EXECUTIVE DYSFUNCTION IN ALZHEIMER'S DISEASE

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ABSTRACT

Executive functioning was examined in 20 patients with Alzheimer's disease (AD) and 20 normal elderly subjects. The results showed that AD patients present lower performance compared to control subjects in all executive tasks, confirming that some executive deficits may be present in the first stages of the disease. A factorial analysis suggested that these deficits can be related to two domains of the executive functions: the inhibition abilities and the capacity to co-ordinate simultaneously storage and processing of information. Moreover, the performance on these factors is correlated to different anterior and posterior cortical areas.

Key-words: Executive functions, Alzheimer's disease, positron emission tomography

INTRODUCTION

Until relatively recently, executive dysfunction was not considered as the main characteristic of Alzheimer's disease (AD). For example, Pillon, Dubois, Lhermitte et al. (1986) have suggested that executive dysfunction tends to be mild and usually occurs relatively late in the disease. Consistent with the hypothesis of a relative preservation of executive function, at least in the early stages of the disease, resting PET studies of AD patients showed decreased metabolism primarily in the parietal and temporal association cortical regions whereas changes in the frontal cortex were less consistent and were found to be associated with more severe cases of the disease (Grady & Haxby, 1995 ; Kennedy & Frackowiak, 1994 ; Morris, 1996).

Recent reports have nevertheless demonstrated that individuals with AD are impaired on a variety of tasks that have been commonly considered as measures of executive control. These studies have compared the performance of AD patients and normal elderly subjects in tasks investigating one specific aspect of executive function. Some of these studies (Baddeley, Logie, Bressi, et al., 1986; Baddeley, Bressi, Della Sala, et al., 1991; Nestor, Parasuman, & Haxby, 1991) used a dual-task paradigm and found that AD patients were particularly impaired when they had to perform simultaneously two different tasks, even when the difficulty of the tasks performed separately was equated across the groups. Such a difficulty to co-ordinate two tasks was also present when subjects do not have to store presented information. Deficits have also been found in AD patients in an alphabetical-span task which requires simultaneous storage and manipulation of information (Belleville, Rouleau, Van der Linden et al., unpublished data; Collette, Van der Linden, Bechet et al., 1998). Several studies have also observed a lower performance by AD patients in verbal fluency tasks (Becker, 1988; Bhutani, Montaldi, Brooks et al., 1992; Lafleche & Albert, 1995; Pasquier, Lebert, Grymonprez et al., 1995). Performance of fluency tasks requires executive functions such as the build-up and the maintaining of an organised search strategy (Baddeley, Lewis, Elridge et al., 1984). Verbal fluency deficits in AD patients were interpreted as a result of their semantic memory impairments (Chertkow & Bub, 1990; Randolph, Braun, Goldberg et al., 1993). However, Troyer, Moscovitch, Winocur et al. (1998) have recently demonstrated that the AD deficit observed on semantic fluency tasks could in fact be due to a difficulty to use an efficient search strategy in semantic memory. AD patients also exhibited deficits affecting planning abilities, as indicated by a lower performance on the Tower of London task and the Porteus Maze test (Mack & Patterson, 1995; Rainville, Fabrigoule, Amieva et al., 1998). Such planning difficulties have also been observed in ecological situations. Passini, Rainville, Marchand et al. (1995) showed that AD patients experienced difficulties in developing decisions plans for solving wayfinding problems in unfamiliar settings. Higher-order decisions are more affected (e.g. to reach the correct floor), while decisions made in direct relation to explicit environmental information is still possible (e.g. taking the elevator). Another executive function relates to inhibition processes. Indeed patients with frontal lobe lesion have difficulty inhibiting non-relevant responses (e.g. Shallice & Burgess, 1993). The presence of inhibition processes deficits have been demonstrated by Spieler, Balota and Faust (1996) who showed the presence of a slightly larger Stroop interference effect and more intrusion errors (naming the word when the task was naming the color) in AD patients. Recently, Sullivan, Faust and Balota (1995) showed that the inhibitory component underlying selective attention is impaired in individuals with AD. Finally, another way to investigate executive functions is to administer random generation tasks, which involve the capacity to switch retrieval strategies in order to avoid redundancy and alphabetical stereotypes. Brugger, Monsch, Salmon et al. (1996) demonstrated that during a random generation task, AD patients' subjective random sequences were more stereotyped than those of control subjects and that this difference in response stereotypy was due to AD patients' enhanced tendency to arrange consecutive numbers in an ascending series ("counting bias"). Moreover, these stereotypes were positively correlated with overall severity of dementia.

Few studies have simultaneously investigated a large range of executive functions in a same group of AD patients. A first study was that of Bhutani et al. (1992) who administered to minimally, mildly and moderately AD-affected patients and elderly control subjects, four very different executive tests, namely a delayed alternation task, a subject-ordered pointing task, the Wisconsin card-sorting task (WCST) and a verbal fluency task. On the Wisconsin card-sorting test, results were characterized by clear floor effects in both AD patients and control subjects. The three remaining tests produced performances by the AD patients which were significantly lower in comparison to control subjects. Only the word fluency task failed to show a significant difference between controls and minimally demented patients. In a more recent study, Lafleche and Albert (1995) administered to mildly AD patients a series of tasks involving various aspects of executive function (the self-ordering test, the verbal fluency, the trail-making test, the Hukok logical matrix[1], a proverb interpretation test, the similarities subtest of the WAIS and a cued reaction time). Only the executive function tasks which primarily required concurrent manipulation of information and emphasize cognitive flexibility (namely, the self-ordering, Hukok, trail making and fluency) were impaired in AD patients. Finally, Binetti, Magni, Padovani et al. (1996) showed that mild AD patients, with and without executive dysfunction, were not distinguishable from each other on tasks assessing short- and long-term memory, language, attention and visuospatial abilities. From these data, the authors concluded the existence of a subgroup of AD patients who have additional executive deficits unrelated to impairments in other cognitive domains. However, the cut-off score used to identify AD patients with executive dysfunction was defined as a score one standard deviation below the control mean on at least two of the four measures of executive function, which is clearly more lenient than in other studies.

The results of all these studies indicate that executive dysfunction occurs early in the course of the disease. However, several issues regarding the presence of executive dysfunction in AD patients remain unsolved. In particular, the nature and the range of the executive dysfunction have not yet been fully explored, nor their relationships with cerebral pathology . Therefore, the first aim of the present study was to better specify the nature of executive dysfunction in Alzheimer's disease (and also to assess the influence of processing speed and dementia severity on their results). The second aim of this study was to relate the executive deficit of AD patients to their pattern of cerebral metabolism at rest.

METHOD

Subjects

Two groups of subjects participated in this study: patients with dementia of the Alzheimer type (AD) and normal elderly subjects. The AD group consisted of 20 patients (3 men and 17 women) who met the NINCDS-ADRDA criteria for probable (16 patients) or possible (4 patients) Alzheimer's disease (McKhann et al., 1984). All patients had suffered from progressive worsening of memory problems for at least six months. The diagnosis of AD was based on general medical, neurological and neuropsychological examinations. Patients' age ranged from 65 to 84 years (mean age: 72 $\pm$ 5.15 years) and their mean MMSE score was 21.80 $\pm$ 4.75 (range: 15-29). Sixteen of the 20 patients also underwent a positron emission tomography with (18F)fluorodeoxyglucose (18FDG-PET), and the brain metabolism distribution was compatible with AD (Salmon et al., 1994). Scans were acquired during quiet wakefulness with eyes closed, on a Siemens 951/31 R tomograph (CTI, Knoxville, TN), with collimated septa extended. A transmission scan was acquired for attenuation correction using three rotating sources of 68Ge. Emission scans were reconstructed using a Hanning filter at a cut-off frequency of 0.5 Hz, giving a transaxial resolution of 8.7 mm full width at half maximum (FWHM) and an axial resolution of 5 mm FWHM for each of 31 planes, with a total field of view of 10.8 cm in the axial direction. The classical method for 18FDG-PET acquisition and analysis in cognitively normal elderly and in demented subjects has been previously published (Kennedy & Frackowiak, 1994).

Twenty normal elderly subjects, matched for age, sex and sociocultural level, served as control subjects. The normal controls were non-institutionalised, alert, and had no history of neurological problems, alcohol abuse or psychiatric disorders. They had normal or corrected vision and normal or corrected hearing. The average age for the control group was 71.75 $\pm$ 4.83 years. These control subjects did not differ from AD patients with regard to their age [$t(38)=0.16$, $p>0.5$] and their schooling level [$t(38)=1.16$, $p>0.1$].

The Mattis dementia rating scale (DRS; Mattis, 1973) was administered to AD patients and control subjects. All controls had a total score superior to 130 on this scale, which constitutes the cut-off score to discriminate normal aging from dementia (see Monsch et al., 1995). Global performance on the Mattis dementia rating scale was significantly lower for AD patients than for control subjects [$t(38)=-5.82$, $p<0.00001$]. The results of AD patients and control subjects on the different sub-tests are described in Table 1.

[Insert Table 1 near here]

Cognitive assessment

Alpha-span task (Belleville, Rouleau, & Caza, 1998). This task investigated the ability to manipulate information stored in working memory by comparing the recall of information in serial order (implicating only storage of information) and in alphabetical order (implicating storage and manipulation of information). Firstly, a classical word-span task was administered to assess the span level of each subject. Sequences of words were read to the subject at the rate of one word per second, starting with short sequences of two words. The subject was instructed to repeat items orally in serial order. The length of the sequences was progressively increased. Two trials were administered at each level. If one error occurred on one of these two trials, the subject was given two additional trials. Testing was interrupted when the subject failed to report correctly less than two of the four sequences at a particular length. The word span was defined as the longest sequence correctly recalled on at least two trials. After the span measurement, the subject was asked to repeat word sequences in two different conditions: direct recall and alphabetical recall. In both conditions, the number of words to be recalled corresponded to the subject's span minus one item. In the direct condition, the subject performed an immediate serial recall of ten sequences of words. In the alphabetical condition, the subject was asked to recall ten sequences of words in their alphabetical order. In order to control for possible practice or fatigue effects, five trials in the direct condition were firstly administered, followed by the 10 trials in the alphabetical condition, and lastly the five remaining trials in the direct condition. The subject's performance was assessed by comparing the performance in alphabetical recall to that in serial recall. Moreover, a manipulation score was also derived for each individual subject. This score was calculated according to the formula ((direct – alphabetical)/direct)*100. This represents the performance reduction experienced by each subject when performing the alphabetical recall relative to the direct recall.

Dual-task paradigm. This procedure assessed the ability to co-ordinate the simultaneous realization of two tasks. The paradigm used consists of a paper-pencil version of the dual-task paradigm proposed by Baddeley et al. (1986; Baddeley, Bressi et al., 1991). This paradigm compares the performance in a verbal and a motor task carried out separately to the performance when the two tasks are carried out simultaneously (Baddeley, Della Sala, Papagno, & Spinnler, 1997). Firstly, the digit span of each subject was determined by administering strings of digits of increasing length. Three sequences were presented per length. Testing was interrupted when the subject failed to recall correctly at least two of the three sequences. The span was the longest sequence in which at least two sequences had been correctly recalled [2]. Following this span measurement, the verbal and motor tasks were presented successively. During the digit recall task, sequences of digits at the subject's span level were continuously given for 2 minutes and the number of correct sequences was calculated. For the motor task, the subjects were presented with a trail of boxes, and were required to put a cross on each box following the trail as quickly as possible during two minutes. The second part of the paradigm was then administered, whereby the subjects were required to put crosses on the boxes in the trail while simultaneously being presented with sequences of digits to repeat. The ability to divide attentional resources was assessed by comparing the performance in the dual condition with that in the single condition, separately for the digit and motor task. A global measure was also computed expressing an individual's dual-task performance as a percentage of single-task performance, the contribution of the two tasks being equally weighted. This measure (μ score) is defined as: (1-((proportion of lists recalled under the single-task condition – proportion of lists recalled under the dual-task condition) + (number of squares marked under the single-task condition – number of squares marked under the dual-task condition) / number of squares marked under the single-task condition)/2)*100 (Baddeley et al., 1997).

Delayed alternation task (DAT). This reversal learning paradigm assesses the short-term preparation for a specific event and has proven to be sensitive to prefrontal lesions in nonhuman primates (Goldman-Rakic, 1987), as well as in patients with a frontal lobe lesion (Freedman & Oscar-Berman, 1986). The task requires the subject to search for a target stimulus in one of two boxes placed in front of him. Once the subject has found the target, the experimenter replaces the stimulus in the alternative location, out of sight of the subject, who is then required to search again. Whenever the subject successfully identifies the localization of the stimulus, its position is automatically reversed. If, however, the subject fails, the stimulus remains in the same location, and the subject is required to search again. The learning criterion was 12 consecutive correct responses, and the subject was deemed to have failed if this was not achieved in 50 trials. In order to determine the influence of a possible attentional deficit, the performance of the subject was also assessed with a learning criterion of five consecutive correct responses. In a previous study, Bhutani et al. (1992) showed that this task is a very suitable tool for use with a demented population.

Phonemic fluency task. Participants were given 120 sec to generate aloud a list of words beginning with a target letter (letter P) but excluding proper names and variants of a same word. The number of words generated (without errors and repetitions) was recorded. This task requires the ability to initiate and sustain word production while maintaining an organised retrieval strategy, as well as inhibitory and shifting attentional mechanisms, and was classically considered to assess executive function (Baddeley, 1990; Perret, 1974).

Hayling inhibition task (Burgess & Shallice, 1996). This task assesses the capacity to suppress (inhibit) a habitual response and was initially devised in order to examine both initiation and inhibition processes. The Hayling task consists of 30 sentences in which the final word is omitted, but has a particularly high probability of one specific response. The task is composed of two sections (A and B), each containing 15 sentences. In section A (initiation), sentences are read aloud to subjects who have to complete the sentence with the missing word. In section B (response suppression), sentences are read aloud to subjects who this time have to complete the sentence not with the expected word but with a word unrelated to the sentence. If at any time during this stage of the test, subjects give a sentence completion rather than an unrelated word, they are told that the word is too related to the sentence, and the task instructions are repeated. If a subject did not produce a word within 30 sec, that trial was terminated and a response latency of 30 sec was recorded [3]. Different measures of response suppression abilities were used in the analysis. Firstly, section B latencies minus the section A latencies were considered for each subject, which presumably represents the additional thinking time required in having to produce a novel word rather than a straightforward sentence completion. Secondly, each response in section B was classified into one of three groups. Category C comprises the responses which are sensible completions of the sentence, thus clearly violating the task instructions. The second set of responses (category S) includes responses that are semantically related to the sentence in some way. In the last category (category U), are those responses which are unrelated to the sentence, as required by the task instructions. Finally, a semantic score was devised for section B whereby the overall semantic relationship of each response to its stimulus sentence was measured: three points were given if the word was a straightforward completion of the sentence (category C), one point for a word semantically related to the sentence in some way (category S) and no score when the response fulfilled successfully the task requirements (category U).

Self-ordered pointing task (SOPT). This task was initially described by Petrides and Milner (1982), and showed that patients with lesions involving the lateral prefrontal cortex are impaired in tasks requiring to monitor a series of self-generated responses. In this study, the subjects were presented a series of cards, one card at a time. The same set of sixteen abstract designs were printed on each card, but the position of the designs varied randomly from card to card. The subjects were required to inspect the cards one at a time and to point to a different design on each card successively presented. They were not informed of errors. This task is clearly multi-compound and, beside its main objective to assess the ability to plan and organize a sequence and to monitor performance, other cognitive functions are implicated, such as the build-up of proactive interference and storage capacities. A detailed item-by-item scoring procedure served to identify the exact procedure of correct and erroneous responses. This provided the opportunity for measuring the overall erroneous responses for each subject and the build-up of proactive interference between cards 1-4, 5-8, 9-12, and 13-16.

Speed of processing. This task was administered in order to assess general processing speed and to examine the possible contribution of a reduction of processing speed to executive deficits in AD patients. Speed of processing was assessed with a letter comparison task which is a computerized version of the task initially proposed by Salthouse and Babcock (1991). Participants were presented with pairs of letters and their task was to decide as rapidly and accurately as possible whether the letters were the same or different, by pressing a key-response. The test comprised 60 trials, with 30 "same" and 30 "different" pairs. The selected measure was the mean correct latency for "same" pairs.

In order to exclude a possible influence of memory disorders (forgetting the instructions or getting confused) on the performance of AD patients, trials were administered before each task until participants understood perfectly the task and memorized the instructions. Moreover, during the tasks, subjects were reminded of the instructions whenever necessary.

RESULTS

Alpha-span task

The subjects' results are described in Table 2. The AD patients word span was inferior to that of control subjects [$t(38)=-3.24$, $p<0.005$]. The scores for serial and alphabetical recall were then separately analyzed using an ANOVA with group (AD, controls) as a between-subject factor and type of recall (serial, alphabetical) as a within-subject factor. The analysis revealed a significant group effect [$F(1,35)=5.65$, $p<0.05$] and a significant condition effect [$F(1,35)=71.58$, $p<0.000001$]. A significant interaction between group and type of recall was also found [$F(1,35)=18.34$, $p<0.0005$], with AD patients showing a greater decrease of performance from direct to alphabetical recall than control subjects despite a similar performance to control subjects in direct recall. Finally, the manipulation score showed a greater reduction of performance in AD patients than in control subjects [$t(35)=3.95$, $p<0.0005$].

[Insert Table 2 near here]

Dual-task paradigm

The subjects' results in the single- and dual-task conditions are described in Table 3. The digit span performance was lower in AD patients [$t(38)=-3.24$, $p<0.005$]. The proportion of sequences correctly recalled in single- and dual-task conditions was analyzed using an ANOVA with group (AD, controls) as a between-subject factor and condition (single, dual) as a within-subject factor. The analysis revealed a significant condition effect [$F(1,35)=10.64$, $p<0.005$], with digits in the single condition being recalled better than in the dual condition. There was neither a group effect [$F(1,35)=0.16$, $p>0.5$], nor interaction between group and condition [$F(1,35)=0.002$, $p>0.5$]. A similar analysis was carried out with the number of crosses put on the boxes. It revealed a significant group effect [$F(1,35)=10.30$, $p<0.005$] and a significant condition effect [$F(1,35)=76.44$, $p<0.00001$]. An interaction between group and condition was also found [$F(1,35)=4.70$, $p<0.05$], with AD patients showing a larger decrease of performance than control subjects from the single to the dual task. Finally, performance of AD patients appears marginally inferior to that of control subjects with a global measure expressing the individual's dual-task performance as a percentage of single-task performance [$t(35)=-1.99$, $p=0.053$].

[Insert Table 3 near here]

Delayed alternation task

Results of both groups are presented in Table 4. A significant difference was found between AD patients and control subjects on the number of correct guesses with a learning criterion of 12 successive correct trials [t(38)=-3.97, p<0.0005], as well as when a learning criterion of 5 successive correct trials was used in order to avoid the influence of attentional deficits [t(38)=-2.46, p<0.05].

[Insert Table 4 near here]

Verbal fluency

As the data on this task were not normally distributed, the nonparametric Mann-Withney U test was used to analyze inter-group differences. The comparison of the number of words generated by each group showed that AD patient have a lower performance [AD patients: 15.15 (6.28), range: 8-38; control subjects: 20.75 (6.24), range: 5-32; Z=-3.23, p<0.001, Mann-Withney U test].

Hayling task

The raw response latency (sum of latencies across 15 trials) when the suppression time was controlled for the initiation time (B-A), the number of responses in the C, S and U categories and the semantic score (measuring the overall semantic relatedness of the responses to the sentence) are presented in Table 5.

The B-A time was found to be marginally greater in AD patients [t(38)=1.83, p=0.07] and this difference becomes significant with the B-A logarithmic values [t(38)=2.25, p<0.05]. AD patients and control subjects had a similar number of responses semantically related to the sentence (category S) [Z=-0.03, p>0.5; Mann-Withney U test], but control subjects had more unrelated responses (category U) [Z=3.15, p<0.005; Mann-Withney U test] and less completion responses (category C) [Z=3.65, p<0.0005; Mann-Withney U test] than AD patients. Finally, the overall semantic relatedness of the responses to the sentence (semantic score) was higher in the AD patients than in the control subjects [t(38)=5.13, p<0.00001].

[Insert Table 5 near here]

Self-ordering task

The total of erroneous responses (the number of times a design already pointed out was again designated) and their distribution across time are indicated in Table 6. The number of errors was higher in AD patients [t(38)=2.11, p<0.05]. This error score was then analyzed using an ANOVA with group (AD, controls) as a between-subject factor and presentation time (performance on cards 1-4, 5-8, 9-12, 13-16) as a within-subject factor. The analysis again revealed a group effect [F(1,38)=4.47, p<0.05], with AD patients making more errors than control subjects. There was also a highly significant effect of the presentation time [F(3,114)=41.85, p<0.0001], with less errors made for cards 1-4 and the most errors for cards 9-12. No interaction between group and part of the task was found [F(3,114)=0.32, p>0.5].

[Insert Table 6 near here]

Processing speed

Mean response times for correct responses on "same" items were compared between groups. Since a few AD patients had very slow response times, a similar analysis was also computed with the logarithmic value of this measure in order to reduce variability between subjects. AD patients had slower response times (2289 ± 2641 msec., range: 678-6768) than control subjects (967 ± 214 msec., range: 591-1342), for the raw score [t(37)=2.23, p<0.005] and for the logarithmic value [t(37)=2.93, p<0.01].

Factorial analysis

A factorial analysis was carried out in the AD patient group with the following variables: the manipulation score on the alpha-span task, the global performance on the dual-task paradigm, the number of successful trials on the delayed alternation task, the number of words generated on phonemic fluency, the semantic score on the Hayling task and the number of errors in the SOPT. When several measures were available for an executive task (i.e. the delayed alternation and the Hayling task), the measure which better distinguished the two groups was chosen. The raw data in the patient group for these six variables were entered into a principal component analysis. Using varimax rotation, two factors emerged with Eigenvalues > 1, accounting for 58.5% of the variance. The eigenvalues for the two components were 2.24 and 1.27 respectively. The resulting two-component solution is presented in Table 7 with the individual component loading for each variable included. The tests loading heavily on component 1 are the Hayling task (semantic score), the delayed alternation task and the phonemic fluency, while those loading on component 2 are the self-ordering task, the dual-task paradigm and the alpha-span task.

[Insert Table 7 near here]

It should be noted that exploration of the individual patterns of performance revealed different dissociations within and between factors. For example, an AD patient exhibited normal performance on the alpha-span task but impaired performance (defined as inferior to the mean score of control subjects minus 2.5 standard deviations) on the dual-task paradigm while another patient showed the reverse pattern. A similar dissociation was found for the Hayling task and the delayed alternation task. Moreover, such dissociations were also found between tasks of the two factors. For example, an AD patient showed normal performance on the alpha-span task and impaired performance on the Hayling task while another patients exhibited the reverse pattern. A similar dissociation was found for the dual task and the delayed alternation task. No AD patients showed, nevertheless, a normal performance in all tasks loading on one factor but deficits in all tasks loading on the other factor.

Correlation analysis between measures of executive functions and processing speed

In order to assess the influence of more basic factors on executive function, the speed of processing was correlated to the measures of executive functions described above. There exist significant correlations in AD patients between that measure and the performance on dual-task co-ordination ($r=-0.58$, $p<0.05$), and the performance on the delayed alternation task with a learning criterion of 5 and 12 ($r=-0.52$, $p<0.05$ and $r=-0.57$, $p<0.05$ respectively).

The MMSE score was also correlated to these measures in order to assess the influence of dementia severity on executive function. Significant correlations were found with the delayed alternation task ($r=0.58$, $p<0.008$), the phonemic fluency task ($r=0.44$, $p<0.05$) and the semantic score on the Hayling task ($r=-0.64$, $p<0.005$).

Relations between the two factors and cerebral metabolism

The three variables which loaded respectively on component 1 and on component 2 were each combined and the mean score for each composite was calculated for each AD patient. In order to determine the cerebral areas most related to each factor, a correlation analysis was carried out between the factorial scores and the cerebral metabolism at rest (PET scan examination with 18FDG). Correlations between factor scores and cerebral metabolism were then computed on a pixel by pixel basis by covariance analysis, using age as the covariate, and factor scores as the variable of interest. For both correlation analyses, we used SPM 96 (Friston et al., 1995) with a statistical significance level of $p<0.005$, and a Bonferoni correction for multiple comparisons ($p<0.05$). A significant positive correlation was observed between factor 1 (Hayling, delayed alternation and phonemic fluency tasks) and an area including the left middle and superior frontal gyrus (BA 9/46 and BA 8). With regard to factor 2 (dual-task paradigm, alpha-span and self-ordering tasks), significant negative correlations were observed with three different regions: a cingulate area (BA 31) spreading to the right inferior parietal region (BA 40); a right middle temporal region (BA 21); and finally with a left-sided area including the cingulate gyrus (BA 31) and a region at the junction of the inferior and superior parietal gyrus (BA 40/7).

DISCUSSION

This study investigated the presence of executive dysfunction in Alzheimer's disease using six different tasks assessing the ability to divide attentional resources (the dual-task paradigm) and to manipulate information stored in working memory (the alpha-span task), the short-term preparation for a specific event (the delayed alternation task), the capacity to retrieve information in semantic memory (the phonemic fluency task), the inhibition capacity (the Hayling task) and the monitoring of self-generated responses (the self-ordered pointing task). The performance of AD patients is significantly impaired compared to control subjects on all these tasks. Moreover, the speed of processing does not appear to be significantly correlated to executive deficits in AD patients, except for the dual-task paradigm and the delayed alternation task. In a similar way, the dementia severity (assessed by the MMSE score) was found to be correlated only to the delayed alternation, the phonemic fluency and the semantic score on the Hayling tasks.

The existence of a lower performance by AD patients on executive function tasks does agree with previous studies showing such a deficit even in mildly-affected AD patients (e.g. Bhutani et al., 1992; Brugger et al., 1996; Lafleche & Albert, 1995; Spieler et al., 1996). Moreover, we also showed that processing speed and dementia severity are correlated with only a few tasks, suggesting that all executive impairments are not a consequence of deficits affecting more general factors.

The results of the principal component analysis demonstrated that executive tasks administered to AD patients load mainly on two factors, which could be respectively associated to inhibition processes and the co-ordination between the storage and processing functions. Indeed, the first factor is made up of the semantic score on section B of the Hayling task, the number of correct trials on the delayed alternation task and the number of exemplars provided on the phonemic fluency task. The correct performance on these tasks requires, in fact, the necessity to inhibit a predominant response: in the Hayling task, subjects have to complete a sentence with a word unrelated to that sentence, which clearly requires the inhibition of the expected word. In a similar way, the delayed alternation task also requires the inhibition of a predominant response, namely to search for the target stimulus where it had been previously found (Diamond, 1993; see also Houdé, 1996). Finally, performing a phonemic fluency task requires, notably, that subjects inhibit the usual search strategy on the basis of the meaning of the word (Perret, 1974; see also Burgess & Shallice, 1994). The second factor is made up of the performance on the alpha-span task, the dual-task paradigm and the self-ordered pointing task. This factor can be attributed to the co-ordination between the storage and processing functions. Indeed, the alpha-span task clearly requires storage of some information on which alphabetical manipulation will be applied. The dual-task paradigm assesses mainly the capacity to divide attentional resources between two tasks but also requires storage of sequences of digits. Finally, a correct performance on the self-ordering task is based upon the storage in working memory of the items already selected and the reorganization of these items following the presentation of new trials.

Moreover, a correlation analysis between these two factors and cerebral metabolism at rest showed that different cerebral areas are related to the performance on each factor. There exists a significant positive correlation between the inhibition factor and a region including the left middle and superior frontal gyrus (BA 9/46 and BA 8). Previous activation studies with normal subjects also showed that inhibition processes are related to the prefrontal cortex (Bench et al., 1993; Taylor et al., 1997), although the precise localization of these processes does vary between the studies. These data indicate that, even if the main hypometabolic regions in Alzheimer's disease concern the temporal and parietal associative areas, some metabolic changes also exist in other areas which are related to the efficiency of cognitive processes (e.g. inhibition functions). With regard to the factor devoted to the co-ordination of processing and storage function, there exist significant negative correlations with the metabolic values of the posterior cingulate area (BA 31), a right middle temporal region (BA 21) and a left- and right-sided parietal region (BA 40/7). Previous functional PET and MRI studies with normal subjects have attributed storage function in working memory to posterior regions and processing functions to anterior regions (e.g. D'Esposito et al., 1995; Paulesu, Frith, & Frackowiak, 1993; Petrides et al., 1993; Salmon et al., 1996). In a recent well-conducted study, D'Esposito et al. (1995) showed that the coordination of dual tasks involves the dorsolateral prefrontal cortex which could not be accounted for in terms of the relative difficulty of the individual tasks. On the basis of these data, the absence of correlation with frontal regions in the present study seems surprising. However, it should be mentioned that, contrary to the dual task of D'Esposito et al. (1995), the tasks loading on factor 2 require a storage component, which could explain why we observed correlations with posterior areas (mainly parietal region). In addition, concerning the absence of correlation with the dorsolateral prefrontal cortex, a possible interpretation might be that AD patients focus mainly on the storage of information to the detriment of processing function. This predominance of storage function could be a consequence of the reduction of working-memory resources (Baddeley, 1986), or of the presence of a disconnection between anterior and posterior parietal areas (Morris, 1994a, 1994b), or even of a focal prefrontal dysfunction (Waldemar et al., 1994). Further studies will be necessary to investigate more precisely these interpretations.

Taken as a whole, these results are indicative of an executive dysfunction in AD patients which cannot be completely explained by the dementia severity or the presence of a slowing down. The emergence of two factors (inhibition and co-ordination between storage and processing) suggests that different components of cognition contribute to the performance on executive tasks. Moreover, it appears that different cerebral areas are correlated to the performance on these factors. Finally, the analysis of individual patterns of performance showed dissociation not only between tasks loading on the same factor, but also between tasks loading on different factors. These data are consistent with the hypothesis of the fractionation of executive function (Shallice 1994). Such a fractionation has been well illustrated in the memory domain. Indeed, several studies have shown that the encoding of episodic information is dependent upon the left prefrontal dorsolateral cortex while the retrieval of such information relates to the right dorsolateral cortex (for a review, see Nyberg, Cabeza, & Tulving, 1996). In that context, the investigation of executive functions in Alzheimer's disease does appear fruitful since the important heterogeneity presented by these patients will facilitate the emergence of fine-grained dissociations in their executive function.

Finally, it remains to consider the neurobiological substrate of executive dysfunction in Alzheimer's disease. Two different explanations have been proposed for that deficit. The first one refers to a frontal lobe pathology. Indeed, some studies have shown that frontal lobe degeneration is relatively often associated with AD (Waldemar et al., 1994). However, some authors (D'Esposito & Grossman, 1996; Fuster, 1993 ; Weinberger, 1993) have proposed that executive control would require the integration of information coming from different cerebral areas. In that perspective, the central executive deficit observed in AD patients could also be due to a breakdown in connections between the main cortical anterior and posterior association areas (Morris, 1994a, 1994b, 1996). The data of the present study does indicate that both deficits could coexist in Alzheimeir's disease. Indeed, the correlation between the inhibition factor and a middle prefontal area would indicate the presence of frontal lobe degeneration. On the contrary, the correlation between the second factor and metabolism in posterior regions would indicate that AD patients favour storage function, which could be a consequence of an inefficient transfer of information between anterior and posterior association areas.

FOOTNOTES

1. In this test, participants are shown a series of cards one at a time. Each card has a series of visual stimuli at the top, relating to one another. The participants must choose the stimulus item at the bottom that best completes the series of stimuli at the top. The stimulus items vary in terms of colour, shape and size. The cards range from the simple to the complex, depending on the number of stimuli parameters which are varied. This task (Daryn, 1977) assesses the ability to perceive and synthetize patterns of relationships in a sequence of visual stimuli of increasing complexity.

2. It should be noted that we modified the original version of the span task as described by Baddeley et al. (1997), in which the digit span corresponds to the maximum length at which all three lists were reproduced without errors. This criterion of two out the three correct sequences was chosen in order to avoid that the span level of the subjects be lowered by an attentional deficit. This modification does not seem to influence the performance of AD patients and control subjects. Indeed, if we compare the performance in the digit repetition task in isolation to that in the study of Greene, Hodges and Baddeley (1995) also using the Baddeley procedure, results do appear to be very similar (control subjects: 76 ± 17 and 76 ± 20, respectively; AD patients: 74 ± 17 and 77 ± 25, 65 ± 28, respectively; see Table 3).

3. In the original task proposed by Burgess and Shallice (1996), the time allowed to produce a response was 60 seconds, and a latency of 60 seconds was recorded if the subject produced no response in this time. We have reduced the time allowed to 30 seconds in order to lower the anxiety of AD patients when they did not succeed to complete the sentence.

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Table 1
Mean performance (standard deviation) of AD patients and control subjects on the different sub-tests of the DRS

	AD	Controls	
Attention	34.05 (4.05)	36.30 (0.65)	$t(38)=-2.45$, $p<0.05$
Verbal-motor initiation	27.7 (7.15)	34.90 (3.23)	$t(38)=-4.10$, $p<0.0005$
Construction	4.90 (2.07)	5.85 (0.67)	$t(38)=-1.95$, $p=0.058$
Concept	33.35 (6.21)	38.50 (0.83)	$t(38)=-3.68$, $p<0.001$
Memory	14.45 (4.50)	24.45 (1)	$t(38)=-9.70$, $p<0.00001$
DRS overall score	114 (19.62)	140.15 (4.31)	$t(38)=-5.82$, $p<0.00001$

Table 2
Mean performance (standard deviation) and [range score] of AD patients and control subjects on the Alpha span task

	AD	Controls
Word span	3.6 (0.99) [2-5]	4.45 (0.76) [3-6]
Serial recall	9.35 (0.61) [8-10]	9.05 (1) [7-10]
Alphabetical recall	5.23 (2.61) [0-9]	7.70 (1.87) [2-10]
Manipulation score	44.43 (26.28) [10-1000]	15.49 (18.05) [0-71]

Table 3
Mean performance (standard deviation) and [range score] of AD patients and control subjects on the dual task

	AD	Control
Digit span	4.50 (0.95) [3-7]	5.55 (1.10) [4-8]
Digit repetition task-single	73.96 (16.99) [50-93]	76.07 (16.74) [33-100]
Motor task - single	108.71 (40.52) [56-188]	139.40 (34.43) [96-252]
Digit repetition task - dual	61.44 (18.48) [29-100]	63.21 (21.37)[14-84]
Motor task - dual	67.29 (34.15) [29-156]	111.45 (34.32) [53- 210]
Decrease of performance (μ score)	74.22 (13.93) [37-99]	84.27 (16.26) [50-112]

Table 4
Mean performance (standard deviation) and [range of scores] of AD patients and control subjects on the delayed alternation task

	AD	Controls
Correct responses /50 (learning criterion=12)	35.90 (9.08) [13-47]	44.90 (4.47) [30-50]
Correct response /50 (learning criterion=5)	40.02 (9.78) [13-50]	45.80 (2.80) [41-50]

Table 5
Mean performance (standard deviation) and [range of scores] of AD patients and control subjects on the Hayling task

	AD	Controls
Response latencies B-A	83.05 (55.72) [21-263]	54.75 (41.23) [9-178]
Category C (number of responses)	3.10 (2.95) [0-10]	0.15 (0.37) [0-1]
Category S (number of responses)	8.75 (2.51) [4-14]	8.60 (3.07) [3-13]
Category U (number of responses)	3.10 (1.74) [0-7]	6.20 (3.09) [2-12]
Semantic score (overall semantic relatedness)	18.90 (7.46) [8-28]	9.62 (3.11) [4-14]

Table 6
Mean performance (standard deviation) and [range of scores]of AD patients and control subjects on the self ordering task

	AD	Controls
Error score	4.68 (1.40) [2-7]	3.62 (1.54) [1-6]
Error score sheet 1-4	0.20 (0.41) [0-1]	0 (0)
Error score sheet 5-8	0.95 (0.88) [0-2]	0.65 (0.81) [0-2]
Error score sheet 9-12	1.35 (1.04) [0-3]	0.95 (0.94) [0-3]
Error score sheet 13-16	2.15 (0.93) [1-4]	2.10 (0.79) [1-3]

Table 7
Results of the principal component analysis

	Varimax rotated component loadings	
Test	Component 1	Component 2
Hayling (semantic score)	0.87	0.06
Delayed alternation task	-0.86	-0.10
Phonemic fluency	-0.76	0.07
SOT	0.07	0.74
Dual task	0.12	0.61
Alpha span	0.39	-0.57