24) = 12.4$ ,  $p = .0001$ .]

### *Experiment 1: AMI*

*Method.* The AMI is a test of episodic memory in two sections: 'personal semantics' and 'autobiographical incidents.' Each section being divided into three time periods: childhood, early adulthood, and recent life. The group study of Graham and

Hodges found that subjects with SD performed poorly at childhood and early adult periods on both personal semantic and autobiographical incident memory when compared to the recent life period (Graham & Hodges, 1997). To test whether this may also be the case in fvFTD, a group of ( $n = 8$ ) subjects performed the AMI.

*Results.* In the personal semantic section, fvFTD subjects did not differ significantly from controls for childhood, early adulthood, and recent time periods (max. 21, mean  $\pm$  SEM,  $19.5 \pm 0.6$ ,  $17.2 \pm 1.3$ , and  $18.7 \pm 1.3$ , respectively); the same was true of the autobiographical incidents section (max = 9, scores,  $6.9 \pm 0.6$ ,  $6.0 \pm 0.7$ , and  $6.6 \pm 0.8$ ). Repeated measures ANOVA demonstrated no significant difference in scores by time period for either section; i.e., there was no gradient in the memory scores, which contrasts with the poor performance for the childhood and early adult time periods described previously in SD.

### *Experiment 2: 20-Item Crovitz*

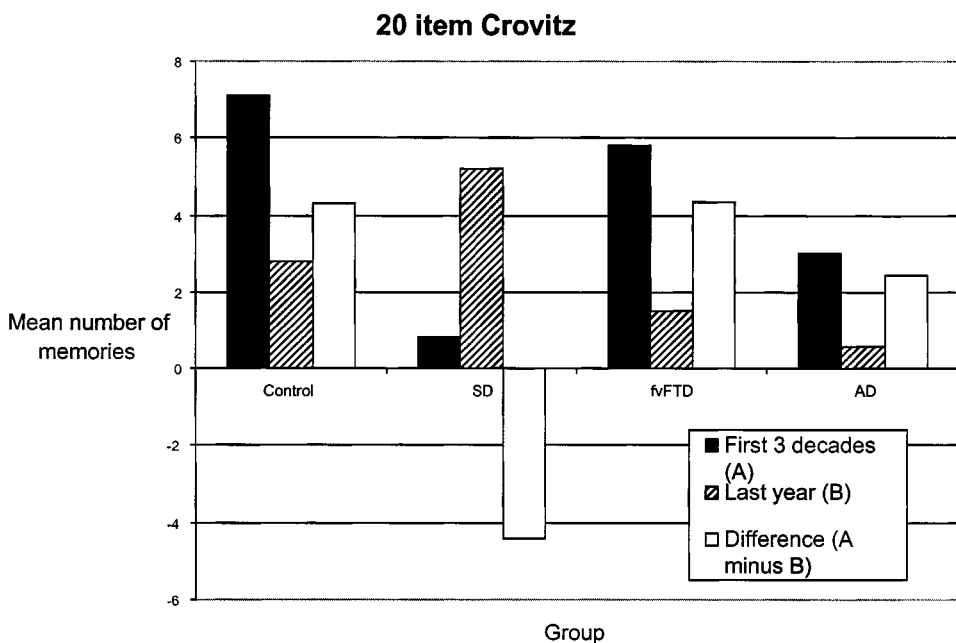
*Method.* Groups of SD ( $n = 5$ ), fvFTD ( $n = 6$ ), AD ( $n = 7$ ), and controls ( $n = 10$ ) were compared on a 20-item Crovitz test. Subjects were presented with cue words (e.g., train, book) and asked to relate a personal memory pertaining to each; they were encouraged to be specific and detailed in their recollection.

Only specific memories (judged by  $n = 2$  raters) were included for further analysis. This was for two reasons, generic memories (e.g., book: ‘I’ve always enjoyed reading thrillers’) do not constitute recollection of a particular autobiographical incident and generally cannot be placed to a specific time period. No explicit instruction was given as to whether the memory should come from any particular period of life; in other words they were ‘free’ to produce any relevant memory that came to mind. If the raters considered that the tester had lead the subject to a particular time period (e.g., . . . ‘well what about the last thriller you read’), then the response was discarded.

To test whether groups showed a preference for retrieving memories from recent or distant past, the number of memories recalled from the first three decades of life was compared to those from recalled from the previous year. This allowed comparison of strongly consolidated memory with memories from after disease onset. As all subjects were well over the age of 31 years, it also meant that subjects of varying ages could be directly compared. Total number of memories recalled (any time period) was also analyzed to ensure that no group produced a disproportionate number of memories from the life period between those in question.

*Results.* On total number of memories produced (max = 20), controls scored (mean  $\pm$  SEM),  $17.7 \pm 0.2$ ; fvFTD,  $13.0 \pm 1.6$ ; SD,  $10.2 \pm 1.7$ ; and AD,  $5.86 \pm 1.5$ . Single-factor, independent-measures ANOVA showed a significant group difference  $F(3, 24) = 22.1$  ( $p = .0001$ ). Post hoc  $t$  tests showed no significant difference between fvFTD and SD groups. However, between all other groups results were significant: e.g., controls versus fvFTD,  $p < .01$ ; controls versus SD,  $p < .01$ ; and SD versus AD,  $p < .05$ .

The results of comparison of memories recalled from the first three decades to the year previous are summarized in Fig. 1. To produce a distant–recent index, the number of memories dated to the past year was subtracted from the number dating to the first three decades for each individual. This gave a ‘number of memories difference’ score (0–30 years minus past year) for each subject. Mean difference score for controls (mean  $\pm$  SEM) was  $+4.3 \pm 1.7$ ; fvFTD,  $+4.3 \pm 1.9$ ; SD,  $-4.4 \pm 1.5$ ; and AD,  $+2.4 \pm 0.5$ . Single-factor independent-measures ANOVA showed a significant group effect,  $F(3, 24) = 5.305$ ,  $p < .01$ . Post hoc  $t$  tests showed a significant difference in ‘memory difference’ score for SD when compared controls, fvFTD, or AD



**FIG. 1.** Results of 20-item Crovitz experiment showing mean number of memories recalled from the first three decades (solid), year previous (hatched), and the difference between these (unfilled). SD, semantic dementia; fvFTD, frontal variant of frontotemporal dementia; AD, Alzheimer’s disease.

( $p < .01$  for each). No other groups differed significantly on this measure and specifically there was no difference between fvFTD and controls.

*Discussion*

Experiment 2 offers, using a novel method, further evidence that SD subjects retrieve more memories from recent as opposed to distant past. The hypothesis that this may be a consequence of concomitant frontal lobe damage in the SD group was not substantiated by the results of the fvFTD group in either experiment 1 or experiment 2.

It is of interest, however, that in experiment 2, total number of memories produced (regardless of time period), for SD and fvFTD groups, did not differ significantly; moreover, the fvFTD group performed significantly worse than controls. These findings are not at odds with the proposed role of the frontal lobes in forming retrieval strategies in that this may indeed be the explanation for the impaired performance of the fvFTD group. It would be difficult, though, to disentangle a deficit of strategic retrieval from nonspecific effects of the frontal syndrome such as apathy or impulsivity.

The findings do, however, challenge the hypothesis that frontal pathology is the explanation for the reversed temporal gradient seen in SD. Instead we propose, as before, that this phenomenon relates to the pattern of temporal damage per se. Perhaps the assumption that recall from very distant compared to recent past requires a greater strategic effort is not correct in this circumstance. While intuitively it would seem plausible that recall of what one ate for lunch yesterday compared to 5 days ago requires a less demanding retrieval strategy; what one chooses to recall (spontaneously without prompting to specific time period) from ones childhood may actually constitute something analogous to ‘cue-dependant’ rather than strategic retrieval.

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## 81. Cingulate and Attentional Correlates of Apathy in Alzheimer's Disease

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Apathy is a frequent behavioral disturbance in AD. We hypothesized that apathy was related to cingulate hypoperfusion and to divided attention impairment. (1) Using the Neuropsychiatric Inventory 28 AD patients were divided into apathetic ( $n = 14$ ) and nonapathetic ( $n = 14$ ) subgroups. Brain perfusion was measured by SPECT and the images were compared using the Statistical Parametric Mapping software. The apathetic patients showed a significant hypoperfusion in the anterior cingulate (Talairach coordinates:  $x = 0$ ,  $y = 22$ ,  $z = 28$ ). (2) Using the same procedure 22 AD patients (apathetic,  $n = 10$ ; nonapathetic,  $n = 12$ ) were tested with the dual-task paradigm (Baddeley). The dual task decrement measure was significantly larger in apathetic AD subjects. © 2001 Academic Press

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Apathy was defined as a syndrome of diminished motivation and includes symptoms such as reduction or lack of interest, productivity, will, initiative, and affective responses toward positive or negative events, leading to decreased goal-directed activities. Apathy is one of the most frequent behavioral symptoms in Alzheimer's disease. Alexander (1986) described five frontal–subcortical circuits implicated in movement, cognition, and behavior. The anterior cingulate circuit mediates motivated behavior, and apathy betrays damage to the structures of this circuit.

Evidence from animal studies, functional brain imaging, and clinical evaluation of patients with focal brain lesions indicates that the cingulate is involved in both cognitive and behavioral disorders. Following a review of the efferent and afferent connections, it is possible to describe four cingulate regions. The three anterior effector regions integrate ascending input coming from the visceral motor system and the cognitive-attentional networks, in order to produce affective motivation.

Reviewing attention and executive deficits in AD, Perry and Hodges (1999) reported that selective and divided attention were particularly vulnerable in the early stages of the disease. Divided attention has been studied in AD by using the dual-task paradigm. This task requires the subject to perform two tasks separately before performing the two tasks simultaneously. AD patients showed a marked impairment compared with elderly and young control subjects (Baddeley et al., 1986).

We hypothesized that in AD the presence of apathy is related (1) to cingulate hypoperfusion and (2) to divided attention impairment taking into account the influence of cingulate area on attention processes and the fact that clinical experience shows that apathetic AD patients are less attentive to environmental stimulation. In order to provide evidence for these two hypotheses, the present poster uses data coming from two different studies.

### *Experiment 1*

**Population.** Twenty-eight subjects with AD according to ICD 10 diagnostic criteria (World Health Organization, 1992) were evaluated in the Nice University Memory Center and gave their informed consent to participate in the study.

Apathy was assessed with the neuropsychiatric inventory (NPI) (Cummings et al., 1994). The purpose of the NPI is to obtain information on the presence of psychopathology in patients with brain disorders. Information for the inventory may be obtained from the spouse or another person intimately familiar with the patient's behavior; information may be increased by direct observation and by questioning the patient. The 12 behavioral domains to be assessed were chosen after a comprehensive review of the literature. For each domain a screening question was first asked to determine if the behavioral changes were present or absent. If the answer was positive, the category was explored in depth with a list of subquestions following NPI instructions, yielding a frequency  $\times$  severity score.

A subject was allocated to the AD apathetic subgroup (AD/A) if the NPI interview detected the presence of apathy and if the NPI score was higher than 2/12. The screening items for the apathetic domain were:

- Less spontaneous to initiate a conversation and less active than usual (e.g., contributes less to household chores);
- Less affectionate or lacks emotions when compared to his/her usual self;
- Less interested in the activities and plans of others or has lost interest in friends and family members; and
- Less enthusiastic about his/her usual points of interest.

AD without these apathetic characteristics was allocated to the nonapathetic subgroup (AD/NA). Global cognitive performance was assessed in all subjects with the Mini-Mental Score Evaluation (MMSE).

**Brain imaging method.** In a quiet dark room, each patient received 1100 mBq of  $^{99m}\text{Tc}$ -ECD via an iv line in order to avoid noxious stimuli. One hour later, 120 projections of 55 s were gathered using a three headed gamma camera (Prism 3000 XP, Picker, Cleveland, OH) equipped with LEUHR fan beam collimators (focus 50 cm). Reconstruction was performed by filtered back projection with a 3D postfiltering (Butterworth filter, order = 6, cutoff frequency = 0.4). This led to a spatial resolution of 8 mm on the reconstructed cuts.

The two groups (A and NA) were compared by Statistical Parametric Mapping (SPM96). In summary, this software works as follows: after realignment, spatial normalization, spatial smoothing, and modelization, a  $t$  statistic is performed on a voxel-by-voxel basis constituting the SPM. To make statistical inferences, the theory of the Gaussian fields is used and creates the SPM. The resulting foci are characterized in terms of spatial extent and peak height.

**Results.** The A/NA groups were comparable in terms of age (mean, A = 77.4/NA = 76.9) and MMSE (mean, A = 20/NA = 22). The Z map showed a significant decrease ECD uptake for the apathetic patients in the anterior cingulate ( $Z = 3.15$ ,  $p < .001$  for peak height;  $k = 302$ ,  $p < .05$  for spatial extent) (Talairach coordinates,  $x = 0$ ,  $y = 22$ ,  $z = 28$ ).

## Experiment 2

Using the same procedure as in experiment 1, 22 AD subjects (10 with apathy and 12 without apathy) were included.

*Dual performance task.* This task, modified from Baddeley et al.'s visual tracking-digit span test, has been used by Greene (1995) and more recently by Baddeley, Della Sala, et al. (1997).

*Memory span.* First, a standard procedure was used to measure digit span. A list of digits was read aloud by the examiner at a rate of one digit per second, and subjects were asked for immediate ordered recall. The number of digits was gradually increased by one item. Three lists at each length were given. Span was taken as the maximum length at which the patient recalled all three lists without making mistakes.

*Single-task condition/digit span.* Subjects were then presented with lists of digits at their own span, continuously for 2 min. Performance was measured as the percentage of sequences repeated correctly.

*Single-task condition/tracking.* Patients were required to cross out, using a felt pen, a chain of 1-cm<sup>2</sup> boxes linked to form a path on an A4-size sheet of paper. All the patients first performed practice tests using a 10-box path, until the examiner was sure they understood the task. There were 80 boxes on each experimental sheet. Patients were asked to start at one end of the chain and place a cross in each successive box as rapidly as possible. If the patients managed to cross all the boxes within the time limit of 2 min, a second sheet was presented. The total number of crossed boxes was taken as the score.

*Dual-task condition/digit span.* Subjects were again shown lists of sequences at their own span, for 2 min, while simultaneously performing the tracking task. Once again, performance was measured as the percentage of complete sequences correctly recalled.

*The dual-task performance decrement* was calculated by using the boxes and digit span information, with the following formula: dual-task decrement = (120 s/number of boxes during the dual task) (proportion of digit span sequences correct in the dual task) – (120 s/number of boxes crossed during the single task) (proportion of digit span sequences correct in the single task).

*Results.* There was no difference in age or years of education between the C AD A/NA groups. Table 1 summarizes the neuropsychological data. One ANOVA with an "apathy" factor (apathy/nonapathy; A/NA) indicated that apathetic AD subjects showed a significantly higher impairment for the dual task decrement ( $F = 11.65$ ;  $df = 20$ ;  $p .002$ ).

## Discussion

These results indicate that in AD subjects, apathy was related to (1) anterior cingulate hypoperfusion and (2) divided attention impairment. These results are important since the relationship between apathy, attentional processes, and the cingulate region also have pharmacological implications for AD. The cholinergic neurons of the basal forebrain have recently attracted a great deal of attention in dementia. A marked decrease in cortical cholinergic innervation is one of the most consistent features of Alzheimer's disease. There is also marked cell loss in the nucleus basalis-CH4 complex, which provides most of the cholinergic projections to the medial frontoparietal regions as well as to the cingulate gyrus.

This could be related to the fact that along with the cognitive effects, behavioral improvement in AD patients (and particularly resolution of apathy) occurs during cholinesterase inhibitor therapy, just as with patients' and caregivers' comments sug-

TABLE 1  
Neuropsychological Performance of the Control and AD  
Subjects with and without Apathy

	Alzheimer's disease (AD)	
	Apathetic <i>n</i> = 10	Nonapathetic <i>n</i> = 12
Age (years)	75.1 (3.9)	72.1 (5.2)
Mini-Mental test	23.2 (3.66)	25.7 (3.1)
Span	4.9 (0.5)	4.9 (0.5)
Single task		
Digit span	0.81 (0.1)	0.74 (0.1)
Tracking	87 (43)	135 (33)
Dual-task		
Digit span	0.62 (0.2)	0.64 (0.1)
Tracking	77 (41)	126 (32)
Dual-task decrement	1.27 (0.8)	0.37 (0.31)

*Note.* The digit span measure is the percentage of correct digit sequences. The tracking score is the total number of boxes crossed in the 2 min allocated for the task.

gesting that positive responses to cholinergic therapy are mainly associated not only to memory improvement, but also with greater implication in interpersonal relations and daily activities. However, results of this study must be confirmed in merging within the same study and with the same patient's brain imaging and neuropsychological data.

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