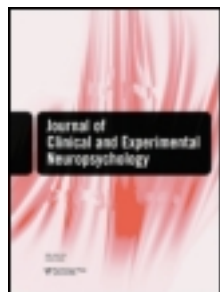


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### Exploring recollection and familiarity impairments in Parkinson's disease

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# Exploring recollection and familiarity impairments in Parkinson's disease

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There is conflicting evidence on whether patients diagnosed with Parkinson's disease (PD) have cognitive deficits associated with episodic memory and particularly with recognition memory. The aim of the present study was to explore whether PD patients exhibit deficits in recollection and familiarity, the two processes involved in recognition. A sample of young healthy participants (22) was tested to verify that the experimental tasks were useful estimators of recognition processes. Two further samples—one of elderly controls (16) and one of PD patients (20)—were the main focus of this research. All participants were exposed to an associative recognition test aimed at estimating recollection followed by a two-alternative forced-choice (2AFC) test designed to estimate familiarity. The analyses showed a deficit in associative recognition in PD patients and no difference between elderly controls and PD patients in the 2AFC test. By contrast, young healthy participants were better than elderly controls and PD patients in both components of recognition. Further analyses of results of the 2AFC test indicated that the measure chosen to estimate conceptual familiarity was adequate.

**Keywords:** Familiarity; Recollection; Recognition memory; Associative recognition; Parkinson's disease.

Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by motor deficits such as resting tremor, bradykinesia, rigidity, and postural instability. The neurodegenerative processes associated with PD begin in the dorsal motor nucleus and the intermediate reticular zone, extending to the substantia nigra, and showing a progression towards subcortical and cortical structures of the midbrain at more advanced stages of the disease (Braak et al., 2003). PD also implies a dysfunction of the dopaminergic system that connects the dorsolateral prefrontal cortex and orbitofrontal and ventrolateral structures (Alexander, Crutcher, & DeLong, 1990) and a

deficit in the cholinergic pathways that causes a dysfunction in frontal-subcortical circuits (Bohnen et al., 2003).

The diagnosis of PD is based on the presence of tremors combined with rigidity and akinesia. Although this disease has a heterogeneous clinical presentation, contemporary research has shown that cognitive deficits can be observed from the earliest stages of the disease (Aarsland, Bronnick, Larsen, Tysnes, & Alves, 2009) and fluctuate depending on the progression of the neuropathological lesions. Around 24% of patients with newly diagnosed PD show some form of cognitive dysfunction (Muslimovic, Post, Speelman, &

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Schmand, 2005). In these patients, neuropsychological tests revealed deficits in several cognitive domains of executive function, immediate and delayed memory, and attention; smaller deficits have been found in processing speed, visual-spatial skills, and language (Muslimovic et al., 2005). As the disease progresses, it also affects patients' semantic fluency, temporal orienting, visual search, and object/action naming (Rodríguez-Ferreiro, Cuetos, Herrera, Menendez, & Ribacoba, 2010). A recent review of PD suggest that cognitive deterioration present in the early stages involves deficits in maintaining attention and performing dual tasks, speech fluency, daily life activities, free/cued recall, and verbal and visual memory. The majority of initial deficits can be attributed mainly to a failure of frontostriatal circuits, although nondemented PD patients also exhibit visuospatial and memory deficits more related to posterior-cortical alterations. The dementia associated with PD is characterized by more severe cognitive impairment including deficits in semantic verbal fluency, confrontation naming, and recognition memory (see Pagonabarraga & Kulisevsky, 2012). In addition, the cumulative incidence of dementia increases with age and duration of Parkinson's disease. According to a prospective longitudinal study with 20 years' follow-up, about 80% of surviving PD patients developed dementia (Hely, Reid, Adena, Halliday, & Morris, 2008). The presence of deficits in immediate and delayed memory and executive function processes has also been associated with the later development of dementia in PD patients (Levy et al., 2002).

Nondemented PD patients show an impairment in episodic memory tasks but often not in recognition (Whittington, Podd, & Kan, 2000). This discrepancy may be due to the lack of statistical power of the studies conducted. Yet, a meta-analysis (Whittington et al., 2000) identified the factors most likely involved in the detection of deficits in PD patients who participated in a classical recognition experiment or whose recognition was measured through neuropsychological tests. Such factors were cognitive state, signs of dementia, medication status, disease stage and duration, depression, motor disability, sample size, and task difficulty. However, an additional factor may explain the inconsistent results obtained regarding PD patients' deficits in recognition memory: Most researchers have failed to acknowledge the specific processes involved in recognition in the neuropsychological or experimental paradigms used to measure such deficits. According to the dual process theory (Yonelinas, 2002), recognition can be achieved through a combination of familiarity (F)

and recollection (R). *Familiarity* is defined as the feeling that an event has been previously experienced combined with the inability to identify the specific context in which it occurred. By contrast, *recollection* is based on conscious retrieval of information supported by specific details of the past event. Taking this dichotomy into account, tasks with lower cognitive demands could be completed by using familiarity while more complex situations might require the use of recollection, which is more effortful.

The procedures more commonly used to measure R and F fall into three categories: remember/know judgments, the process dissociation procedure, and the study of the pattern of experimental effects. In the remember/know procedure, participants are asked whether the recognized stimulus is accompanied by contextual information or not, leading to so-called "know" or "remember" judgments. This procedure has been heavily criticized because it relies on the subjective experience of participants (e.g., Wixted, Mickes, & Squire, 2010). In the process dissociation paradigm, participants are required to study stimuli in two conditions and are later asked to perform inclusion and exclusion tests. In inclusion tests, participants are instructed to accept stimuli studied in either of the two study conditions; in exclusion tests, participants must reject all the stimuli that do not correspond to one of the specific study conditions. This experimental procedure makes it possible to estimate R and F when both processes are assumed to be independent. The process dissociation procedure may be difficult to apply with older people, requiring also an assumption of independence between the processes measures. A third, very indirect, procedure is based on the use of differential experimental effects in purported R and F situations.<sup>1</sup> Such is the case when the mirror effect (i.e., the mirror pattern of hits and false-alarm rates in two different conditions) is used. The few studies in which researchers have experimentally analyzed the performance of PD patients in recognition tasks have been conducted using one of these techniques.

When R and F are independently estimated in older populations, participants tend to exhibit deficits in the R component (Duarte, Graham, & Henson, 2010; Jennings & Jacoby, 1997) but perform similarly to younger adults in F (Parkin et al., 2001; Yonelinas, 2002). This pattern of deficits is

<sup>1</sup>For the sake of simplicity we do not mention the analysis of receiver operating characteristic (ROC) curves that could be subsumed into the latter category of procedures.

also prevalent in patients with impaired frontal lobe function (Davidson & Glisky, 2002), although patients with poor medial temporal function have also shown deficits in familiarity. In PD patients, Davidson, Anaki, Saint-Cyr, Chow, and Moscovitch (2006) observed a decline in recognition memory and attributed it exclusively to a deficit in F using the three methods described above. More recently, Weiermann, Stephan, Kaelin-Lang, and Meier (2010) found similar results in a sample of PD and control subjects using two methods: the word-frequency mirror effect and remember/know judgments. The analysis of remember/know judgments suggested that PD patients were able to distinguish between new and old words in remember judgments, indicating intact R; however, they were not able to make this distinction in know judgments, revealing a deficit in F only with low-frequency words. These data demonstrated a deficit in familiarity but not in recollection estimates. Results of these two studies differ considerably from those of three studies whose authors used similar paradigms (Edelstyn, Mayes, Condon, Tunnicliffe, & Ellis, 2007; Edelstyn, Shepherd, Mayes, Sherman, & Ellis, 2010; Hay, Moscovitch, & Levine, 2002). Hay et al. (2002) used a process-dissociation procedure and did not find any impairment in R or F in early PD, whereas more advanced PD patients showed deficits in both. Edelstyn et al. (2007) used the remember/know technique and found deficits in R but not in F in PD patients. In a further study in which the effect of disease stage and medication was considered, Edelstyn et al. (2010) found no deficits in R or F in early PD but observed an impairment in R in moderate PD patients. In their sample, more advanced disease stages and medication intake were associated with poorer performance. To our knowledge, only one study has used an associative recognition task with a Parkinson's disease sample (Cohn, Moscovitch, & Davidson, 2010) as a way of assessing deficits in R. In their study, PD patients showed impaired R but intact F under deep encoding conditions but exhibited the opposite pattern under a shallower condition.

This contradictory state of affairs could be clarified by generally assessing the performance of PD patients in episodic tasks other than recognition. As previously stated, PD patients tend to perform poorly in free recall tasks. This has theoretically been attributed to a deficit in retrieval (Tröster & Fields, 1995). According to this hypothesis, memory deterioration is caused by a selective impairment at the retrieval stage due to problems evoking the information learned. If this is the case, deficits

should be found in R but not in F, as in the above-mentioned studies (Edelstyn et al., 2007; Edelstyn et al., 2010; Hay et al., 2002). Even if this hypothesis is considered less credible by arguing that possible deficits in the encoding process have more weight, this should still be differentially reflected in the R component of recognition (Bronnick, Alves, Aarsland, Tysnes, & Larsen, 2011; Higginson, Wheelock, Carroll, & Sigvardt, 2005) when measured. This is our interpretation of the data obtained by Higginson et al. (2005) using the California Verbal Learning Test, in which PD patients showed deficits in free recall, cued recall, and delayed recognition. The fact that patients were unable to use the help of cues suggests the existence of a deficit in R rather than F (see also Bronnick et al., 2011).

Finally, if R were impaired in PD, deficits in prospective memory should also be found. Prospective memory is the ability to remember future intentions. It is therefore a very conscious process that is closely related to R. Foster, McDaniel, Repovs, and Hershey (2009) suggested that early PD patients have impaired prospective memory for intention retrieval.<sup>2</sup> However, Katai, Maruyama, Hashimoto, and Ikeda (2003) found impairment only in event-based tasks, whereas Costa, Peppe, Caltagirone, and Carlesimo (2008) found impairment in the prospective component only in time-based tasks and impairment in the retrospective component in both tasks.

Estimating R and F involves methodological difficulties due to the use of indirect and sometimes subjective measures. Because of this, we used a very specific paradigm (Parkin et al., 2001) in a previous study (Algarabel et al., 2010) to assess whether F and R processes are preserved in PD patients or not. In this paradigm, subjects study words composed of a restricted set of letters of the alphabet (a, e, u, r, n, d, b, g, z, j, x, k, w) that are mixed in the recognition test with other words composed of an alternative set of letters (o, i, c, t, s, l, p, m, v, f, h, q, ñ). This nonoverlapping (NO) condition is compared to a condition in which the letters play no differential role in distinguishing studied words from nonstudied words (i.e., overlapping condition, O). Recognizing words composed of overlapping letters implies using R and F in an unspecified combination. Yet, recognition in the nonoverlapping condition involves an

<sup>2</sup>Prospective memory can be studied using time-based tasks (i.e., the subject has to perform an action at a given time) or event-based tasks (i.e., the subject has to perform an action when a specific event occurs).

additional type of F based on the perceptual fluency<sup>3</sup> that results from letter manipulation. Such manipulation is under precise experimenter control. The difference between participants' results in the overlapping and nonoverlapping conditions yields an estimate of the generated perceptual F that participants are using to respond. If we assume that patients with PD are able to benefit from this perceptual fluency, we can expect to find intact F. If, on the other hand, patients have deficits in the F process (as in Davidson et al., 2006; Weiermann et al., 2010), we should find no differences or smaller differences between the NO and O conditions. We assessed patients with early PD, advanced PD, dementia with Lewy bodies, and PD with dementia. Results indicated that patients with early PD, advanced PD, and dementia with Lewy bodies used F to improve recognition to a similar extent as control groups. Unlike these groups, PD patients with dementia were not able to benefit from F (Algarabel et al., 2010). However, some of the groups that exhibited similar F scores had lower general recognition scores. We attributed this deficit indirectly to a decline in R.

### THE PRESENT STUDY

As described above, the literature on Parkinson's disease shows many inconsistencies. Some studies support the idea of a deficit in F but not in R (Davidson et al., 2006; Weiermann et al., 2010); others confirm the existence of a deficit in R (Edelstyn et al., 2007; Edelstyn et al., 2010; Hay et al., 2002); finally, the results of our previous study (Algarabel et al., 2010) demonstrated the ability of PD patients to use perceptual F. Considering the previous state of affairs, the aim of the present study was to determine whether PD patients show deficits in R but not in F when both are based on conceptual grounds (see, for example, Lanska, Olds, & Westerman, 2014). We estimated R directly by using an associative recognition paradigm that it is typically considered to involve only R when applied with the appropriate parameters (Wixted et al., 2010). We extended our research on perceptual F (Algarabel et al., 2010) to the study of conceptual F in PD by using a modified two-alternative forced-choice (2AFC) test. According to the rationale explained in this

introduction and the results of our previous study (Algarabel et al., 2010), we expected to find deficits in R (associative recognition phase) and intact conceptual F (2AFC phase).

## Method

### Participants

The study sample included 20 patients diagnosed with idiopathic Parkinson's disease, 16 elderly healthy controls, and a group of 22 young healthy controls. The group of young healthy individuals was included in the study as a reference to clarify the response pattern expected in this experimental task in a population with optimal cognitive performance. All participants except young healthy controls underwent a thorough neuropsychological assessment. This evaluation was conducted in a single experimental session of about two and a half hours or two sessions if participants showed fatigue. Participants were tested in a quiet room at the outpatient clinic or at home. All PD patients were tested during the "on" state of their medication cycle. Both groups of interest (i.e., elderly controls and PD patients) were equated in age, education, and general intelligence. Demographic data on the three groups are provided in Table 1.

Patients with PD were recruited from the Neurology Unit of the General Hospital of Valencia, Spain, and the Provincial Association of Parkinson's Disease Patients in Linares, Jaén

**TABLE 1**  
Demographic data of the different experimental groups

Demographic characteristics	Controls		
	Young healthy (n = 22)	Elderly healthy (n = 16)	Parkinson's disease (n = 20)
Age (years)	21.68 (7.6)	72.31 (13.2)	71.45 (7.4)
Education in years	16.14 (4.4)	7.84 (4.9)	6.05 (4.3)
Sex (M/F)	5M/17F	4M/12F	10M/10F
MMSE score	—	27.19 (2.5)	26.60 (1.7)
GDS-15	—	2.50 (2.2)	4.15 (2.2)
I subtest of WAIS-III <sup>a</sup>	—	10.93 (2.6)	9.67 (2.6)
Duration of illness (years)	—	—	5.32 (3.0)
Hoehn and Yahr rating	—	—	1.95 (0.9)

*Notes.* Means; standard deviations in parentheses. M = male; F = female; GDS-15 = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; I subtest = Information subtest.

<sup>a</sup>Thirty participants out of a total of 36 completed this test.

<sup>3</sup>Fluency is defined as the easiness with which we process a particular stimulus. It could have several origins. In this paper we are interested in the fluency originated by perceptual quality or by the meaning of the stimulus. Fluency is an important contributor to the sense of familiarity.



province, Spain. PD diagnosis was based on the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria (Hughes, Ben-Shlomo, Daniel, & Lees, 1992; Hughes, Daniel, Kilford, & Lees, 1992). These criteria require the presence of at least two of the following three symptoms: (a) resting tremor, (b) rigidity, and (c) bradykinesia. In addition, (d) a good response to levodopa is a further criterion. The average score for describing the severity of PD symptoms using the Hoehn and Yahr rating scale (Hoehn & Yahr, 1967) was 1.95 ( $SD = 0.9$ ; range = I to III) with a mean of 5.32 years since initial diagnosis ( $SD = 3.0$ ). At the time of the assessment, all PD patients were outpatients receiving medical treatment with a dopamine agonist and/or L-dopa. We used the following exclusion criteria for this group: suspicions of Parkinsonism conditions other than Parkinson's disease, such as Parkinson-plus syndromes or pharmacological parkinsonism; inadequate response to antiparkinsonian medication; cognitive impairment defined by a score less than 24 in the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975); diagnosis of Parkinson's disease with dementia based on the recommendations of the Movement Disorder Society (Emre et al., 2007); other neurological diseases such as degenerative dementia or cerebrovascular disease; a history of visual hallucinations; or the presence of depression. The elderly control group was composed of people living independently in their community or in a nursing home. They all had good hearing and vision. Exclusion criteria for this group were an MMSE <24, use of psychotropic medication, or presence of a neurological disease. Informed consent was obtained from all participants prior to their inclusion in the study.

For the purposes of the present study, PD patients and elderly healthy participants underwent the following psychometric tests:<sup>4</sup> (a) MMSE (Folstein et al., 1975; 36); (b) a short version of the Geriatric Depression Scale (GDS-15; Sheikh & Yesavage, 1986; 36); (c) the Information and the Digit Span subtests of the Wechsler Adult Intelligent Scale-III (I and DS; Wechsler, 1997a; 30 & 27, respectively); (d) the Logical Memory subtest of the Wechsler Memory Scale-III (LM of WMS-III; Wechsler, 1997b; 31), and the *Test de Aprendizaje Verbal España-Complutense* (Spanish

Complutense Verbal Learning Test, TAVEC; Benedet & Alexandre, 1998; 28); (e) the Rey-Osterrieth Complex Figure Test (ROCF; Rey, 1941; 35); (f) the Trail Making Test (TMT; Reitan, 1958; 36 Part A, and 26 Part B); (g) the Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993; 35), and the Stroop Color-Word Test (SCWT; Golden, 1978; 30); and (h) the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983; 29).

### Materials and procedure

We created a task in which participants had to complete two phases in sequence uninterruptedly. In the first phase, participants were exposed to a seven series of associative recognition study-test cycles in order to estimate their R abilities. In the second phase, participants had to perform a 2AFC test to estimate conceptual F. We defined conceptual F as the increased fluency originated by the processing of meaning. If the processing of a specific meaning increases its fluency, such fluency is likely to extend to related concepts, which should benefit from it.

Materials included 238 Spanish nouns of between three and eight letters long, selected from an initial database of 14,000 words (Alameda & Cuetos, 1995). A total of 196 of these words were used to create seven study lists composed of 14 word pairs each. Words in the study lists were selected minimizing the semantic or phonological relationships among them. To achieve this, each word was compared one by one with the remaining words in the study lists according to association norms (Algarabel, Sanmartin, Garcia, & Espert, 1986). Additionally, two of the authors independently checked each word in the experiment database trying to minimize the semantic relationships between them. All study lists were equated in mean frequency and length (Alameda & Cuetos, 1995).

In the associative recognition phase, participants were instructed to read all the word pairs (14 word pairs in each list) and try to memorize them together in preparation for a subsequent memory test. One of these 14 word pairs was included at the beginning and another at the end of each list to mitigate the primacy and recency effects, but these were never tested. Word pairs were presented side by side in the center of the computer screen for 2 seconds. The experimenter read each pair of stimuli aloud to the elderly healthy and PD participants to ensure that all the stimuli were studied. Following each study list, participants completed an associative recognition test that consisted of presenting the same word pairs, half of them intact

<sup>4</sup>Not all participants completed the neuropsychological assessment in full due to motor, visual, or hearing alterations or because they failed to keep the second appointment to conclude the assessment. Therefore, the last number in the parentheses indicates the total number of participants who completed each test.

and the other half rearranged (6 intact and 6 rearranged pairs). Participants were required to decide whether the word pair had appeared together previously as such or not. As in the previous case, the experimenter read the stimuli aloud to ensure that all stimuli were understood and that participants responded to them. Young healthy controls (or the experimenter in the elderly and PD patient groups) pressed the letter “K” for “intact pair” and the letter “D” for “rearranged pair.”

The 2AFC phase consisted of the random appearance of 42 additional word pairs divided into two conditions: “old–new” (O–N) and “new’–new” (N’–N). The O–N condition included 21 word pairs composed of a studied word and a completely new word that was unrelated to other word presented in the experiment. Studied words in the O–N word pairs were selected from each of the seven studied lists (i.e., three words from each list) and were presented in the same position in which they had been studied (i.e., right or left in the original word pair). The N’–N condition included 21 word pairs. One of the words in each pair (N’ word) of this condition in the 2AFC test was conceptually related to a previous studied word presented in the studied lists presented in the associative recognition phase (three words from each studied list to make the final 21 trials). The other word of the N’–N pair (N word) was new and minimally related to the rest of words presented in the experiment. Examples of associated words selected are “*griego–latín*” (“Greek–Latin”), “*día–fecha*” (“day–date”), or “*lápiz–*

*punta*” (“pencil–tip”). Thus, participants could have studied words like “*latín*” (“Latin”), “*fecha*” (“date”), or “*punta*” (“tip”) in the study lists and subsequently be tested with “*griego*” (“Greek”), “*día*” (“day”), or “*lápiz*” (“pencil”) in the 2AFC test (see Table 2). These words were selected according to the Spanish association norms (Algarabel et al., 1986), which provide the most frequent associatively related word responses given by a sample of university students.

In sum, the 2AFC test consisted of 42 randomized trials. In half of those trials, one of the words had been studied while the other word was new (21 O–N word pairs); in the other half, one of the words (N’ word) was conceptually related to a studied word while the other was new (21 N’–N word pairs). Thus, three words were selected from each study list, making a total of 21 O words, which were used to generate the O–N word pairs. Three additional words were selected also from each study list to generate 21 N’ words, which made up the N’–N word pairs.

For the 2AFC phase, participants were led to believe that in all cases one of the words had been studied but the other had not. Participants had to choose which of two words now presented had been “studied” in the associative recognition phase. They had to decide whether the previously “studied” word was the one presented to the left or right of the pairs using the “D” and “K” keys, respectively. Each word pair appeared on screen until a response was given. Elderly participants gave their answer aloud, and the experimenter

TABLE 2  
General experimental procedure with a study-test example list and partial 2AFC test

<i>Associative recognition phase</i>									
<i>Study 1</i>	<i>Test 1</i>	<i>Study</i>	<i>Test</i>	<i>Study 7</i>	<i>Test 7</i>	<i>2AFC phase</i>			
1 cactus–miner	1 speck–tapestry	R	...	...	...	1	may–pencil	N’–N	
2 thorn–hoop	2 <b>Latin</b> –scratch	I	...	...	...	2	mind–parrot	O–N	
3 eye–tip	3 puzzle–date	R	...	...	...	3	cigarette–scarf	O–N	
4 cigarette–twin	4 cigarette–twin	I	...	...	...	4	grandfather–day	N’–N	
5 lead–dowry	5 moneybox–rise	R	...	...	...	5	<b>Greek</b> –war	N’–N	
6 <b>Latin</b> –scratch	6 eye–tip	I	...	...	...	6	dolphin–cherry	O–N	
7 sauna–parrot	7 trophy–dowry	R	...	...	...	7	...		
8 wheel–leg	8 dolphin–palm	R	...	...	...	8	...		
9 dolphin–rise	9 sauna–parrot	I	...	...	...	9	...		
10 speck–date	10 lead–germ	R	...	...	...	10	...		
11 puzzle–palm	11 wheel–leg	I	...	...	...	11	...		
12 moneybox–germ	12 thorn–hoop	I	...	...	...	12	...		
13 trophy–tapestry	...	...	...	...	...	13	...		
14 canopy–oak	...	...	...	...	...	...	...		
						42			

Note. 2AFC = two-alternative forced-choice; R = rearranged pair; I = intact pair; N’–N = new’–new condition; O–N = old–new condition. Words in bold correspond to the selected pair according to the association norms for Spanish words (Algarabel, Sanmartín, García, & Espert, 1986); words in italics are studied words used in the “O–N” condition.

pressed the appropriate key to avoid errors. The O–N and N’–N word pairs were combined to prevent participants from discovering that some word pairs did not include “studied” stimuli. The “conceptually” related words presented in the N’–N condition—which participants selected thinking that they had studied them—allow us to obtain an estimate of conceptual F. If these N’ words elicited a feeling of F, they should be easily processed without evoking any past specific contextual detail. To test this, after each pair was presented in the 2AFC test, participants estimated the list position they thought the chosen word occupied in the associative recognition phase (i.e., whether the word selected by the participants as the studied word appeared in Study Lists 1, 2, 3, 4, 5, 6, or 7). Since F is an automatic process without any contextual information, the procedure was expected to correctly estimate F if participants selected the conceptually related word and were not able to provide accurate contextual information about it. If this were the case, we would confidently conclude that participants were responding based on F. Each answer given by the participant was hand-recorded by the experimenter. After the test, participants were asked about the task to try to find out whether any of them had any suspicions about the presentation of the stimuli. None of them expressed that they thought both words were new in any pair.

In conclusion, participants were exposed to seven study–test lists in the associative recognition phase and to the 42 trials of the 2AFC phase, with 21 word pairs in the O–N condition and another 21 in the N’–N condition. Stimulus presentation was randomized and conducted by a computer running E-Prime software (Schneider, Eschman, & Zuccolotto, 2002) in Courier New 35-point font in black letters on a white background. Two versions of the task, which only differed in the tested stimuli, were created and were counterbalanced across subjects. Elderly participants were tested individually. Young controls were tested in groups of up to eight participants.

### Statistical analysis

We compared the neuropsychological performance of PD patients and healthy controls using *t* tests. The basic dependent variable in the analysis of associative recognition data was hits (i.e., proportions of trials in which a studied pair was identified as “studied together”) minus false alarms (i.e., proportions of trials in which unpaired words were identified as “studied together”). To

better interpret the results of the associative recognition test, we also analyzed hits and false alarms separately. We compared the performance of elderly controls and PD patients using independent *t* tests. In all cases *t* tests were one-tail because we always expected to show a deficit in the case of the contrasts between healthy and PD patients and a superiority in the contrast between the young and elderly healthy samples. We tested the equality of variances assumption every time and applied the appropriate corrections when the assumption was not met. In the 2AFC test, we used proportion correct as a discrimination index.<sup>5</sup> Effect sizes are shown when appropriate (Cohen’s *d* for *t* tests and  $\eta^2$  for analyses of variance, ANOVAs). We compared list position estimation data using within-subject analyses of variance. The significance level was established at .05 unless otherwise indicated.

We defined false alarms arbitrarily as the proportion of times that participants chose the left response when the right response was the correct one (see Macmillan & Creelman, 1991, p. 121). As we obtained exactly the same results as when using raw proportion correct, and the latter is user friendlier, we conducted the analysis with proportion correct.

### Results

The neuropsychological evaluation indicated that PD patients showed more depressive symptoms (GDS-15), poorer executive function (WCST), and deficits in attentional set-shifting ability (TMT, Part B), as well as learning and memory (LM of WMS–III), than did their controls. By contrast, both groups were equal in denomination (BNT), visuoconstructive skills (ROCF), sustained attention (TMT, Part A), working memory (DS), and interference control ability (SCWT). Overall, PD patients exhibited poorer performance in tests assessing frontal cognitive functions and measures of recall.

As indicated previously, the young control group was mainly introduced as an important reference to compare list position estimation data to those of both elderly samples. Preliminary

<sup>5</sup>For the 2AFC test, several raw data transformations can be performed to analyze the effect of the independent variables (see Macmillan & Creelman, 1991, p. 120 on). First, we analyzed the data transforming the choice proportions:

$$d' = \frac{1}{\sqrt{2}}(Z(\text{Hits}) - Z(\text{False Alarms}))$$



TABLE 3

Means in associative recognition and two-alternative forced-choice tests on old–new and new’–new words for the three samples of participants

Groups	Associative recognition			2AFC test	
	Hits	False alarms	Hits – false alarms	Old–new	New’–new
Young controls	.83 (.12)	.13 (.11)	.72 (.18)	.93 (.05)	.65 (.11)
Elderly controls	.68 (.18)	.48 (.24)	.20 (.24)	.72 (.15)	.56 (.13)
PD patients	.61 (.19)	.56 (.18)	.06 (.09)	.69 (.10)	.55 (.10)

Note. Means; standard deviations in parentheses. 2AFC = two-alternative forced-choice; PD = Parkinson’s disease; new’ = related word.

analyses indicated that elderly controls and PD patients were equal in age,  $t(34) < 1$ , *ns*, education,  $t(34) = 1.17$ ,  $p = .25$ , and general intelligence,  $t(28) = 1.32$ ,  $p = .20$ . However, young healthy controls had more years of education than elderly controls,  $t(36) = 7.09$ ,  $p < .01$ . Below, we analyze the associative recognition data (i.e., R estimation). Next, we discuss participants’ performance in the 2AFC test of O words followed by the choice of N’ words (i.e., F estimation). Finally, we analyze position estimation data to operationally reinforce the F dependent measure. Table 3 shows the main results obtained in the experimental task as a function of group and condition.

As expected, young healthy controls performed better than elderly controls in the associative recognition test, a critical measure that has revealed that performance declines with age. This is shown by the analysis of hits minus false alarms,  $t(36) = 7.48$ ,  $p < .01$ ,  $SEM = .07$ ,  $d = 2.4$ . This significant effect<sup>6</sup> was due to the fact that young healthy controls had fewer false alarms,  $t(29) = 5.50$ ,  $p < .01$ ,  $SEM = .06$ ,  $d = 1.89$ , and a greater number of hits,  $t(36) = 3.13$ ,  $p < .01$ ,  $SEM = .05$ ,  $d = 0.99$ . After comparing the young and elderly healthy samples, we compared both elderly samples to determine whether PD patients showed any deficits in R according to this test. The analysis showed that PD patients performed worse in hits

minus false alarms,  $t(18) = 2.30$ ,  $p < .05$ ,  $SEM = .06$ ,  $d = 0.81$ , although neither hits,  $t(34) = 1.01$ ,  $p = .16$ , nor false alarms,  $t(34) = 1.15$ ,  $p = .13$ , showed any significant differences.

The analysis in the 2AFC test indicated that young controls were more accurate than elderly controls in the condition in which one of the words had been studied,  $t(18) = 5.42$ ,  $p < .01$ ,  $SEM = .04$ ,  $d = 1.89$ , replicating the difference previously found in the associative recognition test (i.e., that recognition abilities decline with age). However, PD patients performed similarly to controls,  $t(25) < 1$ ,  $p = .24$ . More importantly, our estimate of F in the 2AFC test conducted with N’ words showed significant differences between both healthy samples,  $t(36) = 2.27$ ,  $p < .05$ ,  $SEM = .04$ ,  $d = 0.73$ , but did not show any differences between the PD sample and its control group,  $t(34) < 1$ ,  $p = .37$ . A one-tailed *t* test comparing the performance of PD patients against chance (.50) revealed significant differences,  $t(19) = 2.04$ ,  $p < .05$ ,  $SEM = .02$ ,  $d = 0.46$ , indicating that PD patients were able to respond on the basis of F. It should be noted that the null difference between both elderly samples was recorded in the context of a significant effect found as a function of age (young vs. old control groups). Most studies do not find F differences as a function of age (e.g., Parkin et al., 2001; Yonelinas, 2002), suggesting that we had enough experimental sensitivity to detect an effect. A power analysis of this null effect indicated that, within the conditions of the experiment, we had a power of .80 to detect a .10 difference between both conditions. We should also point out that in a previous paper (Algarabel et al., 2010) we observed a nonsignificant tendency to get a F deficit in PD when years from initial diagnosis increased.

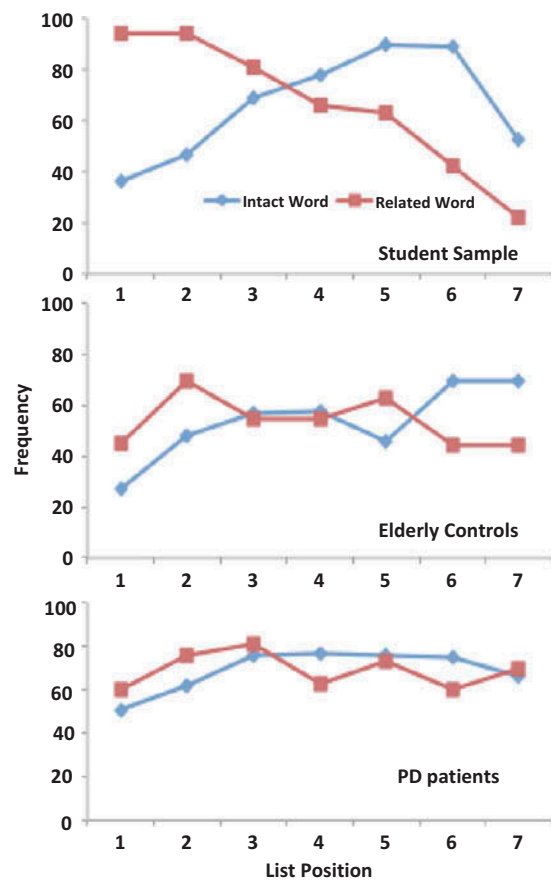
A possible criticism of the operational definition of conceptual F used in this study could be that participants may bring to mind the original studied word related to the new word presented rather than use F as a basis for their responses. If this were the case, the response would not reflect F but rather

<sup>6</sup>An analysis of covariance (ANCOVA) controlling for education yielded the same result—that is, a significant effect,  $F(1, 35) = 8.78$ ,  $MSE = .04$ ,  $p < .01$ . The use of an ANCOVA may be debatable (see Miller & Chapman, 2001), given that the independent variable was selected and not experimentally manipulated. It should be noted that the use of an ANCOVA is appropriate despite the selected nature of the independent variable when the covariate is not part of the definition of the independent variable. We consider that this was the case. Yet, as indicated in the text, the comparison of interest was between the two elderly groups that were equated. Nevertheless, the ANCOVA of hits was marginally significant,  $F(1, 35) = 3.27$ ,  $MSE = .023$ ,  $p = .079$ , and very similar to that of false alarms,  $F(1, 35) = 3.25$ ,  $MSE = .025$ ,  $p = .08$ .

some sort of R of the originally studied word. If so, we should find a similar pattern of list estimations as a function of choice test condition (O–N vs. N’–N), given that a word had been presented in one condition (O word) but no words had been presented in the other (N’ word). In other words, the estimation function for actually presented words should be similar to that of totally new words, except perhaps with a difference in accuracy. Figure 1 shows these functions separately for each group and type of test. To clarify this important point, we analyzed position estimation provided by participants as a function of original list position in the associative study phase. We hypothesized that if new related words were reminders of each actually presented stimulus, the function relating list position and frequency would be similar. By design, the number of “parent” words chosen across list position was identical (i.e., 3 per studied list). If subjective and objective estimations were similar, we expected to find a nonsignificant interaction between list position and word status (i.e., “N’ word” vs. “O word”). The 2 (2AFC condition) × 7 (list position) within-subject ANOVA of proportion of correct responses revealed a highly significant interaction in healthy young participants,  $F(6, 126) = 10.40, MSE = .008, p < .01, \eta^2 = .72$ , and elderly controls,  $F(6, 90) = 3.00, MSE = .006, p < .01, \eta^2 = .17$ , but not in PD patients,  $F(6, 114) = 1.08, MSE = .008, ns$ . These interactions are displayed in Figure 1, showing very clearly that the better the memory of participants, the more dissimilar were the estimation functions built from the position information provided by the participants.

As regards the performance of young participants, regardless of their accuracy, they biased the location responses of studied words to the most recent list positions. Participants probably consider that if they remember anything about a word it is because it was recently viewed. The opposite pattern was observed in words that had never been presented but were related to studied words (i.e., words used to estimate conceptual F). This response pattern changed with group because participants’ memory of word presentation declined, and responses to conceptually related words that were based on F alone declined as well.

We were also able to compute an objective measure of error, taking into account participants’ estimate and the actual position of the presented word in absolute terms.<sup>7</sup> The 2 (2AFC condition)



**Figure 1.** List position estimation given by all participants in the two-alternative forced-choice (2AFC) test as a function of study status. The rhombus line refers to actually studied and presented word in the associative recognition phase; the square line refers to related but not actually presented words (new’–new words). To view a color version of this figure, please see the online issue of the Journal.

× 7 (list position) interaction with the Greenhouse–Geisser correction produced a significant effect,  $F(4, 84) = 12.42, p < .01, MSE = .94, \eta^2 = .37$ . This indicates that the computed error was greater in the last positions of the list in conceptually related words than in studied words. This pattern of errors was reversed in the early positions of the list. The interpretation of this interaction is that most participants considered that related words were presented in the initial position of the lists because they were not able to recall anything about them. Again, this confirms that participants chose the related word even though they did not have accurate information about a very relevant contextual detail: the list position of the word used as stimulus. A similar although less marked result was found in healthy elderly controls,  $F(6, 120) < 1, ns, MSE = 0.91$ . This pattern of results was not found in the PD group,  $F(6, 120) < 1, MSE = 1.18, ns$ .

<sup>7</sup>Absolute values are greater at the extremes than at the center of the lists. This is why we only based our interpretations on the List × Study interaction as a function of group.

## Discussion

Our study was designed to explore R and F processes in patients with nondemented Parkinson's disease using associative recognition and 2AFC tests. As expected, our results confirm that PD patients show deficits in memory performance when these tasks draw heavily on R but show little or no impairment when responses are based on F. Our data support the conclusions reached in the meta-analysis conducted by Whittington et al. (2000). These authors identified the presence of dementia, disease stage, and task difficulty, among others, as major factors associated with studies revealing statistically significant deficits in PD patients responding to a recognition test (Whittington et al., 2000). Our previous study (Algarabel et al., 2010) indirectly revealed a non-significant trend toward observing deficits in R with number of years since diagnosis. We expected episodic memory to be the same in PD patients as in the general population at very early stages of the disease, as shown by Hay et al. (2002) or Edelstyn et al. (2010), who found no difference between the performance of patients with early PD and that of their control groups, and the memory deficits begin to appear as the disease progresses, as seen in patients with advanced PD (Edelstyn et al., 2007; Edelstyn et al., 2010; Hay et al., 2002). These deficits are more visible in tasks that rely heavily on R or have greater difficulty. Thus, the more R is involved in a task, as happens with associative recognition, the more self-initiated strategies participants must bring into play to generate a response. However, when it is possible to use F for recognition because the task requires fewer cognitive resources, it is more difficult to detect possible deficits.

Several temporal medial lobe regions are crucial in recognition memory. Neuroimaging studies have shown that activity in the hippocampus and the parahippocampal cortex is related to R, while activity in the perirhinal cortex is associated with F (Davachi, Mitchell, & Wagner, 2003; Ranganath et al., 2004). According to the Braak model (see Braak et al., 2003), the alterations begin in the dorsal motor nucleus and the intermediate reticular zone (Stage 1), affecting the caudal raphe nuclei, the gigantocellular nucleus, and the coeruleus-subcoeruleus complex at Stage 2. The pathological process extends into the substantia nigra of the midbrain at Stage 3. At this point, there is also damage in the hippocampus, extending to the anteromedial temporal mesocortex at Stage 4. However, there is relative sparing of lateral perirhinal areas. In the two final stages (Stages 5 and

6), the lesions reach from anteromedial temporal mesocortex into the sensory association areas of the neocortex, the prefrontal neocortex, and premotor areas. The severity of lesions in the amygdala, the hippocampal formation, and the anteromedial temporal mesocortex increases during these final stages. We believe that this model is consistent with the idea that, if recognition memory is impaired, the impairment should be primarily in the R component.

The finding of deficits in R is also congruent with the well-established fact that PD is generally characterized by deficits in executive function. Therefore, a possible explanation for the inconsistent results about R and F processes found in the literature could be related to the executive deficit variability shown by these patients. PD patients are characterized by a loss of dopamine that causes frontostriatal dysfunction (Cools, Stefanova, Barker, Robbins, & Owen, 2002; Owen, 2004). This explains their pattern of executive deficits. Dopamine also plays an important role in human episodic memory formation (Schott et al., 2006). A functional magnetic resonance imaging study (Yonelinas, Otten, Shaw, & Rugg, 2005) has revealed the involvement in the R process of various brain regions including the anterior medial area of the prefrontal cortex, the lateral parietal/temporal region, the posterior cingulate, and the hippocampus; by contrast, the anterior and dorsolateral prefrontal cortex, the superior parietal region, and the precuneus have been associated with F (Yonelinas et al., 2005). It is known that dorsolateral areas are involved in executive function and working memory (Petrides & Milner, 1982).

Concerning F and taking into account the methodological problems associated with its measurement, we decided to design a similar procedure to that used with perceptual F (Algarabel et al., 2010; Parkin et al., 2001). We tried to minimize the chances that patients "had seen the word" previously by ensuring that there was no relevant contextual information from the study situation. Our estimate of conceptual F was based on the proportion of times that each participant selected the new and conceptually related word compared to an also new and unrelated word in a 2AFC test. We introduced the additional constraint that the participant should not notice that the word had not been previously presented and that the list location information was inaccurate. This latter restriction was set to counteract the possible criticism that participants really had in mind the original word we had used to find the related word. The statistical analysis revealed a nonsignificant drop in

conceptual F as a function of group, as expected according to our literature review (Algarabel et al., 2010; Edelstyn et al., 2007; Edelstyn et al., 2010; Hay et al., 2002; Weiermann et al., 2010).

Results obtained in the 2AFC test on studied words are also discussed below. This condition was mainly introduced to reduce the chances that participants would notice that both members of some pairs were new in the F estimation condition. It is worth noting that, given the difficulty in selecting the appropriate number of stimuli for the experiment, the 2AFC test included words already tested in the associative test. Therefore, we ran two consecutive tests with some stimuli in common. In the first, some words were associated with one another, and the association was tested; in the second, those words were tested individually. Therefore, on both occasions a restricted set of stimuli was tested for two different aspects of the memory trace: an associative dimension and an item dimension. The fact that these two stimuli dimensions were available to participants in the 2AFC test strengthened the view that the more R plays a role in recognition, the greater the chances of finding a significant difference when comparing the performance of young participants to that of elderly participants. In this case, young participants may have used their better associative capabilities to confirm the previous presence of a stimulus in the 2AFC test with greater accuracy.

Several previously reviewed studies support the idea that F is more impaired than R in patients with PD (Davidson et al., 2006; Weiermann et al., 2010). Such results are contrary to others that confirm that F is intact while R is impaired (Edelstyn et al., 2007; Edelstyn et al., 2010; Hay et al., 2002). Our analysis of the performance of PD patients in episodic tasks other than recognition also suggests that, if recognition memory is impaired, the impairment should primarily be found in the R component. A possible explanation for this conflicting evidence may be related to the possible different encoding strategies that participants may have used in different experiments. This is the possible explanation for the results obtained by Cohn et al. (2010). When the encoding of information is intentional and targeted, R seems to be altered but F is preserved; by contrast, when encoding is shallow, the opposite pattern is found. This pattern of results is also congruent with the simultaneous presence of deficits in executive function and the subsequent difficulties of using encoding strategies. However, another possible explanation for the conflicting evidence found in the literature is methodological, as argued above. Consequently, one of the purposes of this

study was to assess R and F using direct tasks that minimized the number of assumptions made. This is why we chose an associative recognition test to assess R. Our results confirm the appearance of a R deficit with age and PD. In our study, participants were also instructed to read the word pairs and try to remember them in a later recognition test (similarly to the “read” condition of Cohn’s study). We were not able to confirm Cohn’s results. Yet, the differences in performance between both healthy groups replicated previous results (Naveh-Benjamin, 2000; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003; Overman & Becker, 2009), showing that elderly people exhibit deficits in the R component (particularly in explicit long-term memory tasks) but not in F.

Several authors have considered the possibility that certain associative recognition tasks may be based on F when participants form associations between items with the help of unitization (Giovanello, Keane, & Verfaellie, 2006; Quamme, Yonelinas, & Normani, 2007). This is a possible explanation for the results found in Cohn’s study, in which participants had to encode word pairs as sentences and may have stored this information as a unit (Cohn et al., 2010). Recently, Ford, Verfaellie, and Giovanello (2010) found that distinct cerebral regions support retrieval of related versus unrelated stimulus compounds; recognition of related stimuli was associated with activity in the left perirhinal cortex, while recognition of unrelated stimuli was associated with activity in the left hippocampus. If this is the case, participants who are able to associate both words in a stimulus pair are using F completely or partly in their responses.

Finally, we would like to point out some of the possible limitations of the present study. First, from the statistical point of view, we have argued repeatedly about the consistency of the present results with regard to the experimental literature and in relation to the steps taken to warrant the power requirement to defend a null effect. However, our reasoning may not be accepted by everyone. Therefore, further confirmatory studies underway may settle this possible issue in the near future. This issue may be complicated by the fact that familiarity effect sizes, as measured in the experimental task used in this research, are weak and therefore difficult to detect in older populations. Secondly, Parkinson’s population is heterogeneous, and the existence of cognitive impairment or dementia associated with Parkinson’s disease in some of these patients may be a factor that needs to be taken into consideration to explain the contradictory data reported in the literature.

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