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Improving Delayed Face Recognition in Alzheimer's Disease by Differential Outcomes

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Objective: Previous studies have demonstrated the benefit of the differential outcomes procedure (DOP) in human learning. In the present study we aimed to explore whether the DOP might also help to overcome the face recognition memory deficit commonly observed in Alzheimer's disease (AD) patients. ***Method:*** A delayed matching-to-sample task was used. Participants were instructed to choose which of the 4 alternative faces (comparison stimuli) matched the previously seen face (sample stimulus). Either short (5 seconds) or long (25 seconds) delays were interposed between the sample and the comparison stimuli. In the differential outcomes condition each sample face was paired with its own outcome. In contrast, in the nondifferential condition, outcomes were randomly arranged. ***Results:*** The differential outcomes effect (DOE) was evident in the AD patients with both accuracy and latency data. That is, they showed a significantly better and faster delayed face recognition when differential outcomes were arranged. The analyses also revealed a significant main effect of delay; participants were slower in the 25 seconds condition than in the 5 seconds condition, but the difference was higher in the patients than in the controls. ***Conclusions:*** These findings demonstrate, to our knowledge for the first time, that face recognition memory in patients with Alzheimer is improved when differential outcomes are used and draw attention to the potential of this procedure as a therapeutic technique.

Keywords: Alzheimer's disease, differential outcomes effect, memory, therapeutic aid

It is well known that Alzheimer's disease (AD) is the most common form of dementia, affecting millions of older people around the world. Since the initial phases, the progressive decline of memory has been the symptom usually detected and associated with this disease. Memory, however, has multiple components and processes, and not all of them are affected to the same degree in AD. It has been demonstrated that explicit memory deficit is common in Alzheimer's disease patients. In fact, the loss of episodic memory, one type of explicit memory, is considered the cardinal symptom usually detected and associated with this disease (Gainotti, Marra, Villa, Parlato & Chiaretti, 1998; Grady et al., 1988). This kind of memory refers to autobiographical information for specifics events embedded in a temporal context. Another type of explicit memory, semantic memory (stored information about ideas, meanings, and concepts which are not related to personal experiences), is also disrupted in AD (Alathari, Ngo & Dopkins, 2004). By contrast, implicit memory system, which refers to the automatic acquisition of verbal and nonverbal knowledge or skills (i.e., procedural knowledge) in the absence of conscious recollection of the content, and the circumstances in which learning has taken place, has been shown to be relatively well preserved until the later stages of the disease (Rogers et al., 2000).

Intact implicit memory has been exploited by different authors for memory rehabilitation purposes (for a review, see De Vreese, Neri, Fioravanti, Belloi & Zanetti, 2001). The procedures include the expanding rehearsal technique (Landauer & Bjork, 1978), the method of vanishing cues (Glisky, Schacter & Tulving, 1986), and the errorless learning procedure (Wilson, 1999). In the present study we aim to explore a simple procedure that has been stated to rely on the implicit memory system that might be useful to ame-

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liorate some of the explicit memory deficits commonly associated with AD, we refer to the differential outcomes procedure (DOP).

The DOP comes originally from the animal learning tradition (Goeters & Blakely, 1992; Trapold, 1970). Basically the procedure consists in associating a sample stimulus/correct choice combination of a discrimination task with a distinct outcome. When this training procedure is applied, learning is faster and final accuracy is higher than when the outcomes are randomly presented (the nondifferential outcomes control procedure) (for a review, see Urcuioli, 2005).

The differential outcomes effect has been accounted for on the basis of the expectancy theory originally proposed by Trapold and Overmier (1972). According to this theory, under differential outcomes conditions, a conditioned expectancy of the upcoming reward is learned as a result of the unique discriminative stimulus-outcomes association. Such specific outcomes expectancies have functional stimulus-like properties than can serve as discriminative cues for guiding choice behavior. When nondifferential outcomes are used, the associations between the discriminative stimuli and the outcomes are not unique; that is, there is no predictive relation about what outcome will be given based on the discriminative stimulus, so that reward expectancies cannot be evoked to direct behavior.

The benefits of using the DOP have also been demonstrated in human populations (for a review, see Mok, Estévez & Overmier, 2010). With one exception (Dube, Rocco & McIlvane, 1989), it has been observed that normal children (Estévez, Fuentes, Mari-Beffa, González & Alvarez, 2001; Maki, Overmier, Delos & Gutman, 1995), children and adults with Down's syndrome (Estévez, Fuentes, Overmier & Gónzalez, 2003), children born prematurely (Martínez et al., 2012), adults with Prader-Willi syndrome (Joseph, Overmier & Thompson, 1997), and adults without mental handicaps (e.g., Miller, Waugh & Chamber, 2002; Mok & Overmier, 2007) learned conditional discriminations more readily when they received specific outcomes (a particular reinforcer) after their correct responses than when nondifferential outcomes were arranged.

Importantly for the purposes of the current study is that the DOP has also been used successfully in memory tasks (Savage & Langlais, 1995; Savage, Pitkin & Careri, 1999; Savage & Ramos, 2009). The mechanisms by which the DOP produces enhanced learning and memory performance are thought to rely on prospective memory. Retrospective recall of the particular discriminative stimulus (a cholinergic-dependent explicit memory system) is the only source of information that can guide correct choice behavior when nondifferential outcomes are arranged. In contrast, implicit memory processes can be used to solve the task when training under differential outcomes procedures, concretely prospective memory of what the upcoming reward will be (a glutaminergic-dependent memory system) (e.g., Overmier, Savage & Sweeney, 1999; Ramirez, Buzzetti & Savage, 2005; Savage, 2001; Savage & Parsons, 1997). Such prospective memory (or reward expectancy) elicited by the discriminative stimulus is thus critical to the enhancement of choice behavior observed in the differential outcomes condition. Given that performance based on reward expectancies appears to be less dependent on cholinergic mechanisms in animals (see Savage, 2001; Savage & Parsons, 1997; Savage & Ramos, 2009), the differential outcomes procedure might help to overcome memory deficits on those populations in which the cholinergic system is deteriorated, as in normal aging and AD (Schliebs & Arendt, 2006; Wenk, 2003). Accordingly, a recent study demonstrated that aged people trained with the DOP did not show the delay-related decline observed when nondifferential outcomes were used in an every-day task such as facial recognition. In fact, their performance was comparable to the level shown by younger adults (López-Crespo, Plaza, Fuentes & Estévez, 2009).

Two other published studies have explored the role of the DOP to improve memory in humans. In the first one, four patients with alcohol-related amnesia were trained to recognize which of two faces matched a previously seen face, a task that these patients found difficult to solve. Three of the patients showed improved recognition memory at a delay of 5 seconds when differential outcomes were arranged, and their performance did not differ from that of controls at that delay. At longer delays, however, patients showed low accuracy regardless of the type of training used (Hochhalter, Sweeney, Bakke, Holub & Overmier, 2001). More recently, in a study with healthy adults (Plaza, Estévez, López-Crespo & Fuentes, 2011), participants performed a face recognition memory task under four memory intervals (5, 10, 25, and 32 seconds). The results showed that when a difficult task was used, a significantly better delayed face recognition was observed under differential outcomes conditions.

Given the dramatic consequences that memory loss associated with AD has in patients' lives, more research is necessary to develop the potential utility of the DOP as a therapeutic technique to promote patients autonomy in daily activities to improve their quality of life. In the experiment reported here, we tested whether AD patients would improve their facial recognition memory when differential outcomes were arranged.

Method

Participants

Participants were eight healthy controls (HC) and eight patients with AD. The HC participants were recruited from the community and were free from serious medical conditions (i.e., heart disease, cancer, stroke, dementia, or drug and alcohol abuse). The AD participants were patients from the Dementia Unit at the University Hospital Virgen de la Arrixaca (Murcia, Spain). The diagnosis of AD was established at the Dementia Unit by an experienced neurologist (C.A.) and was based on a comprehensive evaluation protocol that included neurological and neuropsychological tests. The diagnosis was determined according to the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and Alzheimer's disease and Related Disorders Association (ADRDA) (McKhann, Drachmann, Folstein, Katzman, Price & Stadlan, 1984). For sake of exclusion/inclusion criteria, participants with AD also underwent MRI, CT, or SPECT to exclude other neurological causes of their cognitive deficits, and only patients in phase 4 of the Reisberg's global deterioration scale (Reisberg, Ferris, De Leon & Crook, 1982) were included in the study. Demographic information, cognitive functioning scores, and statistical differences between the two groups are presented in Table 1. All participants were equated in age and education, and all of them had normal or corrected-to-normal vision. We obtained written informed consent to participate in the study from the participants and patient's caregivers. The ethics committees of

Table 1

Demographic Information, Means of Neuropsychological Testing, and GDS Scores for Each Group

Socio-demographic data and tests	Maximum	HC	AD
n		8	8
Sex (F/M)		4/4	4/4
Age		75 (5)	76 (6)
Education (years)		7 (4)	7 (3)
MMSE***	30	29 (1)	17 (3)
GDS***	7	1 (0)	4 (0)
CERAD Battery			
Boston Naming test**	15	14 (1)	12 (3)
Word List Memory**	10	7 (1)	4 (2)
Word List Recall***	10	6 (1)	1 (2)
Word List Recognition***	20	19 (1)	15 (2)
Constructional Praxis*	11	11 (0)	9 (1)
Recall of Constructional Praxis***	11	10 (1)	3 (2)
Trail Making Test (part A)***		75 (24)	149 (36)
Trail Making Test (errors)		0 (0)	2 (2)
Barcelona Test (Subtests)			
Imitation of postures (Praxis)*	8	8 (0)	7 (1)
Semantic Fluency**		15 (4)	10 (3)
Phonological Fluency (P)**		13 (5)	5 (4)
Forward Digits Span**	9	5 (1)	4 (1)
Backward Digits Span***	8	4 (1)	2 (1)
Abstraction***	12	9 (1)	4 (1)
Random Letters Test (Errors)		0 (0)	1 (1)

Note. Figures in parentheses are *SD*. Trail Making Test Part B was not included because of the small number of records in this condition as a consequence of the low academic level of the patients and controls. The MMSE was corrected by age and education (24). MMSE = Mini-Mental State Examination; GDS = Global Deterioration Scale; CERAD = The Consortium to Establish a Registry for Alzheimer's disease; HC = healthy controls; AD = Alzheimer's disease.

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

both the Virgen de la Arrixaca Hospital and the University of Murcia approved this study.

Stimuli and Materials

The stimuli were eight half-length photographs of Spanish men dressed in suits, taken from a front perspective. They were grouped in two sets of four photographs each that served as the sample and the comparison stimuli for the two versions of the recognition task. All stimuli were presented on a white background on a tactile screen (15″ Active Matrix TFT-LCD monitor). The photographs measured 5.5 × 6.5 cm and could be displayed either individually in the center of the screen (sample stimulus), or grouped in a 2 × 2 grid (comparison stimuli) equidistant from the borders. The position of the photographs on the 2 × 2 virtual square was randomly arranged. Stimulus presentation and data collection were controlled by the E-Prime v. 1.1 software (Psychology Software Tools, 2002).

Primary and secondary reinforces served as outcomes. Four photographs of the prizes or primary reinforces (an umbrella, a scarf, a perfume, and a mug) that would be raffled off at the end of the experiment were used as secondary reinforces. They measured approximately 10 × 13 cm and were presented individually and immediately on the center of the screen along with the text "You may win a:" above the picture after a correct response. As previous studies have demonstrated raffling off the prizes is an effective way of assessing the effects of the differential outcomes procedure (López-Crespo et al., 2009; Miller et al., 2002; Plaza et al., 2011) that can avoid some undesired effects of delivering primary reinforces for each correct response such as satiation. Moreover, by using this methodology the training can be designed as a motivating game in which accuracy is encouraged. Accordingly, participants in the present study were told that the more accurate they were on their response, the more tickets for the raffle they would win and the more probabilities to win one of the prizes they would have. At the end of the study, all the participants received one of the prizes and an acknowledgment diploma for their participation.

Procedure

Pilot study: Two versions of the task. Because a within-subject design was used in the present study, two versions of a facial recognition memory task were designed by using two different set of four faces, regardless of which would be used in the differential outcomes or in the nondifferential outcomes condition. To check whether these two set of faces had the same difficulty level, 21 students from the University of Almería (Spain) (*M* age = 23.8, *SD* = 7.28) participated in a pilot study. Participants were asked to perform a delayed face recognition task within a single experimental session that consisted of two blocks of 24 trials each. Each block included faces from one of the two stimuli set. Correct responses were not followed by any outcome. The analysis showed no significant difference between the two blocks when accuracy or latency data were analyzed (91.3% vs. 91.5% and 2423 ms vs. 2330 ms, respectively) (*F*s < 1). This confirmed that both sets of face pictures had a similar level of difficulty.

Pretest. A pretest was administered to all participants before each experimental session to demonstrate that they could discriminate the faces that were to be used in the delayed recognition task. Thus, this phase served to rule out perceptual disorders. A two-choice discrimination task consisted in 12 identity trials was used with no delays and no outcomes provided. Three faces, one located in the top center position of the screen—the sample stimulus—and the other two in the bottom of the screen—the comparisons—, were presented. Participants were instructed to point which of the two alternative faces in the bottom matched the sample stimulus. All participants scored 100% correct.

Matching-to-sample task. The instructions for the experiment were provided both by written text on the screen and verbally by the experimenter. After reading the written instructions, each participant was required to make a practice block of three trials to ensure their correct understanding of the instructions. These practice trials were identical to the training trials (see below). Accuracy and speed in responding were emphasized.

Participants were tested individually in a quiet room. The experiment consisted of a delayed matching-to-sample task involving 48 training trials grouped in three blocks of 16 trials each. The trial sequence (see Figure 1) began with the fixation cross presented for 1000 ms. After an interval of 500 ms a photograph of a man (the sample stimulus) appeared on the center of the screen for 1500 ms. Each sample stimuli was repeated four times per block. Thus, each target face was presented 12 times as a sample stimulus and 48 times as a comparison stimulus. A white screen lasting 5 or 25 seconds, randomly selected, replaced the sample stimulus and

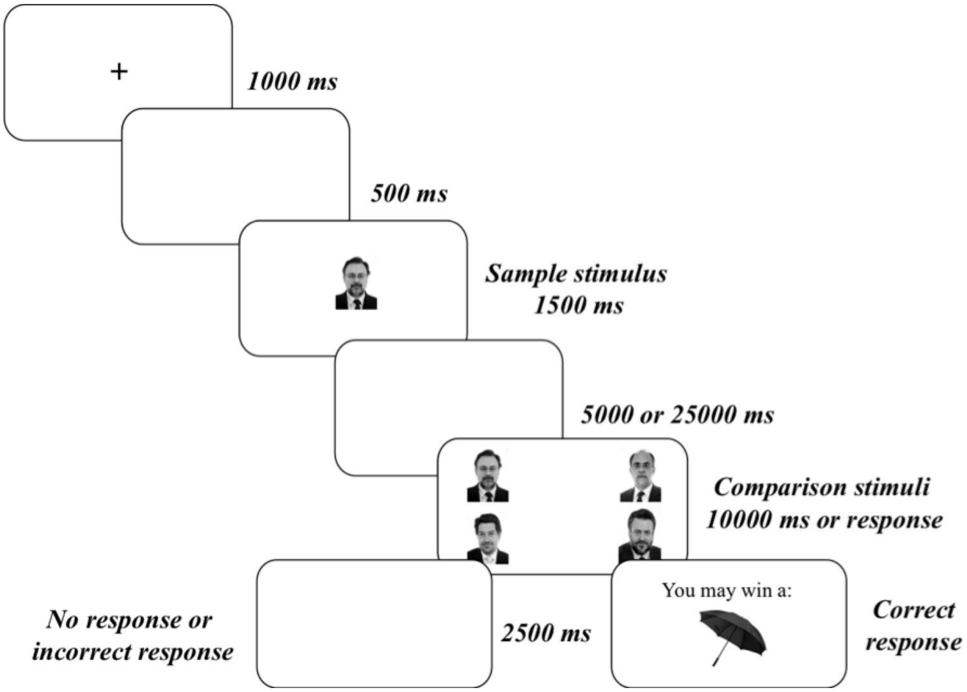

Figure 1. Sequence of stimuli (from left to right).

served as the delay as in López-Crespo et al.' study (2009). After the delay, a set of four photographs was presented (the comparison stimuli). All participants (AD patients and healthy controls) had to choose the comparison stimulus that was the same as the sample stimulus. The comparison stimuli lasted until the participant responded or 10 seconds were elapsed, whichever occurred first.

Correct responses led to the presentation of a secondary reinforcer (both a picture and a phrase indicating the correspondent prize—the primary reinforcer—they would win). The outcome presentation lasted 2500 ms. Incorrect responses were followed by a blank screen during the same time as the outcome presentation. The next trial started immediately after the end of the reinforcer or the time-out period.

The experiment was run in two sessions, separated by one week, to avoid fatigue effects. In the first session, participants were randomly assigned to one of the two experimental conditions, such that half of them served in the differential outcomes condition and the other half in the nondifferential condition. The opposite was true during the second session. Thus, participants performed the delayed recognition task under one training condition (e.g., differential) with one set of four faces and then performed the task under the other training condition (e.g., nondifferential) using the other set of four faces. This procedure allowed us to assess for each participant whether the use of the differential outcomes methodology facilitated delayed face recognition when compared with the traditional nondifferential reinforcement.

For the differential outcomes condition, each sample stimulus was always associated with a specific outcome and correct responses to a particular stimulus led only to its associated outcome. For instance, correct recognition of the man with the beard was always associated with the picture of an umbrella (to be raffled at the end of the study), correct recognition of the man with the glasses was always paired with the picture of a mug (to be raffled at the end of the study as well), and so on. Correct responses in the nondifferential condition were followed by a random presentation of one of the four possible reinforcers. For instance, correct recognition of the man with the beard could be paired with the picture of an umbrella in one trial, the mug on the following one, and so on.

Statistical Analyses

Sociodemographic data, and participants' performance in neuropsychological tests were analyzed by the Mann–Whitney *U* test, a nonparametric two independent samples test.

Percentages of correct responses and median correct RTs were submitted to a $2 \times 2 \times 2$ mixed ANOVA with Group (AD and HC) as the between-subjects factor, and Condition (differential and nondifferential outcomes) and Delay (5 and 25 seconds) as the within-subjects factors. As in a previous study (Estévez et al., 2003) the order of the training condition (whether differential or nondifferential outcomes were arranged in the first session) did not affect to the participant's delayed recognition performance and, therefore, was not further considered in the data analysis. Where necessary, post hoc comparisons were calculated by Newman–Keuls' tests. The significance level was set at $p \leq .05$.

Results

Accuracy Analysis

The analysis conducted on percent of correct responses showed significant main effects of Group, $F(1, 14) = 25.87$, $p < .01$, Condition, $F(1, 14) = 37.98$, $p < .01$, and Delay, $F(1, 14) = 9.71$,

$p < .01$. Healthy controls were more accurate than the patients (93% vs. 80% accuracy, respectively); participants performed the task better in the differential than in the nondifferential outcomes condition (89% vs. 84% accuracy, respectively); and performance was worse with 25 seconds than with 5 seconds delay (84% and 89% accuracy, respectively). The Delay × Group interaction was significant, $F(1, 14) = 4.64$, $p = .049$. Further analyses showed that the effect of the delay was significant only in the AD group, $F(1, 7) = 11.02$, $p < .05$ but not in the control group, $F(1, 7) < 1$. That is, AD patients were less accurate in the 25 seconds delay than in 5 seconds delay (75% vs. 85% accuracy; see Figure 2).

The Condition × Group interaction was also significant, $F(1, 14) = 40.78$, $p < .01$. As it is shown in Figure 2a, the difference between the DOP and NOP conditions was observed in the AD group, $F(1, 7) = 79.87$, $p < .01$, but not in the NC group, $F(1, 7) < 1$, indicating that only AD patients performed significantly better on the memory task when differential outcomes were arranged (85 vs. 75% accuracy in the differential and nondifferential conditions, respectively). No other interactions reached statistical significance (all ps > 0.05).

Reaction Time Analysis

Latency data were also analyzed. The analysis conducted on percent of median correct reaction times (RTs) showed a significant main effect of Group, $F(1, 14) = 27.05$, $p < .01$, indicating that, in general, the control group was faster than the patient group (2754 ms vs. 5280 ms). The main effect of Delay and the Delay × Group interaction were both significant, $F(1, 14) = 31.47$, $p < .01$ and $F(1, 14) = 7.06$, $p < .05$, respectively. Further analyses of the interaction revealed a significant effect of Delay in both, patients, $F(1, 7) = 17.56$, $p < .01$, and healthy controls, $F(1, 7) = 80.67$, $p < .01$. That is, increasing the delay from 5 to 25 seconds resulted in increased RTs for both groups. However, the reaction time (RT) difference between the 5 and the 25 seconds delays was higher in the patients (1722 ms) than in the controls (616 ms) (see Figure 2).

Importantly, the main effect of Condition was significant, $F(1, 14) = 5.72$, $p < .05$. This effect was modulated by a significant Condition × Group interaction, $F(1, 14) = 4.88$, $p < .05$. The analysis of the interaction revealed that only AD patients benefited from the DOP, showing faster RTs when differential outcomes were arranged (4634 ms vs. 5926 ms; $F(1, 7) = 6.53$, $p < .05$). No other interactions reached statistical significance all ps > 0.05.

Discussion

This study was designed to test whether the memory improvements observed in some populations (i.e., aged people) after DOP arrangement extend also to AD patients, helping to minimize the memory loss commonly seen in these patients. To explore this issue, we used a delayed matching-to-sample task under conditions in which outcomes were randomized (nondifferential) compared with conditions in which each to-be-remembered face was always paired with its own and unique outcome (differential). Two delays (5 and 25 seconds) between the sample and the comparison stimuli were used.

The results showed that when differential outcomes are used, delayed face recognition performance of AD patients is improved (higher accuracy and faster RTs), as compared with nondifferential outcomes, even at the longer delay. However, when trained with nonspecific outcomes, patients displayed the typical disease-related decline in face recognition memory. It is also noteworthy that patients showed equivalent performance than the control group in the 5 seconds delay under the differential outcomes condition. The healthy controls, in contrast, did not show any advantage of the DOP; that is, they achieved a similar high accuracy (around 90% of correct responses) and low latency (around 2700 ms) under both outcomes conditions irrespective of the delays (5 and 25 seconds), indicating that the recognition task was very easy for them. These results are in agreement with those of previous studies that have demonstrated a modulation of the DOE by task difficulty in children and adults (Estévez et al., 2001; Estévez, Vivas, Alonso, Marí-Beffa, Fuentes & Overmier, 2007; Plaza et al., 2011). Namely, when the task is very easy the effect is not observed (Plaza et al., 2011; Estévez et al., 2001), when it is relatively easy the effect is found only with latency data (Estévez

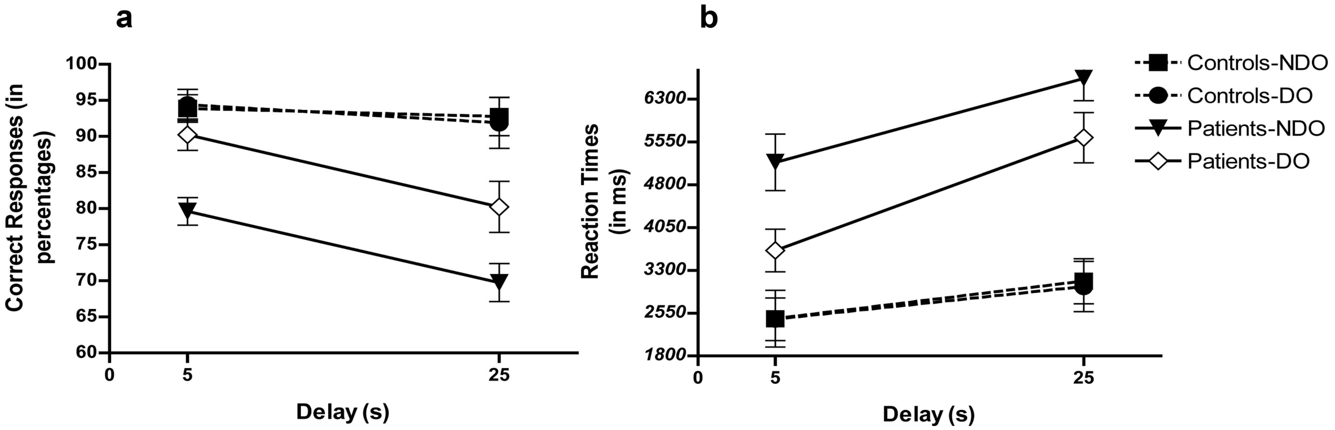

Figure 2. (a) Mean percent of correct responses for controls and AD patients at 5- and 25-second delays under differential and nondifferential conditions. (b) Median correct response times for controls and AD patients at 5- and 25-second delays under differential and nondifferential conditions. DO = differential outcomes; NDO = nondifferential outcomes.

et al., 2007; Plaza et al., 2011), and it is obtained with accuracy data when a more difficult task is used (Estévez et al., 2007; Plaza et al., 2011).

The present findings support the two-memory system model proposed as explanation of the DOE (Savage & Ramos, 2009). According to this model, when nondifferential outcomes procedures are used, the retrospective recall or recognition of the particular discriminative stimulus (a cholinergic-dependent explicit memory system) is the only source of information to solve the task. However, with differential outcomes procedures there is a different memory process that can be used to solve the task: the expectancies of reward or prospective memory of what the upcoming reward will be (a glutamatergic-dependent memory system). These expectancies are formed via classical conditioning associations (i.e., sample stimulus-outcome) in such a way that after several pairings the presentation of the sample stimulus activates the representation of its own and unique outcome. This is an unintentional process characteristic of implicit memory, which is preserved in AD (Rogers et al., 2000). The results obtained in the present study demonstrate that the use of differential outcomes allows AD patients to take advantage of this preserved implicit memory to solve the face recognition memory task more efficiently than when nondifferential outcomes are arranged. As Savage (2001) had hypothesized, the DOP seems to be a simple behavioral manipulation that may enhance memory of specific explicit information in people with memory dysfunction.

This theoretical account has also been supported by some human research exploring the potential of the DOP to improve delayed facial recognition in patients with alcohol-related amnesia (Hochhalter et al., 2001), in aged people (López-Crespo et al., 2009), and in university students (Plaza et al., 2011). Results from these studies indicate that, in general, participants showed improved recognition memory under specific outcomes conditions. Importantly, in a recent study using functional MRI (fMRI), it has also been demonstrated that different brain regions are recruited when differential and nondifferential outcomes are used (Mok, Thomas, Lungu & Overmier, 2009). In agreement with previous findings from animal studies (Savage, Buzzetti & Ramirez, 2004), they found greater hippocampal activation when nondifferential outcomes were arranged, suggesting that the hippocampus plays a role in mediating retrospective rather than prospective memory. In contrast, under differential outcomes, the angular gyrus of the posterior parietal cortex was activated. Thus, this cortical region appears to mediate prospective processing. Brain regions related to sensory-specific cortices were also activated during the delay-period, producing a perceptual representation about what the anticipated outcome would look like (the expectancy of the upcoming reward).

Face recognition is a common and important process to function effectively in everyday life. The results obtained in our study suggest that the DOP can be a useful technique to ameliorate the typical face recognition deficit of AD patients. This enhancement might have a great impact on their daily functioning by improving their social interactions and their interpersonal relationships. A limitation with the present study is that long-term effects of the training were not investigated. Further studies are needed to explore whether the DOP can produce lasting effects in face recognition performance of AD patients and, if so, how many training sessions are needed to observed them. It is also worth noting that although in this study faces were not attached to a meaning, we think that the DOP might also be used in this population to effectively associate a particular face with a name or a relationship (e.g., spouse or grandchildren). This methodology might also extend to other domains as self care (e.g., to improve patient's discrimination of the basic items found in the bathroom and how to correctly use them or to learn their medication schedule or the time schedule of other important daily activities). Future research should investigate the adequacy of the DOP to improve such types of discriminative learning in these patients.

In summary, we can conclude that a little procedural change such as the arrangement of differential outcomes after each correct response can lead to great improvements on a memory task in patients with AD. The present findings are very important because (1) to our knowledge, it is the first time that it has been observed that the DOP helps to overcome the face recognition memory deficit usually observed in this population, and (2) they strongly suggest that this procedure can be a technique to facilitate memory-based performance in humans, especially in those people with memory impairments.

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