CROSS-FORM PRIMING IN NORMAL AGING AND IN MILD DEMENTIA OF THE ALZHEIMER TYPE

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ABSTRACT

Twenty patients at early stages of Alzheimer's disease (AD), 20 elderly control subjects and 20 young subjects completed a cross-form priming task, followed by a free recall task. Results show that patients with mild AD display priming effects, and that these priming effects are strictly comparable to those obtained by elderly and young control subjects. Moreover, while the patients' performances are normal in the implicit part of the task, they are massively impaired in the explicit free recall task. These results don't support the hypothesis of a dissociation of performances between identification tasks and generation tasks in Alzheimer's disease, and show that conceptual priming can be observed at early stages of the disease, despite semantic memory impairments.

Introduction

Patients with Alzheimer's disease (AD) show marked deficits in explicit memory tasks. Unlike normal elderly subjects, who may exhibit a decline of performance only when episodic memory is assessed (Craik and Jennings, 1992; Van der Linden, 1994), they are usually described as severely impaired in episodic memory, and also in semantic memory when direct tasks are involved (i.e. naming, fluency, vocabulary tasks) (Martin and Fedio, 1983; Grober, Buschke, Kawas et al., 1985; Martin, Brouwers, Cox et al., 1985; Kaszniak, Poon and Riege, 1986; for a review, see Nebes, 1992).

However, when assessed with implicit measures of memory, which do not require conscious recollection of any previous experience, AD patients can show intact memory abilities. The most common implicit memory paradigms include procedural learning and direct priming tasks (Schacter, 1987).

Most of the studies concerned with procedural learning in AD have demonstrated preserved abilities, either in motor tasks (Eslinger and Damasio, 1986; Heindel, Salmon, Shults et al., 1989) or in perceptual verbal learning (Moscovitch, Winocur and McLachlan, 1986; Deweer, Ergis and Fossati, 1991; Ergis, Deweer and Fossati, 1992; Grober, Gitlin, Bang et al., 1992; Deweer, Ergis, Fossati et al., 1994). In contrast, many discrepancies are found when examining direct priming effects in AD. Different procedures have been used to study such effects. Among them, identification of words, non-words or pictures, which essentially rely on the analysis of the physical properties of stimuli, assess perceptual priming. Perceptual identification of words and pseudo-words briefly presented

on a computer screen has been examined in AD patients (Keane, Gabrieli, Fennema et al., 1991; Keane, Gabrieli, Growdon et al., 1994). Although patients were significantly slower at identifying both targets and distractors than controls, both groups displayed significant priming effects, and they did not differ from each other. Perceptual priming in AD has also been studied with fragmented pictures from Gollin's task (1960). Corkin (1982) found priming effects in patients with mild AD, but not in moderately and severely demented patients; Heindel et al. (1990) also observed reduced priming effects in AD.

The word-stem completion paradigm, also generally considered as a perceptual priming procedure, has been frequently used with AD patients, but studies which used this paradigm led to divergent results: some authors found impaired direct priming effects in AD patients (Shimamura, Salmon, Squire et al., 1987; Salmon, Shimamura, Butters et al., 1988; Bondi and Kaszniak, 1991; Keane et al., 1991). By contrast, other studies showed comparable levels of priming in AD and age-matched normal subjects (Grosse, Wilson and Fox, 1990; Lussier, Belleville, Peretz et al., 1990; Partridge, Knight and Feehan, 1990; Deweer, Ergis and Fossati, 1991; Ergis et al., 1992; Deweer, Ergis, Fossati et al., 1994).

Moreover, a similar pattern of results in direct priming has been observed in normal aging: many studies report preserved perceptual priming abilities in tasks such as perceptual identification of words (Light and Singh, 1987) and picture naming (Mitchell, 1989; Mitchell, Brown and Murphy, 1990). On the other hand, contrasting results have been found with word-stem completion paradigms: some authors demonstrated normal priming effects (Light, Singh and Capps, 1986; Java and Gardiner, 1991), while others found decreased effects in elderly controls (Chiarello and Hoyer, 1988; Davis, Cohen, Gandy et al., 1990).

Among the potential explanations for such discrepancies found in word-stem completion tasks are (a) procedural differences, concerning the orienting tasks during the study phases, or the degree of perceptual similarity of stimuli presented at the study and test phases; (b) the severity of dementia; (c) the size and homogeneity of patient groups. Furthermore, according to Moscovitch and Winocur (1992), such discrepancies suggest that word-stem completion is not a purely perceptual task like perceptual identification of words or figures, but also involves strategic, lexical or conceptual components. Moreover, Nelson et al. (1992) showed that word-stem completion, unlike word-fragment completion, is affected in normal subjects by the number of possible completions and the number of semantic associates, which suppose then the involvement of both lexical and semantic processes.

While perceptual priming tasks rely on the analysis of the physical properties of stimuli, and require that their format remain identical between study and test, in conceptual priming tasks retrieval cues provide information conceptually related to the target information, and identical format presentation of stimuli between study and test is then not necessary.

Investigation of conceptual priming in Alzheimer's disease has been reported in some studies, in which a paired-associate procedure was used (Brandt, Spencer, McSorley et al., 1988; Huff, Mack, Mahlman et al., 1988; Salmon et al., 1988; Grober et al., 1992). In this kind of paradigm, subjects have to judge semantically related word pairs, and later to "free-associate" with the first words of the previously presented pairs. Results showed that AD patients were less likely to produce the second word of the semantically related pairs than were amnesic patients, patients with subcortical disease

and control subjects.

Few studies were aimed at assessing conceptual priming in normal aging, and used different paradigms. Light and Albertson (1989) showed that prior study of a list of words increased, in both young and elderly subjects, the probability that they produce these words when asked later to generate category members. Van der Linden et al. (1993) used a cross-form priming task similar to that of Hirshman et al. (1990) in order to examine conceptual priming effects in normal aging. Subjects were asked to complete a sentence by generating the final missing word. They were later presented fragmented pictures of objects, one half corresponding to the generated names (targets), the other half to new words. A conceptual priming effect was evidenced, since elderly subjects, like young ones, identified target pictures faster than the new ones.

Two alternative hypotheses were proposed by Gabrieli and his co-workers (Gabrieli, Keane, Stanger et al., 1994; Monti, Gabrieli, Wilson et al., 1994) to account for the discrepancies of performance observed across different priming tasks in AD patients. These authors suggested to focus (1) on the nature of the priming tasks at *test phase:* according to them, identification tasks (i.e. reading words presented tachistoscopically, lexical decision, naming pictures of familiar objects) are preserved in AD patients, while generation priming task (i.e. word-stem completion, word associate generation, category exemplar production) are impaired; (2) on the requirements of the tasks at study and test phases: implicit memory is spared when the study and test phases of an experiment are similar (i.e. reading and re-reading words, making and re-making lexical decisions), in other words in tasks labelled as *repetition* priming tasks (see Roediger and MacDermott, 1993); in contrast, standard word-stem completion, word associate generation, category exemplar production priming paradigms, which are impaired, involve different tasks at study and test phases *(direct* priming).

For the present experiment, a cross-form priming task similar to the one used by Hirshman et al. (1990) was designed, in order to examine whether mild AD patients, as compared to elderly and young control subjects, are able to obtain priming effects. This task was chosen to allow a further assessing of the two hypotheses of Monti et al. (1994) because (1) it involves the generation of objects names from incomplete drawings, and (2) there is no similarity between the study and test phases. Moreover, this task is considered as conceptual: Hirshman et al. (1990) showed that semantic processing of words can facilitate identification of their corresponding pictures in young subjects. These facilitation effects were not observed when the words were simply read in the context of a sentence, instead of being generated. Since semantic representations are generally considered to mediate performance in cross-form priming, such a task allows exploration of conceptual priming in Alzheimer's disease. Tulving and Schacter (1990) suggested that conceptual priming relies on the modification of, or the addition of new information to semantic memory. As these patients display impairments of semantic memory, even at early stages of the disease, we expect to find abnormal — if any — priming effects.

MATERIALS AND METHODS

SUBJECTS

Twenty patients with probable Alzheimer's disease (16 females and 4 males), 20 elderly adults (14 females and 6 males) and 20 young subjects (16 females and 4 males) participated in this study. AD patients were all outpatients, recruited from the Department of Geriatry, Hôpital Broca, Paris, and

from the Department of Neurology, Hôpital Henri Mondor, Créteil. The diagnosis of AD was made by senior staff neurologists according to the NINCDS- ADRDA criteria (McKhann, Drachman, Folstein et al., 1984). Patients with a history of head injury, alcoholism, psychiatric illness or neurological disease were excluded from this study. All patients had a metabolic screening (serology, B12 and folates levels, tests of thyroid function). Computed tomographic scans (and/or MRI) were available for all patients but one; most of them showed atrophy, without further significant abnormalities; the presence of any focal lesion was an exclusion criterion. The duration of the disease was 2.9 (±1.1) years. No patient was diagnosed as depressed, on the basis of a psychiatric interview guided by the DSM III-R (1987) criteria for depression; the Montgomery and Asberg scale (1979) score was 5.80 ± 2.82. These patients were mildly demented: their mean MMS (Folstein, Folstein and McHugh, 1975) score was 23.55 (± 2.44) and their mean score on the Dementia Rating Scale (Mattis, 1976) was 118.15 (±7.9) out of 144.

The elderly control subjects were either patients' spouses or volunteers recruited among relationships. Controls with a current medical illness, a history of alcoholism, head trauma, neurological or psychiatric disorder were excluded from the experiment.

The young control subjects were recruited at Henri Mondor Hospital. They were working in the Hospital, or having a training session as students at the Nursing School. They were all in good health.

Table I shows the mean age, years of education, fluency scores in the three groups, and MMS and DRS scores of the first two groups. These two groups significantly differed in terms of MMS and DRS scores (respectively, F= 105.1; d.f. = 1, 39; p < 0. 0001; F= 162.3; d.f.= 1, 39; p<0.0001), but not for age (F = 0.16; d.f. = 1, 39; ns). There was no significant difference among the three groups with regard to the length of formal education (F = 0.71; d.f. = 2, 59; ns).

This experiment was part of a larger study including a complete neuropsychological assessment and the following priming paradigms: perceptual identification of words, nonverbal perceptual priming, word-stem completion, and priming for new associations of words (Ergis, Van der Linden, Boiler et al., in preparation).

TABLE I *- Demographic and Psychometric Characteristics of the 3 Subjects Groups: Mean (SD)*

	AD patients		Elderly controls		Young controls	
Number	20		20		20	
Age	71.3	(6.41)	70.35	(9.17)	23.9	(3.26)
Education (yrs)	10.65	(3.18)	11.65	(2.78)	11.2	(1.8)
MMS	23.55	(2.44)	29.55	(0.6)		
DRS (Mattis, 1976)	118,15	(7.9)	142	(2.05)		
Category naming (animals, 1 minute)	12.70	(4.88)	24.35	(5.62)	26.7	(7.4)
Category naming (supermarket, 1 minute)	13.60	(6.93)	26.30	(6.2)	28.35	(9)

MATERIALS

This experiment was adapted from the Hirshman et al. (1990) study on conceptual priming. The material consisted of three sets of 10 sentences, and 22 series of fragmented pictures of common objects. The pictures were selected from the series of standardized (Snodgrass and Vanderwart, 1980) and fragmented (Snodgrass, Smith, Feenan et al., 1987; Snodgrass and Corwin, 1988) images of Snodgrass and her co-workers. Each picture was fragmented in 8 stages numbered 1 to 8 (l=most fragmented stage; 8 = complete picture). Two parallel sets of 10 series of pictures were constructed (the 2 remaining series were used as examples) and matched in terms of visual complexity, according to Snodgrass and Vanderwart (1980) norms (mean visual complexity: respectively 2.98 and 2.79 on a five- point scale). These sets were also matched in terms of identification threshold: in a pilot study conducted with 10 control subjects, the mean identification threshold was the same for each set (4.66). The two sets were counterbalanced between subjects: during the test phase, the 20 picture series were mixed and shown to each subject, half of the picture series as targets, the other half as distractors. In the present experiment, the material was displayed on white index cards.

Among the three sentence sets which were constructed for the study, one corresponded to the pictures of one set, one to the pictures of the other set, and the third was used as distractors. The distractors were the same for all subjects. Thus, two parallel lists of 20 sentences were constructed, each comprising of 10 targets and 10 distractors, and counterbalanced between subjects. Each sentence included a specific word denoting a common object, but this word was actually missing and replaced by a broken line indicating its length (number of letters). The sentences were constructed so that the missing words could be found unequivocally. Each sentence was written on a A4 format paper sheet, and the to-be- found word was printed on the other side.

PROCEDURE

Each subject was successively given a word generation task, a priming task, and an explicit memory task.

Study Stage

Each subject was first shown the two examples, and instructed that s(he) had to find the last word of each sentence, which was missing and replaced by a broken line indicating its length. Then, s(he) was successively shown each of 20 sentences, and asked to discover and say aloud the missing word. When s(he) found the critical word, it was then shown for one second. When s(he) produced a wrong response, s(he) was told the correct answer, and then the target word was shown for one second. The subject was not aware that these items would be tested later in implicit and explicit tasks.

Test Stage

After a 3-minute letter cancellation task, the subject was shown the example series of fragmented pictures, and asked to name the picture as quickly as possible. The most fragmented level of a picture was shown first for five seconds, then the next level for five seconds, and so on up to the correct response. After the completion of examples, the subject was given the 20 series of fragmented pictures, with the same procedure. S(he) was encouraged throughout the session to guess what the picture represented, and to give responses, even if s(he) was not sure that it was the correct one.

The dependant variable was the level of fragmentation reached when the correct naming took place (identification threshold). Threshold 1 meant that the picture was identified at the most fragmented level, threshold 8 meant that it was only identified at its most complete level. The measure of priming was the difference of mean identification thresholds between the 10 targets and the 10 distractors.

Explicit Memory Task

After another 3-minute letter cancellation task, the subject was asked to recall as many words as possible among those s(he) had generated during the first part of the experiment.

Statistical Analyses

Data were submitted to analyses of variance (ANOVA), t-tests, correlation tests, and Newman-Keuls tests (post hoc analysis), performed with Statview II.

Results

NEUROPSYCHOLOGICAL ASSESSMENT

Statistical analyses performed in the general study, including this experiment, showed that AD patients were significantly impaired in all neuropsychological tests, except for attentional tasks. Patients were also impaired for all measures of explicit memory tasks. Some results from the Grober and Buschke (1987) memory procedure are summarized in Table I.

IMPLICIT PART OF THE EXPERIMENT: CROSS-FORM PRIMING

The identification thresholds for the pictures were analyzed by means of a 3 (groups: young/old/SDAT) X 2 (stimulus: target vs distractor; repeated measures) analysis of variance. Target pictures were identified faster (5.11) than the distractor pictures (5.36) by all subjects. This cross-form priming effect was underscored by a highly significant stimulus effect ($F = 26.47$; d.f. = 2, 57; $p<0.0001$). Data analysis also showed a significant group effect ($F = 22.7$; d.f. = 2, 57; $p<0.0001$), indicating that the pictures were not identified at the same level in the three groups (AD patients: 5.79; elderly controls: 5.36; young controls: 4.56). Newman-Keuls post-hoc analysis ($p<0.05$) indicates that the 3 groups differ significantly: young controls identified the pictures at a lower level than the aged ones; elderly controls identified them at a lower level than AD patients. The group X stimulus interaction was not significant ($F = 0.68$; d.f. = 2, 57; ns).

Although the picture identification level varied among groups, the amplitude of the priming effect (mean target identification threshold minus mean distractor identification threshold) did not significantly differ among groups ($F = 0.67$; d.f. = 2,57; ns). This measure of the priming effect amplitude is an *absolute* one, calculated for each subject as follows: distractors minus targets (D — T). However, Snodgrass (1989) showed that the amplitude of priming is proportional to the level of distractor identification (baseline), and that a *relative* measure of the priming effect amplitude is therefore more appropriate. As the baseline differed between groups, we computed a relative measure as follows, using Snodgrass' method: we divided the difference between distractors and targets by the maximal potential difference: (D — T)/(D— 1); as 1 is the first level of fragmented pictures identification, D — 1 corresponds to the maximal potential priming effect for each subject. No significant interaction between groups and stimuli was obtained, which confirms a normal

priming effect in AD patients and elderly normal subjects.

Moscovitch and Winocur (1992) suggested that frontal lobes may contribute to performance on conceptual priming. In order to assess their hypothesis, correlations between cross-form priming and different measures of executive functions (Stroop test, Trail making Test B, WAIS-R Similarities subtest) were examined. Correlations with semantic tasks (category naming) were also examined. No significant relationship between these measures was found in any of the 3 groups.

EXPLICIT PART OF THE EXPERIMENT: FREE RECALL

Unlike the priming effect, the explicit recall of the words generated during the first part of the experiment was affected by age: there was a significant group effect ($F = 21.79$; d.f. = 2, 59; $p<0.0001$). In fact, young subjects recalled more words than elderly subjects (respectively, 4.85 and 2.10; $t = 3.89$; d.f. = 38, $p<0.0002$), and elderly subjects recalled more words than AD patients (respectively, 2.10 and 0.05; $t = 4.3$; d.f. = 38; $p<0.0001$).

Additional analyses indicate that the explicit and implicit memory measures are independent: the priming effect was not significantly correlated with the free recall score of the generated words, in none of the control groups (young controls: r = .O2, ns; elderly controls: r = .11, ns). No correlation could be examined in the AD patient group, since only one patient could recall words; this observation supports also the independence of measures. Furthermore, the identification thresholds for recalled and non recalled pictures were compared in both, control groups. No significant difference in the mean identification threshold of recalled pictures vs non recalled pictures was found, either in the young control group (respectively 4.6 and 4.36: $t = 0.79$; d.f. = 19, ns), or in the elderly control group (respectively 4.77 and 5.3: $t= 1.34$; d.f. = 19, ns), indicating that the explicit and implicit performance were independent. Finally, all subjects were interviewed after completing the task, and none of them reported that (s)he discovered that some pictures corresponded to previously generated words.

Discussion

The results of this study are particularly striking: first of all, patients with mild AD display priming effects; secondly, these priming effects are strictly comparable to those obtained by elderly and young control subjects. Moreover, while the patients' performances are normal in the implicit part of the task, they are massively impaired in the explicit free recall task.

On the other hand, elderly control subjects show quite a similar pattern of performances, with normal conceptual priming effects, and significantly — although not as drastically as the AD patients' ones — diminished performances in free recall, as compared to young controls.

At a general level, our results are not consistent with the two interpretations proposed by Gabrieli and his co-workers (Gabrieli et al., 1994; Monti et al., 1994): firstly the task we used involves the generation of objects names from incomplete drawings, secondly the study and test phases are different, but nevertheless normal priming effects are obtained by AD patients. Moreover, the authors' hypotheses can't account for the results of others studies showing preserved priming abilities of AD patients in word-stem completion tasks, which are also generation tasks, and differ between study and test phases (Grosse et al., 1990; Lussier et al., 1990), Partridge et al., 1990; Deweer et al., 1991; Ergis et al., 1992; Deweer et al., 1994).

At a more specific level, our results suggest that conceptual priming is preserved in AD patients. In fact, several data allow the assumption that the cross-form priming task we used in this experiment is conceptual: (1) a task is considered as conceptual when the cue presented at the test phase provides information conceptually linked to the information-target presented at the study phase, in the absence of any physical similarity between the two informations (Roediger and McDermott, 1993). The task responds to this first criterion, since words are generated in the study phase, and pictures are presented in the test phase; to identify more rapidly a picture whose name has been generated implies semantic processing of a concept, allowing access to different representations of this same concept; (2) unlike perceptual tasks, a conceptual task is affected by manipulations of levels of processing at encoding. Hirshman et al. (1990) obtained priming effects in their study when the words were generated by the subjects at the study phase, but not when they were simply read.

One possible objection is that when subjects generate a word, they construct a mental image of the referent of this item; given that imagery produces representations that are similar to the pictures presented at the test phase, the priming effect would be then perceptual — or data-driven —, and not conceptual. Hirshman et al. (1990, experiment 4) showed that a conceptual priming effect could be obtained in such conditions where there was no possible similarity between mental images constructed after generating a word, and the stimuli presented at test.

Furthermore, several findings of selective interference experiments suggest that words would only activate pictures nodes if specific instructions are given that require such an activation of picture nodes, for example an imagery instruction (Engelkamp and Zimmer, 1994). Our task's instructions don't require imagery generation.

Researchers who studied until now conceptual priming in Alzheimer's disease used a paradigm of word associations (Brandt et al., 1988; Huff et al., 1988; Salmon et al., 1988; Grober et al., 1992), and they all observed that the patients obtained impaired conceptual priming effects. This kind of paradigm is different from the one we used: targets-words are not presented at the test phase, even under an uncomplete format, since subjects are asked to produce them in response to a semantic cue. The second difference — and the most important one — is that subjects are asked either to produce a semantic associate of the presented word (Brandt et al., 1988; Huff et al., 1988; Salmon et al., 1988), or to produce category exemplars when given a semantic category name (Salmon et al., 1988; Grober et al., 1992). Since AD patients' impairments in semantic memory can disrupt their abilities to generate conceptual associations (Martin and Fedio, 1983; Gewirth, Shindler and Hier, 1984), these authors suggest that the disorganization of their semantic network is responsible for the lack of conceptual priming effects. According to Salmon and Heindel (1992), the alteration of the hierarchical associative network which constitutes the structure of semantic knowledge prevents the presented cues from activating the trace of the studied stimuli. For example, the cue "bird" can't produce an unconscious activation of the word "robin", because the association between these two words is weakened.

In that perspective, spared performance of AD patients in our cross-form priming task could be explained by the fact that this task doesn't require the activation of semantic associates, but the activation of a concept representation. It seems that at early stages of the disease AD patients would be able to perform this kind of task, and not those involving the production of semantic associates. We are presently studying this task with moderately demented AD patients, and preliminary results

seem to indicate that at more advanced stages of the disease, patients don't show anymore conceptual priming effect. However, it should be mentioned that, like Salmon & Heindel (1992), we didn't find any correlations between conceptual priming and category naming, although the patients were significantly impaired in the naming task. It is possible then that category naming is not the most appropriate task to assess semantic memory, since it relies strongly on language production, and that association or categorization tasks would be more appropriate.

Our study also shows that elderly normal subjects demonstrate a priming effect strictly comparable to the one obtained by young normal subjects. These results supports those observed by Van der Linden et al. (1993). Light et Singh (1989) also showed normal performances of elderly normal subjects in a conceptual priming task using familiar material, which allows to suggest that normal aging doesn't affect the activation of pre-existing semantic representations.

It is also important to emphasize that this priming task is much less *contaminated* by explicit processes than other ones. To change the physical format of stimuli between study and test, and to propose a distracting task between the two parts of the task made impossible any intentionality of using explicit recollection strategies: each subject was asked at the end of the task if (s)he noticed any link between the two parts of the task, and all of them answered that they did not notice that the same items were used at study and at test, and that these two parts were belonging to the same task. We could establish independence measures between the implicit part and the explicit one in 3 ways: (1) nineteen out of 20 patients did not recall any studied word, and the only one who could do it recalled only one word; (2) no correlation was found between priming and free recall in young and elderly control subjects; (3) target-pictures whose previously generated name was recalled were not identified faster than the others, neither by young controls, nor by elderly ones.

Two kinds of approaches have been proposed to account for the dissociations between explicit and implicit memory tasks. The first one postulates a unique memory system involving different processes (see Roediger, Weldon and Challis, 1989; Jacoby and Kelley, 1992). According to the transfer-appropriate procedure approach, memory performances in explicit tasks are impaired in AD because they are conceptually-driven, while memory performances in implicit tasks should be spared because most of them are data-driven. However, the fact that patients show massive impairments in explicit memory tasks and normal conceptual priming is in contradiction with such an approach. The priming effects of elderly normal subjects should also be subnormal, which is not the case. The second approach postulates the existence of multiple memory systems (see Tulving and Schacter, 1990). According to this approach, perceptual priming reflects the operation of a presemantic perceptual representation system (PRS), that can function independently of the episodic and semantic systems. On the other hand, conceptual priming reflects the modification or the addition of new information to semantic memory. It seems then that elderly normal subjects and AD patients are able to normally activate pre-existing semantic representations, which implies that at early stages of the disease, existing semantic memory impairment is not severe enough to impair such automatic processing.

Two important questions concern (1) how long conceptual priming involving familiar material can be spared in the course of Alzheimer's disease; (2) if mild AD patients are able to show priming effects for materials that don't have preexisting representations in memory.

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