A qualitative impairment in face perception in Alzheimer's disease: Evidence from a reduced face inversion effect

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Abstract

Prevalent face recognition difficulties in Alzheimer disease have typically been attributed to the underlying episodic and semantic memory impairment. The aim of the current study was to determine if AD patients are also impaired at the perceptual level for faces, more specifically at extracting a visual representation of an individual face. To address this question, we investigated the matching of simultaneously presented individual faces and of other nonface familiar shapes (cars), at both upright and inverted orientation, in a group of mild AD patients and in a group of healthy older controls matched for age and education. AD patients showed a reduced inversion effect (i.e. larger performance for upright than inverted stimuli) for faces, but not for cars, both in terms of error rates and response times. While healthy participants showed a much larger decrease in performance for faces than for cars with inversion, the inversion effect did not differ significantly for faces and cars in AD. This abnormal inversion effect for faces was observed in a large subset of individual patients with AD. These results suggest that AD patients have deficits in higher-level visual processes, more specifically at perceiving individual faces, a function that relies on holistic representations specific to upright face stimuli. These deficits, combined with their memory impairment, may contribute to the difficulties in recognizing familiar people that are often reported in patients suffering from the disease and by their caregivers.

Introduction

Alzheimer's disease (AD) accounts for approximately 60% of all dementia cases and is by far the most prevalent form of dementia. Considering the general aging of the population and the fact that age is the greatest risk factor for AD, the expected number of cases is going to double between 2020 and 2040 [1]. Consequently, there is an important need to better understand the nature of the cognitive symptoms that occur in the disease. Ultimately, this may lead to the development of specific cognitive interventions aimed at remediating the difficulties experienced by individuals living with AD.

AD is typically characterized by memory problems [2]. However, one of the most striking symptoms of AD is the failure to recognize familiar people [3, 4], a function that relies heavily on visual inputs, especially the persons' faces, rather than auditory inputs (i.e., voices). In AD, the impaired ability to recognize familiar persons has typically been attributed to the underlying memory impairment [5]. Indeed, deficits in both anterograde episodic memory of faces [6, 7] and retrograde semantic memory of famous persons [8-10] are present in AD and are thought to account for the difficulties in recognizing familiar faces.

In addition to their memory impairment, however, deficits in visual tasks are also commonly reported in AD [11]. For instance, individuals suffering from AD have difficulties in color and depth perception [11], visuospatial organization [12], control of visual attention [13] and in visual search tasks with simple stimuli [14]. These low-level visual deficits occur independently of memory problems in AD [15] and may result from the concentration of neuropathology in the visual cortex [16].

A number of studies have also found deficits at processing pictures of unfamiliar faces. One line of evidence comes from studies which have demonstrated difficulties in the categorization of facial emotions in AD [17-22]. Another line of evidence involves studies that have shown deficits in the processing of non-emotional features of faces such as age

estimation [23] and mental rotation of faces [24]. AD patients also show poorer accuracy at the Benton Facial Recognition Test (BFRT) [25], a test which requires matching unfamiliar faces simultaneously presented under identical and different views [26-28], this impairment being observed even when visual contrast has been increased [29].

However, even when unfamiliar faces are used in simple matching tasks minimizing memory processes, there is no evidence that AD's deficits at such tasks reflect an impairment that is specific to faces, i.e., which would not concern other visual shapes. Most importantly, such explicit matching tasks require attention, complex stimulus comparison and decision processes. Hence, reduced performance at such tasks does not provide unambiguous evidence that AD patients are impaired at the *perceptual* level for faces, i.e. that they are impaired at building a *visual representation* of an individual face (irrespective its long-term familiarity).

One way to address these important issues is to compare AD patients' processing of simultaneously presented individual faces to other nonface familiar shapes, at both upright and inverted orientation. Starting with Yin [30], many studies have shown that the processing of individual faces is much more severely impaired by picture-plane inversion than the processing of other objects [31-43]: this effect has been coined the Face Inversion Effect (FIE) [30, 43, 44 for review]. Although the original study of Yin [30] and others [42] relied on old/new paradigms involving an important memory component, studies have shown a large decrease of performance for inverted unfamiliar faces in delayed or even simultaneous matching tasks with unfamiliar faces [e.g., 32, 33, 40, 45-53], suggesting that the source of the FIE lies at the perceptual level [48, 54, 55]: the visual representation of an individual face, irrespective of its long-term familiarity, appears to be qualitatively different for upright and inverted faces.

Given these well-established findings in the typical population, the FIE offers a unique opportunity to test whether, in addition to their memory impairment, AD patients have

deficits in higher-level visual processes such as the perception of individual faces. This is the main goal of the present study. In addition, providing that the answer to this question is positive, we were also interested to test whether such impairments may possibly account in part for the commonly reported difficulties of patients in recognizing familiar persons. Such findings would shed light on the nature of the face processing impairment in AD.

Materials and methods

Participants. Two groups of participants took part in the study: 25 mild AD patients and 23 healthy older controls (HE). All participants gave written consent before participation, and the research protocol was approved by the Research Ethics Board of the Institut Universitaire de Gériatrie de Montréal (IUGM) and the Centre Hospitalier Universitaire de Montréal (CHUM).

The twenty-five persons (15 women and 10 men) who received a diagnosis of AD were referred by the Cognition clinic of the IUGM and CHUM. Diagnosis of AD complied with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [56]. All patients were in a mild stage of the disease [57] (see Table 1 for details). AD patients completed a neuropsychological assessment, results of which are presented in Table 1. In addition, 23 HE (13 women and 10 men) participated in the study. They were recruited from a pool of volunteer participants at the CRIUGM. All HE showed normal performance on neuropsychological tests (see Table 1). As part of the neuropsychological assessment, one HE did not complete the Stroop Test. In addition, one AD patient did not complete the Stroop Test; another did not complete the Stroop Test and the Trail Making Test; finally, one AD patient was only able to complete the MMSE, the BLOT, and the VOSP subtests as part of the neuropsychological assessment. These patients were not able to complete all neuropsychological assessment due to fatigue/lack of motivation. HE and AD participants

were matched for age and level of education. We excluded HE and AD participants who had a presence or history of neurological disorder excluding AD, psychiatric disorder, closed-head injury, a history of alcoholism, substance abuse, general anaesthesia in the past 12 months, an untreated medical or metabolic condition with a potential impact on cognition, uncorrected hearing or vision impairment, as well as eye diseases such as age-related macular degeneration and cataracts.

Neuropsychological assessment. Both groups underwent a general neuropsychological assessment, which included standard measures of memory, language, attention, executive functions, visuoconstructional, visuoperceptual and visuospatial skills. Episodic memory was assessed with the RL/RI 16 [58], a verbal free and cued recall test of single words widely used in the French speaking population. Visual memory was tested using the immediate and delayed recall conditions of the Rey complex figure [59], as well as the immediate and delayed conditions of the DMS48 [60], a visual recognition memory test. Language was assessed with the DO80 picture naming test [61], lexical fluency (letter P) and categorical fluency (animals) [62]. Executive functions were measured using the Trail Making Test A and B [63] and the Victoria Stroop Test [64]. Short term/working memory was assessed using the forward and backward digit span subtest of the Wechsler Memory Scale-III [65]. Visuoconstructional skills were measured with the copy of Rey-Osterrieth figure [59]. Visual perceptual skills were assessed using the Shape detection, Silhouettes, Object decision, and Cubes subtests of the Visual Object and Space Perception battery (VOSP) [66]. In addition, basic-level face recognition abilities were tested using the Benton Facial Recognition test (BFRT) [25]. Finally, visuospatial skills were assessed with the Benton Line Orientation Test [67]. Results are presented in Table 1.

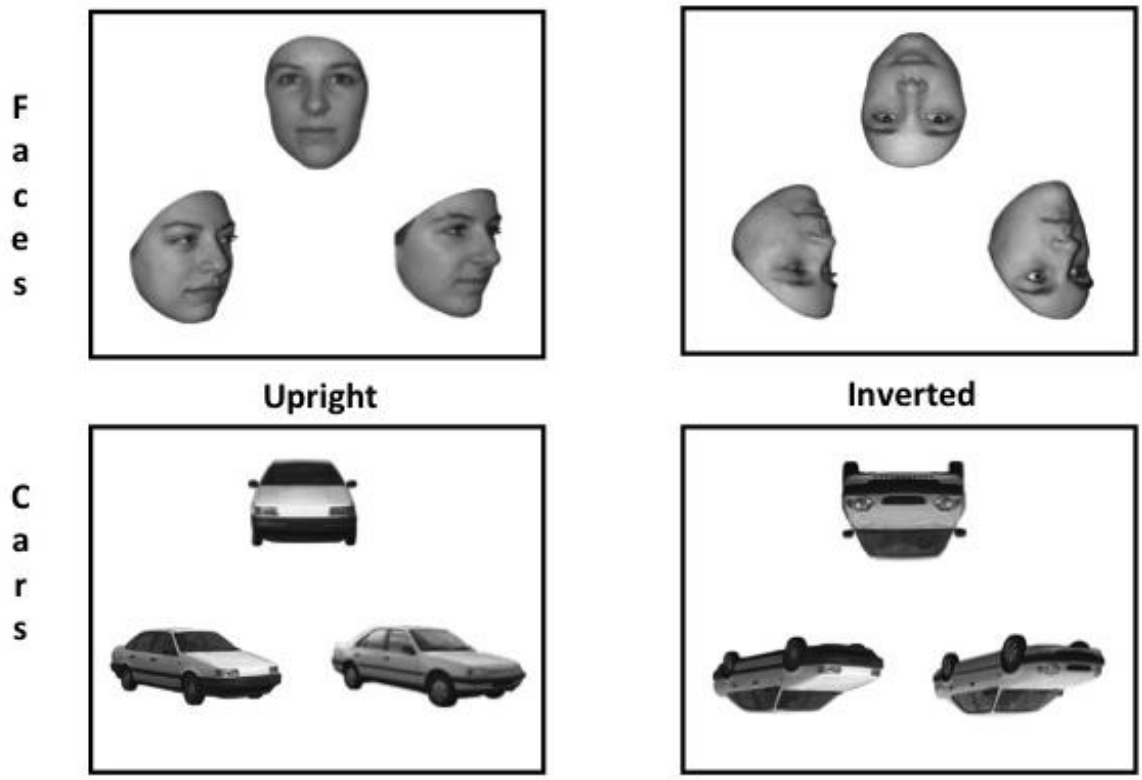
Table 1. Neuropsychological results of participants.

	Control Mean (S.D.) [Range]	AD Mean (S.D.) [Range]	*p* value for group effect
Demographic data			
Age	77.82 (6.4) [65-87]	77.07 (7.62) [54-85]	n.s.
Education	14.23 (2.9) [9-20]	12.71 (3.8) [6-20]	n.s.
General cognitive functioning			
MMSE	28.76 (1.1) [26-30]	25.17 (2.5) [20-29]	$p < 0.01$
Memory			
RL/RI 16			
Immediate free recall of a word list (16)	8.40 (2.3) [4-13]	2.55 (1.8) [0-6]	$p < 0.01$
Immediate total recall of a word list (16)	14.40 (2.4) [7-16]	6.5 (2.6) [2-11]	$p < 0.01$
Delayed free recall of a word list (16)	12.24 (2.9) [3-16]	1.36 (1.5) [0-5]	$p < 0.01$
Delayed total recall of a word list (16)	15.56 (1.3) [10-16]	6.50 (3.3) [0-12]	$p < 0.01$
Visual memory			
DMS48 Set 1	95.15 (5.1) [83-100]	76.17 (13.5) [50-98]	$p < 0.01$
DMS48 Set 2	93.52 (5.9) [83-100]	72.30 (14.0) [48-96]	$p < 0.01$
Rey–Osterrieth immediate recall (36)	14.80 (7.5) [4-30]	4.20 (4.2)[0-13]	$p < 0.01$
Rey–Osterrieth delayed recall (36)	13.64 (7.1)[4-28]	3.78 (4.5)[0-14]	$p < 0.01$
Executive function/working memory			
Stroop–Victoria Test			
Part A	51.80 (10.0) [42-85]	61.62 (18.1) [34-101]	$p = 0.03$
Part B	82.64 (16.0)[57-101]	113.57 (36.2) [70-192]	$p < 0.01$
Part C (interference)	138.44 (27.3) [91-177]	219.81 (82.8) [121-392]	$p < 0.01$
Digit span forward	6.52 (1.4) [4-9]	6.14 (1.0) [4-8]	n.s.
Digit span backward	5.04 (1.49)[3-8]	4.18 (1.1) [2-6]	$p = 0.03$
Trail Making Test			
Part A	50.20 (21.20) [17-113]	69.90 (23.4) [32-111]	$p < 0.01$
Part B	103.92 (36.20) [54-183]	248.81 (204.0) [72-919]	$p < 0.01$
Language			
DO80	78.85 (1.7) [75-80]	74.39 (4.5) [63-80]	$p < 0.01$
Verbal fluency "P" in 2 min	23.96 (7.7) [11-42]	14.78 (4.6) [6-25]	$p < 0.01$
Category fluency "animals" in 2 min	26.36 (4.9) [19-35]	16.52 (4.6) [7-26]	$p < 0.01$
Visuoperceptual, visuoconstructional and visuospatial abilities			
Visual object and space perception battery			
Shape detection	19.69 (0.6) [18-20]	19.61 (0.6) [18-20]	n.s.
Silhouette	19.00 (3.9) [10-27]	15.43 (3.8) [7-22]	$p < 0.01$
Object decision	16.85 (1.9) [13-20]	15.48 (3.5) [4-20]	n.s.
Cube	9.31 (0.84) [7-10]	7.87 (2.6) [0-10]	$p < 0.01$
Rey–Osterrieth figure – copy (36)	31.04 (6.2) [24.5-36]	26.83 (7.2) [12.5-36]	$p < 0.01$
Benton line orientation test (30)	23.96 (4.4) [14-30]	20.14 (4.6) [11-29]	$p < 0.01$
Benton facial recognition test	45.58 (3.1) [39-51]	44.0 (4.0) [37-51]	n.s.

Stimuli

In the current study 36 Caucasian unfamiliar individuals (18 women/18 men) presented in both frontal (top) and ¾ views (45° angle, bottom) were used [see Experiment 3 in 33]. These photographs were processed to remove any external cues (such as hair and ears). Thirty-six pictures of cars presented in an upright position in frontal and ¾ views were also used as part of the stimuli and designed in an identical way. Many previous studies have used pictures of cars to isolate the FIE [30, 33, 40, 68]. Pictures of cars were used because they are familiar objects having multiple parts (e.g. headlights, mirrors, windshield, etc.) alike faces (e.g. eyes, nose, mouth). The stimuli were about 7.1 ° × 5.7 ° for faces and 5 × 7.8 ° for cars. Pictures of cars were taken in Belgium 20 years ago (1996) and are mostly photographs of European and Japanese car models unknown to the participants, with car logos removed. All pictures were presented in shades of gray on a white background. From these pictures, 144 displays/trials were created. Each display consisted of 3 stimuli from the same category (faces or cars), one presented at the center of the upper half of the screen, and two horizontally-aligned stimuli presented in the lower half of the screen (left and right) (see Figure 1 for example). The sex was always the same for distractor and target faces. Each stimulus in the upper half of the screen was presented in a frontal view while the 2 stimuli in the lower half were presented in a ¾ view. One of the 2 stimuli presented in the bottom half of each trial matched the stimulus presented in the upper half, while the other stimulus presented in the bottom half was different, but could be the same stimulus shown in the center of the upper half of the screen in another trial. In addition, the exact same displays of faces and cars were presented upside-down, meaning that each face or car in the trial was shown in an inverted position. In total, there were 36 trials of upright cars, 36 of inverted cars, 36 of upright faces and 36 of inverted faces.

Figure 1. Examples of different displays/trials of stimuli.



Procedure

The task was programmed with the E-Prime software (version 2.0.10.353). In this experiment, displays of faces and cars were presented to each participant on the computer screen. Participants had to select which of the two stimuli presented in the lower half of the screen matched the stimulus presented in the upper half of the screen. They were instructed to respond as accurately yet as fast as possible. Each display made of the 3 stimuli remained on the screen until the participant provided an answer by pressing one of the two response keys on the keyboard. The participant had to press the *S* button if the corresponding stimulus was on the bottom left-hand side of the screen, and the *L* button if it was on the right-hand side. Stimulus displays (i.e., one trial) were separated by 1,000 msec. The experiment was divided into 3 blocks containing 12 trials of each category (upright cars, inverted cars, upright faces and inverted faces) presented at random. The experiment began with a practice session

consisting of 6 trials of upright and inverted faces, followed by the 144 trials of the experiment.

Statistical analyses

Statistical analyses were conducted with IBM SPSS Version 21.0 (Statistical Package for the Social Sciences). Practice trials were not included in the analyses.

The mean error rates (ER) and the mean response times (RT) were calculated for each condition and for each participant. RT were only used for successful trials and if RT did not exceed 1.96 standard deviations below or above a participant's own mean. Outliers were then replaced by the participant's mean RT (across all conditions), accounting for 5.5% of the data [69, 70].

In regard to ER, we first verified whether scores exceeded 3.29 standard deviations above the mean and SD of all participants, which was not the case [71]. We also verified the normality of our variables according to Kline's criteria [72]. Only ER for inverted cars in HE exhibited abnormal kurtosis. However, as there were no participants with extreme scores on this variable, the distribution of this variable was not modified.

Inversion costs ratios (ICR) were also computed for ER and RT using the following formula for faces and for cars: ER or RT difference between upright and inverted condition divided by the sum of ER or RT of both conditions respectively. A negative ICR indicates that a participant performed more accurately with upright pictures than with inverted pictures and a positive ICR indicates the opposite pattern. ICR were used as a way to compare more accurately the difference between HE and AD patients by comparing the IE to its own condition and allowing it to be expressed in terms of a similar amplitude across individuals (speed/accuracy ratio, reduced speed of processing in AD, etc.). Also, by first comparing the

participants with themselves, we can reduce the statistical bias that may be induced by a greater variance in AD.

Analysis of variance for repeated measures (ANOVA) was performed separately for non-transformed data and ICR on both ER and RT. Mauchly's test for sphericity was conducted for each ANOVA to assess the homogeneity of variance and the analyses did not reveal any significant effect. Therefore, the ANOVAs were not corrected. ANOVAs on non-transformed data were run with *Group* (Controls *vs.* AD patients) as between subjects and *Category* (Cars *vs.* Faces) and *Orientation* (Upright *vs.* Inverted) as within subjects. ANOVAs on ICR were run with *Group* as between subjects and *Category* as within subjects.

Significant three-way interactions for non-transformed data were subsequently analyzed by running separated ANOVAs for each group with *Category* and *Orientation* as within subjects. Planned *t* tests between upright cars and inverted cars, between upright faces and inverted faces, between upright cars and upright faces and between inverted cars and inverted faces were used as posthoc analysis to decompose significant interactions on non-transformed data and on ICR.

Finally, ICR were used to compute z scores for each AD patient compared to HE for cars and faces on both ER and RT according to this formula: (HEmean – ADratio)/HEsd with HEmean and HEsd reflecting the mean and standard deviation of the HE group for a given ICR and ADratio the specific value of a given AD patient for the given ICR.

A $p < .05$ was used as a significant threshold for all analyses.

A correlation analysis was also conducted between the ICR on ER for cars and faces and the different neuropsychological scores in the AD group and in the HE group in order to better understand the relations between performance on the task and specific cognitive processes. Due to the exploratory nature of this analysis, the threshold for significance was not corrected for multiple comparisons. The results are thus discussed accordingly.

Results

The mean accuracy rates and correct RTs are illustrated in Figure 2A and 2B, respectively.

Error Rates (ER)

There were significant main effects of all factors: *Group* ($F(1, 46) = 11.68$, $p < .05$, $\eta^2_g = .14$) *Category* ($F(1, 46) = 142.47$, $p < .05$, $\eta^2_g = .30$) and *Orientation* ($F(1, 46) = 74.78$, $p < .05$, $\eta^2_g = .12$), these effects being qualified by significant interactions between *Orientation* and *Group* ($F(1, 46) = 4.82$, $p < .05$, $\eta^2_g = .01$), as well as between *Orientation* and *Category* ($F(1, 46) = 16.59$, $p < .05$, $\eta^2_g = .05$). Most importantly, the three-way interaction between *Category*, *Orientation* and *Group* was significant ($F(1, 46) = 4.07$, $p < .05$, $\eta^2_g = .01$) (all other effects, $F<1$). This interaction, which was due to the much larger face inversion effect in HE participants (18.63% for faces *vs.* 3.03% for cars) as compared to AD participants (9.22% *vs.* 3.77%), was decomposed by running separate ANOVAs for each group.

For HE, there was a main effect of *Category* ($F(1, 22) = 64.47$, $p < .05$, $\eta^2_g = .37$) and of *Orientation* ($F(1, 22) = 61.73$, $p < .05$, $\eta^2_g = .25$) and the *Category* by *Orientation* interaction was also significant ($F(1, 22) = 27.92$, $p < .05$, $\eta^2_g = .15$), reflecting the much larger decrease in performance for faces than cars with inversion, even if there was a decrease in performance with inversion for both cars ($t(22) = 2.39$, $p < .05$) and faces ($t(22) = 7.26$, $p < .05$).

For AD patients, there was a main effect of *Category* ($F(1, 22) = 78.03$, $p < .05$, $\eta^2_g = .26$); cars were significantly better processed than faces, and a main effect of *Orientation* ($F(1, 22) = 20.92$, $p < .05$, $\eta^2_g = .05$), whereby upright stimuli were better processed than inverted stimuli. However, the inversion effect did not differ significantly for faces and cars (i.e., non-significant interaction between *Category* and *Orientation* ($F(1, 22) = 1.81$, $p = .19$). It should be noted that even in the inverted faces condition, which was the more difficult

condition, AD patients performed well above chance level ($t(24) = 4.20$, $p < .01$; patients' percentage error against 50% chance to choose the correct response).

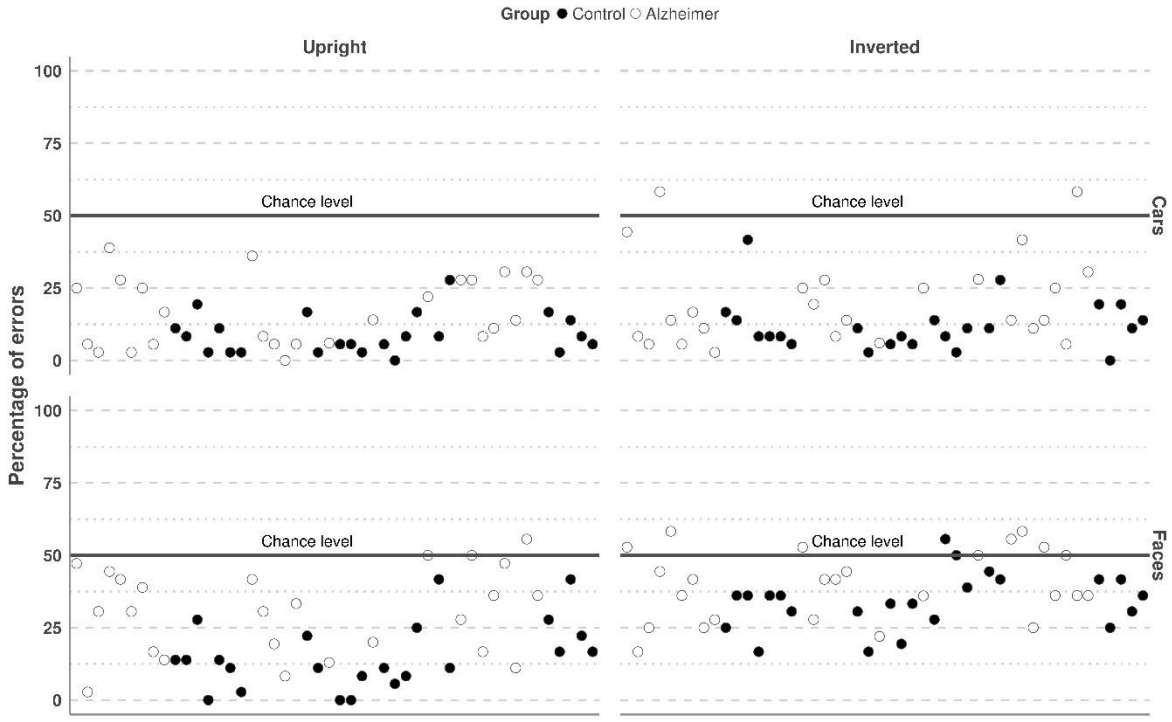
Response Times (RT)

In regard to RT, there was a main effect of *Group* ($F(1, 46) = 7.82$, $p < .05$, $\eta^2_g = .13$), *Category* ($F(1, 46) = 21.57$, $p < .05$, $\eta^2_g = .02$) and *Orientation* ($F(1, 46) = 34.31$, $p < .05$, $\eta^2_g = .02$), qualified by a significant three-way interaction between *Group*, *Category*, and *Orientation* ($F(1, 46) = 4.15$, $p < .05$, $\eta^2_g = 0$). All other interactions were not significant ($F < 1$). The three-way interaction was due to the much larger face inversion effect in HE participants (1,266.43 ms for faces *vs.* 545.03 ms for cars) as compared to AD participants (1,003.68 ms *vs.* 788.36 ms respectively). This interaction was decomposed by running an ANOVA in both groups separately.

For HE, there was a main effect of *Category* ($F(1, 22) = 23.68$, $p < .05$, $\eta^2_g = .09$) and *Orientation* ($F(1, 22) = 32.33$, $p < .05$, $\eta^2_g = .05$), qualified by a significant interaction between *Category* and *Orientation* ($F(1, 22) = 6.42$, $p < .05$, $\eta^2_g = .01$), due to the relatively larger increase of RT with inversion for faces ($t(22) = 4.43$, $p < .05$) than cars ($t(22) = 5.60$, $p < .05$).

For AD patients, the main effect of *Category* was significant ($F(1, 24) = 4.57$, $p < .05$, $\eta^2_g = .01$) revealing that faces were processed more slowly. The main effect of *Orientation* ($F(1, 24) = 12.27$, $p < .05$, $\eta^2_g = .02$) was also significant indicating the upright stimuli were processed more quickly. Contrary to the HE group, however, the *Category* by *Orientation* interaction was not significant ($F < 1$), indicating that the inversion effect did not differ for faces and cars in AD.

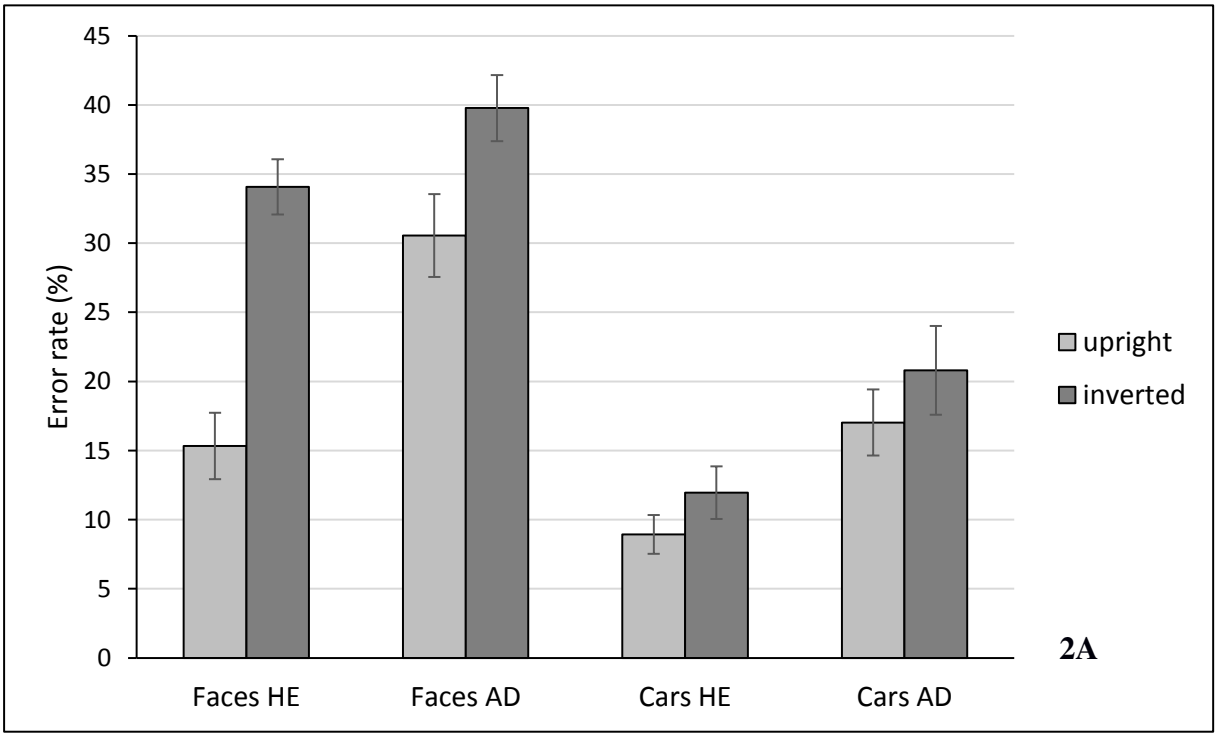
Supplementary Figure 1. Percentage of errors for each control and patient as a function of the experimental condition.

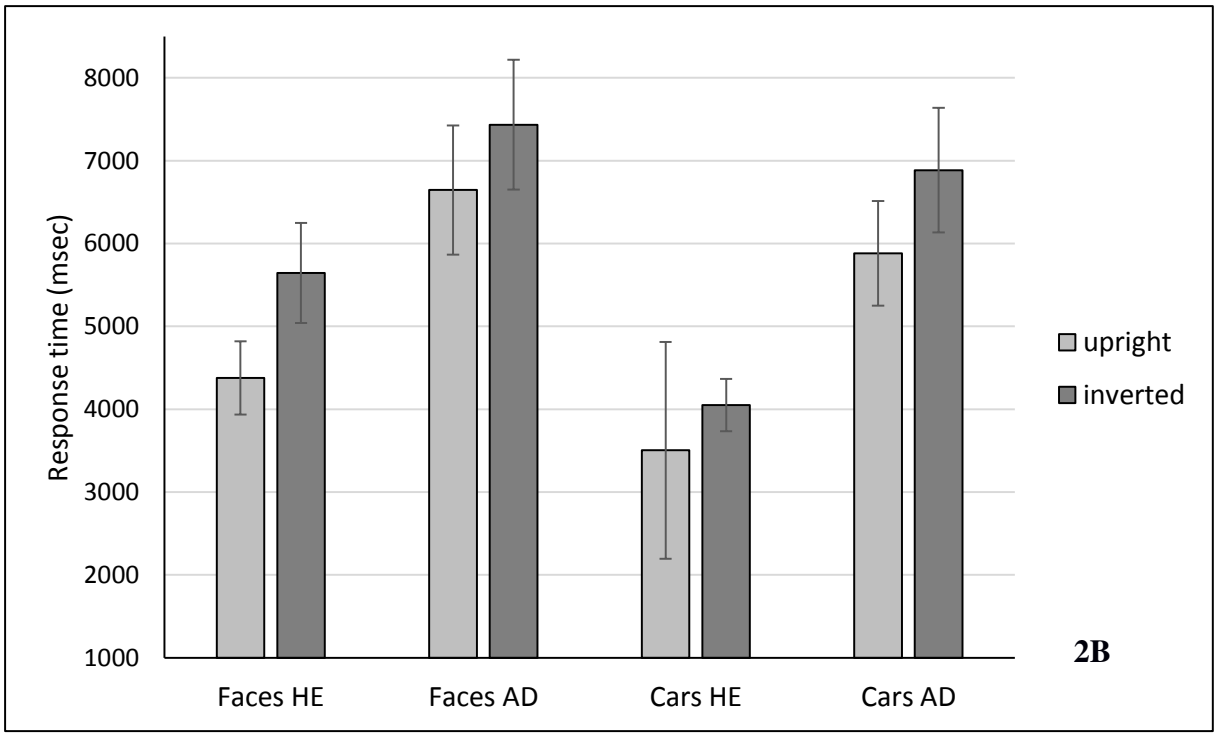


Inversion Cost Ratio (ICR) analyses

Since AD patients made many more mistakes and were much slower than normal controls, we also computed an inversion cost ratio (see methods) to normalize for general performance and speed. These inversion cost ratios are illustrated for the categories and groups in Figure 3.

Figure 2. Mean error rates (Fig. 2A) and mean response time (Fig. 2B) of HE and AD participants across conditions (standard errors corrected for within participant design).





Error Rates (ER)

The main effect of *Group* showed a non-significant trend ($F(1, 46) = 3.74$, $p = .06$, $\eta^2_g = .05$) and the main effect of *Category* was significant ($F(1, 46) = 8.35$, $p < .05$, $\eta^2_g = .07$), these effects being qualified by the significant interaction between *Group* and *Category* ($F(1,46) = 4.66$, $p < .05$, $\eta^2_g = .04$). To better understand this interaction, planned *t* tests were performed for each category with group as the grouping variable. For cars, there was no significant difference between AD patients and HE ($t(44) = .07$, $p = .95$), whereas the ratio was significantly higher in HE (-0.45) than in AD (-0.17) for faces ($t(40) = 3.37$, $p < .05$).

This pattern of results was confirmed by a z-score analysis on ICR. AD patients were relatively evenly distributed around the performance of HE participants for cars (13 AD patients above 0) whereas only three AD patients were above the HE's performance for faces. In other words, almost all AD patients presented a diminished FIE compared to HE.

Response Times (RT)

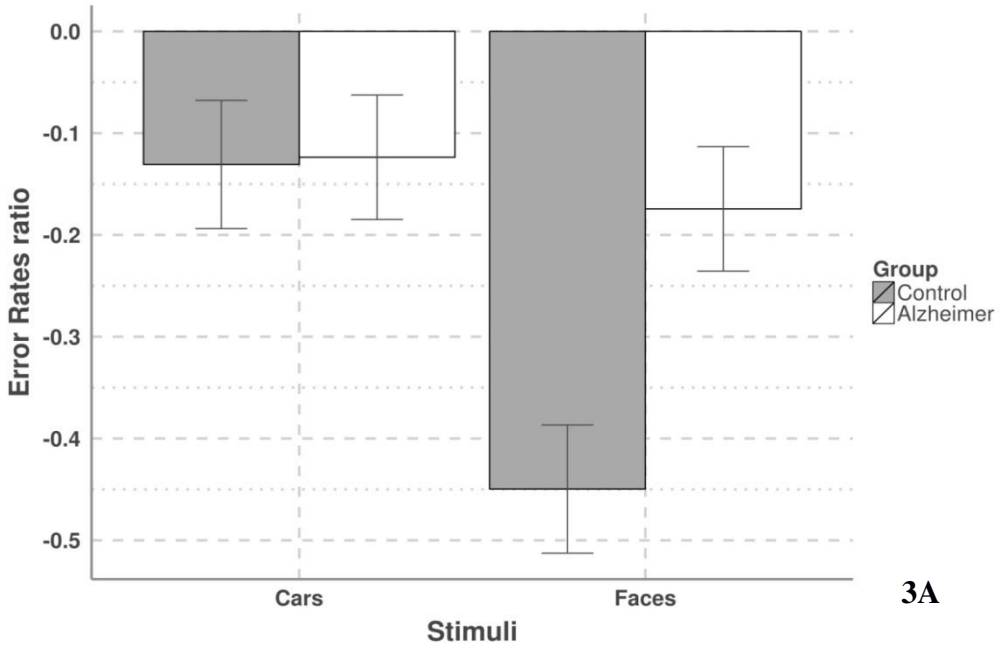
The main effect of *Group* was not significant ($F(1, 46) = 1.50$, $p = .23$) nor was the main effect of *Category* ($F<1$). However, the *Group* by *Category* interaction showed a non-significant trend ($F(1, 46) = 3.20$, $p = .08$, $\eta^2_g = .03$). Due to our a priori hypothesis and the trend for the interaction, this interaction was further explored with planned *t* tests for each category with *Group* as the grouping variable. Results are presented in Figure 6.

As for ER, there was no significant difference between groups in ICR for cars, $t(45) = 0.27$, $p = .79$. In line with error rate measures, the ICR, however, was higher for faces in the HE group (-0.11) compared to the AD group (-0.06) ($t(45) = 1.70$, $p < .05$).

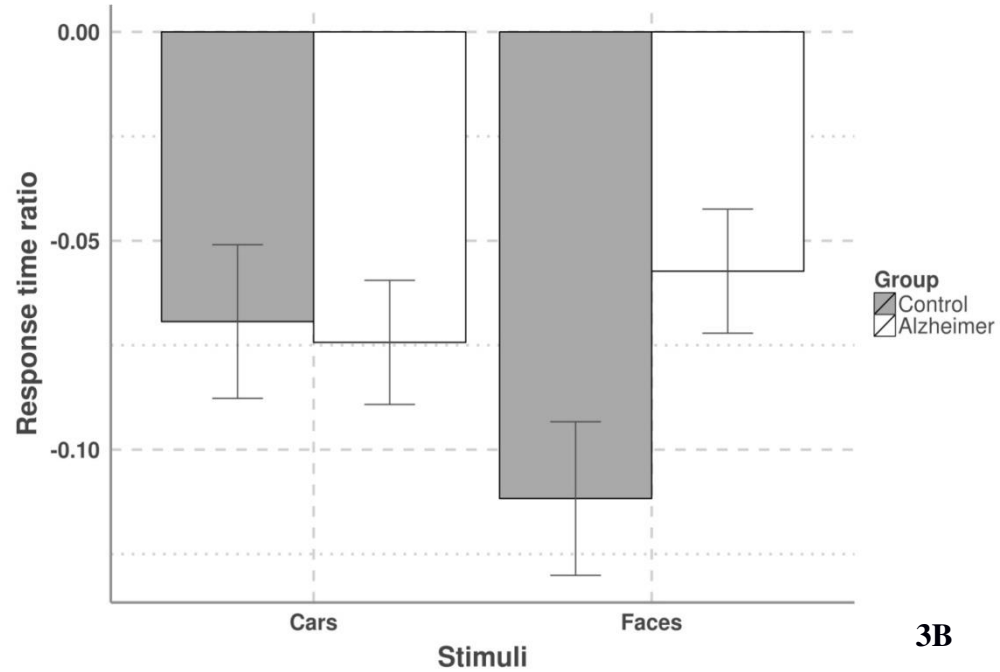
This pattern of results was once again observed by the z-score analysis on ICR. AD patients were relatively evenly distributed around the performance of HE participants for cars

(14 AD patients above 0) whereas only five AD patients were above the HE's performance for faces. As for ER, most of the AD patients presented a diminished FIE compared to HE.

Figures 3A and 3B. Mean inversion cost ratios (ICR) for error rates (ER) and response times (RT) in AD and HE participants (standard errors corrected for within participant design).



3A



3B

Correlation analysis

Pearson coefficients were computed to assess the relationship between the ICR on ER for cars and faces and neuropsychological tests in the AD group. A significant correlation was found between the ICR on ER for faces and performance on the Benton Facial Recognition Test ($r = -.48$, $p < .05$), copy of the Rey Figure ($r = -.50$, $p < .05$), recognition of words in the RL/RI 16 ($r = -0.50$, $p < .05$), and word-color interference in the Stroop test ($r = -0.53$, $p < .05$). All other correlations with neuropsychological tests were non-significant. Concerning cars, a significant correlation was found between the ICR on ER and performance on the Benton Line Orientation Test ($r = -.44$, $p < .05$). The same correlations were also computed in the control group. A significant correlation was found between the ICR on ER for faces and performance on recognition of words in the RL/RI 16 ($r = 0.43$, $p < .05$). All other correlations with neuropsychological tests were non-significant. Concerning pictures of cars, a significant correlation was found between the ICR on ER and performance on the Trail Making Test part A ($r = .43$, $p < .05$).

Discussion

This study aimed to investigate if AD patients are specifically impaired at face perception. We addressed this question by comparing the matching/discrimination of simultaneously presented individual faces to other nonface familiar shapes, at both upright and inverted orientation. Most interestingly, AD patients had a reduced face inversion effect (FIE) both in terms of error rates and response times. Healthy participants showed a much larger decrease in performance for faces than for cars with inversion, while in AD the inversion effect did not differ significantly for faces and cars.

It is important to note that AD patients generally made more mistakes and were slowed down in all conditions tested in the study. In this respect, their impairment was not

specific to (upright) faces. Even a simultaneous matching task such as the task used here involves many processes (attention, decision making, motor response, etc.) contributing to performance, so that any impairment at this task cannot be attributed unambiguously to perceptual processes. Since AD patients have a lower general cognitive functioning than typical participants, this factor may well account for the general increase of error rates and RTs in the different conditions. However, a strength of the present study is that these general processes are neutralized by comparing the different conditions, in order to isolate the specific processes involved in upright face perception. Moreover, the reduced FIE in AD cannot be accounted for in terms of a floor effect. AD's accuracy rates are low for upright faces (69%) but they remain well above chance for inverted faces (61%), indicating that there was still room for further decreases. Moreover, the FIE was also reduced when measures in correct RTs in AD patients. Therefore, the significant interactions between object categories, orientation and the two groups tested suggest that, in addition to their general difficulties and slowing down at performing behavioral tasks requiring matching complex visual stimuli, AD patients present with a specific impairment at building a visual representation of an (upright) individual face.

Face inversion deficits have been previously documented in other clinical populations, most notably patients suffering from acquired prosopagnosia, who show an absence or reduced face inversion effect [32, 33, 73-76]. Persons with unmedicated schizophrenia have also been documented to show lower FIE than controls [77], and a reduction of the FIE has also sometimes been reported in neurodevelopmental disorders such as autism, Down syndrome and Williams syndrome [78] although the vast majority of studies investigating the FIE in autism spectrum disorder (ASD) have concluded for a typical effect, despite lower overall performance and general cognitive functioning [79]. To our knowledge, however, no prior study has shown a reduced FIE in Alzheimer's disease. The current study provides new

insights into the nature of the face processing difficulties encountered in AD and may explain, at least to a certain extent, some of the difficulties patients have in recognizing and identifying familiar and famous persons. Difficulties in recognizing familiar persons in AD are more often attributed to memory loss. Although AD patients undoubtedly show significant memory difficulties which may impair their ability to recognize recently-encountered individuals (episodic memory) as well as previously familiar and famous individuals (semantic memory), the results of this study suggest that even in the mild stage of the disease, patients also present with deficits in higher level visuoperceptual processes required to process faces. It is worth pointing out that facial skills are rarely assessed in clinical practice, although these skills are critical in the lives of persons with AD. Indeed patients need to recognize familiar persons in various contexts and be able to distinguish familiar from unfamiliar individuals. The development of new clinical tools that allow assessing various aspects of visuoperceptual face processes may thus be particularly relevant and useful to clinicians.

Interestingly, AD patients in the current study were not impaired on the Benton Facial Recognition Test (BFRT). The BFRT is a commonly used clinical tool used to test the ability of an individual to match faces presented in identical and different perspectives. These results contrast with other studies that have shown significant differences between HE and AD participants on this test [26-28]. The absence of impairment on the BFRT in our AD group may have different explanations. First of all, AD patients in the current study were in a mild stage of the disease, while previous studies included patients in a more advanced stage [27]. Second, as in most studies we did not measure response times for the BFRT. However, there is evidence that this variable is important in assessing face matching ability using the BFRT, since some patients with acquired prosopagnosia can achieve reasonable scores at this test if they are given unlimited time [74]. Therefore, if we had measured RT it is possible that we

may have obtained significantly slower RT in AD relative to HE on the BFRT despite not finding a significant difference in accuracy.

Despite the lack of difference between AD and healthy controls on accuracy rates at the BFRT, performance on the BFRT was significantly and specifically correlated with the ICR for faces in AD patients: the weaker the performance at the BFRT, the lower the FIE. This suggests that processes involved in the BFRT and the face inversion test are related, but that the face inversion test used here is more sensitive in detecting face perception difficulties in mild AD.

In the current study, AD patients showed a specific significant decrement in matching/discriminating upright faces relative to inverted faces and nonface shapes. There is overwhelming evidence that the processing of upright faces differ from other types of stimuli – including inverted faces – since it involves fine-grained holistic representations: the multiple parts of an individual face are perceived as integrated, or as a single unit, rather than as separate representations [44, 45, 80-83]. Our original data suggest that this process may be partly compromised in AD patients, who may rely to a greater extent on analytical (i.e., par-by-part) processes in order to recognize faces (i.e. relying to a greater extent on isolated features such as the eyes, the nose and the mouth). A deficit in forming individualized, integrated representations of faces based on their local features may in turn impede the identification of faces.

At the neuroanatomical level, one possible explanation for the difficulties in face perception observed in AD patients in the current study is that regions specifically associated with face perception may be affected during the course of the disease. An important region involved in face processing is the fusiform face area [FFA, 84], located in the lateral section of the posterior/middle fusiform gyrus, with a right hemispheric dominance. This region is sensitive to differences between individual faces [e.g., 85, 86] and shows a large inversion

effect (i.e. reduction of release from adaptation to presentation of the same face when it is presented upside-down) [87-89]. One study, which used functional magnetic resonance imaging (fMRI) during a face-matching task, detected a weaker correlation between activation of the right and left fusiform gyrus in patients with Mild cognitive impairment (MCI, considered to be a prodromal stage of AD) and healthy controls [90]. This suggests that the fusiform gyrus is less activated in MCI during the task, even though there was no difference in behavioral performance between the two groups in that study [90]. Another fMRI study showed that the patterns of activation in the right FFA and right occipital face area (OFA), a face-selective area of the lateral part of the inferior occipital gyrus that is also critically involved in individualization of faces [85, 86, 89], were abnormal in MCI [91]. In fact, these regions were activated more strongly in response to scrambled faces vs. real faces, showing a pattern opposite to that of controls participants. Interestingly, the authors explained this pattern by suggesting that the holistic processing controlled by these regions was impaired in MCI [91]. More recently, a meta-analysis of gray matter volume in AD detected that AD individuals, unlike HE, usually have right fusiform gyrus atrophy [92]. Difficulties in recognizing faces for AD also seem consistent with studies showing that the N170, an early ERP component that is larger to faces than objects [93] and sensitive to individual face repetition [94 for review], is of reduced amplitude in AD [95, 96]. Thus, these alterations in face-selective brain regions and scalp electrophysiological responses could possibly subtend the behavioral face perception deficit that we report in AD.

Finally, some limitations need to be mentioned in the current study. Although we showed a reduced FIE in AD patients, the study did not include a questionnaire to assess face recognition difficulties of patients in everyday life situations [e.g., 97]. Therefore, it is difficult to determine if the reduced FIE is actually related to real-life difficulties in AD patients (even though we assume this is the case), and whether there is a given FIE cut-off

beyond which face recognition difficulties become apparent and have a functional impact on the lives of patients. Future studies should address this question in order to better understand the functional impact of face-processing difficulties in the everyday life of AD patients. Finally, the correlation analyses carried out in the current study were exploratory in nature and for this reason were not corrected for multiple comparisons. Therefore they need to be considered as preliminary results and will need to be further supported in future studies.

In conclusion, results of the present study suggest that, in addition to their memory impairment, AD patients have deficits in higher-level visual processes, more specifically at the level of the perception of individual faces. Future studies should help at better characterizing and pinpointing the nature of the face recognition deficits in this clinical population. Finally, future functional and structural neuroimaging studies should investigate the neural correlates of this reduced face inversion effect in AD.

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