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Preserved Extra-Foveal Processing of Object Semantics in Alzheimer's Disease

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The data and R script to reproduce visualisations and models are available at: https://osf.io/gyutd/

Abstract

Alzheimer's disease (AD) patients underperform on a range of tasks requiring semantic processing, but it is unclear whether this impairment is due to a generalised loss of semantic knowledge or to issues in accessing and selecting such information from memory. The objective of this eye-tracking visual search study was to determine whether semantic expectancy mechanisms known to support object recognition in healthy adults are preserved in AD patients. Furthermore, as AD patients are often reported to be impaired in accessing information in extra-foveal vision, we investigated whether that was also the case in our study. Twenty AD patients and twenty age-matched controls searched for a target object among an array of distractors presented extra-foveally. The distractors were either semantically related or unrelated to the target (e.g., a car in an array with other vehicles or kitchen items). Results showed that semantically related objects were detected with more difficulty than semantically unrelated objects by both groups, but more markedly by the AD group. Participants looked earlier and for longer at the critical objects when these were semantically unrelated to the distractors. Our findings show that AD patients can process the semantics of objects and access it in extra-foveal vision. This suggests that their impairments in semantic processing may reflect difficulties in accessing semantic information rather than a generalised loss of semantic memory.

Keywords: Visual search; Alzheimer's disease; semantic processing; eye-tracking

Preserved Extra-Foveal Processing of Object Semantics in Alzheimer's Disease

A hallmark of Alzheimer's disease (AD) and degenerative cognitive deficits leading to AD (e.g., Mild Cognitive Impairment - MCI) is their detrimental impact on semantic memory (Chan et al., 1993; Daum, Riesch, Sartori, & Birbaumer, 1996; Hodges & Patterson, 1995; Martin & Fedio, 1983; Mulatti, Calia, De Caro, & Della Sala, 2014), defined as conceptually organised knowledge not tied to specific episodes (Gold & Budson, 2008; Nebes, 1989). From an early stage of the disease, AD patients present with disruptions in word finding abilities (Bandera, Della Sala, Laiacona, Luzzatti, & Spinnler, 1991; Spaan, Raaijmakers, & Jonker, 2003), name fewer pictures in object naming tasks than age-matched controls (Holmes, Fitch, & Ellis, 2006), underperform on word-to-picture matching tasks (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006) and their verbal recall does not benefit from cues (Ivanoiu et al., 2005; Spaan, Raaijmakers, & Jonker, 2005). In addition, relative to healthy controls, AD patients produce more semantic-superordinate errors when asked to generate names of objects belonging to a specific semantic category (see Salmon et al., 1999, for a review) or they generate less words of a particular semantic category than words beginning with a particular letter (Phillips, Della Sala, & Trivelli, 1996), which suggests specific difficulties with semantic knowledge rather than generic disruptions linked to lexical retrieval (Monsch et al., 1994).

The findings reported above have at times been interpreted as reflecting a breakdown of semantic knowledge in AD (Adlam et al., 2006; Hodges, Salmon, & Butters, 1992; Salmon et al., 1999), but AD patients have shown normal semantic abilities when tested on tasks which can be performed more automatically and include a priming component. Semantic priming implies the automatic activation of information related to a processed stimulus, which results in faster responses when, for example, a stimulus is preceded by a semantically related cue compared to when the preceding cue is unrelated to the target stimulus (e.g., Gold & Budson, 2008). Studies that have used semantic priming in AD have reported levels of performance comparable to – or higher than –

those achieved by age-matched controls (Chertkow et al., 1994; Hernández et al., 2008 and Nakamura et al., 2000).

The control of selective attention is also known to decline starting from the early stage of AD, and this is mediated by task requirements (Baddeley, Baddeley, Bucks, & Wilcock, 2001). Therefore, evidence of preserved semantic abilities in AD may be linked to tasks that can be performed more automatically and require reduced attentional control (Ober, 2002; Perri et al., 2003). Consistent with the distinction between automatic and controlled memory processes (Jacoby, 1991; Moscovitch, 1992), AD may, in fact, induce a selective impairment in the explicit access and intentional retrieval of semantic knowledge (Nebes, 1992; Ober, 2002; Rogers & Friedman, 2008), rather than its indiscriminate loss. Tippett and colleagues (2004), for example, tested AD patients and healthy age-matched individuals on a lexical fluency task, a comparison task and a verb generation task, and systematically varied the number of alternatives participants were faced with. In the verb generation task, participants had to produce a verb related to a visually presented noun; in the high selection condition the noun was associated with many appropriate responses (e.g., *boat* -> *sail, dock, capsize*), whereas in the low selection condition the noun could only be matched with one or few responses (e.g., *piano* -> *play*). The results of this study showed that AD patients were disproportionately impaired in the high-selection conditions, but performed closely to healthy controls when the demands on selective attention were reduced (Tippett et al., 2004). Similarly, Rich and colleagues (2002) showed that semantic judgements of AD patients in a sorting task were impaired when the retrieval context was unstructured (i.e., when the number of groups to sort items into was not specified), but performed normally under more structured conditions (i.e., when instead the number of groups was specified by the experimenter).

When investigating semantic mechanisms and their functioning in healthy and neuro-pathological ageing, it is also important to consider the type of stimuli used (e.g., verbal vs. non-verbal). As argued by Paivio's Dual Coding theory (Paivio, 1991; Paivio & Csapo, 1973), words have a mnemonic disadvantage over pictures because they are encoded into the semantic system through a verbal route only, whereas pictures rely on an additional visual route. Thus, words can be mainly accessed through conceptual processing, whereas pictures can also benefit from perceptual processing (O'Connor & Ally, 2010), which facilitates their subsequent retrieval[1] (Ally, McKeever, et al., 2009). The mnemonic superiority of pictures over words is already present in childhood (Whitehouse, Maybery, & Durkin, 2006), it becomes increasingly pronounced as we age (Ally et al., 2008) and it is particularly evident in AD patients (Ally, Gold, et al., 2009b), probably due to the fact that pictures allow AD patients to access semantic information that is less accessible with lexical stimuli (Rich et al., 2002). In support of this, some AD patients show preserved information about the use of objects that they cannot name (Bartolo, Della Sala, & Cubelli, 2016). Therefore, it is possible that AD selectively impairs the top-down access to – and retrieval of – lexical information, and that this impairment may account for previous findings of reduced performance on semantic memory tasks that have used verbal stimuli (Cuetos, Arce, Martínez, & Ellis, 2017).

As such, the main objective of the present study was to determine whether AD patients utilise semantic knowledge when asked to perform a visual search for pictorial stimuli. To this aim, we also examined patients' eye movement behaviour, which can be taken as an implicit index of semantic processing and help unveil its more automatic functioning (see Ramzaoui et al., 2018 for a recent review on the topic). Eye movement responses can index memory processes even when explicit conscious recollection seems to fail (Hannula et al., 2010). For instance, in visual search tasks with complex scenes, target detection is affected by previous knowledge of the specific contexts in which objects are more likely to occur (Henderson & Hayes, 2017; Loftus & Mackworth, 1978), which indicates that semantic knowledge affects the way in which we extract visual information. In particular, overt attention appears to be guided by a top-down analysis of the conceptual features that are shared (or not) between the search target and the other objects in the

[1] A lengthy discussion of Dual Coding theory is beyond the scope of this study, hence we refer interested readers to previous literature on the topic (e.g., McBride and Dosher, 2002; Nelson, Reed and McEvoy 1977; or Paivio, 2014).

visual scene (e.g., Belke, Humphreys, Watson, Derrick, Meyer, & Telling, 2008; Nuthmann, de Groot, Huettig, & Olivers, 2019; Ruotolo, Kalénine, & Bartolo, 2020). The guidance provided by the object features can also be visual, as observers searching for a cued target (e.g., a red ball) can preferentially look at visually similar (e.g., a red apple) than dissimilar (e.g., a yellow banana) objects (Alexander & Zelinsky, 2011; Schmidt & Zelinsky, 2009). Moreover, eye movements on a target object precede its explicit identification by as many as 25 fixations (Holm, Eriksson, & Andersson, 2008), and longer fixations are observed when a target object embedded into a scene is changed, even when the change is not consciously detected by the participant (Hollingworth, Williams, & Henderson, 2001). Gaze patterns are also particularly revelatory about cognitive and attentional processes in patient populations (Hannula et al., 2010; Molitor, Ko, & Ally, 2015), and they can be used to discriminate between healthy older adults and individuals suffering from neurodegenerative disease such as MCI and AD (Crutcher et al., 2009; Oyama et al., 2019) or to identify those individuals at risk of developing such diseases (Ryan et al., 2019; Zola et al., 2013).

It is generally agreed that objects are recognised through the activation of their conceptual representations and of related concepts sharing similar features (Chertkow et al., 1994; Kiefer & Pulvermüller, 2012). It has been shown that AD patients underperform in detecting, recognising and categorising objects (Laatu, Revonsuo, Jäykkä, Portin, & Rinne, 2003), which supports the hypothesis of a generalised impairment in semantic memory. However, as already discussed above, the semantic impairment observed in AD may more specifically relate to the explicit top-down selection of a single object among a pool of co-activated semantic competitors. Evidence in support of this proposition comes from a recent eye-tracking study conducted by Seckin and colleagues (2016). In this study, healthy older adults, patients with a generalised object naming impairment (non-semantic aphasia) and patients with a semantic variant of the object naming impairment (semantic aphasia) were asked to search for a target object in an array with fifteen other distractor objects placed in an imaginary circle at extra-foveal distance from the centre of the display. The critical manipulation of this study was that half of the distractors belonged to the same semantic category as the target, whereas the remaining distractors belonged to different semantic categories than that of the target. A key finding was that, although all participants tended to fixate more on the distractors that were semantically related to the target object, this behaviour was particularly pronounced in the patients with semantic aphasia. This result probably reflected the difficulty of semantic aphasia patients in isolating the target object from its competitors, as their explicit knowledge of its word denotation was blurred by the co-activated semantically related distractors.

As well as issues related to semantic processing, AD patients may display additional difficulties in visual search due to reductions in their field of focal attention (Rösler et al 2000), which may specifically disrupt processing of information in extra-foveal vision. Boucart and colleagues (2014) investigated this question in AD patients by using a categorization task (i.e., spot-the-animal) in which they presented participants with pairs of natural images displayed to the right and left side of a central fixation cross. Their results showed that AD patients were less accurate than healthy older adults, who were in turn less accurate than younger adults, in the categorization task. As argued by Boucart et al., this impairment may stem from deficits in the magnocellular pathway of AD patients (Gilmore & Whitehouse, 1995; Kergoat et al., 2002; Sartucci et al., 2010), which result in degraded extra-foveal processing of objects' features. In sum, even though mechanisms of semantic processing have often been shown to be impaired in AD patients, it is not yet clear whether the reported impairments are due to a generalised loss of semantic knowledge or whether they may specifically relate to the explicit control and access of this information. Moreover, despite evidence of reduced extra-foveal information intake in this group, it is yet to be established whether this also occurs when the semantics of the visual context is manipulated to generate a more automatic and implicit "pop-out" effect.

Therefore, the aims of the present study were twofold: (1) to establish whether processing of semantic information about objects is preserved in AD and, if so, (2) to determine whether it can occur through extra-foveal vision, as shown in our previous work on healthy younger adults (Cimminella, et al. 2020). We used the experimental paradigm we previously developed, reported in observed ceiling search performance on young adults in our previous study, but for older adults, a semantically related search object (e.g., a car) in target-absent trials may lead to greater memory demands, i.e., the object is not present in the context. This, in turn, may result in a higher rate of false detections due to co-activation of semantically homogenous distractors (e.g., other vehicles) that need to be suppressed.

Cimminella et al., which we adapted to make it suitable for use with participants with AD and healthy older adults (see the Methods section for further details). In this paradigm, participants search for a target object, which is either related (e.g., *a car*) or unrelated (e.g., *a banana*) to other semantically homogenous distractors (e.g., *other vehicles*; see Figure 1 for an example of the design). This manipulation critically differs from Seckin et al., (2016), where distractors belonging to different semantic categories were presented together with semantically related distractors. We previously showed that in young adults, our manipulation led to a "semantic pop-out" effect whereby participants looked at a critical object earlier, and for longer, when it was semantically unrelated than related to the other distractors (Cimminella et al, 2020). This finding indicated that, in young adults, the rapid and complex extraction of object semantics occurs in extra-foveal vision, and it influences the early allocation of overt attention (see also Nuthmann et al., 2019; and Borges et al., 2020, for corroborating results in healthy older adults using naturalistic scenes).

In the context of a neuropathology associated with semantic impairment, such as AD, if semantic processes are compromised, we should not observe any effect of semantic relatedness on either manual responses or eye movements. In practice, the time taken to visually identify and accurately recognize the search target should not vary depending on the semantic context in which it is presented. In contrast, if semantic processes are, to a certain degree, preserved, we would expect search responses to be mediated by the semantic relatedness of the objects in the array, consistent with previous findings on younger adults. We reasoned that, if AD patients' attentional abilities are sufficiently preserved to enable them to process information extra-foveally, then we would expect shorter latencies to first fixations onto semantically unrelated objects. This would indicate that object semantics are accessed in extra-foveal vision, with parafoveal semantic processing driving target selection in AD patients and healthy older adults alike. If processing also continued during foveation, we would expect unrelated objects to be looked at for longer due to the heightened complexity of the semantic context. Evidence of this integration cost in AD would suggest that retrieving operations to identify the search object are also partly preserved. Finally, we

Figure 1

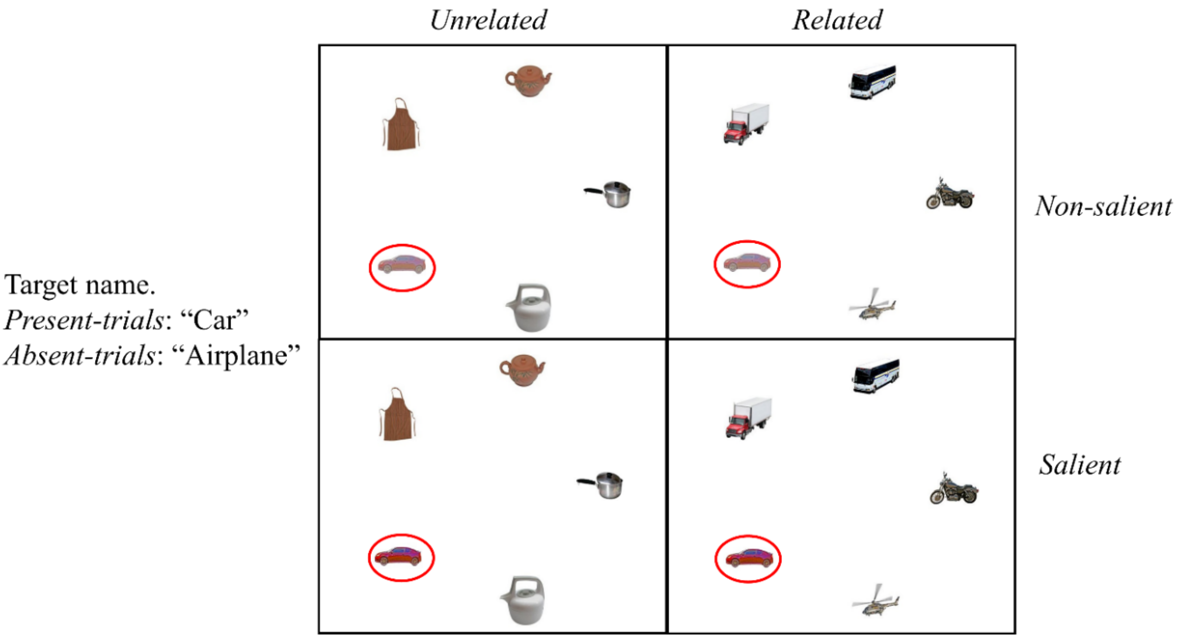

Figure 1. Experimental design and example of an object array, which included a critical object (e.g., ***car***, highlighted in red) plus 4 distractors. In target-present trials, the target name cued the critical object as the target. In target-absent trials, the target name cued an object that was not visually depicted in the array, but it was semantically related to the critical object and thus to the distractors in the semantically related but not the unrelated condition (e.g., airplane). The written cues for the targets were presented in Italian.

Methods

Participants

A group of 20 patients with a diagnosis of mild to moderate AD (14 women) and a group of 20 healthy controls (9 women) took part in the study. Both patients and controls were native Italian speakers recruited from the Neurological and Stroke Unit at CTO Hospital, Naples (15 patients and 10 controls) and the Alzheimer's Disease Italian Association AIMA Campania (5 patients and 10 controls). The two groups were matched on age (AD: $M = 71.15$, $SD = 8.50$; Control: $M = 69.35$, $SD = 5.52$; $t(32.60) = .79$, $p = .43$) and years of education (AD: $M = 8.90$, $SD = 4.29$; Control: $M =$

Table 1

Neuropsychological Test		Minimum	Maximum	Mean	SD
RAVLT	IR	6	31	19.90	7.97
	DR	0	4	1.15	1.39
WF		5	35	21.40	9.08
FAB		7	15	10.37	2.09
RCPM		9	31	17.32	5.09
CD		0	11	6.32	2.85
CDL		21	70	58.53	11.35

Table 1: Minimum, Maximum, Mean, and Standard Deviation (SD) of the Neuropsychological Tests' Scores (Raw) of the AD group. *Note.* RAVLT: Rey's auditory verbal learning test (IR, immediate recall; DR, delayed recall); WF: word fluency; FAB: frontal assessment battery; RCPM: Raven's coloured progressive matrices; CD: freehand copying of drawings; CDL: copying drawings with landmarks.

Table 2

Variables		AD	Control	t-value	p-value
MMSE	Raw	20.85 (2.68)	28.40 (1.35)	- 11.24	**< 0.001**
	Corrected	21.46 (2.37)	28.86 (2.08)	- 11.36	**< 0.001**
WR		9.61 (0.50)	9.85 (0.37)	- 1.66	0.11
ON		9.56 (0.78)	9.85 (0.37)	- 1.46	0.16
DSF		4.83 (0.99)	5.65 (0.93)	- 2.62	**0.01**

Table 2: Means, Standard Deviations (in parenthesis), t-values, and p-values for the Scores on MMSE, Word Reading Test, Object Naming Test, and Digit Span Forwards. *Note* The word reading (WR) test, the object naming (ON) test, and the digit span forwards (DSF) were administered to 18 (out of 20) AD patients, and all the healthy controls.

10.50, *SD* = 4.37; $t(37.99) = -1.17$, $p = .25$). The diagnosis of AD was based on family and medical history interview and neuroimaging evidence (available for 16[2] out of 20 patients), according to the NINCDS-ADRDA criteria (McKhann et al., 1984). The diagnosis was also based on neuropsychological testing, including the Italian version of the mini-mental state examination (MMSE, Folstein, Folstein, & McHugh, 1975; Frisoni, Rozzini, Bianchetti, & Trabucchi, 1993), the frontal assessment battery (FAB, Dubois, Slachevsky, Litvan, & Pillon, 2000; Iavarone et al.,

[2] MRI and PET: 3 patients; MRI and CAT: 1 patient; only MRI 8 patients, only PET 4 patients.

2004), the Rey's auditory verbal learning test (Ricci, Graef, Blundo, & Miller, 2012), word fluency (Costa et al., 2014), Raven's coloured progressive matrices (Ambra et al., 2016), freehand copying of drawings, and copying of drawings with landmarks (Gainotti, Miceli, & Caltagirone, 1977). We refer the reader to Table 1 for descriptive statistics of these neuropsychological. Inclusion criteria for both AD patients and healthy controls were: 1) MMSE raw score ≥ 16; 2) between 50 and 90 years of age; 3) no less than 3 years of schooling; 4) normal or corrected-to-normal vision with no history of eye surgery; 5) no history of neurological (other than AD) and/or psychiatric disorders; 6) no history of alcohol or substance abuse and/or use of medications likely to affect cognitive functioning; 7) able to understand the instructions and perform the task.

Eighteen AD patients[3] and all healthy controls also completed a neuropsychological battery of tests at the end of the eye-tracking visual search task (refer to Table 2 for descriptive and inferential t-test statistics comparing the two groups). Specifically, they completed: (1) the Albert's line cancellation task (Fullerton, Mcsherry, & Stout, 1986), which tests for spatial neglect; (2) a word reading and an object naming task from the "Esame Neuropsicologico Per l'Afasia" (neuropsychological test battery for aphasia - ENPA, Capasso & Miceli, 2001), to evaluate potential impairments in reading and object recognition (i.e., agnosia) and (3) the forward digit span from the Wechsler adult intelligence scale (WAIS-IV, Wechsler, 2008), which tests short-term memory, to examine the capacity of our participants to retain the identity of the cued object across the search task. All participants were at ceiling on the Albert's task and displayed similar performances on word reading and object naming. Even though healthy controls had a significantly higher digit span than AD patients, we note that this latter group was able to correctly remember an average of 4.83 digits, which suggests that their short-term working memory was sufficiently preserved to cope with the visual search task. All participants were naive to the purpose of the study and unfamiliar with the stimulus material. The study was approved by the Psychology Research Ethics Committee at the

[3] Two AD patients reported fatigue and did not want to continue with the additional neuropsychological assessments.

School of Philosophy, Psychology and Language Sciences at the University of Edinburgh (Ref: 12-1617) prior to starting the data collection; written consent was collected at the beginning of each session.

Design

A 2x2x2x2 mixed factorial design was used with *Semantic Relatedness* (unrelated, related), *Visual Saliency* (non-salient, salient), and *Target* (absent, present) as within-participant variables, and *Group* (control, AD) as a between-participant variable.

Stimuli

We used the 128 five-object arrays from Cimminella et al. (2020) and created a further 32 arrays (i.e., a total of 160 items) by crossing the visual saliency (non-salient, salient) and the semantic relatedness (unrelated, related) of 40 critical objects (i.e., 40 * 4); refer to Supplementary Material A for miniatures of the experimental arrays. The position of the critical object in the array was rotated across items to prevent location biases. A total of 200 objects were taken from the Bank of Standardized Stimuli (BOSS) database (Brodeur, Dionne-Dostie, Montreuil, & Lepage, 2010; Brodeur, Guérard, & Bouras, 2014), and used to create the experimental arrays (i.e., 40 as critical objects and 160 as distractors). All objects were univocally classifiable into 20 semantic categories (see Cimminella et al., 2020, for details on the semantic category norms). In addition, all objects were named by a sample of Italian participants to obtain naming norms in Italian (the reader is referred to Supplementary Material B for the norming of the materials). No object picture was presented more than once to avoid any uncontrolled effect that may derive from repeated exposures to the same stimulus.

The arrays were presented on a uniform white background, at a resolution of 1024 x 768 pixels and at a viewing distance of 75 cm. Object pictures measured 150 x 150 pixels (4.25° x 4.47° of visual angle) and were arranged on an imaginary circle such that the midpoint of each object was equidistant from the centre of the array (corresponding to the central fixation cross) and from the two adjacent object midpoints. The circle had a fixed radius of 344 pixels (9.75°), while the distance between objects was 404.40 pixels (11.46°).

We manipulated the visual saliency of the critical object by changing its brightness/contrast and hue/saturation with GIMP (Version 2.8.2) to make it visually more conspicuous in the salient than in the non-salient condition. We validated the effectiveness of our manipulation with the Walther and Koch's Matlab Saliency Toolbox (2006): a Wilcoxon signed-rank test confirmed that the critical object was ranked among the most visually conspicuous regions of the array in the salient condition (*Mdn* = 1) and the least in the non-salient condition (*Mdn* = 4), $p < .001$, z-coefficient = -7.98.

We implemented the semantic relatedness manipulation by creating object arrays with all objects belonging to the same semantic category (related), or all distractors of the same semantic category but the critical object of a different one (unrelated). To validate the semantic relatedness manipulation, we computed the mean of the semantic similarity score of the critical object with every other distractor in each experimental array using Latent Semantic Analysis (LSA, Landauer & Dumais, 1997; Landauer, Foltz, & Laham, 1998), trained on co-occurrences of words (as implemented by Hoffman, Lambon Ralph, and Rogers 2013) and on labels of objects (as normed by Brodeur et al. 2010, 2014). A t-test confirmed that semantic similarity between the critical object and all other distractors was significantly higher in the semantically related (*M* = .44, *SD* = .24) than unrelated condition (*M* = .01, *SD* = .08), $t(39) = 10.52$, $p < .001$, Cohen’s d = 1.66.

We also included 40 five-object filler arrays, 32 arrays from Cimminella et al. (2020), and 8 new arrays created using objects from the BOSS database (Brodeur et al., 2010, 2014). The filler items ensured a balanced distribution of target detection response (i.e., 50% object present, 50% object absent); and were not systematically manipulated in semantic relatedness or visual saliency nor will they be analysed. Each participant saw the same 40 fillers and 40 unique experimental arrays, which were counterbalanced across the conditions of visual saliency, semantic relatedness, and target (absent, present) using a Latin square rotation. In the target-present condition, the cue word of the search target, i.e., the target name, always referred to a critical object depicted in the array. In the target-absent condition, the cue word did not refer to any object in the arrays, but it was either semantically related to the critical object depicted in the display and unrelated to all other semantically homogenous distractor objects (M = .03, SD = .11), or semantically related to all objects (M = .30, SD = .21), t(39) = 7.02, p< .001. Cohen's d = 1.11 (the reader is referred to Supplementary Material C for the full list of target-present and target-absent experimental arrays used in this study). Finally, we used the Bank of Local Analyzer Responses (BOLAR) method (Zelinsky, 2003) to examine whether the critical object was visually more similar to the distractors when semantically related rather than unrelated to them (Cimminella et al., 2020). We found that this was indeed the case (related: *M* = .52, *SD* = .13; unrelated: *M* = .49, *SD* = .13; *t*(39) = 2.39, *p* = .02, Cohen's *d* = 0.38) and so controlled for the potential confounding effects of visual similarity on search by including it as a quasi-experimental predictor in our models (see the Statistical Analysis sub-section below for details).

Apparatus

Visual stimuli were displayed on a 19-inch Sony SDM E96D monitor, and eye movements were recorded using a Gazepoint GP3 HD 150 eye-tracker (150 Hz sampling rate). A pilot study on a pool of young participants ensured that the Gazepoint GP3 HD 150 eye-tracker was able to detect semantic relatedness effects on eye movements in a similar way to the EyeLink 1000 (SR Research, 1,000 Hz), used in Cimminella et al. (2020), despite its lower sampling rate; see Supplementary Material D for the pilot study. A forehead and chin rest were used to stabilise participants' viewing position. The experiment was built using OpenSesame (Version 3.1.9, Mathôt, Schreij, & Theeuwes, 2012) and the PyGaze Python plug-in (Dalmaijer, Mathôt, & Van der Stigchel, 2014) was used to acquire the eye-movement data.

Procedure

At the beginning of each experimental session, the eye tracker was calibrated using a 9-point grid appearing on the monitor. Each trial began with a fixation cross at the centre of the display; as

Figure 2

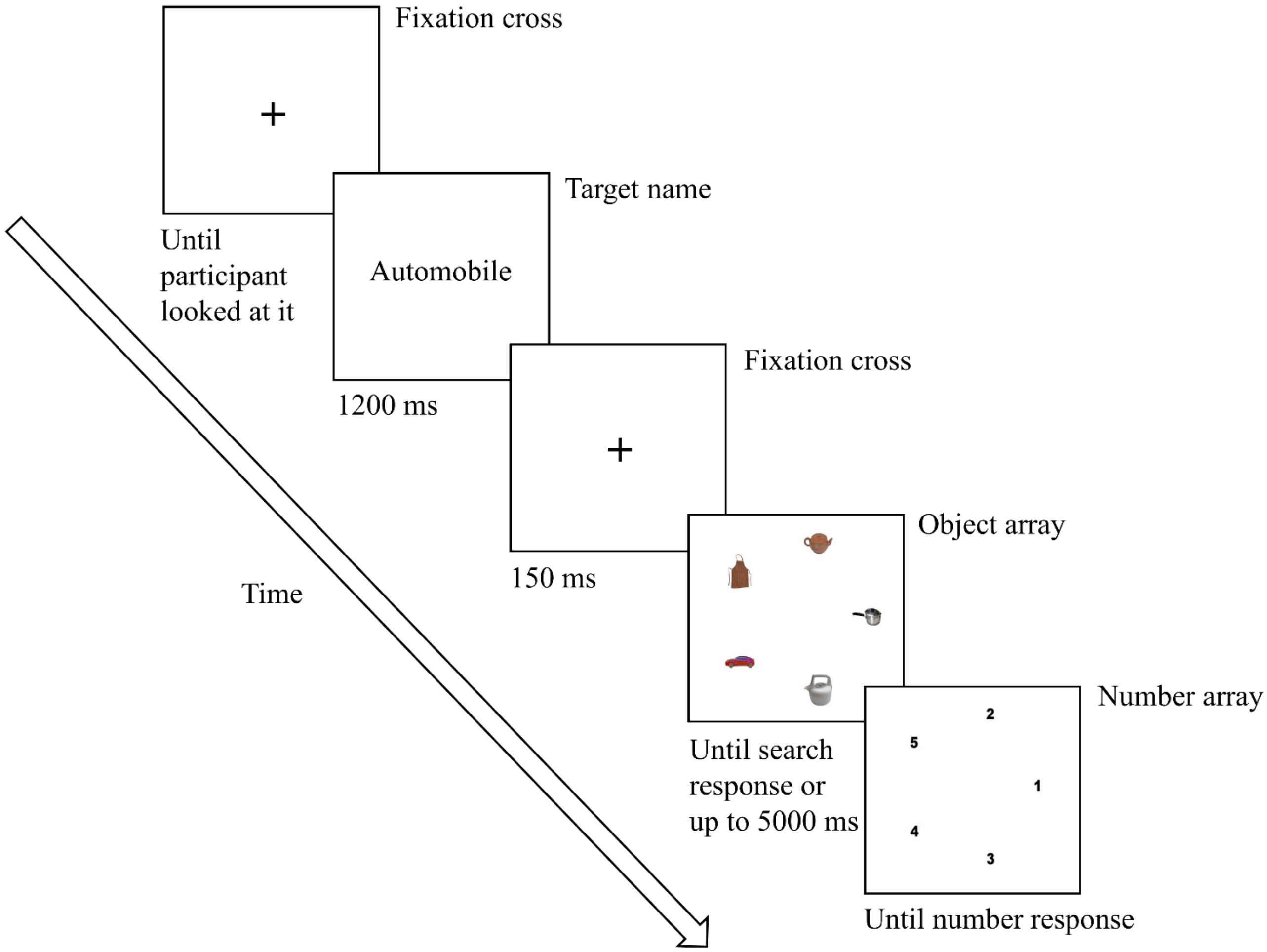

Figure 2. Example of a trial. The target name was cued ("automobile" is the Italian translation for "car") after the presentation of a fixation cross. Then, the same fixation cross appeared for 150 ms, followed by the object array. If the participant indicated that a target was found, the object array was replaced with a number array, and she/he was asked to remember the location of the object by verbally indicating the corresponding number in the array. When the participant responded that the target was not found, the object array was immediately followed by the next trial.

soon as participants looked at it, the experimenter, who was monitoring their gaze position, manually pressed the F key on their keyboard to trigger the cue word indicating the search target. The word was visible on the screen for 1,200 ms, followed by another central fixation cross for 150 ms, and then the object array was displayed. Participants received written and verbal instructions and were asked to perform the task as quickly and accurately as possible by verbally responding *sì* (Italian for *yes*) if the target was present in the array, or *no* if it was not. The experimenter recorded participants' responses by pressing the left or the right arrow key, respectively. If the participant answered *no,* the experiment progressed to the next trial. If the participant answered *yes*, the object array was replaced by a number array, and the participant was asked to verbally indicate the number matching the target location. This provided us with an additional verification of the search accuracy; responses were regarded as correct only if both the search response and the number response were accurate. If participants did not respond within 5,000 ms, a null response was logged (see Figure 2 for an example of a trial run). Each participant completed 4 practice trials and 80 randomized trials (40 experimental and 40 filler trials). If a patient could not remember the task, the experiment was stopped, and the instructions and the practice session repeated before continuing the session. The experimental session lasted approximately 45 minutes.

Data Analysis

Data processing

Fixations and saccade events were extracted from the raw eye movement samples with the I2MC algorithm, which is particularly suitable for noisy and low frequency data (Hessels, Niehorster, Kemner, & Hooge, 2017), using MATLAB (R2016b). Out of the 1,600 experimental trials considered in the analysis (i.e., 40 trials x 40 participants), we discarded 4 trials because of machine error (no eye movement was recorded) and 57 trials of the target-present condition where the number responses were inaccurate. On the remaining trials (1,539), we analysed the response accuracy. The eye-movement measures were computed only on accurate trials in which the critical object was fixated at least once (1,178 trials).

Dependent variables

We considered *response accuracy* to measure the target detection performance (a binary variable coded as 0 = Incorrect; 1 = Correct), and the following measures from the fixation data: *latency to first fixation*, which is the time (in ms) between the onset of the array and the first fixation on the critical object; and *first-pass dwell time*, that is the ratio between the sum of all fixations during the first inspection of the critical object and all other fixations during the trial. The latencies to first fixation were z-scored to account for general slowing effect associated to AD (Faust, Balota, Spieler, & Ferraro, 1999).

Statistical analyses.

Linear and generalised linear mixed-effects models (G/LMM), as implemented by the lme4 package (Bates et al., 2015) in R (version 4.0.0), were used to analyse the data. We adopted the same forward best-path model selection procedure as in Cimminella et al. (2020), whereby we start by evaluating the random variables and then proceed by adding the predictors as main effects and in interaction, one-by-one, while testing whether the inclusion of each new parameter would significantly improve the log-likelihood of the model fit using chi-square tests. The only difference here with this approach is that the fixed effect of group was retained during model selection even when found non-significant to test for its potential interactions with the variables of interest of our study. The fixed effects considered, and centred to reduce co-linearity, were: *Semantic Relatedness* (Unrelated, Related), *Visual Saliency* (Non-salient, Salient), *Target* (Absent, Present), *Group* (Control , AD), and *Visual Similarity*, which was obtained by splitting the 160 items into two groups (Dissimilar, Similar) based on the median score obtained with the BOLAR (i.e., .52). The random variables included in the models, both as intercepts and slopes, were Participant (40) and Item (160). We report the coefficients[4], standard errors, t-values (LMM), and z-values (GLMM) of those predictors that were retained in the final models. The p-values were based on Satterthwaite approximation for denominator degrees of freedom for LMMs models, on asymptotic Wald tests for GLMM models, and computed using the lmerTest R package (Kuznetsova, Brockhoff, & Christensen, 2017).

The data and R script to reproduce visualisations and analyses are available in the Open Science Framework (https://osf.io/gyutd/)

[4] Bi-variate correlation matrices detailing the association of all predictors in each G/LME model are reported in Supplementary Material E.

Figure 3

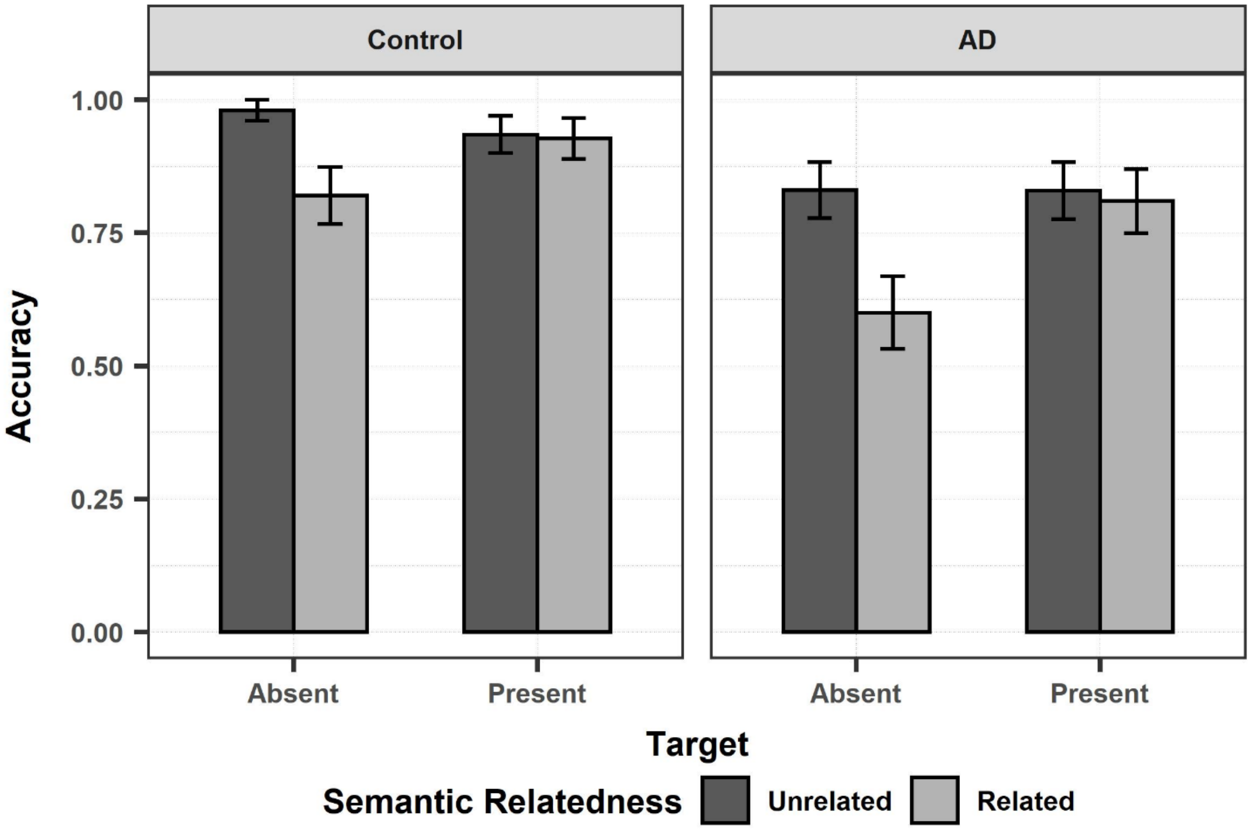

Figure 3. Mean response accuracy (proportions) for the Control (Left Panel) and AD group (Right Panel), in Target-Present and Absent trials (on the x-axis), in the Semantically Unrelated (dark grey) vs. Related (light grey) condition. Error bars represent 95% confidence intervals around the mean.

Results

Model coefficients for response accuracy[5], latency to first fixation and first-pass dwell time are reported in Table 3. On response accuracy (Figure 3), we found a significant main effect of group, whereby AD patients performed less accurately than healthy controls. There was also a significant main effect of semantic relatedness, and a significant interaction between semantic relatedness and target: accuracy was higher when the critical object was semantically unrelated than related to the distractors, with this difference being greater in target-absent than target-present trials.

[5] On this measure, we demonstrated using a binomial test that the performance of AD patients was significantly higher than chance across all experimental conditions (p <. 01), indicating that they were able to complete the task.

Figure 4

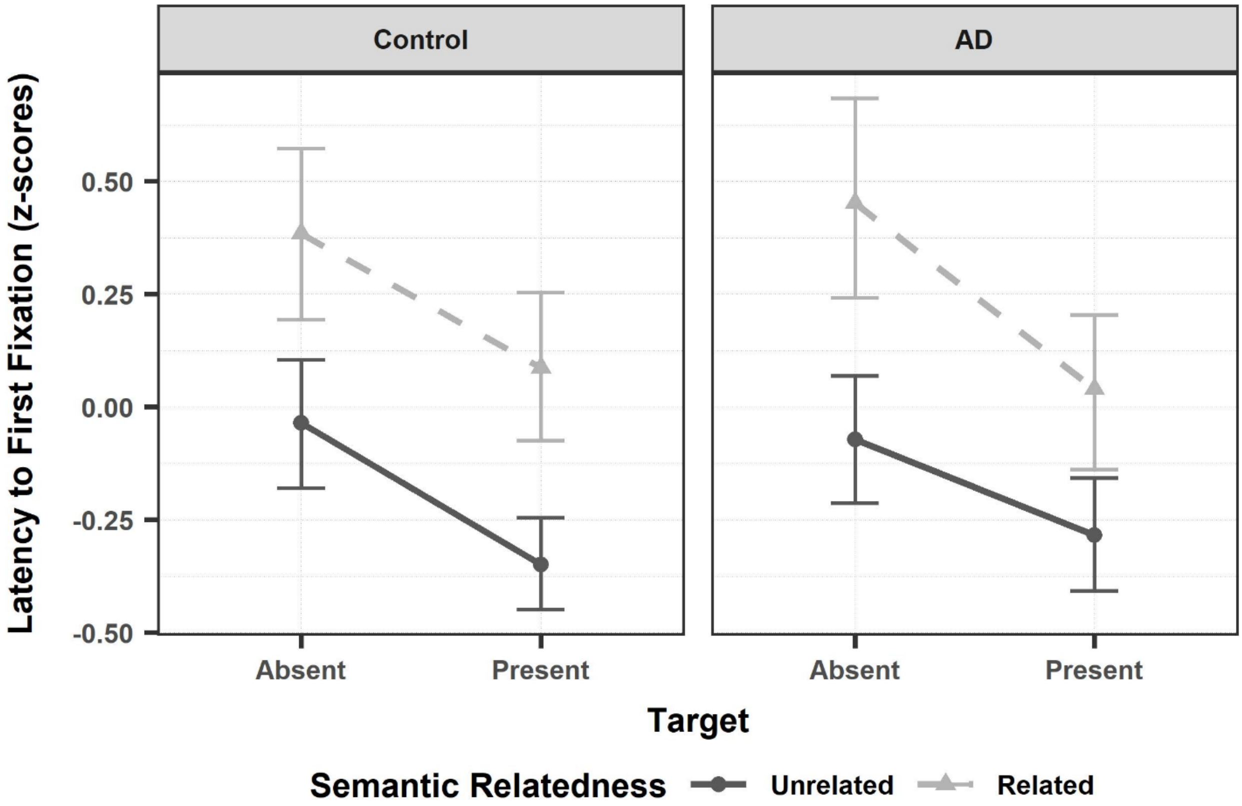

Figure 4. Mean latency to first fixation (z-scores) on the critical object for the control (Left Panel) and AD group (Right Panel), in Target-Present and -Absent trials (on the x-axis), with the Semantic Relatedness of the critical object marked using line types and colours (Unrelated: dark grey, solid line; Related: light grey, dashed line). Error bars represent 95% confidence intervals around the mean.

When looking at latency to first fixation (Figure 4), we found that the critical object was looked at earlier when it was semantically unrelated to the other distractors than when it belonged to the same semantic category, and on target-present compared to target-absent trials. No other predictor (e.g., visual saliency or visual similarity) was found to be significant, either as main effect or interaction.

On first-pass dwell time (Figure 5), we found longer dwell times for the healthy age-matched controls than for the AD patients, when the critical object was semantically unrelated rather than related to the distractors and in target-present trials compared to target-absent trials. Moreover, when the critical object was semantically unrelated to the distractors, this resulted in longer dwell times in the healthy control group than in the AD group, and in target-present

Figure 5

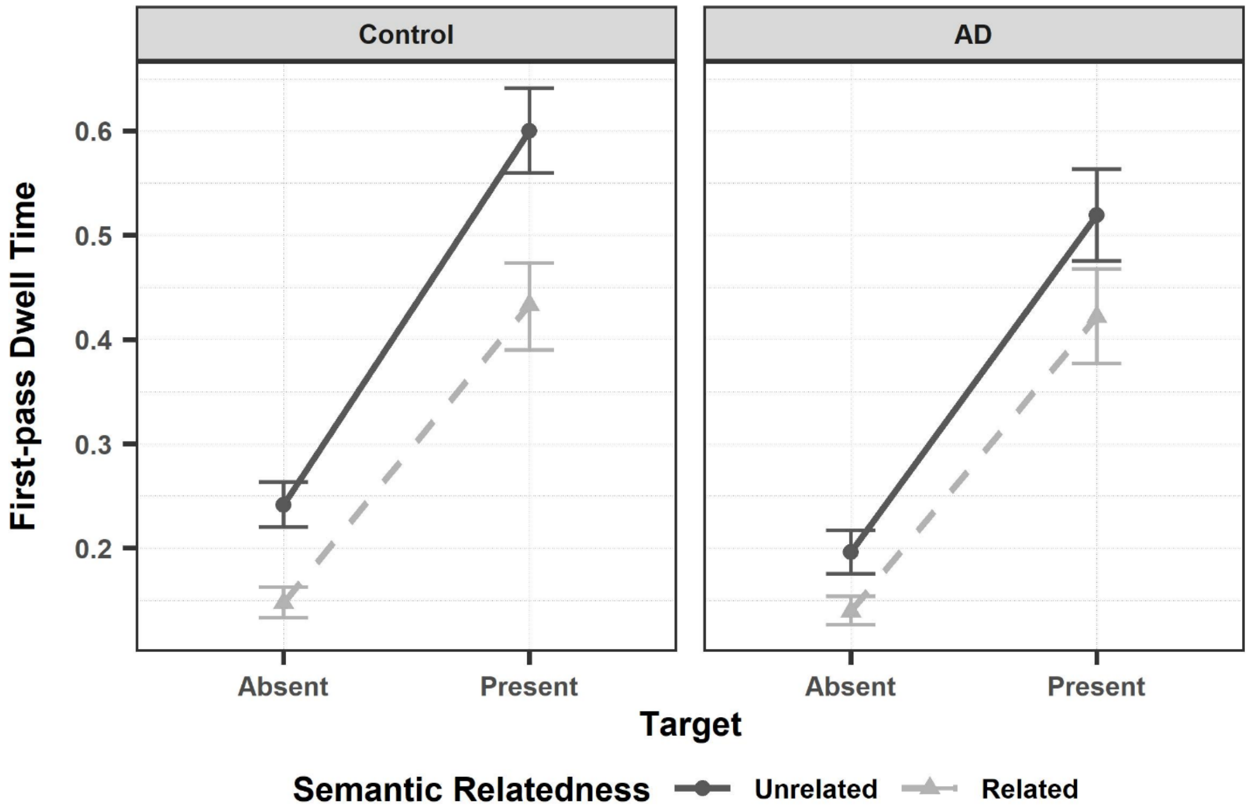

Figure 5. Mean first-pass dwell time (proportions) on the critical object for the control (Left Panel) and AD group (Right Panel), in Target-Present and -Absent trials (on the x-axis), with the Semantic Relatedness of the critical object marked using line types and colours (Unrelated: dark grey, solid line; Related: light grey, dashed line). Error bars represent 95% confidence intervals around the mean

compared to target-absent trials. Importantly, we did not find any effect of visual saliency or visual similarity, either as main effect or as interaction, in any of the measures reported herein[6].

[6] We replicated the significant main effects of semantic relatedness and target when analysing overall dwell time, i.e., the ratio between the sum of all fixations on the critical object and the sum of all remaining fixations occurring during the trial (unrelated: $M = .47$, $SD = .26$; related: $M = .39$, $SD = .24$; $\beta = -.10$, $SE = .01$, $t = -7.79$, $p < .001$; target-absent: $M = .24$, $SD = .14$; target-present: $M = .61$, $SD = .21$; $\beta = .36$, $SE = .01$, $t = 27.32$, $p < .001$).

Table 3

Dependent Variable	Predictor	β	SE	z-value or t-value	p-value
Accuracy	Intercept	2.21	0.15	14.50	**< 0.001**
	Semantic Relatedness	- 0.93	0.21	- 4.56	**< 0.001**
	Group	- 1.32	0.23	- 5.70	**< 0.001**
	Target	0.22	0.24	0.95	0.34
	Visual Similarity	- 0.36	0.20	- 1.80	0.07
	Semantic Relatedness:Target	1.58	0.34	4.67	**< 0.001**
Latency to first fixation (z-scores)	Intercept	0.02	0.04	0.41	0.68
	Group	0.04	0.05	0.74	0.46
	Target	- 0.31	0.05	- 6.06	**< 0.001**
	Semantic Relatedness	0.43	0.09	4.91	**< 0.001**
	Visual Similarity	0.15	0.08	1.80	0.07
	Group:Target	- 0.01	0.10	- 0.14	0.89
	Group:Semantic Relatedness	0.02	0.13	0.20	0.84
	Group:Visual Similarity	0.09	0.10	0.90	0.37
First-pass dwell time	Intercept	0.35	0.01	36.01	**< 0.001**
	Target	0.31	0.02	18.46	**< 0.001**
	Semantic Relatedness	- 0.11	0.01	- 7.53	**< 0.001**
	Group	- 0.03	0.02	- 2.30	**0.02**
	Semantic Relatedness:Target	- 0.05	0.02	- 2.30	**0.02**
	Semantic Relatedness:Group	0.05	0.02	2.26	**0.02**

Table 3: Linear and Generalised Linear Mixed-effects Model Outputs. *Note*. Predictors are listed in the table in the same order as they were entered in the models. The predictors used in the different models are: Semantic Relatedness (Unrelated = -.49, Related = .51), Group (Control = -.49, AD = .51), Target (Absent = -.48, Present = .52), and Visual Similarity (Dissimilar = -.51, Similar = .49). The z-value is reported for the generalised linear mixed-effects model with binomial link of the response accuracy, and t-values instead are reported for all other linear mixed-effects models (i.e., latency to first fixation and first-pass dwell time).

Discussion

A frequent feature of AD patients' cognitive profile is an impairment in tasks requiring explicit access to semantic knowledge, such as category fluency (Salmon et al., 1999), word-to-picture matching (Adlam et al., 2006) and object naming (Holmes et al., 2006). There is evidence, however, that some implicit semantic abilities related to automatic processing may be preserved (e.g., Chertkow et al., 1994; Perri et al., 2003; Perry & Hodges, 1999), and eye-movement responses can be revelatory of such implicit processes (Hannula et al., 2010).

In the present study, we investigated whether AD patients' ability to process semantic information of visual objects is preserved, and whether such processing can occur in extra-foveal vision. AD patients and healthy age-matched controls searched for a target (e.g., a car), which was either semantically related or unrelated to a set of semantically homogenous distractors (e.g., an array of vehicles or kitchen utensils, respectively). The target object was either visually available in the display (target-present trials), or it was replaced by a semantically related competitor of the target (target-absent trials), and it was either visually salient or non-salient to evaluate potential bottom-up stimulus driven effects. So, if the semantics of objects were processed in extra-foveal vision, we expected semantically unrelated targets to be prioritised in early overt attention and be easier to recognize as deviant from the context of the array. On the contrary, we expected that a semantically related critical object would be recognized with more difficulties in target-absent trials, as the on-going competition of co-activated semantic distractors would increase the chance of false detection, i.e., it requires the involvement of memory processes.

Results revealed a significant main effect of group on search accuracy, with AD patients performing worse than age-matched controls, even if significantly above chance across all experimental conditions, which is in line with previous evidence that AD can lead to impaired object identification (Porter et al., 2010; Laatu, et, al., 2003; Tales et al., 2002). However, regardless of the group, all participants detected the critical object more accurately when it was semantically unrelated to the distractors compared to when it belonged to the same semantic category. This result indicates that the semantic information of the critical object was processed enough to lead to a significant difference in its identification, and crucially, this effect was also observed in the AD group. In contrast to Seckin, et al., 2016, we did not observe greater difficulty to recognize semantically related objects in our neuropathological population, i.e., AD, compared to healthy older adults, which may reflect underlying differences between our patients and individuals with more specific conditions such as semantic aphasia. Another important finding was the poorer recognition performance for semantically related objects in target-absent trials, which indicates that our participants found it harder to resolve the ongoing competition of semantically related distractors, especially because they needed to rely more strongly on memory for the critical object, which was no longer visually available in the context. Note that we did not find any difference associated with the semantic relatedness of the critical object on the detection accuracy of young participants in Cimminella et al. (2020), but this discrepancy can be accounted for by the fact that performance was at ceiling in that study.

On eye-movement measures, we found that both AD patients and healthy controls looked at the critical object significantly earlier, and for longer, when it was semantically unrelated compared to when it was related to the other distractors. These findings align with our previous work on healthy young participants which used the same experimental paradigm (Cimminella et al., 2020), and complement previous work using naturalistic scenes that also demonstrated extra-foveal processing in healthy older adults (Borges, Fernandes, & Coco, 2020) and unravelled the links to the brain activity time-locked to it (Coco, Nuthmann, & Dimigen, 2020). These results strongly suggest that extra-foveal processing of object semantics occurred in AD patients, and as for the healthy older adults and the younger adults of our previous studies, it contributed to guiding overt visual attention. The solid evidence of intact processing of object semantics observed on both the allocation of visual attention and the target detection accuracy suggests that the semantic deficits found in previous studies of AD patients may be associated with factors other than a complete loss of semantic knowledge. This core finding has important methodological, theoretical, and practical implications for AD research.

Methodologically, our results point to two key factors that call for attention when assessing semantic abilities in AD patients: whether the task requires explicit or implicit access to semantic knowledge; and the nature of the stimuli used, i.e., verbal or non-verbal. Semantic impairments in AD have been typically reported in category fluency, object naming and word-to-picture matching tasks (Holmes et al., 2006; Monsch et al., 1994; Salmon et al., 1999; Spaan et al., 2003), which require participants to intentionally access their semantic knowledge and retrieve relevant information. In contrast, in the present study we used a visual search task, which effectively entails a cueing component, i.e., the target of the search is prompted to the participant, whereby explicit retrieval of semantic information is not required. We argue that this resulted in the relatively automatic activation of a specific target template that facilitated processing of the associated semantic information, thus leading to the emergence of preserved semantic abilities in AD patients. The other factor that may have contributed to our findings is that the stimuli in our task consisted of non-verbal material (i.e., pictures of objects), which is known to have a cognitive advantage over verbal material that demands more complex strategies of lexical matching and retrieval (Ally, Gold, & Budson, 2009a; Ally et al., 2008). It is possible that studies that employ verbal material, which requires additional processing effort and resources compared to pictures, may find AD-related semantic impairments which would not be observed in studies that employ the same tasks but with visual material (see O'Connor & Ally, 2010 for an example of a study about the effects of stimulus format on memory tasks). In fact, a limitation of the present study is that we did not directly compare semantics relatedness effects using both verbal and non-verbal material. One objective of our current investigations on this topic is to utilise a similar experimental paradigm as in this study, but to probe search using verbal stimuli only, i.e., a target word followed by an array of words. We trust this will help elucidate the role played by the stimulus material on semantic processing in AD patients.

Our study also highlights the methodological usefulness of eye-movement responses in research on clinical populations, because they can index implicit mechanisms of semantic processing (Hannula et al., 2010). In the present study, eye movements revealed preserved extra-foveal capture by object semantics in AD patients, which counters previous evidence of impaired extra-foveal processing in this population (Boucart, Bubbico, Szaffarczyk, & Pasquier, 2014; Rösler, Mapstone, Hays-Wicklund, Gitelman, & Weintraub, 2005). We attribute this discrepancy to the semantic pop-out effect induced by our experimental paradigm: when patients were faced with a single object that was semantically divergent from the surrounding context, this facilitated its covert processing in extra-foveal vision and elected it as a possible target to saccade to. This explanation would align with previous evidence of similar performance in AD patients and healthy controls in instances where the selective demands of the task are reduced (e.g., Tippett et al., 2004). An important question that stems from this finding is whether similar evidence of preserved semantic processing would manifest if all objects were clustered around central fixation and placed within foveal vision. This experimental manipulation would remove the need for overt eye-movements, whereby performance would depend solely on covert attention. Given the current results, we would expect target detection accuracy to show the same advantage for a semantically unrelated compared to a related critical object in AD patients, as such a measure is independent of the overt allocation of visual attention.

Analysis of the first-pass dwell times also indicated preserved semantic abilities in the AD group, as a semantically unrelated critical object was looked at more than a semantically related one, although this difference was less pronounced in the AD patients than it was in the healthy controls. The evidence of longer foveation mediated by object semantics hints at other mechanisms of target identification, closely related with linguistic processing, which may be spared by AD too. Psycholinguistics research on young adults has, in fact, clearly shown effects of semantic relatedness during spoken language situated in a visual context (e.g., arrays of visual objects; Huettig & Altmann, 2005; or Coco et al., 2016, for photo-realistic stimuli); which has led to integrative proposals about the relationship between attention, memory and language (see Huettig et al., 2011, for an example of an integrative theoretical framework). Future research on AD should address questions about situated language processing, focusing on whether evidence of spared semantics would also emerge when language and vision are synchronously active.

Theoretically, our findings argue against a generalised loss of semantic memory in AD (Adlam et al., 2006; Hodges et al., 1992; Salmon et al., 1999), and suggests that semantic processing may be spared, at least in part, when the task can be performed relatively automatically (Ober, 2002; Perri et al., 2003). Moreover, our results seem to align with a two-stage model of recollection (Moscovitch, 2008), even if we realise that such a model was mainly conceived to describe episodic memory. In the first-stage, semantic information is implicitly retrieved from memory, which is reflected in the responses indirectly associated to memory processes (e.g., eye movement). Then, in a second slower stage, such retrieved information becomes explicitly available, influencing downstream responses (e.g., the manual response of target detection). This would be consistent with evidence of gradual semantic degradation in patients with semantic aphasia (Seckin et al., 2016): as the pathology degrades semantic memory, concepts become progressively more blurred rather than being entirely lost.

Our results also have implications for neuropsychological diagnostics criteria and theoretical accounts of semantic memory. Additional correlation analyses of the AD patients' neuropsychological profiles and semantic relatedness effects on their search responses, in fact, failed to show any significant association between the two (see Appendix for a description of this analysis and their results). A key implication of this dissociation is that visual guidance by object semantics during a search task is an index of cognitive functioning which escapes what is assessed using classic neuropsychological tests. Additionally, the lack of an association between verbal semantic abilities of our AD patients (e.g., RAVLT) and visual guidance by object semantics may argue against the notion of a unitary semantic memory system (Bright, Moss, & Tyler, 2004; Lambon, Patterson, & Hodges, 1997) and suggests instead that the semantic system may be divided into modality-specific subsystems, which interact with one another but separately deal with pictures and words (Paivio, 2014; Saffran, Branch Coslett, Martin, & Boronat, 2003). If we assume this division, it follows that AD may involve preserved semantic processing for visual material and a specific impairment in the semantic processing of verbal material.

As a point of discussion, and differently from our previous study on young participants, the analysis of the probability that the first fixation would fall on the critical object did not show any effect of semantic relatedness[7]. This suggests that, regardless of pathology, older adults require more fixations to orient their gaze in the visual scene, which is in line with the general slowing associated with cognitive aging (Crawford, Smith, & Berry, 2017; Rösler et al., 2005). Moreover, our study did not show any other key difference in fixation behaviour between the healthy control participants and the AD group, beyond the significantly decreased first fixations time on the critical object in patients (see Fernández et al., 2018 for a similar finding). That being said, differences on eye-movement responses of AD patients have mostly been found on saccades (e.g., Fletcher & Sharpe, 1986; Yang, Wang, Su, Xiao, & Kapoula, 2013). Our analysis comparing the mean saccade amplitude of the two groups did not show any significant difference and hence it was not reported. This result must be taken cautiously due to the relatively low sampling rate of our eye-tracker that may not have been sensitive enough to detect finer differences, which calls for future research specifically looking at saccade measures in visual search paradigms adapted to the purpose (e.g., by varying systematically the distance of the target and distractor objects in the arrays).

In sum, our study suggests that AD patients retain semantic knowledge and are able to access it when the task involves more implicit processes and utilises non-verbal stimuli, probably indicating that they present deficits when this knowledge has, instead, to be intentionally and explicitly retrieved. These findings also have some practical implications, as determining which conditions can enable the emergence of preserved semantic processes in AD patients may allow the development of strategies aimed at facilitating their access to and use of semantic knowledge more effectively, which in turn could increase patients' quality of life.

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Conflict of Interest Statement

The authors declare that there is no conflict of interest.

[7] We did not include the full description of this analysis, as it was not significant.

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Appendix

Pearson correlation was used to determine whether the neuropsychological performances of the AD patients were related to their manual and eye-movement responses to the visual search task. The aim of this analysis was to qualify the nature of semantic processing during visual search in relation to neuropsychological performance. Evidence of a dissociation between neuropsychological results and search responses would suggest that visual guidance by object semantics may be independent from what is classically assessed by off-the-shelf tests.

To get at a synthetic measure of semantic relatedness effects on search responses (i.e., accuracy, latency to first fixation and first-pass dwell time), we first computed by-participant averages across trials and separately for the two conditions of Semantic Relatedness and then calculated their difference (Unrelated - Related). This difference score reflects the amount of change that a semantically unrelated critical object implied on search responses compared to a semantically related object. For example, if a semantically unrelated object were expected to be looked at earlier than a semantically related object, we would expect the difference score for latency of first fixation to be negative. All measures were standardised and centred prior to this analysis.

Results revealed significant positive correlations between the mini mental state examination and two tests of short-term memory (RAVLT.IR and DSF), which is congruent with the type of functions assessed by the MMSE. Likewise, we observed significant positive correlations between RCPM, CD and CDL which are all tests tapping into visuo-spatial functions. Most importantly, however, we did not observe significant correlations between any of the neuropsychological tests and search responses. The only significant negative correlation observed on search responses was between the latency of first fixation and first-pass dwell time, which aligns with the main results reported on these measures: an unrelated object is looked at earlier but for longer compared to a semantically related object. Correlations which were significant at $p < .05$ are displayed in Figure 6, and the full results of these correlation analyses are reported in Table 4.

Table 4

	MMSE	FAB	RAVLT (IR)	RAVLT (DR)	WF	RCPM	CD	CDL	WR	ON	DSF	Accuracy	Latency to First Fixation
MMSE													
FAB	0.00												
RAVLT (IR)	**0.51***	0.14											
RAVLT (DR)	0.28	-0.34	**0.62****										
WF	0.27	0.40	0.18	-0.15									
RCPM	0.36	**0.55***	**0.56***	0.15	0.43								
CD	0.31	0.22	0.28	0.03	**0.54***	**0.69*****							
CDL	0.13	0.07	0.12	-0.03	0.32	0.45	**0.69****						
WR	0.07	0.29	0.15	-0.04	0.32	0.13	-0.05	-0.24					
ON	-0.09	0.16	0.23	0.20	-0.01	0.12	-0.07	-0.10	-0.02				
DSF	**0.76*****	0.46	0.33	-0.06	0.38	0.40	0.35	0.01	0.34	-0.03			
Accuracy	-0.28	-0.03	-0.06	-0.03	-0.09	-0.07	-0.08	-0.12	0.46	-0.09	-0.14		
Latency to First Fixation	-0.11	-0.29	-0.16	0.22	-0.02	-0.27	0.13	0.22	-0.23	-0.04	-0.27	-0.12	
First pass Dwell Time	0.07	0.06	-0.10	-0.23	-0.04	-0.14	-0.05	-0.11	0.33	0.25	0.38	0.08	**-0.53***

Table 4: Pearson correlation analysis examining the neuropsychological profiles of AD participants together with their responses to the visual search task (accuracy, latency to first fixation, first-pass dwell time). On search responses, we first computed by-participant averages across trials for the two conditions of Semantic Relatedness then derived a difference score (Unrelated - Related). This measure reflects the differential that semantic relatedness had on search responses. All measures have been standardised and centred before correlating them. Significant correlations are marked using bold face, and the associated p-value indicated using asterisks ($^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$).

Note. MMSE: Mini mental state examination; FAB: frontal assessment battery; RAVLT: Rey's auditory verbal learning test (IR, immediate recall; DR, delayed recall); WF: word fluency; RCPM: Raven's coloured progressive matrices; CD: freehand copying of drawings; CDL: copying drawings with landmarks; WR: word reading; ON: Object naming; DSF: Digit span forwards. The horizontal line in the table distinguishes between neuropsychological and search responses.

Figure 6

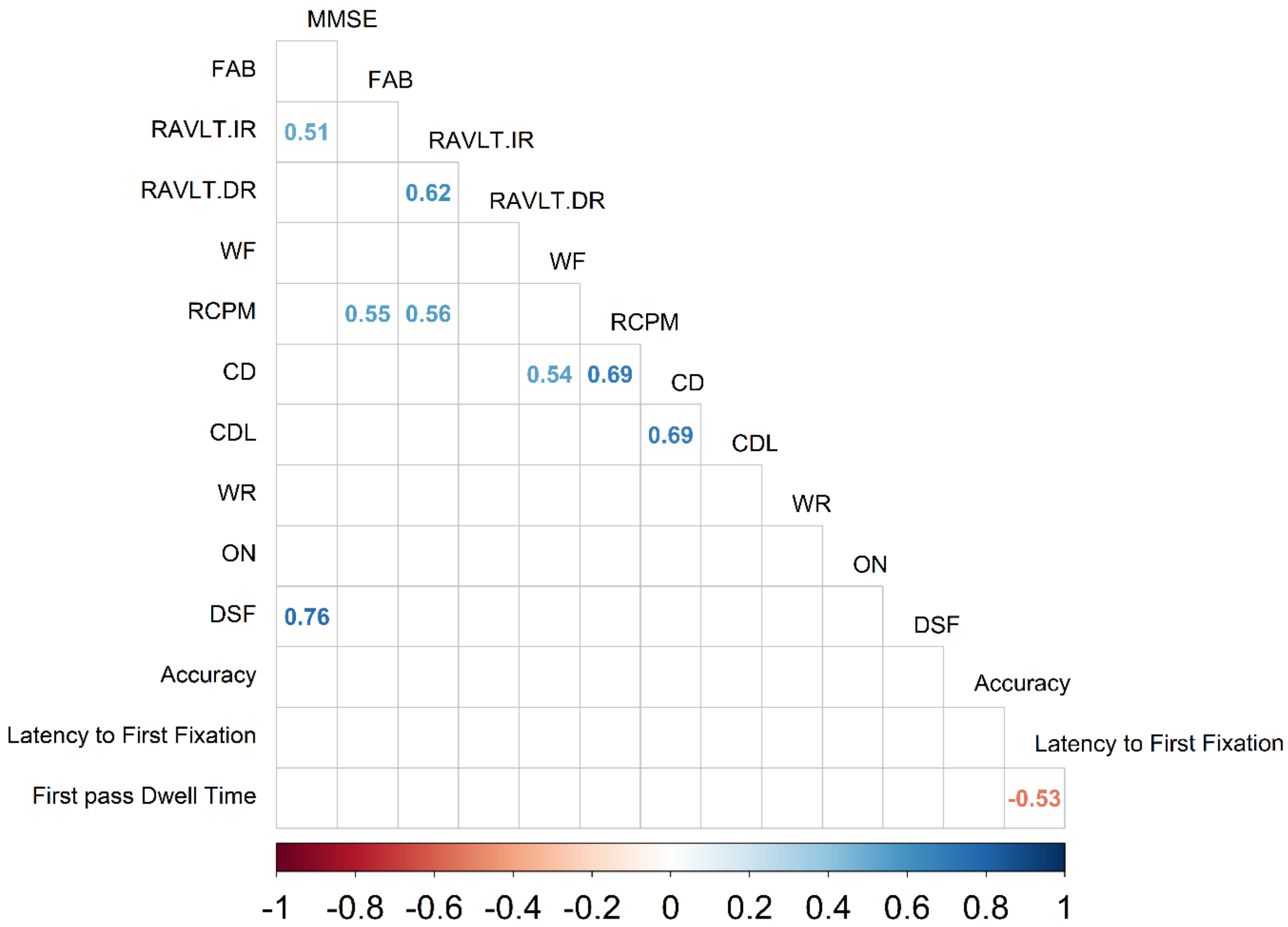

Figure 6: Pearson correlation plot examining the neuropsychological profiles of AD participants and their responses to the visual search task (accuracy, latency to first fixation, first-pass dwell time). On search responses, we first computed by-participant averages across trials for the two conditions of Semantic Relatedness then calculated a difference score (Unrelated - Related). This measure would reflect the differential that semantic relatedness had on search responses for each participant. All measures have been standardised and centred before correlating them. Only correlations significant at $p < 0.05$ are presented and empty cells indicate non-significant correlations. The colour indicates the strength of the correlation from red (−1) to blue (1). *Note.* MMSE: Mini mental state examination; FAB: frontal assessment battery; RAVLT: Rey's auditory verbal learning test (IR, immediate recall; DR, delayed recall); WF: word fluency; RCPM: Raven's coloured progressive matrices; CD: freehand copying of drawings; CDL: copying drawings with landmarks; WR: word reading; ON: Object naming; DSF: Digit span forwards.