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Reading Disorders in Primary Progressive Aphasia: a behavioral and neuroimaging study

SM Brambati^{1,2}, J Ogar^{1,3}, J Neuhaus⁴, BL Miller¹, and ML Gorno-Tempini¹

¹UCSF Department of Neurology, San Francisco, CA

²CRIUGM, Université de Montréal, Montréal, QC

³Center for Aphasia and Related Disorders, Veterans Administration Northern California Health Care Service, Martinez, CA, USA

⁴UCSF Department of Epidemiology and Biostatistics, San Francisco, CA

Abstract

Previous neuropsychological studies on acquired dyslexia revealed a double dissociation in reading impairments. Patients with phonological dyslexia have selective difficulty reading pseudo-words, while those with surface dyslexia misread exception words. This double dissociation in reading abilities has often been reported in brain damaged patients, but it has not been consistently shown in patients with neurodegenerative diseases.

In this study, we investigated reading impairments and their anatomical correlates in various neurodegenerative diseases. First, we performed a behavioral analysis to characterize the reading of different word types in primary progressive aphasia (PPA). Then, we conducted a voxel-based morphometry neuroimaging study to map the brain areas in which gray matter volume correlated with accurate reading of exception and pseudo-words.

The results showed a differential pattern of exception and pseudo-word reading abilities in different clinical variants of PPA. Patients with semantic dementia, a disorder characterized by selective loss of semantic memory, revealed a pattern of surface dyslexia, while patients with logopenic/phonological progressive aphasia, defined by phonological loop deficits, showed phonological dyslexia. Neuroimaging results showed that exception word reading accuracy correlated with gray matter volume in the left anterior temporal structures, including the temporal pole, the anterior superior and middle temporal and fusiform gyri, while pseudo-word reading accuracy correlated with left temporoparietal regions, including the posterior superior and middle temporal and fusiform gyri, and the inferior parietal lobule.

These results suggest that exception and pseudo-word reading not only rely upon different language mechanisms selectively damaged in PPA, but also that these processes are sustained by separate brain structures.

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Corresponding author: Maria Luisa Gorno-Tempini, MD, PhD, Memory and Aging Center, Department of Neurology, UCSF, 350 Parnassus Avenue, Suite 905, San Francisco, CA 94143-1207, E-mail: marilu@memory.ucsf.edu; Phone: 415-476-1895, Fax: 415-476-0213.

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Keywords

exception words; pseudo-words; neurodegenerative diseases; voxel-based morphometry

INTRODUCTION

Neuropsychological studies on brain damaged patients with acquired dyslexia have revealed a double dissociation in reading of different word types. Patients with phonological dyslexia show a discrepancy between reading regular words (e.g., words with regular spelling-to-sound correspondence, such as ‘apple’) and pseudo-words (e.g., pronounceable letter string with no semantic representation, such as ‘voot’ and ‘yull’), with relatively preserved reading of exception words (e.g., words with atypical spelling to sound correspondence, such as ‘yacht’ and ‘colonel’). On the other hand, patients with surface dyslexia show a discrepancy in their reading of regular and exception words, with relatively preserved reading of pseudo-words.

Different computational models have tried to account for this neuropsychological dissociation by postulating the existence of at least two means by which reading aloud can occur. The **dual route cascaded (DRC) model** (Coltheart, 2006; Coltheart, Curtis, Atkins, & Haller, 1993; Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001) postulates the existence of two distinct reading-specific pathways that work independently from other language and cognitive systems; 1) the *non-lexical route* relies on a system of grapheme-to-phoneme conversion rules and it is employed in the reading of pseudo-words; 2) the *direct lexical route* retrieves a word’s sound representation from the phonological lexicon by first accessing its whole orthographic representation. This route is believed to be employed in the reading of regular and exception words. According to this model, the reading deficits characteristic of phonological and surface dyslexia would be caused by the disruption of the non-lexical and lexical route respectively, and they would be isolated from other language and cognitive impairments.

A second theory, the **connectionist triangle model** (Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989; Woollams, Lambon Ralph, Plaut, & Patterson, 2007) proposes that the reading of words is determined by the modulation of connections between orthography, phonology and the semantic system. The strength of connections is determined by both the proficiency of the reader and word features, such as word type and frequency. Within this framework, two serially-working pathways contribute to the reading of different word types: 1) the direct pathway from orthography to phonology ($O \rightarrow P$) is more involved in regular and pseudo-word reading; 2) the indirect pathway from orthography to phonology mediated via the semantic system ($O \rightarrow S \rightarrow P$) is more involved in less frequent and exception word reading. According to this model, a pattern of phonological dyslexia would be associated with a defective phonological system, while a pattern of surface dyslexia would arise in the case of a defective semantic system.

The hypothesis of an association between semantic memory impairments and surface dyslexia is supported by evidence in patients with semantic dementia (SD), a variant of primary progressive aphasia (PPA) characterized by progressive loss of semantic memory and anterior temporal lobe degeneration (Chan et al., 2001; Galton et al., 2001; Gorno-Tempini et al., 2004; Mummery et al., 2000; Rosen et al., 2002). In fact, patients with SD not only present with surface dyslexia (Caine, Breen, & Patterson; Graham, Patterson, & Hodges, 2000; Hodges, Patterson, Oxbury, & Funnell, 1992; Hodges et al., 1999; Neary et al., 1998; Woollams et al., 2007), but there is also a strong association between the severity of the reading deficit and the extent of the semantic loss (Graham et al., 2000; Jefferies, Lambon Ralph, Jones, Bateman, & Patterson, 2004; Patterson & Hodges, 1992; Woollams et al., 2007). A pattern of surface dyslexia has also been reported in Alzheimer’s disease, but only in patients manifesting

semantic deficits (Patterson, Graham, & Hodges, 1994; Strain, Patterson, Graham, & Hodges, 1998).

On the other hand, the presence of a pattern of phonological dyslexia has not been described in other neurodegenerative syndromes characterized by language deficits. This absence in the literature of a double dissociation in reading disorders could be partly due to the lack of studies investigating reading abilities in other clinical variants of PPA, besides SD. To our knowledge, no studies specifically investigated reading abilities in patients with progressive nonfluent aphasia (PNFA), which is characterized by apraxia of speech, agrammatism and inferior frontal and insular atrophy (Gorno-Tempini et al., 2004; Grossman et al., 1996; Hodges & Patterson, 1996). We also know of no such studies in patients with logopenic/phonological progressive aphasia (LPA), another variant of PPA, in which patients present with phonological loop deficits and atrophy in left temporoparietal structures (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2004).

From an anatomical point of view, previous functional imaging studies have attempted to identify brain areas differentially involved in exception and pseudo-word reading. A pattern of activation consistent among studies has been found for reading of pseudo-words compared to exception words, but the pattern associated with the reverse comparison is less defined (for a discussion, see (Mechelli et al., 2005)). In general, the data suggest that the inferior parietal regions and the posterior inferior frontal gyrus (IFG) are more involved in pseudo-word reading (Jobard, Crivello, & Tzourio-Mazoyer, 2003; Mechelli et al., 2005; Mechelli, Gorno-Tempini, & Price, 2003; Wilson et al., 2008), while the anterior portion of the IFG is involved in exception word reading (Mechelli et al., 2005; Mechelli et al., 2003). Moreover, a differential involvement of the left fusiform gyrus has been reported in the reading of different word types, with the anterior portion underpinning the reading of exception words, while the posterior portion is involved with the reading of pseudo-words (Brunswick, McCrory, Price, Frith, & Frith, 1999; Mechelli et al., 2005; Mechelli et al., 2003; Price et al., 2003).

In order to better define the nature of reading impairments and to determine their anatomical correlates, we studied patterns of reading deficits and associated anatomical changes in patients with various neurodegenerative diseases. First, we performed a behavioral study to characterize the profile of reading impairments for different word types (regular/exception/pseudo-words) in patients with different clinical variants of PPA. A voxel-based morphometry (VBM) neuroimaging study was then conducted on a subset of participants in order to map the neurological correlates of exception and pseudo-word reading disorders.

METHODS

Pattern of Reading Impairments in Primary Progressive Aphasia

SUBJECTS—Sixty-six subjects (mean age=61.7±8.0 years, F/M= 36/30) were recruited through University of California San Francisco (UCSF) Memory and Aging Center (MAC). The group of participants included 10 cognitively normal subjects and 56 patients with a diagnosis of neurodegenerative disease. A detailed medical history, comprehensive neurological and standardized neuropsychological and language evaluations (Gorno-Tempini et al., 2004) were used by a team of clinicians to formulate a consensus diagnosis for each patient, according to the currently published criteria (Litvan et al., 1997; McKeith et al., 1996; McKhann et al., 1984; Mesulam, 1987; Neary et al., 1998). Twenty-six patients with PPA, comprising seven with PNFA, 14 with SD, and five with LPA (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2004), were included in the study.

Data were also collected from 14 patients with Alzheimer's disease (AD) and from a group of neurodegenerative patients reporting no primary language symptoms ('dementia control

group', DCG). The DCG included six patients with the fronto temporal dementia variant of frontotemporal lobar degeneration (FTD-FTLD), three with dementias with predominant motor symptoms (PSP/CBD/ALS), and seven who did not meet any research criteria (MNRC). Demographic characteristics of each group are reported in Table 1.

The study was approved by the UCSF Committee on Human Research. All subjects provided written informed consent.

NEUROPSYCHOLOGICAL AND LANGUAGE ASSESSMENT—All participants underwent a neuropsychological and language battery for diagnostic purposes as previously described (Gorno-Tempini et al., 2004). General functional level was assessed by means of the Clinical Dementia Rating (CDR) (Morris, 1993) and the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975). Standard tests were used to assess semantic skills (Boston Naming Test (BNT)), phonological abilities (number of D-words in one minute) and semantic category fluency (number of animals in one minute), sentence repetition abilities (WAB repetition), verbal working memory (digits forward and backward), visual memory (Modified Rey-Osterrieth Delay), verbal memory (California Verbal Learning Test Mental Status Edition - CVLT), visuospatial functions (Modified Rey-Osterrieth Copy), verbal executive functions (Modified Trail Making – number of errors). Apraxia of speech and dysarthria were assessed by an experienced speech-language pathologist (JO) using severity rating scales.

Neuropsychological data for participant groups were compared with normative data obtained from a group of more than 100 cognitively unimpaired individuals enrolled in studies of normal aging at the UCSF MAC and matched by age, gender and education level. Only three out of ten normal subjects included in this study were part of the normative population. A score of two standard deviations below the mean was considered impaired.

READING TEST—Each patient's reading abilities were assessed using the word (subtest 35) and pseudo-word (subtest 36) lists of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) battery (Kay, Lesser, & Coltheart, 1992). Specifically, the subtests included:

1. 30 regular words, e.g., words with regular grapheme-to-phoneme correspondence, such as 'rub', 'navy', and 'chicken' (subtest 35);
2. 30 exception words, e.g., words with inconsistent grapheme-to-phoneme correspondence, such as 'sew', 'iron', and 'ceiling' (subtest 35);
3. 24 pseudo-words, e.g., pronounceable strings of letters with no semantic representation, such as 'ked', 'snite' and 'dringe' (subtest 36).

Regular and exception words were randomly presented in subtest 35, while pseudo-words were presented separately in subtest 36. The number of correctly read items was recorded for each list and a percentage index of accuracy was derived for regular words, exception words and pseudo-words.

STATISTICAL ANALYSIS OF READING ACCURACY—All statistical analyses were performed using SPSS 12.0 software package for Windows (release 12.0.0, SPSS Inc., Chicago, IL).

Group Analyses: Specific statistical group analyses were performed in order to test the significance of the effect of word type (regular, exception and pseudo-words) and group (PNFA, SD, LPA, AD, DCG, NC) on reading accuracy scores. In particular, the following effects were tested:

1. Group effect for each word type reading accuracy, by means of three separate one-way ANOVA models (one for each word type) entering the reading accuracy score as dependent variable and the 'group' as six-level factor.
2. Group effect for the differences between regular and exception word reading, by means of a one-way ANOVA model entering the differences between regular and exception reading accuracy score as dependent variable and the 'group' as six-level factor.
3. Group effect for the differences between regular and pseudo-word reading, by means of a one-way ANOVA model entering the differences between regular and pseudo-word reading accuracy score as dependent variable and the 'group' as six-level factor. For each analysis, post hoc pair-wise comparisons were performed using Tukey's method.

Correlation Analysis: In order to test the hypothesis of an association between exception word reading and semantic memory impairments (Plaut et al., 1996; Seidenberg & McClelland, 1989), a bivariate correlation analysis between reading accuracy and BNT scores was performed. The hypothesis of an association between pseudo-word reading impairments and phonological deficits (Plaut et al., 1996; Seidenberg & McClelland, 1989) was not tested, because our neuropsychological test did not include specific measures of phonological abilities.

Neural correlates of exception and pseudo-word reading

SUBJECTS—All subjects of the behavioral study, from whom a high-quality MRI scan was acquired within six months of the reading assessment, were included in the imaging study. The group was composed of 54 subjects. As highlighted in the 'Voxel-based morphometry analysis' section (see below), the subjects were not sub-grouped on the basis of their diagnosis in the VBM correlation analysis. Subjects with heterogeneous reading scores and with different patterns of gray matter atrophy (Baron et al., 2001; Boxer et al., 2006; Gorno-Tempini et al., 2004; Mummery et al., 2000; Rosen et al., 2002) were entered as a single-group in the statistical model in order to provide variability in the sample and thus to increase the power of the correlation analysis. However, for sample characterization purposes, we report that the subject group included five patients with PNFA, 13 with SD, five with LPA, 14 with AD, three subjects of the normal control group (NC), and 14 of the dementia control group (DCG).

IMAGE ACQUISITION—MRI scans were obtained on a 1.5T Magnetom VISION system (Siemens, Iselin, NJ). A volumetric magnetization prepared rapid gradient-echo MRI (MPRG, TR/TE/TI = 10/4/300 milliseconds) was used to obtain T1-weighted images of the entire brain, 15-degree flip angle, coronal orientation perpendicular to the double spin-echo sequence, 1.0 × 1.0 mm² in-plane resolution and 1.5 mm slab thickness, as described in a previous study (Brambati, Myers et al., 2006).

VOXEL-BASED MORPHOMETRY ANALYSIS—VBM analysis included two steps: spatial preprocessing (normalization, segmentation, Jacobian modulation and smoothing) and statistical analysis. Both steps were implemented in the SPM5 software package (Wellcome Department of Imaging Neuroscience, London; <http://www.fil.ion.ucl.ac.uk/spm>) running on Matlab 6.5.1 (MathWorks, Natick, MA).

Image pre-processing: Anatomical MRI images were spatially pre-processed using standard procedures (Good et al., 2001). *Ad hoc* template and *a priori* images were created by averaging 30 age-matched normal control scans that had been normalized and segmented in the MNI (Montreal Neurological Institute) stereotaxic space. All T1 structural images were segmented, bias corrected and spatially normalized to the Montréal Neurological Institute space using the

unified segmentation procedure (Ashburner & Friston, 2005). The VBM analysis was based on modulated gray matter images, whereby the gray matter value in each voxel is multiplied by the Jacobian determinant derived from the spatial normalization in order to preserve the total amount of gray matter from the original images. These modulated gray matter images were smoothed with a Gaussian kernel (8 mm FWHM).

Statistical Analysis: Exception and pseudo-word reading accuracy were entered in a single multiple regression statistical model as separate covariates of interest. Age and gender were entered as nuisance covariates. Global nuisance effect was accounted for by scaling all images to the same global volume. Smoothed gray matter images of all subjects, irrespective of their diagnosis, were entered as a single group in the statistical model. This statistical model of VBM correlation analysis has already been successfully applied to patients with various neurodegenerative diseases in order to test the association between the voxelwise gray matter volumes and specific behavioral and cognitive abilities (Amici et al., 2007; Brambati, Myers et al., 2006; Rankin et al., 2006; Rosen et al., 2005).

Specific contrasts were set in order to identify the brain regions that correlated with exception (*effect of exception word reading*) and pseudo-word reading accuracies (*effect of pseudo-word reading*). The correlation was tested using a [1] t-contrast, assuming that decreased reading abilities would be associated with decreased gray matter volumes. The significance of each effect of interest was determined using the theory of Gaussian fields (Friston et al., 1995). When the whole brain was explored, a statistical threshold of $p < 0.05$ corrected for multiple comparisons (SPM family-wise error – FWE) was accepted. Based on previous work, a less conservative threshold of $p < 0.001$ uncorrected for multiple comparisons was adopted within a region of interest (ROI) comprising the network of regions that have been previously implicated in reading (Mechelli et al., 2005; Mechelli et al., 2003; Price et al., 2003; Price, Wise, & Frackowiak, 1996). The ROI included the left inferior frontal gyrus, inferior parietal lobule/angular gyrus, superior and middle temporal gyri and fusiform gyrus. It was created from the AAL brain atlas (Tzourio-Mazoyer et al., 2002) and applied to the SPM dataset using WFU Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003).

RESULTS

Pattern of Reading Impairments in Primary Progressive Aphasia

NEUROPSYCHOLOGICAL AND LANGUAGE ASSESSMENT (Table 1)—The neuropsychological and language evaluation broadly revealed the expected pattern of impairments for each PPA variant: motor speech disorder (apraxia of speech and dysarthria rating) in PNFA, semantic impairment in SD (semantic fluency, BNT), short-term phonological memory disruption in LPA (digits backward, WAB repetition, verbal executive functions – Modified Trials), and impaired construction ability and visuo-spatial memory in AD (Modified Rey-Osterrieth Copy and Delay Recall). The dementia control group (DCG), as by inclusion criteria, showed an aspecific, mild profile of cognitive impairments, due to the heterogeneity of the sample.

READING ACCURACY RESULTS (Table 2 and Figure 1)

Group Analysis: 1) Group effect for each word type reading accuracy: The one-way ANOVA analyses revealed a significant group effect of word type in word reading accuracy of exception ($F(5,60)=18.6$, $p<0.001$) and pseudo-words ($F(5,60)=9.5$, $p<0.001$), but not of regular words ($F(5,60)=2.2$, $p=0.06$). In the post-hoc analysis of exception word reading scores, SD patients presented with significantly lower reading accuracy with an overall type error 1 of 0.05 when compared to all other groups (SD<NC, 95% Confidence Interval – Lower Bound (LB) = -53.2, Upper Bound (UB) = -24.7; SD<PNFA, LB=-42.4, UB=-10.4; SD<LPA, LB=

−37.3, UB=−1.3; SD<AD, LB=−45.2, UB=−19.1; SD<DCG, LB=−46.3, UB=−21.0). Moreover, LPA showed a poorer performance than NC (LPA<NC, LB=−38.6, UB=−0.8).

In order to test the differences in exception word reading that could not be explained by general functional level, we re-ran the analysis controlling for MMSE scores (weighted least-squares (WLS) analysis within a GLM Univariate Model). The performance of those with SD remained significantly lower than all other groups, while the difference between LPA and NC was no longer significant.

In the post-hoc analysis of pseudo-word reading scores, AD, LPA, PNFA and SD showed significantly lower accuracy when compared with either dementia (DCG) and normal (NC) controls (SD<NC, 95% Confidence Interval - LB=−42.6, UB=−5.3; PNFA<NC, LB=−47.1, UB=−2.7; LPA<NC, LB=−68.0, UB=−18.7; AD<NC, LB=−44.4, UB=−7.1; SD<DCG, LB=−36.2, UB=−3.2; PNFA<DCG, LB=−41.0, UB=−0.2; LPA<DCG, LB=−62.1, UB=−16.0; AD<DCG, LB=−38.0, UB=−5.0). The differences remained significant even when we controlled for MMSE scores.

2) Group effect for the differences between regular and exception word reading: The one-way ANOVA analyses revealed a significant group effect on the difference of regular and exception word reading ($F(5,60)=23.9$, $p<0.001$). The post-hoc analysis revealed that the discrepancy between regular and exception word reading abilities was larger in the SD group when compared to all the other groups (SD>NC, 95% Confidence Interval - LB=19.4, UB=39.0; SD>PNFA, LB=8.5, UB=30.5; SD>LPA, LB=5.8, UB=30.5; SD>AD, LB=16.7, UB=34.7; SD>DCG, LB=18.5, UB=35.9). The differences remained significant even when we controlled for MMSE scores.

3) Group effect for the differences between regular and pseudo-word reading: The one-way ANOVA analyses revealed a significant group effect on the difference of regular and pseudo-word reading ($F(5,60)=7.4$, $p<0.001$). The post-hoc analysis revealed that the discrepancy between regular and pseudo-word reading abilities was bigger in LPA and AD compared to both NC (LPA>NC, 95% Confidence interval - LB=10.7, UB=58.6; AD>NC, LB=4.3, UB=40.6) and DCG (LPA>DCG, LB=11.3, UB=56.1; AD>DCG, LB=5.5, UB=37.5). The differences remained significant even when we controlled for MMSE scores.

Correlation Analysis: Correlation analysis showed a significant association between naming abilities, as assessed by the BNT, and accuracy in reading of exception words ($r=0.69$, $p<0.01$), but not regular ($r=0.25$, $p=0.7$) nor pseudo-words ($r=0.17$, $p=0.21$). In order to exclude the possibility that the correlation results were driven by a diagnosis effect or by an effect of general functional decline, we ran two separate partial correlation analyses controlling for SD diagnosis and MMSE. Yet when we controlled for SD diagnosis or general functional level (MMSE), we observed that BNT scores selectively correlated with reading of exception words (controlling for SD diagnosis: $r=0.41$, $p<0.05$; controlling for MMSE: $r=0.68$, $p<0.01$), but not regular (controlling for SD diagnosis: $r=0.14$, $p=0.32$; controlling for MMSE: $r=0.18$, $p=0.18$) nor pseudo-words (controlling for SD diagnosis: $r=0.18$, $p=0.20$; controlling for MMSE: $r=0.05$, $p=0.70$).

Neural correlates of exception and pseudo-word reading (Table 3 and Figure 2)

Effect of Exception Word Reading—A positive correlation between exception word reading accuracy and gray matter (GM) volume was observed in the left anterior temporal lobe, at the level of the anterior superior and middle temporal gyri, anterior fusiform gyrus and temporal pole ($p<0.05$ FWE). No significant correlation was revealed between exception word

reading accuracy and the GM volume in the posterior fusiform gyrus, even when the threshold was lowered to $p < 0.1$ uncorrected for multiple comparisons (see Figure 3).

The left anterior temporal lobe area that correlated with performance on exception word reading was located in regions commonly atrophied in SD (Chan et al., 2001; Galton et al., 2001; Gorno-Tempini et al., 2004; Mummery et al., 2000; Rosen et al., 2002), raising the question of a diagnosis-related effect. When we re-ran the analysis entering the SD diagnosis as nuisance variable, the correlation persisted, albeit at a predictably lower level of significance (superior temporal gyrus (22/38), anterior portion: $x = -36$, $y = -2$, $z = 0$, $Z = 3.6$, $p < 0.001$ uncorrected; middle temporal gyrus (21), anterior portion: $x = -60$, $y = -10$, $z = -16$, $Z = 2.8$, $p < 0.005$ uncorrected; fusiform gyrus (20), anterior portion: $x = -42$, $y = -36$, $z = -26$, $Z = 3.6$, $p < 0.005$ uncorrected; temporal pole (38): $x = -40$, $y = 8$, $z = -22$, $Z = 1.9$, $p < 0.05$ uncorrected). This result showed that an SD group effect alone cannot explain our findings.

Effect of Pseudo-Word Reading—A positive correlation between pseudo-word reading accuracy and GM volume was observed in the left inferior parietal lobule/angular gyrus ($p < 0.001$ uncorrected), in the posterior portion of the middle and superior temporal gyri ($p < 0.05$ FWE) and in the posterior fusiform gyrus ($p < 0.001$ uncorrected for multiple comparisons). No significant correlation was observed between pseudo-word reading and GM volume in the anterior fusiform gyrus even when the threshold was lowered to $p < 0.1$ uncorrected for multiple comparisons ($p < 0.1$ uncorrected) (see Figure 3).

The left inferior parietal and posterior temporal regions that correlated with performance in pseudo-word reading was located in regions that are commonly atrophied in LPA (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2004), raising the question of a diagnosis-related effect. When we re-ran the analysis entering the LPA diagnosis as nuisance variable, the correlation persisted at the pre-established threshold of $p < 0.001$, uncorrected for multiple comparisons (inferior parietal lobule/angular gyrus (39/40): $x = -54$, $y = -58$, $z = 38$, $Z = 3.8$; $x = -52$, $y = -70$, $z = 24$, $Z = 4.2$; superior temporal gyrus (21/22), posterior portion: $x = -60$, $y = -50$, $z = 14$, $Z = 3.3$; middle temporal gyrus (21), posterior portion: $x = -58$, $y = -56$, $z = 18$, $Z = 4.7$; fusiform gyrus (19), posterior portion: $x = -42$, $y = -80$, $z = -16$, $Z = 3.5$). This result showed that an LPA group effect cannot explain our findings.

DISCUSSION

In this study we showed that patients with different clinical forms of PPA and AD show a differential pattern of relative double dissociation in their ability to read exception and pseudo-words. Specifically, patients with SD were mainly impaired in exception word reading, while those with LPA and AD were mainly impaired pseudo-word reading. Moreover, exception word reading impairments correlated with the severity of semantic impairment. A VBM correlation analysis showed that exception word reading accuracy correlated with the integrity of left anterior temporal and fusiform regions, while pseudo-word reading abilities correlated with the integrity of the left temporoparietal structures and the posterior portion of the fusiform gyrus.

Analysis of behavioral data showed that clinical variants of PPA present with different patterns of reading impairments. Patients with SD, a PPA variant defined by progressive semantic loss (Gorno-Tempini et al., 2004; Hodges et al., 1992; Mummery et al., 2000; Neary et al., 1998; Rosen et al., 2002), demonstrated a difference in performance between regular and exception word reading abilities that could not be ascribed to a general cognitive decline.

Previous studies have consistently reported an effect of word frequency and length on exception word reading accuracy in SD (Jefferies et al., 2004; Patterson & Hodges, 1992; Patterson et

al., 2006; Wilson et al., 2008; Woollams et al., 2007). In particular, long, low-frequency exception word reading was characterized by frequent over-regularization errors (e.g., 'sue' for 'sew') (Patterson et al., 2006; Wilson et al., 2008; Woollams et al., 2007), supposedly due to a compensatory mechanism in which sub-word processes for regular mapping of orthography-to-phonology normally employed in reading pseudo-words is extended to exception words. Based on reports involving patients with SD, it has been hypothesized that there is an association between exception word reading and semantic abilities. Consistent with this view, we observed that the severity of semantic loss, as measured by the BNT, correlated with the accuracy in reading of exception words, but not of other word types, even when we controlled for general cognitive status and an SD diagnosis.

On the other hand, patients with LPA, defined by phonological loop impairment (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2004), showed a symmetrical pattern of reading disorders, characterized by a discrepancy between regular and pseudo-word reading abilities, but not between regular and exception words. These findings suggest that reading disabilities in these forms of neurodegenerative diseases are not determined by general cognitive decline, but by specific damage to different language mechanisms sustaining exception and pseudo-word reading.

Although our study was not specifically designed to test cognitive models of reading, these results seem to be better explained by the connectionist triangle model (Plaut et al., 1996; Seidenberg & McClelland, 1989), assuming that the reading of words and pseudo-words is determined by a graded division of labor between phonology, semantics and orthography within the general language architecture, more than by two distinct reading-specific routes. From a clinical point of view, these results provide further evidence to the hypothesis that SD and LPA are distinct variants of PPA (Gorno-Tempini et al., 2008; Gorno-Tempini et al., 2004) and suggest that reading evaluations could provide a valuable tool for differential diagnosis.

A pattern characterized by a discrepancy between regular and pseudo-word reading abilities was also found in AD patients, who most likely show pathological changes similar to LPA (Josephs et al., 2008; Mesulam et al., 2008; Rabinovici et al., 2008). Moreover, it must be noted that the AD group included in this study was mostly formed by AD at early age of onset (mean age of the AD group: 62 years). Early onset AD has been characterized by a pattern of cortical atrophy involving bilateral temporoparietal regions, similar to that observed in LPA (Frisoni et al., 2007; Frisoni et al., 2005), as opposed to late stage AD, which has been associated with hippocampal atrophy (Frisoni et al., 2007; Frisoni et al., 2005). The heterogeneity of the AD patients included in previous reading studies could explain why the phonological dyslexia pattern has not been consistently reported in AD and why the presence of pseudo-word reading deficits is still controversial (Colombo, Fonti, & Cappa, 2004; Friedman, Ferguson, Robinson, & Sunderland, 1992; Glosser, Friedman, Kohn, Sands, & Grugan, 1998; Noble, Glosser, & Grossman, 2000).

The results of our neuroimaging study showed that exception and pseudo-word reading rely not only upon different language mechanisms, but are also sustained by separated brain regions. Even when we controlled for potential diagnosis effect, exception word reading accuracy showed a significant correlation with the integrity of the left antero-lateral temporal cortex, representing a crucial structure of the anatomical network underpinning the semantic system (Devlin et al., 2000; Gauthier, Anderson, Tarr, Skudlarski, & Gore, 1997; Lambon Ralph, Pobric, & Jefferies, 2008; Mummery, Patterson, Hodges, & Price, 1998; Noppeney & Price, 2002b; Pobric, Jefferies, & Ralph, 2007; Ricci et al., 1999; Vandenberghe et al., 1996; Vandenberghe, Nobre, & Price, 2002).

Although patient testing consistently pointed to an association between damage in the antero-lateral temporal cortex and pattern of surface dyslexia, this region was not found to be activated in functional imaging studies investigating the neural correlates of exception word reading in healthy controls (Wilson et al., 2008). This discrepancy may be explained by different methodological factors. First, it is notoriously difficult to get a strong signal from the anterior temporal lobes in functional MRI (Devlin et al., 2000). Secondly, nearly all functional neuroimaging studies on reading have employed monosyllabic and high-frequency word stimuli, mostly representing high-familiar concepts. It is possible that the processing of these stimuli can be successfully achieved without the engagement of the left anterior lateral temporal cortex, usually more involved in semantic processing of less prototypical stimuli (Brambati, Narvid et al., 2006). In contrast, the activation of the anterior fusiform gyrus during exception word reading has been observed in both normal readers and patients with acquired dyslexia (Brunswick et al., 1999; Mechelli et al., 2005; Mechelli et al., 2003; Price et al., 2003). Since this area also responds during semantic tasks (Mummery et al., 1998; Noppeney & Price, 2002a), it has been proposed that the anterior fusiform gyrus semantically mediates the translation from orthography to phonology.

Pseudo-word reading accuracy correlated with the GM volume in the left inferior parietal lobule, in the posterior portion of the superior and middle temporal and fusiform gyri. Although the selective activation of the left temporoparietal regions during pseudoword reading is not consistent among different studies, its involvement in the mechanisms of direct translation from orthography-to-phonology is supported by three separate lines of evidence: 1) studies on stroke patients, showing that lesions of the temporoparietal regions often result in deficits in pseudo-word processing (Hillis et al., 2001; Philipose et al., 2007; Price et al., 2003); 2) studies on neural correlates of developmental reading ability, showing activation of temporoparietal regions has been associated with the maturation of phonological processing and the development of orthographic-phonological reading strategies in young readers (Schlaggar & McCandliss, 2007; Turkeltaub, Eden, Jones, & Zeffiro, 2002; Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003); 3) previous functional neuroimaging study on the neural basis of the reading network in semantic dementia, showing the engagement of this area when over-regularization errors (e.g., 'sue' for 'sew') occurred during reading of exception words (Wilson et al., 2008). On the other hand, converging evidence has reported a selective activation of the posterior fusiform gyrus during pseudo-word reading (Mechelli et al., 2005; Mechelli et al., 2003; Price et al., 2003). It has been proposed that this area acts as an interface between abstract visual form information and higher order stimulus properties such as its associated sound. However, this function would not be specific to reading (McCrory, Mechelli, Frith, & Price, 2005; Price & Devlin, 2003) (for an alternative view, see also (Cohen et al., 2000).

Taken together, these anatomical findings suggest that in neurodegenerative diseases, the selective loss of exception and pseudo-word reading abilities is associated with progressive loss of integrity of brain areas sustaining semantic and orthographic-phonologic systems respectively. Even if testing theoretical models of reading goes beyond the aims of the present study, we suggest that the present anatomical findings could be better explained by the connectionist triangle model of reading.

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Figure 1.
Reading accuracy scores in each group.

Figure 2.

Brain areas showing (A) Independent effect of exception word reading; (B) Independent effect of pseudo-word reading. Maps of significant correlation are superimposed the 3D rendering of the Montreal Neurological Institute standard brain. The threshold for display is $p < 0.05$ FWE corrected for multiple comparisons.

Figure 3. Representative axial ($z = -17$) and coronal ($x = -28$) slices showing the differential involvement of the anterior and posterior portions of the left fusiform gyrus in exception (green) and pseudo-word (red) reading. Maps of significant correlation are superimposed on a canonical template image at a display threshold of $p < 0.1$ uncorrected.

Table 1
Demographic and neuropsychological screening information in each patient subgroup
Scores are reported as mean raw score (standard deviation).

	PNEA n=7	SD N=14	LPA n=5	AD n=14	DCG n=16	NC n=10
<i>Demographic and Functional Information</i>						
Age (years)	68.7 (9.7) ^a	63.6 (6.8)	62.0 (4.3)	62.0 (8.3)	57.3 (6.1)	60.9 (9.1)
Gender (F/M)	5/2	4/10	2/3	9/5	8/8	8/2
MMSE (max=30)	25.4 (5.2)	22.1 (6.0)	17.2 (5.1)	20.4 (5.0)	26.9 (3.5)	29.7 (0.6)
CDR Total	0.4 (0.4)	1.0 (0.5)	0.7 (0.3)	0.8 (0.3)	0.8 (0.4)	0.0 (0.0)
CDR Box Scores	2.6 (2.6)	5.1 (2.7)	3.6 (2.1)	4.6 (2.0)	5.3 (3.3)	0.2 (0.3)
<i>Neuropsychological Screening</i>						
Apraxia of Speech (7 = max deficit)	3.0 (1.9)	0.0 (0.0)	1.4 (1.9)	0.9 (1.6)	0.1 (0.5)	NA
Dysarthria (7 = max deficit)	1.9 (2.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.5 (1.1)	NA
Phonemic Fluency	5.0 (3.8)	4.9 (3.6)	3.5 (4.4)	8.4 (5.2)	12.1 (7.6)	16 (3.6)
Semantic Fluency	10.3 (6.5)	3.7 (3.6)	6.2 (5.2)	7.8 (3.5)	14.3 (8.6)	26.3 (5.5)
Abbreviated BNT (max=15)	12.4 (2.1)	2.9 (3.2)	8.0 (1.8)	9.5 (4.1)	12.4 (2.9)	14.7 (0.6)
WAB Repetition	80.9(21.7)	85.0(12.2)	63.0(14.5)	80.2(12.2)	92.2(9.5)	NA
Modified Rey-Osterrieth Copy (max=17)	14.6 (2.2)	16.0 (1.4)	15.7 (1.1)	10.1 (6.0)	13.7 (4.3)	15.3 (0.6)
10-min delay	8.6 (5.6)	7.8 (5.4)	8.3 (5.7)	4.1 (4.8)	8.6 (4.9)	10.3 (0.6)
CVLT-MS Trials 1-4 Total (max=36)	23.7 (9.8)	12.6 (7.4)	13.0 (9.4)	13.6 (6.4)	22.3 (8.0)	NA
30-sec delay (max=9)	6.4 (2.9)	1.7 (2.3)	3.0 (3.2)	2.8 (2.1)	6.0 (3.0)	NA
10-min delay	5.7 (3.5)	1.3 (2.2)	2.8 (2.6)	1.8 (2.3)	5.4 (3.0)	NA
Digit Forward	5.7(2.2)	6.1(1.4)	3.6(0.9)	5.2(1.2)	6.1(1.5)	6.7(2.5)
Digit Backward	3.1 (2.0)	4.5 (2.0)	1.8 (1.1)	2.7 (1.2)	4.3 (1.4)	7.3 (0.6)
Modified Trails-no. of correct lines (max=14)	8.6 (6.8)	12.9 (2.6)	2.7 (2.4)	5.9 (5.3)	10.4 (5.6)	14.0 (0.0)

Abbreviations: PNEA = Progressive Non-Fluent Aphasia; SD = Semantic Dementia; LPA = Logopenic Progressive Aphasia; AD = Alzheimer's Disease; DCG = Dementia Control Group; NC = Cognitively normal subjects.

Bold Italic: score two standard deviations below the mean of normative data

Table 2
Reading accuracy scores in each patient subgroup
Scores are reported as mean percentage (standard deviation).

	PNFA n=7	SD N=14	LPA n=5	AD n=14	DCG n=16	NC n=10
Regular Words	97.1 (2.3)	90.2 (8.9)	91.3 (8.4)	96.7 (4.3)	96.7 (12.5)	100.0 (0.0)
Exception Words	87.1 (15.6)	60.7 (15.8) ^c	80.0 (8.5) ^b	92.9 (6.8)	94.4 (13.3)	99.7 (1.0)
Pseudo-words	72.6 (22.4) ^{a,b}	73.5 (13.9) ^{a,b}	54.2 (21.2) ^{a,b}	71.7 (21.1) ^{a,b}	93.2 (6.6)	97.7 (5.0)

Tukey's *post hoc* pair-wise tests for group factor:

- ^a p<0.05 vs. DCG
- ^b p<0.05 vs. NC
- ^c p<0.05 vs. each of the other groups

Table 3
Results of VBM correlation analysis ($p < 0.05$ SPM family-wise error – FWE, corrected for multiple comparisons)

Brain Regions (BA)	Independent Effect Exception Words				Independent Effect Pseudo-Words			
	x	y	z	Z	x	y	z	Z
Inferior Parietal Lobule (39/40)					-54	-58	38	4.5*
					-48	-76	24	3.3*
					-38	-58	42	3.6*
Superior Temporal Gyrus (22/38), anterior portion	-56	4	-6	5.4				
	-40	-4	-12	5.1				
Superior Temporal Gyrus (21/22), posterior portion					-60	-50	14	3.8*
Middle Temporal Gyrus (21), anterior portion	-58	-10	-14	5.5				
	-54	4	-28	4.6*				
Middle Temporal Gyrus (21), posterior portion					-58	-56	16	5.1
Fusiform Gyrus (20), anterior portion	-40	-32	-24	5.5				
	-30	-8	-40	5.2				
Fusiform Gyrus (19), posterior portion					-42	-80	-16	3.5*
Temporal Pole (38)	-46	14	-26	5.0				

*
 $p < 0.001$ uncorrected for multiple comparisons within the ROI