

Naming unique entities in the semantic variant of primary progressive aphasia and Alzheimer's disease: Towards a better understanding of the semantic impairment

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Abstract

While the semantic variant of primary progressive aphasia (svPPA) is characterized by a predominant semantic memory impairment, episodic memory impairments are the clinical hallmark of Alzheimer's disease (AD). However, AD patients also present with semantic deficits, which are more severe for semantically unique entities (e.g. a famous person) than for common concepts (e.g. a beaver). Previous studies in these patient populations have largely focused on famous-person naming. Therefore, we aimed to evaluate if these impairments also extend to other semantically unique entities such as famous places and famous logos. In this study, 13 AD patients, 9 svPPA patients, and 12 cognitively unimpaired elderly subjects (CTRL) were tested with a picture-naming test of non-unique entities (Boston Naming Test) and three experimental tests of semantically unique entities assessing naming of famous persons, places, and logos. Both clinical groups were overall more impaired at naming semantically unique entities than non-unique entities. Naming impairments in AD and svPPA extended to the other types of semantically unique entities, since a CTRL > AD > svPPA pattern was found on the performance of all naming tests. Naming famous places and famous persons appeared to be most impaired in svPPA, and both specific and general semantic knowledge for these entities were affected in these patients. Although AD patients were most significantly impaired on famous-person naming, only their specific semantic knowledge was impaired, while general knowledge was preserved. Post-hoc neuroimaging analyses also showed that famous-person naming impairments in AD correlated with atrophy in the temporo-parietal junction, a region functionally associated with lexical access. In line with previous studies, svPPA patients' impairment in both naming and semantic knowledge suggest a more profound semantic impairment, while naming impairments in AD may arise to a greater extent from impaired lexical access, even though semantic impairment for specific knowledge is also present. These results highlight the critical importance of developing and using

a variety of semantically-unique-entity naming tests in neuropsychological assessments of patients with neurodegenerative diseases, which may unveil different patterns of lexical-semantic deficits.

Key words: Naming, Semantically unique entities, Semantic variant primary progressive aphasia, Alzheimer's disease, semantics, lexical access

1. Introduction

The semantic variant of primary progressive aphasia (svPPA), also referred to as semantic dementia, is a neurodegenerative disease characterized by a progressive deterioration of semantic memory (Gorno-Tempini, et al., 2011). The core cognitive features of patients with svPPA are impaired confrontation naming and single-word comprehension, most often accompanied with impaired object knowledge as well as surface dyslexia and dysgraphia. While semantic deficits in svPPA patients are relatively isolated, at least in the early stages, Alzheimer's disease (AD) is characterized by a cognitive decline typically beginning with episodic memory impairments but resulting in general debilitating dementia affecting many other cognitive domains (McKhann, et al., 2011). Interestingly, language impairments in AD initially affect confrontation naming and verbal fluency (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Hodges & Patterson, 1995; Huff, Corkin, & Growdon, 1986; Verma & Howard, 2012).

Therefore, both svPPA and AD patients present with impaired confrontation naming. While it is a core symptom of svPPA (Gorno-Tempini, et al., 2011), naming difficulties are much more heterogeneous in AD. Domoto-Reilly and colleagues found that approximately 41% of a large sample of early stages AD patients scored below the normal range when naming common entities (e.g. animals, objects, etc.) on the Boston Naming Test (Domoto-Reilly, Sapolsky, Brickhouse, & Dickerson, 2012). However, deficits in naming semantically unique entities (i.e., entities with a unique semantic and lexical association) such as famous persons have been shown to be more severe than for non-unique entities in AD (Delazer, Semenza, Reiner, Hofer, & Benke, 2003; Joubert, et al., 2010; Joubert, et al., 2008; C. Semenza, Mondini, Borgo, Pasini, & Sgaramella, 2003; Thompson, Graham, Patterson, Sahakian, & Hodges, 2002). Considering that both populations present naming impairments, it appears necessary to compare svPPA and AD patients in terms of their ability to name semantically unique entities. Studies which have investigated semantically

unique entities in dementia so far have largely focused on famous persons. However, it is necessary to determine if naming deficits in svPPA and AD patients extend to other categories of semantically unique entities such as famous places (e.g. landmarks and buildings) and famous logos (e.g. brands or everyday life pictograms). It is also critical to investigate if some types of items are selectively impaired within each population. The characterization of naming impairments across item types in each clinical population could be a valuable tool in clinical settings and contribute to identifying specific anomia profiles (e.g. proper name anomia or prosopagnosia). It also has the potential to improve differential diagnosis. To our knowledge, famous places have only been investigated in some patient populations such as Mild cognitive impairment patients (Ahmed, Arnold, Thompson, Graham, & Hodges, 2008), post-stroke aphasics (Vitali, et al., 2015), traumatic brain injury patients (Milders, 2000), and epileptic patients (Benke, Kuen, Schwarz, & Walser, 2013). Famous logos have never been used with patient populations.

Investigating naming for different types of semantically unique entities is critical for several reasons. First, it is still unclear if famous persons and other entities such as famous places are processed the same way and therefore equally difficult to name for AD and svPPA patients. Previous neuroimaging studies have demonstrated that naming both famous persons and places activate the same brain regions related to semantics (i.e. the left anterior temporal cortex), in addition to brain regions subserving category-specific perceptual processing (i.e. fusiform regions for faces and parahippocampal/lingual regions for places/buildings) (Gorno-Tempini & Price, 2001; Grabowski, et al., 2001). This could suggest that both types of entities would be relatively equally impaired in AD and svPPA, as is the case in mild cognitive impairment patients (Ahmed, et al., 2008) and traumatic brain injury patients (Milders, 2000). In AD, only famous-landmark identification has been investigated and shown to be as impaired as famous-person identification (Sheardova, et al., 2014). Secondly, in comparison to famous persons, famous places might be less time-period sensitive, which might be an advantage for the construction of a validated

neuropsychological test that is durable. Finally, logos are different from other types of semantically unique items in the sense that they are characterized by a very stable and invariable perceptual representation. They also have the potential to be a valuable tool for clinicians as an indication of patients' abilities to identify everyday life stimuli.

Comparing svPPA and AD patients on tests of naming and semantic knowledge of semantically unique entities may also provide insight into the nature of the impairment underlying anomia in these patients. Cognitive models of semantic memory suggest that naming impairments may be caused by either 1) a semantic impairment, in which stored information is lost, or 2) impaired lexical access, in which the access to stored information is dysfunctional (Lambon Ralph, 2014). While it is recognized that svPPA naming deficits result from the disease's characteristic progressive degradation of conceptual knowledge (Gorno-Tempini, et al., 2011; Reilly, Peelle, Antonucci, & Grossman, 2011; Rogers & Friedman, 2008), the nature of the impairment underlying anomia in AD is still a matter of debate. Previous studies have compared naming abilities and semantic knowledge in AD, i.e. the ability to name entities versus the ability to answer semantic knowledge questions about the same entities (Chertkow & Bub, 1990; Joubert, et al., 2010). A correspondence between naming impairments and impaired semantic knowledge in AD patients was observed, suggesting that word finding difficulties were at least in part due to underlying semantic disruption, which could potentially be combined with additional difficulties in the selection, manipulation, and retrieval of knowledge (Joubert, et al., 2010). Other studies observed strong associations between naming abilities and executive functioning in AD patients, suggesting that naming impairments may be associated in part with impaired controlled semantic retrieval (Reilly, et al., 2011). In terms of neuroanatomy, these two mechanisms are associated with different brain regions. Semantic processing has principally been associated with anterior temporal lobes (ATL) and lexical access mainly with the temporo-parietal junction (Gesierich, et al., 2011; Vitali, et al., 2015). While it is widely

acknowledged that naming impairments in svPPA are associated with atrophy in the ATLs (Gorno-Tempini, et al., 2004; Mesulam, et al., 2009), previous neuroimaging results in AD patients have provided support for the role of both regions in naming abilities (Domoto-Reilly, et al., 2012; Grossman, et al., 2004; Lars, et al., 2011; N. Nelissen, et al., 2011; Natalie Nelissen, et al., 2007; Vandenbulcke, Peeters, Dupont, Van Hecke, & Vandenberghe, 2007).

In this study, we aim to characterize and compare naming abilities in 13 AD patients, 9 svPPA patients, and 12 cognitively unimpaired elderly subjects (CTRL). To do so, we used a non-unique-entity naming test (the Boston Naming Test) and experimental semantically-unique-entity naming tests (famous persons, famous places, famous logos). While previous studies suggest that famous-person naming is more impaired than non-unique-entity naming in svPPA and AD, we aimed to evaluate if these impairments also extend to other semantically unique entities such as famous places and famous logos, which have never been studied in this population. In order to provide insight into the nature of the naming impairments observed (i.e. impaired lexical access vs. semantic impairment), semantic knowledge of semantically unique entities (for famous persons and places) was also assessed.

2. Material and methods

2.1 Participants

Thirteen patients with a clinical diagnosis of AD (5 women, 8 men), nine patients with svPPA (2 women, 7 men), and twelve CTRL (4 women, 8 men) took part in this study. Demographics of participants are presented in Table 1. The three groups were matched for age, gender, and education. The svPPA and AD patients were recruited through La Clinique interdisciplinaire de Mémoire du Centre hospitalier universitaire (CHU) de Québec and referred by a behavioral neurologist with expertise in neurodegenerative diseases and cognition (R.J.L.). svPPA patients were diagnosed according to currently accepted criteria (Gorno-Tempini, et al., 2011). Diagnosis of AD was made based on the criteria of the National Institute on Aging and the Alzheimer's Association workgroup (McKhann, et al., 2011). General exclusion criteria were as follows: native tongue other than French, left-handedness, developmental learning disabilities, past psychiatric disorder, history of traumatic brain injury, and uncorrected hearing and vision problems. The study was approved by the research ethics committee of the CHU de Québec (Project #2015-1909) and written informed consent was obtained from all participants.

2.2 Neuropsychological assessment

All participants completed a battery of standard neuropsychological tests to assess general cognitive status (Mini-Mental State Examination (MMSE); (Folstein, Folstein, & McHugh, 1975)), as well as a number of cognitive domains. These domains include nonverbal and verbal episodic memory (Immediate and delayed recall of the Rey Complex Figure Test (Meyers & Meyers, 1995; Osterrieth, 1944); Rey Auditory Verbal Learning Test (Rey, 1964)); language and semantic memory (Pyramids and Palm Trees Test (PPTT) (Howard & Patterson, 1992); Free fluency, orthographic and semantic fluency (Joanette, Ska, & Côté, 2004)), working memory (Forward and Backward Digit-span (Wechsler, 1997)), visual perception (Benton Line Orientation test (Benton, Hamsher, Varney, & Spreen, 1983; Qualls,

Bliwise, & Stringer, 2000); Benton Facial Recognition test (Benton, et al., 1983)), visuoconstructional skills (copy of the Rey Complex Figure Test (Meyers & Meyers, 1995; Osterrieth, 1944); Clock-drawing Test (Rouleau, Salmon, Butters, Kennedy, & McGuire, 1992)); and executive functioning (Trail making test A&B (Tombaugh, 2004); Stroop-Victoria Test (Spreen & Strauss, 1998)). Results are presented in Table 1.

2.3 Naming tasks

2.3.1. Non-unique-entity naming task.

The complete version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) was administered to participants. In this task, subjects are asked to name 60 black and white line drawings of single objects. The total score (out of 60) represents spontaneous correct answers (without cues). Scoring was based on a French-speaking Quebec adults validation study (Roberts & Doucet, 2011).

2.3.2. Semantically-unique-entity naming tasks.

Three semantically-unique-entity naming tasks were created. Twenty high quality color pictures were used in each one of the three tasks. For each task, pictures were displayed one at a time in a Powerpoint slideshow and participants were asked to name the item and to respond to some semantic knowledge questions. They had unlimited time to respond and all responses were recorded using a digital recorder. Items for the famous-person and famous-place tests were selected from a previous study (Vitali, et al., 2015). The semantically-unique-entity tests were intended to be very easy for cognitively unimpaired French-speaking Quebec older adults in order to reduce the impact of education on the tasks. The tests were specifically designed for this age-group and included items that were culturally and time-period appropriate.

2.3.2.1. Naming and semantic knowledge of famous persons.

First, participants were presented with a series of pictures of famous persons (from politics, show-business, and sports) which they had to name. One point was given if at least the family name was correctly mentioned (out of 20). Second, general and specific semantic knowledge for each famous person was assessed by asking the participant 1) the field that the famous person belongs to (e.g. arts, sports or politics; out of 20; general semantic knowledge); and 2) the reason of their celebrity (e.g. an actor; out of 20; specific semantic knowledge).

2.3.2.2. Naming and semantic knowledge of famous places.

First, participants had to name the famous places (buildings or landmarks) and one point was given if the name was correctly mentioned (out of 20). Second, general and specific semantic knowledge for each item was assessed by asking the participant 1) the location of the place (out of 20; general semantic knowledge); and 2) a specific question about the place (e.g. what is the main function of the White House?; out of 20; specific semantic knowledge).

2.3.2.3. Naming famous logos.

In this task, participants only had to name the famous logos (out of 20). Stimuli included logos of brands (e.g. popular restaurant, sports team or company) and everyday life pictograms (e.g. road signs or pictograms). Semantic knowledge was not evaluated in this task since the overlap between the name and the semantic knowledge of the items was for some items too significant (e.g. a no parking or pedestrian crossing sign).

2.4. Statistical analyses

Previous studies have underlined the necessity of controlling for task difficulty when conducting studies on category-specific differences (Joubert, et al., 2010; Lyons, Kay, Hanley, & Haslam, 2006). In order to control for the difficulty of each naming task and to facilitate the interpretation of our results in patient groups, we selected for our analyses 49 items from the Boston Naming Test and 15 items from

each of the three semantically-unique-entity naming tests that were matched for naming difficulty in our CTRL group (e.g. equivalent means and standard deviations). The mean for the CTRLs on each modified test was between 93.0 and 93.3%. Percentage of correct responses on these modified tasks will be used in this study.

3. Results

3.1 Naming performance

3.1.1. Naming non-unique entities vs semantically unique entities

There was a significant interaction between Group (CTRL vs AD vs svPPA) and Item uniqueness (non-unique vs unique) on naming scores, $F(2, 31) = 4.599$, $p < .05$, partial $\eta^2 = .229$ (Table 2).

In terms of intergroup analyses, both non-unique and unique entity naming scores were significantly different for all three groups, (Welch's $F(2, 15.362) = 58.959$, $p < .001$ and Welch's $F(2, 15.985) = 196.161$, $p < .001$, respectively). Games-Howell post hoc analysis revealed that svPPA patients had significantly lower performance on both non-unique and unique entity naming, in comparison to CTRL ($p < .001$) and AD patients ($p < .001$). AD patients also showed significantly lower performance on both non-unique-entity naming ($p < .05$) and semantically-unique-entity naming ($p < .01$), in comparison to CTRLs.

Intragroup analyses showed that in AD patients, performance on non-unique-entity naming was significantly superior to performance on semantically-unique-entity naming, $t(12) = 3.235$, $p = < .01$, $d=.90$, while these tests were controlled for task difficulty on the CTRL group. In svPPA patients, performance on non-unique-entity naming was also significantly superior to performance on semantically-unique-entity naming, $t(8) = 3.016$, $p < .05$, $d=1.00$.

3.1.2. Naming non-unique entities vs. famous persons vs. famous places vs. famous logos

There was a significant interaction between Group (CTRL vs AD vs svPPA) and Item type (non-unique vs famous persons vs famous places vs famous logos) on naming scores, $F(6, 93) = 4.045$, $p < .001$, partial $\eta^2 = .207$ (Table 2, Figure 1).

Intergroup analyses showed that famous-person naming scores were significantly different for all three groups, Welch's $F(2, 18.123) = 264.727$, $p < .001$. Games-Howell post hoc analysis revealed that both AD and svPPA patients had significantly lower performance on famous-person naming than CTRL ($p < .001$), and that svPPA patients had significantly lower performance than AD patients ($p < .001$). A similar pattern was observed on famous-place and famous-logo naming, in which the scores were significantly different for all three groups (Welch's $F(2, 18.593) = 126.922$, $p < .001$; Welch's $F(2, 14.602) = 51.843$, $p < .001$). Games-Howell post hoc analysis revealed that svPPA and AD patients presented lower performance on famous-place naming than CTRLs ($p < .001$ and $p < .05$, respectively) and that svPPA patients had lower performance than AD patients ($p < .001$). On famous-logo naming, svPPA and AD patients also presented lower performance than CTRL ($p < .001$ and $p < .05$, respectively) and svPPA patients also showed lower performance than AD patients ($p < .001$).

For the intragroup analyses, naming scores were significantly different between all item types in the AD group, $F(3,36) = 7.108$, $p < .001$, partial $\eta^2 = .37$. Post hoc analyses revealed that AD patients had significantly lower performance on famous persons, in comparison to non-unique entities ($p < .01$), famous places ($p < .05$) and famous logos ($p < .05$). In svPPA patients, naming scores were also significantly different between all item types, $F(3,24) = 6.084$, $p < .01$, partial $\eta^2 = .43$. Post hoc analyses revealed that svPPA patients had significantly lower performance on famous places, in comparison to non-unique entities ($p < .01$) and famous logos ($p < .05$). They also presented significantly lower performance on famous persons in comparison to non-unique entities ($p < .05$). The other comparisons were non-significant.

3.2 Naming vs. semantic knowledge

3.2.1. Naming vs. general vs. specific semantic knowledge (Famous persons)

There was a significant interaction between Group (CTRL vs AD vs svPPA) and Condition (naming vs. general semantic knowledge vs. specific semantic knowledge), $F(2.5, 38.7) = 34.115$, $p < .001$, partial $\eta^2 = .688$ (Table 2, Figure 2).

Intergroup analyses showed that both general and specific semantic knowledge of famous persons was significantly different for all three groups ($F(2, 31) = 23.542$, $p < .001$; Welch's $F(2, 15.814) = 54.088$, $p < .001$, respectively). For general and specific semantic knowledge, svPPA patients presented significantly lower performance than both AD patients ($p < .01$ and $p < .001$, respectively) and CTRLs ($p < .01$ and $p < .001$, respectively). However, while AD patients had lower performance than CTRLs for specific semantic knowledge ($p < .05$), their performance was equivalent to CTRLs on general semantic knowledge ($p = .376$).

For the intragroup analyses, scores for the famous persons were significantly different between all conditions in CTRLs, $F(2, 22) = 8.407$, $p < .01$, partial $\eta^2 = .433$. Post hoc analyses revealed that in the CTRL group, general and specific semantic knowledge for famous persons was equivalent ($p = .287$) but superior to naming ($p < .05$). In AD and svPPA scores were also significantly different between all conditions ($F(1.1, 13.3) = 34.996$, $p < .001$, partial $\eta^2 = .745$; $F(2, 16) = 130.339$, $p < .001$, partial $\eta^2 = .942$, respectively). Post hoc analyses revealed that AD and svPPA patients presented a similar pattern with better performance for general semantic knowledge ($p < .001$) than for specific semantic knowledge, and with both types of knowledge superior to naming ($p < .001$; $p < .05$, respectively).

3.2.1. Naming vs. general vs. specific semantic knowledge (Famous places)

There was a significant interaction between Group (CTRL vs AD vs svPPA) and Condition (naming vs. general semantic knowledge vs. specific semantic knowledge), $F(4, 62) = 10.263$, $p < .001$, partial $\eta^2 = .398$ (Table 2, Figure 2).

Intergroup analyses for semantic knowledge of famous places yielded similar results to semantic knowledge of famous persons. Both general and specific semantic knowledge of famous places was significantly different for all three groups (Welch's $F(2, 14.878) = 19.717, p < .001$; Welch's $F(2, 18.021) = 48.423, p < .001$, respectively). For general and specific semantic knowledge, svPPA patients presented significantly lower performance than AD patients ($p < .01$ and $p < .001$, respectively) and CTRLs ($p < .001$). However, while AD patients had lower performance than CTRLs for specific semantic knowledge ($p < .05$), their performance was equivalent to CTRLs on general semantic knowledge ($p = .268$).

Intragroup analyses showed that CTRLs and AD patients had a similar pattern of results. In both groups, scores were significantly different between all conditions ($F(2, 22) = 27.107, p < .001$, partial $\eta^2 = .711$; $F(2, 24) = 22.723, p < .001$, partial $\eta^2 = .654$, respectively). Furthermore, post hoc analyses showed that in these two groups, naming and general knowledge for famous places was equivalent ($p = .815$ for CTRL and $p = .186$ for AD), but superior to specific semantic knowledge ($p < .001$). svPPA patients' scores were also significantly different between all conditions ($F(1.2, 9.5) = 25.612, p < .001$, partial $\eta^2 = .762$). However, they showed lower scores on naming in comparison to both specific and general semantic knowledge ($p < .05$ and $p < .01$, respectively). Specific semantic knowledge scores were also significantly lower than general semantic knowledge scores in svPPA patients ($p < .01$).

3.3. Rates of impairments on naming tests

Impaired performance was defined as 2 SDs below the CTRLs mean. On the non-unique-entity naming test, 100% of svPPA patients and 46.2% of AD patients showed impaired performance. On the famous-person test, 100% of svPPA patients and 69.2% of AD patients had impaired performance. On the famous-place test, 100% of svPPA patients and 38.5% of AD patients showed impaired performance. On the famous-logo test, 100% of svPPA patients and 61.5% of AD patients had impaired performance.

Looking at the overlap of impairment across the unique-entity naming tests, the performance of 100% of svPPA patients was impaired on all 3 tests. Of the AD patients, 15.4% showed unimpaired performance on any of the tests, 38.5% had impaired performance on one test only, 7.6% on two tests and 38.5% on all three tests.

3.4. Post-hoc voxel-based morphometry analysis

The behavioral results of the intragroup analyses revealed a selective vulnerability for famous-person naming in AD patients (in comparison to other types of entities). In order to provide further insight into the nature of the famous-person naming impairments observed (i.e. impaired lexical access vs. semantic impairment), a voxel-based morphometry analysis was conducted. Based on previous studies, we hypothesized a significant correlation between the famous-person naming scores and the temporo-parietal junction gray matter (GM) volume if the naming impairments were related to impaired lexical access, and a correlation with the ATL GM volume if they were related to a semantic impairment (Gesierich, et al., 2011; Vitali, et al., 2015). Therefore, we correlated the GM volume in two regions of interest (left ATL (-39, 15, -33) and left temporo-parietal junction (-42, -60, 48)) with the famous-person naming scores in the AD group. The regions of interest were 10 mm spheres based on coordinates obtained in a previous fMRI study investigating famous-person naming and semantics (Gesierich, et al., 2011).

3.4.1. Image acquisition.

Out of our 13 AD patients, 12 underwent a Magnetic Resonance Imaging protocol including a high-definition T1 brain image. The brain structural MRI scans were obtained with a 3T Philips Achieva TX scanner at IRM Québec-Mailloux in Quebec City. A volumetric magnetization prepared rapid gradient echo (MP-RAGE) sequence was used to acquire a high-resolution T1 3D structural image (TR = 8.2 ms, TE = 3.7 ms, FoV= 250 mm, flip angle = 8°, 256×256 matrix, 180 slices/volume, slice thickness = 1mm, no gap).

3.4.2. Image preprocessing.

The structural images were preprocessed using voxel-based morphometry (VBM) implemented in SPM12 using MATLAB 7.14.0.739 (Mathworks, Natick, MA). The images were segmented into gray (GM) and white (WM) matter. Affine registered tissue segments were used to create a custom template using the DARTEL (diffeomorphic anatomical registration using exponentiated lie algebra) approach (Ashburner, 2007). For each participant, the flow fields were calculated during a template creation, which described the transformation from each native GM image to the template. These were then applied to each participant's GM image. The VBM analysis was based on modulated GM images, where the GM value for each voxel was multiplied by the Jacobian determinant derived from spatial normalization to preserve the total amount of GM from the original images (Ashburner & Friston, 2000). The resulting modulated and normalized images were then smoothed with a Gaussian kernel of 8 mm FWHM.

3.4.3. Statistical analysis.

The VBM analysis was performed on smoothed GM images. First, the famous-person naming scores were entered as covariate of interest in a multiple regression statistical model, with age and gender as nuisance covariates. A contrast was set to identify voxels that correlated with famous-person naming scores in each of our regions of interest.

The correlation was tested using a [1] t-contrast, assuming that decreased naming scores would be associated with decreased GM volumes. The significance of each effect of interest was determined using the theory of Gaussian fields (Friston et al., 1995). Statistical threshold of $p < 0.05$ corrected for multiple comparisons was used.

3.4.4. Voxel-based morphometry results

In AD patients, famous-person naming scores correlated with the ROI in the left temporo-parietal junction ($x=-42$, $y=-51$, $z=51$, $T=5.45$, number of voxels=6, $p<.05$ FWE corrected within our ROI), but not with the ROI in the left ATL (figure 3).

In order to demonstrate that this result in the left TPJ was specific to the naming performance, and not an effect of semantic processing or dementia severity, we re-ran the analyses including the famous-person specific semantic knowledge and the MMSE scores as nuisance covariates in the model. The correlation between famous-person naming and GM atrophy in the left TPJ remained significant. Finally, to further demonstrate that the correlation observed in the left TPJ was not an effect of a general semantic impairment, we ran a correlation analysis using the PPTT score as the covariate of interest with age and gender as nuisance covariates. No significant correlation was observed in the left TPJ as a result of this analysis.

Table 1 : Demographic and neuropsychological characteristics

| | CTRL (<i>n</i> = 12) | AD (<i>n</i> = 13) | svPPA (<i>n</i> = 9) | <i>p</i> value | Intergroup differences |
|---|--------------------------|------------------------|--------------------------|-------------------|---------------------------------------|
| Demographics | | | | | |
| Gender (F/M) | 4/8 | 5/8 | 2/7 | NA | NA |
| Age (in years) | 66.8 (8.7) | 70.6 (8.0) | 65.2 (11.2) | = .36 | CTRL = AD = svPPA |
| Education (in years) | 16.9 (3.4) | 15.5 (4.1) | 16.1 (4.1) | = .65 | CTRL = AD = svPPA |
| Neuropsychological assessment | | | | | |
| <i>Global cognitive status</i> | | | | | |
| MMSE | 29.0 (0.7) | 25.0 (2.7) | 25.2 (2.1) | < .001 | CTRL > AD = svPPA |
| <i>Episodic memory</i> | | | | | |
| RCFT (Immediate recall) | 19.5 (4.1) | 6.0 (3.7) | 9.6 (5.7) | < .001 | CTRL > AD = svPPA |
| RCFT (Delayed recall) | 20.5 (4.5) | 5.5 (4.7) | 8.4 (5.2) | < .001 | CTRL > AD = svPPA |
| RAVLT (Trials 1-5) | 52.9 (7.1) | 27.8 (5.9) | 29.5 (7.8) | < .001 | CTRL > AD = svPPA |
| RAVLT (Immediate recall) | 10.9 (2.6) | 3.2 (2.6) | 4.8 (2.3) | < .001 | CTRL > AD = svPPA |
| RAVLT (Delayed recall) | 10.8 (2.6) | 1.9 (2.8) | 4.7 (2.7) | < .001 | CTRL > AD = svPPA |
| RAVLT (Recognition) | 46.8 (2.1) | 32.3 (7.8) | 41.0 (5.7) | < .001 | CTRL = svPPA > AD |
| <i>Language and semantic memory</i> | | | | | |
| Pyramids and Palm Trees Test | 50.3 (1.4) | 48.1 (2.4) | 31.7 (12.5) | < .001 | CTRL = AD > svPPA |
| Free Fluency | 66.5 (17.0) | 39.0 (14.8) | 30.7 (12.0) | < .001 | CTRL > AD = svPPA |
| Letter Fluency - P | 27.3 (8.4) | 19.7 (8.1) | 13.2 (5.7) | < .001 | CTRL = AD CTRL > svPPA; AD = svPPA |
| Semantic Fluency - Clothing | 25.7 (4.7) | 14.2 (6.8) | 9.1 (7.8) | < .001 | CTRL > AD = svPPA |
| Similarities subtest - WAIS-III | 18.9 (4.3) | 15.3 (4.9) | 6.1 (2.9) | < .001 | CTRL = AD > svPPA |
| <i>Visual perception</i> | | | | | |
| Benton Line Orientation test | 27.7 (2.2) | 24.5 (6.6) | 26.6 (2.4) | = .23 | CTRL = AD = svPPA |
| Benton facial recognition test | 47.8 (2.9) | 45.3 (3.1) | 44.4 (3.4) | < .05 | CTRL = AD = svPPA |
| <i>Visuoconstruction</i> | | | | | |
| RCFT (copy) | 32.4 (2.6) | 27.5 (7.7) | 29.7 (4.5) | = .10 | CTRL = AD = svPPA |
| Clock-drawing test | 9.3 (1.0) | 7.5 (2.3) | 7.8 (1.9) | < .05 | CTRL = svPPA > AD |
| Clock-copy test | 9.7 (0.5) | 9.3 (0.8) | 9.7 (0.4) | = .20 | CTRL = AD = svPPA |
| <i>Executive functions / working memory</i> | | | | | |
| Trail making test A (s) | 30.0 (5.7) | 76.3 (88.1) | 47.9 (13.0) | = .12 | CTRL = AD = svPPA |

| | | | | | |
|----------------------------------|--------------|------------------|--------------|--------|--|
| Trail making test B (s) | 61.5 (20.0) | 238.8 (141.8) | 113.4 (66.8) | < .001 | CTRL = svPPA > AD |
| SVT Word-color interference task | 127.2 (31.1) | 221.0 (108.7) | 135.1 (35.8) | < .01 | CTRL = svPPA > AD |
| Digit span | 18.7 (4.4) | 15.8 (2.5) | 14.6 (3.7) | < .05 | CTRL = AD CTRL > svPPA; AD = svPPA |

MMSE = Mini-Mental State Examination; RCFT: Rey Complex Figure Test; RAVLT: Rey Auditory Verbal Learning Test;

SVT = Stroop-Victoria Test

Table 2 : Summary of intergroup and intragroup differences for all naming tests

| | CTRL (n = 12) | AD (n = 13) | svPPA (n = 9) | p value | Intergroup differences |
|---|---|---|---|--------------------------|---|
| Naming non-unique entities vs semantically unique entities | | | | | |
| Non-unique entities | 93.0 (6.4) | 79.3 (16.4) | 25.3 (17.6) | < .001 | CTRL > AD > svPPA |
| Unique entities | 93.3 (5.4) | 69.9 (19.5) | 14.7 (10.7) | < .001 | CTRL > AD > svPPA |
| p value | ≥ .05 | < .01 | < .05 | | |
| Intragroup differences | Non-unique = Unique | Non-unique > Unique | Non-unique > Unique | | |
| Naming non-unique entities vs. famous persons vs. famous places vs. famous logos | | | | | |
| Non-unique entities | 93.0 (6.4) | 79.3 (16.4) | 25.3 (17.6) | < .001 | CTRL > AD > svPPA |
| Famous persons | 93.3 (7.0) | 59.0 (25.1) | 10.0 (8.8) | < .001 | CTRL > AD > svPPA |
| Famous places | 93.3 (10.3) | 74.9 (23.4) | 8.9 (12.9) | < .001 | CTRL > AD > svPPA |
| Famous logos | 93.3 (5.7) | 75.9 (18.0) | 25.2 (19.7) | < .001 | CTRL > AD > svPPA |
| p value | ≥ .05 | < .001 | < .01 | | |
| Intragroup differences | Non-unique = Persons = Places = Logos | Persons < Non-unique = Places = Logos | Places < Non- unique = Logos; Persons < Non- unique | | |
| Naming vs. general vs. specific semantic knowledge (Famous persons) | | | | | |
| Naming | 93.3 (7.0) | 59.0 (25.1) | 10.0 (8.8) | < .001 | CTRL > AD > svPPA |
| General SK | 100.0 (0.0) | 98.5 (4.0) | 77.5 (15.3) | < .001 | CTRL = AD > svPPA |
| Specific SK | 97.3 (5.3) | 89.7 (8.9) | 28.3 (19.1) | < .001 | CTRL > AD > svPPA |
| p value | < .01 | < .001 | < .001 | | |
| Intragroup differences | Naming < Specific SK = General SK | Naming < Specific SK < General SK | Naming < Specific SK < General SK | | |
| Naming vs. general vs. specific semantic knowledge (Famous places) | | | | | |
| Naming | 93.3 (10.3) | 74.9 (23.4) | 8.9 (12.9) | < .001 | CTRL > AD > svPPA |
| General SK | 95.0 (8.1) | 83.6 (24.0) | 39.3 (25.5) | < .001 | CTRL = AD > svPPA |
| Specific SK | 80.0 (11.4) | 59.0 (24.3) | 16.3 (16.3) | < .001 | CTRL > AD > svPPA |
| p value | < .001 | < .001 | < .001 | | |
| Intragroup differences | Naming = General SK > Specific SK | Naming = General SK > Specific SK | Naming < Specific SK < General SK | | |

SK = Semantic Knowledge

Figure 1: Performance of CTRL, AD and svPPA groups at naming non-unique entities, famous persons, famous places and famous logos.

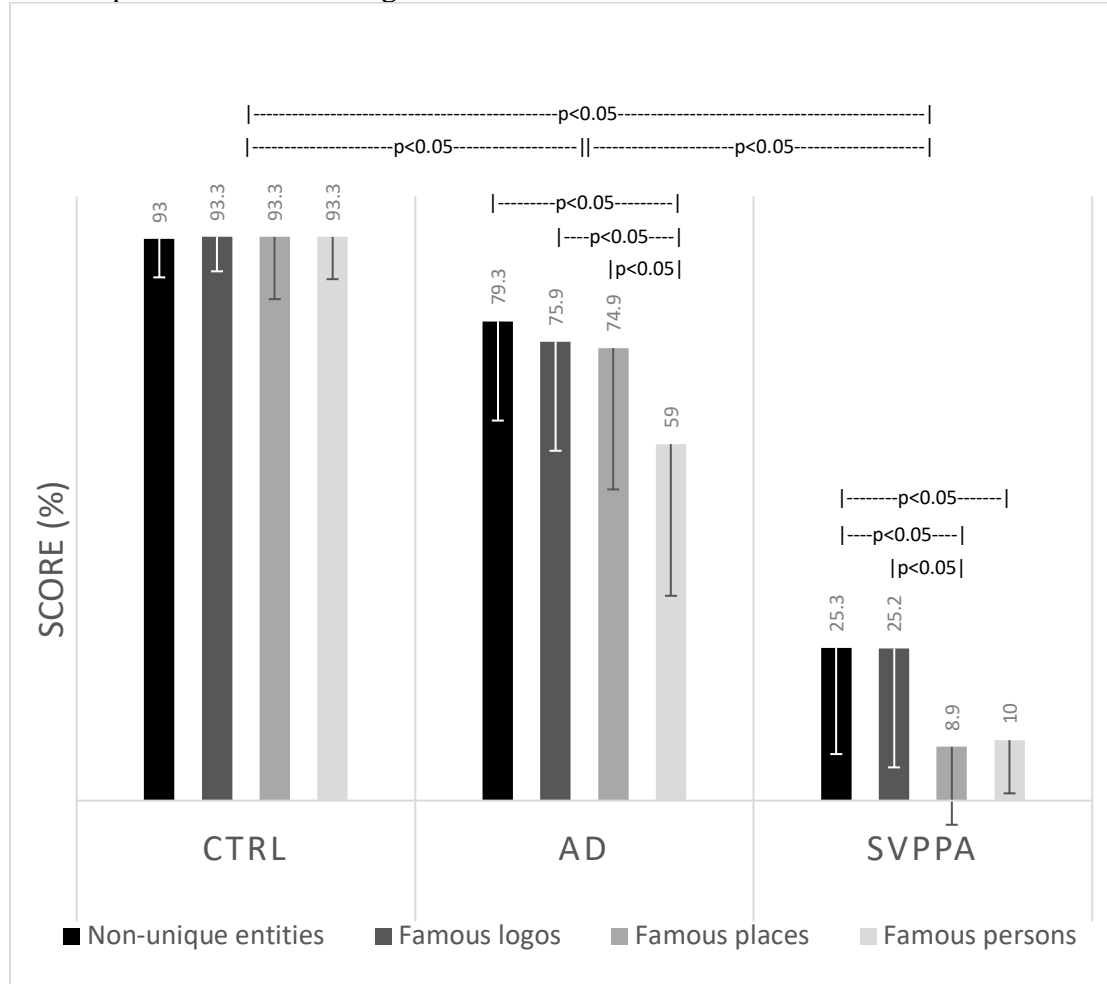


Figure 2: Performance of CTRL, AD and svPPA groups at naming vs. general semantic knowledge vs. specific semantic knowledge for A) famous persons B) famous places.

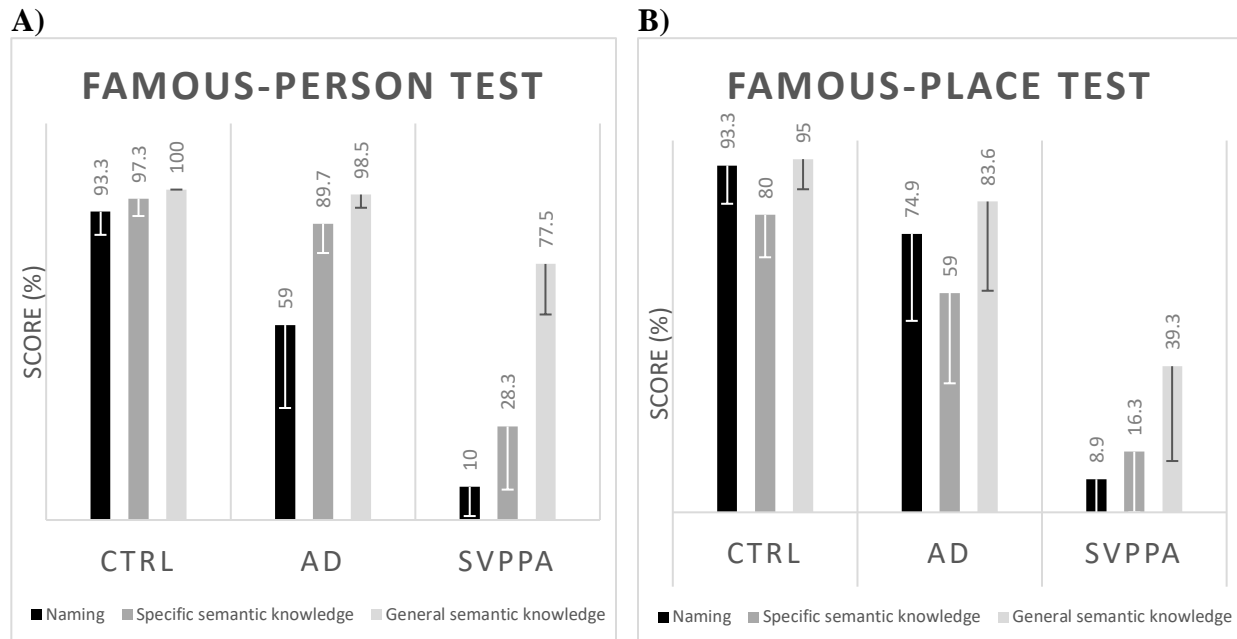
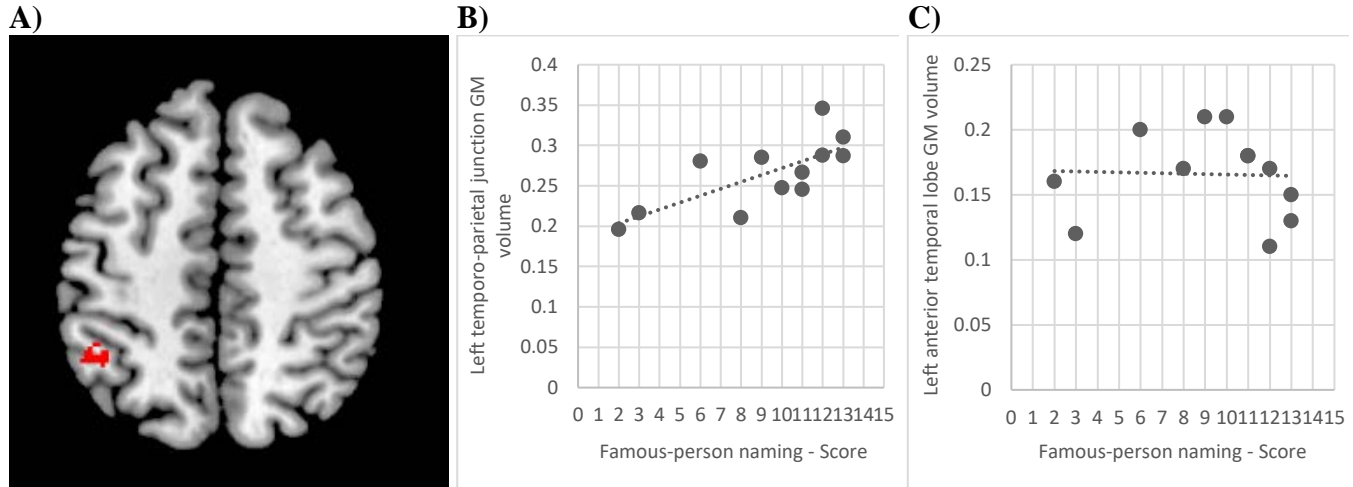


Figure 3: A) Voxels in which the gray matter (GM) volume positively correlate with the performance on the famous-person naming task in AD patients (for display $p < 0.01$ uncorrected; the results is significant at $p < 0.05$ corrected within our ROI); B) Significant relationship between GM volume in the left temporo-parietal junction significant cluster and famous-person naming scores in AD patients; C) Absence of relationship between GM volumes of the left anterior temporal lobe ROI and famous-person naming scores in AD patients.



4. Discussion

In the present study, we aimed to characterize and compare the ability to name non-unique and unique entities (famous persons, famous places, famous logos) in CTRL, AD and svPPA participants. Our behavioral results showed that both AD and svPPA patients were overall more impaired at naming semantically unique entities than non-unique entities on tests that were controlled for difficulty in the CTRL group. We also showed that naming impairments in AD and svPPA extend to different types of semantically unique entities, since a CTRL > AD > svPPA pattern was found on the performance of all naming tests (famous persons, famous places, famous logos). However, all types of entities were not equally impaired within each group. Analyses comparing item types in each group showed that famous-person naming was particularly impaired in AD, revealing a profile similar to what has been previously described as prosopagnosia (Carney & Temple, 1993; Geva, Moscovitch, & Leach, 1997; C. Semenza, Sartori, & D'Andrea, 2003). In svPPA patients, our results showed that famous-place naming was particularly impaired, as well as famous-person naming. In terms of the comparison between naming and semantic knowledge, svPPA patients were impaired on all conditions (naming, specific and general semantic knowledge) on both famous-person and famous-place tests. However, although AD patients were most significantly impaired on famous-person naming, they showed preserved general semantic knowledge for these items, suggesting that their naming difficulties might be related, at least in part, to impaired lexical access. Our post-hoc analysis was in line with this idea, since the severity of deficits for naming famous persons in AD correlated with GM volume in the left temporoparietal junction, a region that is functionally associated to lexical access (and not with the left ATL, which has been found to be correlated with semantic knowledge, i.e. see Joubert et al. 2010).

The findings reported here replicate earlier studies documenting more severe naming impairments for semantically unique entities in neurodegenerative diseases (Delazer, et al., 2003; Joubert, et al., 2010; Joubert, et al., 2008; C. Semenza, Mondini, et al., 2003; Thompson, et al., 2002). Several studies have investigated what makes semantically unique items special and therefore harder to name in certain diseases. In terms of neuroimaging, it has been suggested that processing semantically unique entities and linking them with their names requires a greater amount of metabolic resources (Gorno-Tempini & Price, 2001; Ross & Olson, 2012; Carlo Semenza, 2009). More precisely, the uniqueness of semantic associations and the presence of a proper name associated with the semantically unique item modulates brain activity in the left ATL, overall involving a wider left-hemispheric cortical network (Ross & Olson, 2012). Other authors have also suggested that semantic breakdown may be more important for unique entities than for non-unique entities due to the idiosyncratic features of the former (Joubert, et al., 2010; Joubert, et al., 2008). In our study, all famous persons and places and some famous logos (e.g. brands of well-known restaurants or companies) were associated with a proper name. This could, in part, account for our results. Retrieval of proper names is thought to be more difficult than retrieval of common nouns (even in cognitively unimpaired elderly subjects), which could be due to the less frequent association between a proper name and what it refers to (Bredart, 1993; Bredart, Brennen, & Valentine, 2002; C Semenza, Nichelli, & Gamboz, 1996)). In the context of neurodegenerative diseases in which cerebral resources are limited, this discrepancy between unique and non-unique-entity naming might be amplified.

Since all previous studies in AD and svPPA have focused on famous-person naming, the novelty of this study consisted in evaluating if semantically-unique-entity naming impairments in these populations extend to other types of items such as famous places and logos and to investigate if some types of items are selectively impaired within each population. The characterization of naming impairments across item types in each clinical population could be an invaluable tool in clinical settings

and contribute to identifying specific anomia profiles (e.g. proper name anomia or prosopagnosia). Indeed, both AD and svPPA patients exhibited impairments, to different degrees (CTRL>AD>svPPA), on all types of semantically unique entities. However, all types of entities were not equally impaired within each group.

Famous-person naming appears to be a very sensitive measure to detect naming impairments in neurodegenerative patients. AD patients presented a significantly greater vulnerability for famous-person naming in comparison to all other types of items, while in svPPA patients, famous persons were some of the most difficult items to name along with famous places. We hypothesize that this selective vulnerability for famous persons might be due to the fact that out of all the semantically unique entities evaluated in this study, famous-person names appear to present the less frequent association with their referent. Conversely, a lot of famous-place names include (and begin with, in French) a common noun describing what the place is (e.g. Tower in Eiffel Tower, Falls in Niagara Falls) which might also serve as a cue to retrieve the appropriate name. Similarly, some of the items on our famous-logo naming test also include a common noun in their name (e.g. Pedestrian crossing, No smoking). Another hypothesis to explain the selective impairments for naming famous persons in AD is the fact that face perception has recently been shown to be affected to some extent in this disease (Lavalley, et al., 2016). In our sample, AD patients did not present a significant impairment on the Benton facial recognition test, even though a trend towards lower scores was observed. However, this hypothesis remains unlikely in our sample, since AD patients were successful in responding to our general semantic knowledge question (and 89.7% for the specific semantic knowledge question), which confirms that AD patients were able to recognize the famous persons presented to them. Our results for the AD group correspond to prosopagnosia, a category-specific anomia for faces (Carney & Temple, 1993; Geva, et al., 1997; C. Semenza, Sartori, et al., 2003). It is

described as a condition in which naming persons based on their faces is impaired, but in which face perception and access to semantic knowledge or autobiographical information from faces is preserved.

In addition to their impairment in famous-person naming, famous-place naming was also significantly impaired in svPPA patients in comparison to the other types of entities. These results suggest that naming deficits in svPPA are more severe and less selective, which is in line with svPPA's characteristic progressive degradation of conceptual knowledge (Gorno-Tempini, et al., 2011; Reilly, et al., 2011; Rogers & Friedman, 2008). AD patients were not specifically impaired on famous-place naming in comparison to other types of items, which is not in line with findings suggesting that famous buildings/places are a similarly vulnerable category to famous persons in mild cognitive impairment individuals (Ahmed, et al., 2008), and traumatic brain injury patients (Milders, 2000). However, the naming tests in these studies were not controlled for difficulty in CTRL, which makes the interpretation of their results and the comparison with our results more complex. While previous neuroimaging studies have demonstrated that processing famous persons and places activates the same brain regions related to semantics (i.e. the left anterior temporal cortex) (Gorno-Tempini & Price, 2001; Grabowski, et al., 2001), it remains unclear if naming both types of items activates similar brain regions. While our study does not provide a clear explanation for this discrepancy between famous-person and famous-place naming in AD, the differences between these two types of entities might provide hypotheses to explore in future studies. While all famous persons are natural entities, famous places can be either natural (e.g. Niagara Falls) or man-made artefacts (e.g. the Eiffel Tower) (Tranel, Enekeuchi, & Manzel, 2005). Also, famous persons, in comparison to famous places, might more importantly involve processes related to social and affective associations (Ross & Olson, 2012; Simmons, Reddish, Bellgowan, & Martin, 2010). These differences between famous persons and places underline the relevance of combining the use of these two types of items in clinical settings. Finally, famous logos yielded mixed results. Even though they proved to be

helpful in detecting naming impairments in svPPA and AD in comparison to CTRL, they only provided limited additional information beyond commonly used naming tests such as the Boston Naming Test. These results obtained for famous-logo naming are not in line with the specific impairment for semantically-unique-item naming. Even though the naming tests used were matched for difficulty in the CTRL group, we hypothesize that famous logos might be more familiar than famous places or persons and possibly as familiar as non-unique entities. It has previously been shown that svPPA and AD patients are more impaired at naming less familiar entities (Hirsh & Funnell, 1995; Kremin, et al., 2001; Taylor, 1998). Stimuli in this task represented logos that are encountered quite often in daily life (e.g. road signs, popular restaurants, etc.), which might account for the fact that neither AD nor svPPA patients were specifically impaired on this semantically unique entity type in comparison to non-unique entities. Furthermore, tests were not specifically matched on the psycholinguistic characteristics of their stimuli. Even though they were matched for difficulty in the CTRL group, which potentially limits the influence of these variables, this remains a limitation of this study. Future studies investigating semantically-unique-item naming should use items that are specifically matched on familiarity, name agreement, word frequency, visual similarity, and semantic relatedness. These variables have been shown to be important predictors of naming accuracy and speed in individuals with neurodegenerative diseases (Astell & Harley, 1998; Hirsh & Funnell, 1995; Kremin, et al., 2001; Montanes, Goldblum, & Boller, 1996; Taylor, 1998; Tippett, Meier, Blackwood, & Diaz-Asper, 2007). Future neuroimaging studies investigating famous-logo processing and naming could also help us determine if these processes require greater cognitive resources in a similar way to famous persons and places (Gorno-Tempini & Price, 2001; Ross & Olson, 2012; Carlo Semenza, 2009).

Although both clinical groups present with naming impairments, one of the remaining debates in the literature relates to the mechanisms underlying them (i.e. semantic impairment vs. impaired lexical

access), especially in AD. While previous behavioral studies support both the semantic impairment hypothesis (Chertkow & Bub, 1990; Giffard, et al., 2002; Laisney, et al., 2011; Predovan, et al., 2013) and the inefficient retrieval hypothesis (Nebes, Martin, & Horn, 1984; Ober & Shenaut, 1995; Rich, Park, Dopkins, & Brandt, 2002), some authors have actually suggested that naming impairments might reflect both mechanisms (Joubert, et al., 2010; Rogers & Friedman, 2008). Unfortunately, traditional explicit naming tasks present the limitation of not providing information on the underlying nature of naming impairments. However, we conducted two additional analyses suggesting that famous-person naming impairments in AD might at least in part arise from impaired lexical access. First, at the behavioral level, we added a second part to our famous-person and famous-place naming tasks, in which both general and specific semantic knowledge were assessed. In comparison to both CTRL and AD patients, svPPA patients were affected in naming, as well as for general and specific semantic knowledge for both famous persons and famous places. Overall, these results on semantic knowledge also demonstrate that the two patient groups, in addition to performing differently on naming tasks, also perform differently on both specific and general semantic knowledge (with svPPA patients being unequivocally more impaired than AD patients). These results are in line with a semantic impairment in svPPA. On the opposite, AD patients were significantly impaired on famous-person and famous-place naming in comparison to CTRL, while presenting preserved general semantic knowledge. Furthermore, on the famous-person test, specific semantic knowledge in AD was significantly inferior to CTRL, but still relatively preserved for the misnamed items (89.7% in comparison to 59% in naming). In contrast to what is observed on the famous-person test, in which naming is more impaired than general semantic knowledge for both svPPA and AD patients, this effect is only observed in svPPA patients for the famous-place test. Second, neuroimaging analyses showed that famous-person naming impairments in AD correlated with atrophy in the temporo-parietal junction, a region functionally associated with lexical access, and not with the ATL. Interestingly,

there is a perfect overlap with the coordinates found in our study and a previous neuroimaging study investigating famous-person processing (Gorno-Tempini and Price 2001). Thus, our results suggest that in AD patients, impaired lexical access significantly contributes to the naming impairments observed for famous persons and that their profile is similar to that of prosopagnosia.

In conclusion, the results presented here have significant clinical implications in the assessment of language and semantic memory in neurodegenerative diseases. First, we characterized for the first time the naming abilities in two neurodegenerative populations across many types of semantically unique and non-unique entities. The pattern of naming performance in each group might be very helpful for differential diagnosis purposes. Our results also provide insight into the nature of the naming impairments observed (i.e. impaired lexical access vs. semantic impairment), with the help of additional questions assessing general and specific semantic knowledge as well as neuroimaging. These results suggest that naming difficulties for famous persons in AD might be related at least in part to impaired lexical access, while svPPA patients' naming impairments are associated with a semantic impairment. Finally, our results highlight the critical importance of adding a variety of semantically-unique-entity naming tests in neuropsychological assessments of patients with neurodegenerative diseases, since these tests can inform clinicians on the nature of the naming impairments observed which differ depending on the type of neurodegenerative disease.

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