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Reading words and other people: a comparison of exception word, familiar face and affect processing in the left and right temporal variants of primary progressive aphasia

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Abstract

Semantic variant primary progressive aphasia (svPPA) typically presents with left-hemisphere predominant rostral temporal lobe atrophy and the most significant complaints within the language domain. Less frequently, patients present with right-hemisphere predominant temporal atrophy coupled with marked impairments in processing of famous faces and emotions. Few studies have objectively compared these patient groups in both domains and therefore it is unclear to what extent the syndromes overlap. Clinically diagnosed svPPA patients were characterized as left- (n= 21) or right-predominant (n = 12) using imaging and compared along with 14 healthy controls. Regarding language, our primary focus was upon two hallmark features of svPPA; confrontation naming and surface dyslexia. Both groups exhibited naming deficits and surface dyslexia although the impairments were more severe in the left-predominant group. Familiarity judgments on famous faces and affect processing were more profoundly impaired in the right-predominant group. Our findings suggest that the two syndromes overlap significantly but that early cases at the tail ends of the continuum constitute a challenge for current clinical criteria. Correlational neuroimaging analyses implicated a mid portion of the left lateral temporal lobe in exception word reading impairments in line with proposals that this region is an interface between phonology and semantic knowledge.

Keywords

Primary Progressive Aphasia; Semantic Dementia; Social Cognition; Surface Dyslexia; Anterior Temporal Lobe

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1. Introduction

Semantic variant primary progressive aphasia (svPPA), also known as semantic dementia, is a clinical syndrome characterized by a progressive, generalized loss of semantic memory (or 'conceptual knowledge') that contrasts against a relative sparing of other aspects of perception and cognition (including phonology, executive skills and episodic memory; Gorno-Tempini et al., 2011; Hodges, Patterson, Oxbury, & Funnell, 1992). In the classical clinical presentation, semantic deficits manifest earliest in the form of a profound anomia (naming impairment), but eventually emerge across a range of expressive and receptive tasks in both the verbal and non-verbal domains (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Coccia, Bartolini, Luzzi, Provinciali, & Lambon Ralph, 2004; Lambon Ralph, McClelland, Patterson, Galton, & Hodges, 2001; Luzzi et al., 2007; Piwnica-Worms, Omar, Hailstone, & Warren, 2010). Surface dyslexia is also one of the hallmark features of svPPA. It also typically presents early in the disease course and is included in current clinical guidelines (Gorno-Tempini et al., 2011). Surface dyslexia is characterized as a selective impairment in reading aloud words with exceptional spelling-to-sound correspondences (exception words), where they are typically 'over-regularized' and pronounced as they are spelled (e.g., 'sew' is pronounced as 'sue'). Reading of words with regular sound-spelling relationships (e.g., 'new'), and of pseudo words (e.g., 'lew'), remains largely intact. However, even at later stages of the disease, the degree to which there are clear verbal impairments can vary substantially from patient to patient and this has been most reliably associated with left-right hemisphere distribution of the underlying cortical atrophy (Gefen et al., 2013; Lambon Ralph et al., 2001; Thompson, Patterson, & Hodges, 2003).

The svPPA clinical syndrome falls within the spectrum of frontotemporal dementia (FTD) and is associated with progressive yet relatively circumscribed atrophy and hypometabolism of the rostral temporal lobes (rTL) (Davies et al., 2005; Mummery et al., 2000; Nestor, Fryer, & Hodges, 2006). At initial clinical presentation, atrophy is typically bilateral though usually asymmetric with more extensive left hemisphere involvement. Over time, atrophy spreads through the initially less affected contralateral rostral temporal cortex and also to ipsilateral ventromedial frontal, insular and infero-posterior temporal regions (Brambati, Rankin, et al., 2009; Kumfor et al., 2016; Rogalski et al., 2014). Less frequently (approximately 30% of cases), patients present with greater right than left rostral temporal involvement. The cognitive and behavioral profile of these right-predominant cases is not as well characterized (Babiak, 2014; Chan et al., 2009) and only a few studies have directly and objectively compared their performance to those of left-predominant svPPA. Nonetheless, it has been demonstrated that left-predominant cases exhibit more profound naming impairments than right-predominant patients (Lambon Ralph et al., 2001; Seeley et al., 2005). On the other hand, predominantly right-sided temporal atrophy is associated with disproportionate impairments for person-specific knowledge, processing of affect-related stimuli and socially-salient stimuli and in semantic tasks performed on non-verbal stimuli (Barbarotto, Capitani, Spinnler, & Trivelli, 1995; Gainotti, Barbier, & Marra, 2003; Gorno-Tempini, Rankin, et al., 2004; Henry et al., 2014; Rosen et al., 2002; Snowden, Thompson, & Neary, 2012; Zahn et al., 2009). It has yet to be demonstrated, however, whether

exception word reading impairments reliably feature in right-predominant temporal cases and whether they present to a lesser or equivalent degree to those exhibited in left-predominant svPPA. Given that surface dyslexia is listed as a key feature in consensus diagnostic criteria for svPPA (Gorno-Tempini et al., 2011), a comparison of this nature is of particular clinical import. In particular, it could speak to the sensitivity of surface dyslexia as a diagnostic marker for the temporal variant of frontotemporal dementia, particularly in the earliest stages of the disease. Similarly, it has yet to be clearly demonstrated whether or not socio-emotional deficits feature both in left and in right predominant cases. While prior retrospective case history reviews suggests they are (e.g., Thompson et al., 2003), larger group comparisons utilizing objective quantitative measures are needed to characterize the degree to which these impairments differ in severity.

The present study investigated objective measures of performance in general cognition, language and social cognitive function in the largest well-defined groups of left- and right-predominant temporal variant FTD patients to date. Our primary aims were to establish whether surface dyslexia is a feature of the right-temporal variant of svPPA, to investigate how this particular reading impairment relates to general semantic and language abilities and to identify whether specific temporal lobe regions correlate with exception word reading performance. Furthermore, we evaluated performance across a range of tasks that measure famous face processing and emotion processing in order to objectively compare social cognitive function in left and right temporal variants. We report data from a heterogeneous group of 33 patients clinically diagnosed with svPPA. Given that these patients usually present with varying degrees of asymmetric atrophy, we used a quantitative neuroimaging approach to qualify the status of each patient as being predominately affected in the left or right hemisphere. Moreover, a region of interest volumetric approach was employed to determine the distribution and degree of temporal lobe atrophy in these groups on a rostral-caudal as well as a medial-to-lateral axis. This was followed by a voxel-wise correlation between volume loss and reading performance, the results of which could inform theories of the neural basis of both semantic memory and reading.

2. Materials and Methods

2.1. Participants

Patients with svPPA were recruited through the University of California San Francisco (UCSF) Memory and Ageing Center (MAC) between 2002 and 2012. A diagnosis of svPPA was based on published guidelines (Gorno-Tempini et al., 2011) and followed a comprehensive evaluation by a multidisciplinary team (that included a neurologist, neuropsychologist, neuropsychiatrist and a nurse) who obtained a neurological history and examination and performed standardized neuropsychological and language evaluations as previously described (Gorno-Tempini, Dronkers, et al., 2004; Kramer et al., 2003). Diagnosis was made following a review of the evaluation by a team of clinicians at a consensus diagnostic meeting at the UCSF MAC. Structural neuroimaging was used to classify the cases as imaging-supported svPPA by establishing whether they showed selective anterior temporal atrophy (ATL), as indicated by current guidelines. All patients included in this study met criteria for imaging-supported svPPA, although, as we will

discuss later, some showed some degree of behavioral abnormality early in the course. Subsequent to diagnosis, the clinicians further read the structural MRI and classified patients as having predominantly left hemisphere or right hemisphere ATL atrophy. While this subjective diagnostic evaluation was our initial criteria to divide the patient groups, we further qualified this assignment by means of quantitative imaging-based volumetrics (See below).

Further criteria for inclusion in the present study were (i) a score of at least 15 out of 30 on the Mini-Mental Status Exam (MMSE; Folstein, Folstein, & McHugh, 1975), (ii) a Clinical Dementia Rating (CDR; Morris, 1993) of no greater than 1.0, and (iii) fluent in English. Thirty-three svPPA patients met these additional criteria including 21 with left-predominant ATL atrophy (L-svPPA) and 12 with right-predominant ATL atrophy (R-svPPA). Demographic characteristics of the patients are presented in Table 1.

Behavioral data was also collected from 14 healthy control participants who were verified as neurologically and cognitively normal on the basis of a neurological exam, neuropsychological testing and an MRI. Demographic information for the control participants is shown in Table 1. Although control participants had significantly more years of education than the svPPA patients, this would not account for patterns in the disparity in reading ability subsequently observed. Moreover the comparison of interest was between the two svPPA subgroups who did not differ in years of education, or in age (both P>0.5). Controls were significantly older than svPPA patients.

All patients had a high-quality MRI scan acquired within 3 months of the language and reading assessment. A separate group of 37 controls (herein referred to as the HCi group) were used for imaging analysis to ensure stringent control for age (mean = 62, p>0.6) and gender ratio (17 females, 20 males).

2.2. Neuropsychological screening battery

Patients and controls were administered a broad neuropsychological battery and speech and language tests for diagnostic purposes, as previously described (Gorno-Tempini, Dronkers, et al., 2004; Kramer et al., 2003).

2.3. Face processing and Social Cognitive Function

Processing of person-specific semantic information was evaluated using two tasks from the UCSF Famous Faces battery that have been previously described by Gorno-Tempini, Rankin et al. (2004). The first was famous face confrontation naming. The second was a test of familiarity judgments on famous faces in which the participant has to point to a familiar face, correctly rejecting three other unfamiliar (not famous) faces. Both tests comprised 20 items. Patient performance on famous faces tasks was compared to that of a control group comprising 9 clinically normal participants (3 males, 6 females) with a mean age of 67.1 years (MMSE ≥ 29).

The ability to recognize facial expression of emotions was assessed using the Affect Matching subtest of the Comprehensive Affect Testing System (CATS; Froming, Levy, Schaffer, & Ekman, 2006) whilst controlling for perceptual deficits using the CATS Identity

matching subtest. We also report performance on the Emotion Evaluation subtest from The Awareness of Social Inference Test (TASIT; McDonald, Flanagan, Rollins, & Kinch, 2003). Ability to interpret meaning of social messages from facial expression and other paralinguistic features of communication was assessed using the TASIT Social Inference – Minimal (SI-M) subtest. We report the 'sarcastic' condition and the 'sincere' condition separately such that a deficit in comprehension of paralinguistic cues in particular can be separated from a non-specific language comprehension impairment. We also report the Perspective Taking and Empathic Concern sub-scales from the Interpersonal Reactivity Index (IRI; Davis, 1983), as adapted for completion by the patient's close relative or friend (see Perry et al., 2001; Sollberger et al., 2014). This questionnaire was designed to assess both cognitive and emotional components of empathy and has previously been used to demonstrate a significant loss of empathy in patients with damage to the rostral temporal lobe (Perry et al., 2001; Rankin, Kramer, Mychack, & Miller, 2003).

2.4. Single Word Reading Assessment

Reading abilities were assessed in 22 patients (15 left-predominant and 7 right-predominant) with the "Regularity and Reading" and pseudo-word subtests of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA) battery (Kay, Lesser, & Coltheart, 1992). These tests included thirty regular words (e.g., words with regular grapheme-to-phoneme correspondence, such as 'rub', 'navy' and 'chicken') and thirty exception words (e.g., words with inconsistent grapheme-to-phoneme correspondences, such as 'sew' and 'yacht') randomly presented in a single subtest. Twenty-four pseudo-words (e.g., pronounceable strings of letters with no semantic representation, such as 'ked', 'snite' and 'dringe') were presented in a separate subtest. 11 patients (6 left- and 5 right-predominant) were assessed using Reading List 1 and 2 of the Arizona Battery of Reading and Spelling (ABRS; Beeson & Rising, 2010; Rapcsak & Beeson, 2004) which consist of forty regular and forty exception words randomly presented and the ABRS pseudo-word reading list which consists of 20 items. All control participants were assessed with the ABRS Reading subtests. The PALPA and ABRS subtests are comparable on linguistic parameters, such as regularity, frequency and word length.

The number of correctly read items was recorded and a percentage index of accuracy was derived for regular words, exception words and pseudo-words. Moreover, a measure of 'regularity effect' in reading ability was derived by subtracting the percentage accuracy of reading exception words from that of reading regular words (%regular - % exception). This measure was used as it serves as an internal control, taking into account variability in regular word reading when assessing exception word reading.

2.5. Statistical Analyses on Neuropsychological and Language Data

All statistical analyses on the behavioral data were performed using the SPSS software package (version 21, IBM Corp, Armonk, NY). Two-sample t-tests were used to assess the significance of group differences in accuracy scores. For each behavioral measure we examined differences between (I) All svPPA patients and the healthy control group (HC), (II) the left predominant patient sub-group (L-svPPA) and the HC group, (III) the right predominant patient sub-group (R-svPPA) and the HC group, and (IV) L-svPPA and R-

svPPA. One-tailed distributions were used in the case of single word reading scores as well as face and affect processing tests, in line with the study's core a priori hypotheses. Two-tailed distributions were used in the case of all other behavioral measures and demographics. A threshold of $p = 0.05$ was applied for assessments of statistical significance.

A regression analysis examined a putative association between semantic memory impairment and exception word reading performance (Woollams, Lambon Ralph, Plaut, & Patterson, 2007). 'Regularity effect' was regressed against performance in the picture and word versions of the Pyramids and Palm Trees (PPT; Howard & Patterson, 1992) semantic association task, with repetition performance and sentence comprehension performance as additional regressors to control for pre-semantic language impairments (e.g., phonological impairment) and overall severity of language impairment. All patients were entered as a single group. Controls were not included in this analysis.

2.6. MRI Acquisition

For participants who visited our center prior to 2007, MRI scans were acquired at 1.5 Tesla. Subsequently, MRI was acquired at 3.0 Tesla. In the present study, 13 L-svPPA patients, 6 R-svPPA patients and 22 of the HCi participants underwent MRI at 1.5T. 8 L-svPPA patients, 6 R-svPPA patients and 15 of the HCi participants underwent MRI at 3.0T.

1.5T MRI was acquired on a Siemens Magnetom VISION system (Siemens, Iselin, NJ) equipped with a standard quadrature head coil. A volumetric magnetization prepared rapid gradient-echo (MPRAGE) sequence was used to obtain T1-weighted images of the whole brain (coronal slice orientation; slice thickness = 1.5 mm; in-plane resolution = 1.0 × 1.0 mm; matrix = 256 × 256; time to repetition (TR) =10 ms; echo time (TE) = 4 ms; inversion time (TI) = 300 ms; flip angle = 15°).

3.0T MRI was acquired on a Siemens Tim Trio system equipped with a 12-channel receiver head coil. A volumetric MPRAGE sequence was used to acquire T1-weighted images of the entire brain (coronal slice orientation; slice thickness = 1.0 mm; in-plane resolution =1.0 × 1.0 mm; matrix = 240 × 256; TR/TE/TI = 2300/3/900 ms; flip angle = 9°).

2.7. MRI Pre-processing

All image pre-processing was carried out using statistical parametric mapping (SPM) 12b software, version 5298 (Wellcome Trust Centre for Neuroimaging, London, UK). The T1-weighted MRI image of each participant was bias corrected and partitioned into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) using SPM12b's segmentation procedure. The segments were then registered to a custom template (see below) in Montreal Neurological Institute (MNI) stereotactic space using the DARTEL (diffeomorphic anatomical registration through an exponentiated lie algebra) toolbox, resampling to $1.5mm^3$ with 'volume-preserving' Jacobian modulation (Ashburner, 2007). The resulting images were used to calculate total grey matter (TGM; the sum of voxel values across the GM segment), total intracranial volume (TIV; the sum of values across the GM, WM and CSF segments) and to extract GM volumes from within temporal lobe sub-regions (see below). For the voxel-based VBM analysis, the images were smoothed with an 8 mm full-width half-maximum (FWHM) Gaussian kernel.

We used a custom template created using data processed for longitudinal analysis of svPPA (unpublished data). For each participant, two images acquired at an interval of 6 to 24 months were high-dimensionally registered using SPM12b's longitudinal registration toolbox (Ashburner & Ridgway, 2012) creating a within-participant average image which was then segmented, as above. The GM and WM components of 120 participants' average images were then used to create a custom template using the DARTEL toolbox. The template included 33 left-predominant svPPA patients [mean age at scan 1(range) = 63.0 (50–75); mean scan interval in years (range) = 0.99 (0.56 – 1.40); number of participants scanned at 1.5T/3T = 20/13], 15 right-predominant svPPA patients [mean age at scan 1(range) = 63.3 (50 –72); mean scan interval in years (range) = 1.15 (0.68 – 2.12); 1.5T/3T = 6/9] and 72 healthy control participants [mean age at scan 1(range) = 64.9 (48 – 78); mean scan interval in years (range) = 1.04 (0.52 – 1.47); 1.5T/3T = 36/36].

2.8. Temporal lobe volume of interest (VOI) analysis

GM volumes were extracted from temporal lobe sub-regions in order to (i) quantitatively validate the assignment of patients to the L-svPPA or R-svPPA groups at diagnosis and (ii) further characterize the distribution of temporal lobe atrophy, on average, in each group. For all patients and healthy controls, GM volumes were measured in the rostral[1] and caudal halves of the right and left temporal lobe. The rostral halves were further partitioned according to gyral anatomy and GM volumes were extracted from each rostral sub-region. Anatomical definitions were derived on the basis of the cortical parcellations of Tzourio-Mazoyer et al. (2002) that are distributed as binary masks in the Wake Forest University Pickatlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003). We bisected the superior (STG), middle (MTG) and inferior temporal gyri (ITG), the fusiform gyrus (FG) and the parahippocampal gyrus (PhG) masks perpendicular to and at the approximate midpoint of their rostral-caudal axis. In the case of the rostral STG and MTG VOIs, we also we appended the temporal pole parcellations. The lateral left-hemisphere rostral gyri masks are illustrated as black and white regions in Figure 1, Panel A. We further created a left and a right rostral temporal mask by combining the rostral gyral masks for the respective hemisphere, plus the amygdala. Left and right caudal temporal lobe masks were created by combining the respective caudal gyral masks (the lateral aspect is illustrated as a dark grey region in Figure 1, Panel A).

The volume extracted from each temporal lobe sub-region was scaled by the subject's TIV to control for head size differences. Patients' regional volumes were then divided by the average regional volume across the healthy control participants such that patient volumes represented a proportion of the mean volume in healthy age-matched brains. A lateralization

[1]We use the term *rostral* as opposed to *anterior* when referring to these VOIs in light of an ongoing debate in the literature concerning the definition of the anterior temporal lobe (ATL) (Lambon Ralph, 2014). ATL has been used to refer to the most anterior, polar regions of the temporal lobes in some studies (Ross & Olson, 2010), often in consideration of the fact that it is the earliest and most severely atrophied area in svPPA (Mummery et al., 2000). The cortical region implicated in semantic cognition and language over the course of svPPA, however, extends to include much of the rostral half of the temporal lobe (Nestor et al., 2006). Moreover, correlations between semantic dysfunction and hypometabolism in svPPA as well as functional neuroimaging studies are now implicating regions caudal to the temporal pole, including lateral and ventrolateral temporal lobe neocortex (Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Hoffman, Lambon Ralph, & Woollams, 2015; Mion et al., 2010). The VOIs used in the present study were defined solely for the purpose of grossly examining the distribution of atrophy in the patient groups along an anatomically-defined rostral-caudal axis of the temporal lobe and without particular concern regarding more specific functional definitions of what constitutes the ATL.

index of rostral temporal volume was calculated for evaluating hemispheric predominance of atrophy in each patient with the following formula: (Rostral Right – Rostral Left) – (Rostral Right + Rostral Left). A positive index value therefore indicated left greater than right rostral temporal atrophy and a negative value indicated the opposite lateralization of atrophy with greater values in either direction indicating greater asymmetry. The patient-groups' mean regional proportional volumes were converted to percentage volume loss by multiplying by 100 and then by −1. Differences between patients groups in VOI volumes were assessed with a significance threshold of p=0.05.

2.9. Voxel-Based Morphometry

For between-group VBM analyses, a one-way analysis of covariance (ANCOVA) with 3 levels (L-svPPA, R-svPPA and HCi) was fit at each voxel of the smoothed grey matter segments. Four covariates of no interest were included: MRI field strength, age, total intracranial volume (TIV) to control for head size variability, and total grey matter (TGM) as a control for disease severity across individuals. The search volume was restricted to grey matter using an explicit masking procedure. The mask was created by averaging the normalized modulated grey matter segment of the members of the HCi group and then thresholding at a value of 0.05 to create a binary mask (volume = 205596 voxels). Contrasts were set to examine differences between: a) all svPPA patients and HCi, b) L-svPPA and HCi, c) R-svPPA and HCi, and d) L-svPPA and R-svPPA. The resultant statistical parametric maps (SPMs) were thresholded voxel-wise at p<0.05 corrected for family-wise error (FWE) for comparisons between patients and healthy controls, and p<0.001 (uncorrected) for the comparisons between L-svPPA and R-svPPA. SPMs are overlaid on an average of the HCi group's GM segments, with the exception of a 3D rendering which used the CH2 better template from MRICron (http:// http://www.mccauslandcenter.sc.edu/mricro/mricron/).

The neural correlates of exception word reading were examined by entering 'regularity effect' in a multiple regression model as a covariate of interest. We also included the same covariates of no interest and masking procedure as the group comparisons. All patients, but not healthy controls, were entered as a single group. Contrasts were set to examine the hypothesis that a greater 'regularity effect' (greater relative impairment in reading exception words compared to regular words), would be associated with decreased grey matter volume. Whole-brain statistical maps were initially examined at voxel-wise significance level of p<0.001 uncorrected and a cluster extent threshold of 100 voxels. We subsequently addressed the multiple comparisons problem by applying a voxel-level FWE-correction (P<0.05) within a 'small volume correction' approach. The restricted search volume was defined by the statistical map that resulted from the L-svPPA < R-svPPA group contrast when thresholded at p<0.001 uncorrected.

3. Results

3.1. Characterization of temporal lobe atrophy in left- and right-predominant svPPA

We used a targeted volume of interest (VOI) approach to examine the distribution of temporal lobe atrophy in our group of svPPA patients. We first re-confirmed the patients' diagnoses as imaging-supported svPPA, and quantified the mean (and range) of left and right

temporal lobe percentage volume loss in our undifferentiated svPPA cohort. Figure 1, Panel A depicts the location and coverage of the VOIs; the rostral temporal lobe (rTL) VOI included all of the white and black gyral VOIs and the caudal temporal lobe (cTL) VOI features in dark grey with a black outline.

As an undifferentiated clinical cohort (all svPPA), the patients presented with substantial rostral anterior temporal lobe atrophy in both the left (mean volume loss = 38.8%) and right hemispheres (34.3%). All patients exhibited a left rTL volume loss greater than 20% (range = 22–56%). Only three of thirty-three patients showed less than 5% volume loss in the right rTL (range = 0–67%). Average cTL was 20.3% in the left hemisphere (range 0–38%) and 13.3% in the right hemisphere (0–47%).

We next validated the UCSF MAC's prior clinical diagnostic assignment of each patient to the left-predominant versus the right-predominant variant by calculating an index of the lateralization of rostral temporal atrophy (See Methods). Each and every case assigned to the L-svPPA group did indeed have greater left than right rTL atrophy (index range = 0.22 to 0.48). Eleven of twelve members of the R-svPPA group clearly had right greater than left rTL atrophy (index range of 11 R-svPPA patients = −0.18 to −0.49). The exception case exhibited highly symmetric rTL atrophy with 33% volume loss in the left hemisphere and 35% volume loss in the right.

Indeed, the L-svPPA group, on average, exhibited 43.1% volume loss in the left rTL (range = 26–56%) and 18.9 % in the right rTL (0–41%; Figure 1, Panel B). The R-svPPA group, on average, exhibited 34.4% volume loss in the left rTL (22–50%) and 49.8% in the right hemisphere (35–67%). In accordance with the expected pattern, the L-svPPA and R-svPPA groups differed significantly in both left and right rostral temporal lobe volume. However, it is important to note that overall, the R-svPPA group showed a more symmetric bilateral pattern of rTL atrophy than the L-svPPA group. This may relate to early misdiagnosis of right temporal cases (see Discussion). We also observed evidence of asymmetric spread of atrophy to posterior temporal regions (Brambati, Rankin, et al., 2009; Kumfor et al., 2016; Rohrer et al., 2009). The L-svPPA group, on average, exhibited 22.3% volume loss in the left cTL (range = 0–36%) and 4.3% in the right cTL (0–16%). The R-svPPA group exhibited 16.7% volume loss in the left cTL (3–37%) and 29% in the right cTL (7–47%). Differences between the groups in cTL volume were only significant, however, in the right hemisphere (left hemisphere, $p = 0.2$).

Our next analysis focused on the distribution of atrophy *within* each of the rostral temporal lobes and made group comparisons within each of the constituent gyri with the aim of identifying differences in regional rTL volume loss that might be associated with differential cognitive impairment (the rTL sub-regions are illustrated in Figure 1, Panel A as alternating black and white regions). The pattern of atrophy in the left rTL was consistent across the two patient groups (Figure 1, Panel C), with mean volume loss being greatest in the fusiform gyrus (FG) and inferior temporal gyrus (ITG) and greater relative sparing laterally towards the middle temporal gyrus (MTG) and superior temporal gyrus (STG). Ventro-medially, the parahippocampal gyrus (PhG) is also markedly less affected than the FG and ITG. This pattern was previously observed in an independent patient sample and with analysis

performed on the results of manual tracing of MRI images rather than automated computational approaches (Galton et al., 2001; see also Binney et al., [2010] for a comparable illustration of Galton et al.'s findings). The mean degree of atrophy in the basal-medial rTL (FG and PhG) was not significantly different between patient groups whereas significantly greater volume loss was observed for the L-svPPA group in the ITG, MTG and STG. This was also observed in the VBM analysis (below).

The pattern of graded rTL atrophy (worse medially than laterally) was also present in the right rTL albeit less pronounced in the R-svPPA group where rTL tissue loss was profound (Figure 1, Panel D). Indeed, the difference between the groups was much more striking in the right rTL.

A whole-brain analysis of atrophy across all patients using VBM (Figure 2A) revealed patterns consistent with previous studies in svPPA (Gorno-Tempini et al., 2011). Greater volume loss was observed in the left hemisphere reflecting the larger number of left-predominant patients in the cohort. Extra-temporal lobe atrophy was evident in the insular, ventromedial prefrontal cortices and the left lentiform nucleus. Consistent with the previous VOI analysis, the most severely affected temporal lobe regions included rostral medial cortices (including the length of the hippocampus), the amygdala, the anterior fusiform gyrus, and the polar cortex.

A direct VBM comparison between the L-svPPA and R-svPPA (Figure 2, Row D; $p<0.001$, uncorrected) confirmed results of our VOI analysis in addition to revealing extra-temporal lobe differences in atrophy. The L-svPPA group (displayed in the red-yellow color scale) was significantly more affected in the anterior left superior temporal gyrus, including the pole, and along the entire length of the left infero-lateral temporal lobe (inferior and middle temporal gyri). The posterior insula, lentiform nucleus, caudate head, and the left inferior parietal lobule (all left hemisphere) were also more affected. Regions surviving Family-Wise Error correction at $p < 0.05$ were limited to the lateral temporal cortex, the amygdala and the caudal insula. Significantly greater atrophy in the R-svPPA group (displayed in the blue-turquoise color scale) was observed in a large extent of the right lateral temporal lobe, the hippocampus, the amygdala and other right hemisphere non-temporal regions including the right ventromedial prefrontal cortex, right subgenual cingulate cortex, the caudate, the lentiform nucleus and the insula. With the exception of the caudate, of these regional differences survived Family-Wise Error correction at $p < 0.05$. Like in the VOI analysis, there were no significant differences between the patient groups in the left ventral anterior temporal lobe or left amygdala.

3.2. General Neuropsychological Evaluation (Table 1)

The neuropsychological characteristics of the whole svPPA cohort (Table 1) are consistent with expected pattern for semantic variant PPA as described in current clinical criteria (Gorno-Tempini et al., 2011). Surface dyslexia was present (See below and Table 2). The pattern holds when the left-predominant or the right-predominant group are considered separately and as such both groups individually exhibit the expected pattern for semantic variant PPA (Table 1). However, direct comparisons of the L-svPPA and R-svPPA patients reveal several differences.

The L-svPPA group presented with greater difficulty in tasks involving language. They performed significantly more poorly in object naming (BNT) and the PPVT-R single word comprehension task. Their speech fluency rating, whilst remaining in the 'fluent' range, was also significantly lower which likely reflects a greater degree of naming impairment and circumlocutory speech. While both groups performed poorly in tests of verbal memory, the L-svPPA group was significantly worse. Repetition and performance in following sequential commands was also significantly poorer in L-svPPA, although the difference between groups was small and both groups performed at above 90% accuracy in both tests. Notably, there were no significant group differences, however, in tests of semantic association (PPT). The R-svPPA group presented with greater difficulty in tests of visuospatial reconstruction and memory. They were also significantly worse than their left-predominant counterparts at copying complex figures. Visual memory was impaired in both groups but the R-svPPA group were significantly worse.

The R-svPPA group presented with greater difficulty than the L-svPPA group in tests involving familiar face processing and social cognitive functions. They were significantly worse at identifying a famous face in a four-alternative forced-choice judgment task. Performance was relatively well preserved in L-svPPA as compared to controls ($p = 0.15$). Conversely, there was a near-significant difference, with worse performance of the L-svPPA group, in famous face naming ($p = 0.07$). However, both groups were greatly impaired at this task. This pattern is highly consistent with prior studies in PPA that associated impairment in recognizing famous faces with bilateral temporal atrophy and impairment in naming famous faces with left rostral temporal atrophy (Gefen et al., 2013; Snowden et al., 2012).

The R-svPPA group performed normally in perceptual matching of faces but poorly in matching facial expression of emotion. They were significantly worse than the L-svPPA group who performed at a similar level to control participants. Both groups were poor at recognizing spontaneous emotional expression (TASIT emotion evaluation test) but there was a near-significant difference with R-svPPA being worse at comprehending non-verbal social cues like sarcasm (TASIT-SI M) ($p = 0.07$).

As a whole, the patient group exhibited diminished empathy, particularly in terms of an ability to take the perspective of others (IRI-PT), as did the R-svPPA sub-group (L-svPPA $p = 0.14$). There was no statistically significant difference between the patient groups ($p = 0.11$) although there was a lower average score in R-svPPA (also see Perry et al., 2001). No significant differences were found on the IRI-EC subscale, another empathy-related measure associated with high-agency "other-oriented" feelings and prosocial behavior. This is consistent with prior studies that suggest that these two constructs partially dissociate in terms of their anatomical substrate with scores on the IRI-PT being differentially correlated with right polar and inferolateral rostral temporal atrophy, and the IRI-EC being associated with right fronto-insular atrophy (Rankin et al., 2006; Sollberger et al., 2014; also see Bejanin et al., 2016).

3.3. Comparison of Single Word Reading Accuracy in L-svPPA and R-svPPA (Table 2)

Single word reading performance of patients and controls is reported in Table 3. The svPPA patients, as a single cohort, performed worse than controls at reading aloud all word types.

Their regular word reading was, however, almost at ceiling. Exception word reading was very impaired. A measure of regularity effect in reading (% correct regular word reading - % correct exception word reading) highlighted a substantial advantage (18.8%) for correctly reading regular words over exception words. This was statistically different from healthy controls, who showed very little advantage (0.2%). Therefore, our patient cohort was, by definition, surface dyslexic. We compared the L-svPPA and R-svPPA separately to controls and found that this pattern held in both subgroups. However, the advantage for reading regular over exception words was almost two times greater in L-svPPA (22.5%) than R-svPPA (12.2%). This difference remained even after controlling for disease severity with the CDR sum-of-boxes score.

Both groups were worse than controls at reading pseudo-words, although the magnitude of impairment was considerably smaller than that in exception word reading (average of 88% accuracy compared to 78%). There was no difference between the patient groups. Below normal scores in pseudo-word reading have been reported in previous studies of svPPA cohorts (Graham, Patterson, & Hodges, 2000; Woollams et al., 2007). It has been suggested that this is not a direct effect of semantic impairment (pseudo-word reading performance does not correlate with semantic knowledge impairment in svPPA), but rather it results from noise introduced into the computations for reading aloud novel letter strings as a consequence of partial activation of (degraded) semantic representations for orthographically similar real words (see Woollams et al., 2007). An alternative explanation is that it reflects the beginning of an encroachment of atrophy into regions of the mid-to-posterior temporal lobe that subserve phonology. The cause of this phenomenon remains to be elucidated empirically.

3.4. Evaluation of the association between reading impairment and semantic memory impairment

It has been proposed that surface dyslexia in svPPA is directly associated with and symptomatic of the core semantic memory impairment (Woollams et al., 2007). To test this hypothesis, we regressed all the patients' (no controls) 'regularity effect' (the degree of advantage in reading regular words over exception words) against their performance in the picture and word versions of the PPT semantic association task. Repetition performance and sentence comprehension were included as additional regressors to control for non-semantic language impairment. The regression model explained a significant proportion of variance in regularity effect ($R^2 = 0.59$, $F(4,14) = 4.98$, $p=0.01$). The word version of the PPT significantly predicted regularity effect ($\beta = -0.57$, $t(4,14) = -2.23$, $p = 0.04$) but the picture version did not ($\beta = -0.03$, $t(4,14) = -0.13$, $p = 0.90$), nor did repetition ($\beta = -0.44$, $t(4,14) = -1.69$, $p = 0.11$) nor syntax comprehension ($\beta = -0.12$, $t(4,14) = 0.45$, $p = 0.66$). This suggests that exception word reading impairment is particularly associated with impairment in semantic processing of verbal stimuli. In order to exclude the possibility that the relationship between PPTw and 'regularity effect' is driven by a group effect or by general functional decline, we ran two further regressions, one with svPPA group (left- vs right-predominant) as a nuisance covariate and another with the CDR sum-of-boxes score. PPTw remained a significant predictor of 'regularity effect' in both analyses) while PPTp remained an insignificant predictor. Neither group nor CDR box score predicted 'regularity effect'.

3.5. Correlating grey matter volume with exception word reading performance (Figure 3)

We investigated voxel-wise correlations between patients' 'regularity effect' and grey matter volume across the whole brain. Negative correlations were observed, in the left-hemisphere at the middle MTG (192 voxels, MNI peak coordinates = −66 −34 −17, peak Z = 3.60) and the posterior circular sulcus of the insula (117 voxels, MNI peak coordinates = −36, −24, 16, peak Z = 3.73). Following correction for family-wise error (small volume correction; see Methods) we observed a near-significant correlation in the MTG region ($p = 0.10$).

4. Discussion

The present study is the first to compare quantitative data over an extensive range of neuropsychological measures of language, reading and socio-emotional function in a large group of svPPA patients with left- or right-predominant rostral temporal atrophy. Prior comparisons of the two svPPA variants have mainly relied on clinical case reviews rather than objective measures (with just a few exceptions; e.g., Kumfor et al., 2016; Lambon Ralph et al., 2001). Our primary aims were to investigate reading abilities, relate them to language and semantic impairment and identify which specific temporal regions are associated with ability for reading exception words. Both groups exhibited severe naming and single-word comprehension impairments and surface dyslexic errors in reading, but these impairments were significantly more profound in the L-svPPA group. The R-svPPA group showed greater impairment in performing familiarity judgments on famous faces and in processing socio-affective information such as facial expression of emotion. Quantitative imaging revealed that the L-svPPA group exhibited a greater degree of atrophy in the lateral aspects of the left rostral temporal lobe, while left basal rTL regions were equally affected in both groups. A correlational analysis revealed that the degree to which patients had an advantage for reading regular over exception words was associated with grey matter volume of a left lateral mid temporal region. In the following paragraphs we will discuss both clinical and theoretical implications of our findings.

4.1. Clinical implications

svPPA, also known as semantic dementia, is a clinical syndrome characterized by a progressive and selective impairment of conceptual knowledge. In classical clinical presentations, the earlier stages of the disease feature impairments primarily in the language domain. Patients retain fluent speech but exhibit great difficulty naming objects as well as deficits in single-word comprehension. Through the course of progression, the semantic impairment becomes increasingly evident across all task modalities and domains, including spoken and written words, pictures, environmental sounds, smell, touch, and taste (Bozeat et al., 2000; Coccia et al., 2004; Lambon Ralph et al., 2001; Luzzi et al., 2007; Piwnica-Worms et al., 2010). Surface dyslexia, a selective impairment in reading aloud words with exceptional spelling-to-sound correspondences, also occurs relatively early in the clinical course. It is considered a hallmark feature of svPPA (Patterson & Hodges, 1992; Woollams et al., 2007) and is included within consensus criteria for clinical diagnosis (Gorno-Tempini et al., 2011).

Most semantic variant cases exhibit leftward asymmetric atrophy of the rostral temporal lobes (Mummery et al., 2000). Frontotemporal dementia (FTD) can also present with right greater than left rostral temporal atrophy, although less frequently (approximately 30% of cases). There is less published evidence regarding the clinical presentation of these patients, hindering the establishment of a comprehensive syndromic characterization (Babiak, 2014). Rather than prominent semantic memory deficits, however, right greater than left rostral temporal atrophy has been associated primarily with early changes in personality and behavioral disturbances such as decreased empathy, blunted affect and deficits in receptive emotional processing (Edwards-Lee et al., 1997; Gorno-Tempini, Rankin, et al., 2004; Perry et al., 2001; Rankin et al., 2003) as well as a loss of person-specific knowledge (Evans, Heggs, Antoun, & Hodges, 1995; Gainotti et al., 2003; Joubert et al., 2006; Snowden et al., 2012). Some authors have therefore proposed that the “right temporal lobe variant” of FTD manifests a distinct syndrome to that associated with predominantly left temporal atrophy (Chan et al., 2009; Evans et al., 1995; González-Caballero, Abellán-Miralles, & Sáenz-Sanjuan, 2015) and interpret their difficulties as a selective semantic impairment for socially-relevant information (Irish, Hodges, & Piguet, 2014; Zahn et al., 2009). However, the studies of Chan and colleagues (2009) and Thompson and colleagues (2003) found that these social and behavioral disturbances do in fact present in both left- and right-predominant patients (albeit with more frequency in the latter)(see also Kumfor & Piguet, 2012; Rosen et al., 2002). The extent to which symptoms overlap in the language domain has been less easy to ascertain as the majority of these studies did not also comprehensively compare the language and semantic abilities. Therefore, whether the syndromes resulting from predominantly left or right rostral temporal atrophy should be considered as distinct requires further detailed and quantitative comparison (Adlam et al., 2006; González-Caballero et al., 2015; Thompson et al., 2003), as was the objective of the present study.

All the patients in the present study presented with the core features of svPPA (impaired confrontation naming and single word comprehension; Gorno-Tempini et al., 2011) but 21 exhibited left-ward asymmetry in rostral temporal atrophy and 12 exhibited right-ward asymmetry. We compared the two groups on a wide range of language and cognitive abilities. Consistent with prior descriptions (e.g., Lambon Ralph et al., 2001; Seeley et al., 2005; Thompson et al., 2003), we found that a significant anomia featured in both groups but it was more profound in left-predominant patients. What is more, the left-predominant patients exhibited a more aphasic profile generally when compared to right predominant patients, with scores at least numerically lower in almost all tests of language production and comprehension (see Table 1). We also demonstrated, for the first time, that surface dyslexia is a feature of both L-svPPA and R-svPPA. However, in line with the differential naming impairment, the advantage for reading aloud regular words was of a much greater magnitude in L-svPPA. This observation supports the utility of oral exception word reading assessments as a diagnostic marker of both left- and right-predominant rostral temporal atrophy but with the caveat that it will be less sensitive to R-svPPA, especially at the earliest stages of the disease. Indeed, in cases of R-svPPA, surface dyslexia might only be detectable once the disease has progressed to appreciably affect the left rostral temporal cortex.

Prior studies of svPPA have reported deficits in socio-emotional function on the basis of patient or caregiver interviews or retrospective review of clinical case notes (Chan et al.,

2009; Thompson et al., 2003). Using formal published tests we observed impairments in familiarity judgments on famous faces and in processing affect from facial expression and paralinguistic speech cues (also see Rankin et al., 2009). These difficulties were evident across a range of tasks in both groups, but they were more profound in the R-svPPA group (also see Chan et al., 2009; Gainotti, 2015; Thompson et al., 2003). This supports prior recommendations that assessments of social behaviors and receptive emotion processing are useful tools for detecting both left and right temporal variants of FTD but also indicates that they will be more sensitive in predominantly right-lateralized cases, particularly at earlier stages of the disease (Mychack, Rosen, & Miller, 2001; Rankin et al., 2003; Rosen et al., 2002).

Overall, our data illustrate that the cognitive and behavioral presentation of left- and right-predominant temporal variant FTD are not distinguishable on absolutes, that is, the presence or absence of clinical features. Rather, they share a common overlapping neuropsychological profile and differences are relative and of an order of magnitude. Whilst right-predominant cases may not fit cleanly within diagnostic criteria for svPPA because, for example, behavioral symptoms are the most significant complaint at onset, there is little cause for labeling them as a separate syndromic entity. In almost all cases, as the disease progresses, atrophy becomes increasingly bilateral and symmetric, and patients develop the language or the behavioral symptoms they lacked at onset (Brambati, Rankin, et al., 2009; Kumfor et al., 2016; Rohrer et al., 2009; Seeley et al., 2005). At late stages, both the clinical and anatomical profiles of the left-and right-predominant variants all but completely converge. Moreover, they are both associated with TAR DNA binding protein 43 (TDP-43) Type C pathology (Davies et al., 2005; Henry et al., 2014; Hodges et al., 2004) and, therefore, future pharmaceutical interventions targeting proteinopathy are unlikely to be differentiated on the basis of syndromic sub-classification (but also see Josephs et al., 2009). They are perhaps better considered as alternate trajectories of the temporal variant FTD syndrome that deviate only in the salience of verbal versus behavioral symptoms according to disease severity and the predominantly affected hemisphere at onset (Adlam et al., 2006; Thompson et al., 2003). Our data suggest that early and accurate diagnosis of both left and right temporal variant FTD will be assisted by conjoint evaluation of speech/language and behavioral/socio-emotional symptoms. They further suggest that the next generation of clinical criteria for both PPA and FTD should include a right-temporal variant that emphasizes prominence of impairments in socio-affective processing over (but likely co-existing with) language difficulties.

A caveat that should be considered with regard to this recommendation is that the overlap in the presentation of our two groups could reflect late-stage of progression to bilateral rostral temporal atrophy rendering our patient cohorts unrepresentative of the clinical presentation of early stage temporal variants of FTD. This could be a concern particularly regarding the R-svPPA cohort who exhibited on average a greater total bilateral volume loss and a more symmetric pattern of atrophy. Relative under-reporting of selective right temporal lobe atrophy could reflect the associated clinical features. Language and speech impairments are clear indicators of neurological abnormalities and will likely facilitate early medical investigation. In contrast, behavioral symptoms from right hemisphere damage may go unnoticed in the earliest stages of the disease and/or be initially disregarded as psychological

in nature. Right temporal patients may therefore attend memory clinics later in the disease on average. Self/caregiver-reported disease duration did not significantly differ between our cohorts but this does not completely rule out this potential caveat. However, we do not believe that it could entirely account for the overlap we observed and detract from our study's implications for early diagnostic procedures for two reasons. First, all data was collected during the patients' first visit to the UCSF MAC and the L-svPPA group presented with highly asymmetric atrophy on average (and so are presumably still at earlier stages of the disease) yet still exhibited socio-affective impairments that are typically associated with right frontotemporal atrophy. Second, even the very asymmetric R-svPPA patients exhibited a clear object naming impairment.

4.2. The neural correlates of exception word reading and semantic processing

Our results are indicative of a critical role of the left-hemisphere lateral temporal cortex in exception word reading and are consistent with prior neuropsychological, computational modeling and functional imaging studies (Brambati, Ogar, Neuhaus, Miller, & Gorno-Tempini, 2009; Henry, Beeson, Alexander, & Rapcsak, 2012; Hoffman et al., 2015; Ueno, Saito, Rogers, & Lambon Ralph, 2011; M. A. Wilson et al., 2012; Woollams et al., 2007). This conforms with a recent proposal that the left lateral temporal neocortex plays an intermediary role in mapping between ventrally-situated transmodal conceptual knowledge representation and the frontal speech production network, subtending lexico-semantic processes such as reading and naming (Hoffman et al., 2015; Mehta et al., in press). However, the present study highlights a mid portion of the middle temporal gyrus that is considerably more posterior than the typical area of atrophy observed in svPPA and the region implicated in prior imaging studies of reading. We will discuss both these consistencies and the apparent divergence in the following paragraphs.

The recent inclusion of the left rostral temporal lobe in the language network has been driven primarily by lesion-deficit studies of aphasic patients with stable brain injury (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Drane et al., 2008; Wright, Randall, Clarke, & Tyler, 2015) and investigation of the neural correlates of declining language abilities in progressive neurological disease (Hodges et al., 1992; Mesulam et al., 2009). The semantic nature of the errors that dominate naming performance in the context of damage to this region has led to proposals that it plays an important role in mapping conceptual knowledge (i.e., meaning) to lexical labels (i.e., words) (Mesulam et al., 2013; Schwartz et al., 2009). The tripartite association between rostral left temporal atrophy, semantic impairment and surface dyslexia in svPPA has further led to the suggestion that the region provides inputs from semantic memory into the process of reading aloud (Woollams et al., 2007). According to an influential connectionist model of reading, known as the "triangle model" (Plaut, McClelland, Seidenberg, & Patterson, 1996), mediation of pronunciation from semantic knowledge is especially important for reading words with exceptional spelling-to-sound correspondences that would be poorly served by direct transcoding between orthography and phonology (e.g., "pint"). As such, the model predicts that semantic memory impairments will disproportionately affect exception word reading over regular words and pseudo words (i.e., will result in surface dyslexia). In line with this

hypothesis, our results indeed showed that verbal semantic memory scores predicted the severity of surface dyslexia in our rostral temporal patients.

Both the left and right rostral temporal lobes are implicated in conceptual knowledge representation, not only by patient studies, but also on the basis of recent brain stimulation and functional imaging investigations (Binney & Lambon Ralph, 2015; Lambon Ralph, Pobric, & Jefferies, 2009; Rogers et al., 2006; Visser, Jefferies, & Lambon Ralph, 2010). However, such studies also demonstrate a differential sensitivity of the left rostral temporal lobe to language-mediated information (Marinkovic et al., 2003; Mion et al., 2010; Rice, Lambon Ralph, & Hoffman, 2015; Sharp, Scott, & Wise, 2004; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996). This has been described as a significant challenge (see Gainotti, 2014) to assertions that the left and right rostral temporal lobes constitute a unitary, undifferentiated transmodal semantic system (Patterson, Nestor, & Rogers, 2007). However, they have more recently been characterized as a ‘graded transmodal representational hub’ in which the semantic function of rostral temporal sub-regions varies as a function of proximity and connectivity to different primary inputs (Binney, Parker, & Lambon Ralph, 2012; Lambon Ralph, 2014; Rice, Hoffman, & Lambon Ralph, 2015). Under this framework, a relative specialization of the left rostral temporal lobe for verbally-mediated semantic function arises from greater connectivity (relative to the right temporal lobe) to the predominately left-lateralized perisylvian language network (Hurley, Bonakdarpour, Wang, & Mesulam, 2015; Lambon Ralph et al., 2001; Schapiro, McClelland, Welbourne, Rogers, & Lambon Ralph, 2013). Our results support this notion, demonstrating an association of left-lateralized temporal lobe regions with exception word reading abilities.

It is increasingly apparent that there are differences not only between the left and right temporal lobe but also within each rostral temporal lobe in terms of cytoarchitectonics, connectivity (Binney et al., 2012; Ding, Van Hoesen, Cassell, & Poremba, 2009; Pascual et al., 2015) and functional activation during tasks (Rice, Lambon Ralph, et al., 2015) which further implies intra-hemispheric relative functional specialization of rostral temporal sub-divisions (Binney et al., 2012; Mehta et al., in press; Visser, Jefferies, Embleton, & Lambon Ralph, 2012). For example, within the left rostral temporal lobe, the left basal region (anterior fusiform gyrus) is equally activated by nonverbal and verbal semantic tasks and thus appears to play a role that is transmodal in nature (Shimotake et al., 2014; Visser & Lambon Ralph, 2011). The lateral rostral temporal cortex, on the other hand, exhibits stronger activation when semantic tasks are performed in the verbal relative to non-verbal (e.g., pictures) domain (Hocking & Price, 2009; Scott, Blank, Rosen, & Wise, 2000; Visser & Lambon Ralph, 2011) and, as such, appears to be relatively more specialized for verbally-mediated semantic processes. We provide further evidence for this framework of temporal lobe organization by showing an association between exception word reading difficulties and atrophy of the *lateral* left temporal cortex.

Two recent fMRI studies demonstrated increased activation of the left lateral temporal cortex for reading exception words compared to regular words (Hoffman et al., 2015) and pseudowords (M. A. Wilson et al., 2012), but in an anterior portion of the MTG close to the polar cortex. Our VBM analysis, on the other hand, implicates a mid portion of the middle temporal gyrus that is considerably more posterior. It may be that the involvement of the left

MTG in reading extends quite far posteriorly (Henry et al., 2012). This more posterior lateral region (Figure 3) is in fact strategically placed between, and reciprocally connected with, the anterior MTG, the perisylvian auditory and phonological cortices and ventral visual word processing regions (Binney et al., 2012). It may therefore form a convergence point for integration of the direct pathway between orthography and phonology and the anteriorly situated influences from the semantic system (Plaut et al., 1996). However, we cannot exclude that this more posterior MTG location reflects a statistical artifact of VBM and the tail end of the distribution in which the most catastrophic impairments co-occur with highly advanced disease progression and encroachment of atrophy upon caudal temporal cortices.

The more apparent socio-affective impairment in right-predominant svPPA has been used to argue for a specialization of the right rostral temporal lobe for processing social semantic knowledge (Chan et al., 2009; Kumfor et al., 2016; Olson, Plotzker, & Ezzyat, 2007; Skipper, Ross, & Olson, 2011; Zahn et al., 2009). However, there is evidence to suggest that social cognition is supported by this region bilaterally. For example, Kumfor et al. (2016) observed that atrophy of both left and right rostral temporal sub-regions correlates with the level of behavioral impairment. Furthermore, a recent formal meta-analysis of fMRI studies (Rice, Lambon Ralph, et al., 2015) found little evidence of asymmetry in rostral temporal activations to social stimuli (see Pobric, Lambon Ralph, & Zahn, 2015 for a related TMS investigation). If this is correct, then what is driving the greater social impairment in R-svPPA? One perspective holds that the right rostral temporal lobe subsumes a selective contribution to non-verbal components of semantic representation and therefore this phenomenon reflects differentially impaired comprehension of non-verbal stimuli than contain socially-relevant information (e.g., facial expression of emotion; Gainotti, 2015). However, the fMRI meta-analysis of Rice, Lambon Ralph, et al. (2015) challenges this assertion by demonstrating that semantic processing of non-verbal stimuli engages the rostral temporal cortex bilaterally. fMRI studies of famous face processing also reveal bilateral activation, even when name retrieval is controlled for (Brambati, Benoit, Monetta, Belleville, & Joubert, 2010; Gesierich et al., 2011; Gorno-Tempini et al., 1998; Von Der Heide, Skipper, & Olson, 2013). Another possibility is that the right-lateralized regions are more important for social behaviors because of greater connectivity to high-level social regions in the frontal lobe via the uncinate fasciculus (Highley, Walker, Esiri, Crow, & Harrison, 2002; Papinutto et al., 2016; Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Further research is required in order to fully understand the nature of social-emotional disorders associated with rostral temporal atrophy. Determining whether these deficits reflect high-level social-cognitive dysfunction or instead occur at an earlier stage of receptive semantic processing (see Gainotti, 2015) will help to elucidate the specific contribution of rostral temporal sub-regions to social cognition.

5. Concluding Remarks

In conclusion, we demonstrate that even during early clinical presentation, semantic memory impairments, surface dyslexia and deficits in social cognitive function are features of both the left- and right-predominant svPPA. However, the severity of surface dyslexia and aphasic symptoms is greater when atrophy is predominantly left-lateralized, whereas socio-

behavioral symptoms are most severe when atrophy is predominantly on the right. Early cases at the tail ends of this continuum, with very mild left-only or right-only rostral temporal atrophy, therefore present a challenge for current clinical guidelines regarding differential diagnosis of svPPA and behavioral variant FTD. Our results should be considered in future revisions of these guidelines and in improving the nosology of both left and right temporal variants of svPPA. Our findings also offer support for hypotheses regarding graded specialization of semantic function in the rostral temporal lobes and suggest that the lateral aspects of rostral left temporal neocortex play a role as an interface between phonology and conceptual knowledge representation.

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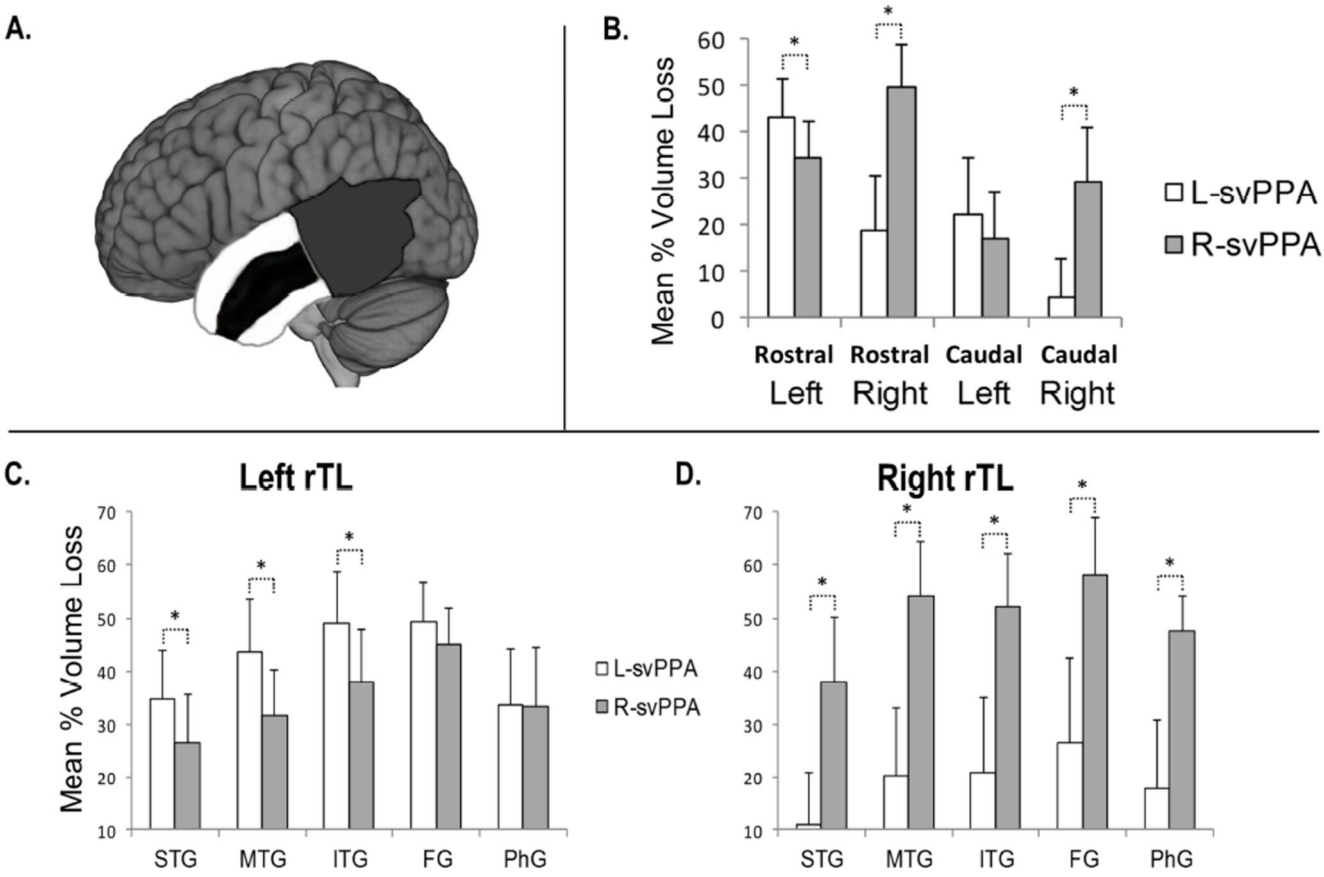

Figure 1.

Distribution of temporal lobe volume loss in left-predominant svPPA and right-predominant svPPA. (A) Illustration of the regions of interest (ROIs) in which mean percentage volume loss was calculated for each patient group. The caudal temporal lobe ROI features in dark grey with a black outline. The rostral temporal lobe (rTL) ROI was the combination of the white and black gyral ROIs. The gyral ROIs were used for a focused rTL analysis featured in the bottom two panels. (B) Rostral vs. caudal temporal lobe volume loss in the left and right hemispheres, by patient sub-group. (C) Gyral distribution of left rTL volume loss in left- and right-predominant svPPA. (D) Gyral distribution of right rTL volume loss in left- and right-predominant svPPA. * $p<0.05$ (error bars display one standard deviation). STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; FG = fusiform gyrus; PhG = parahippocampal gyrus.

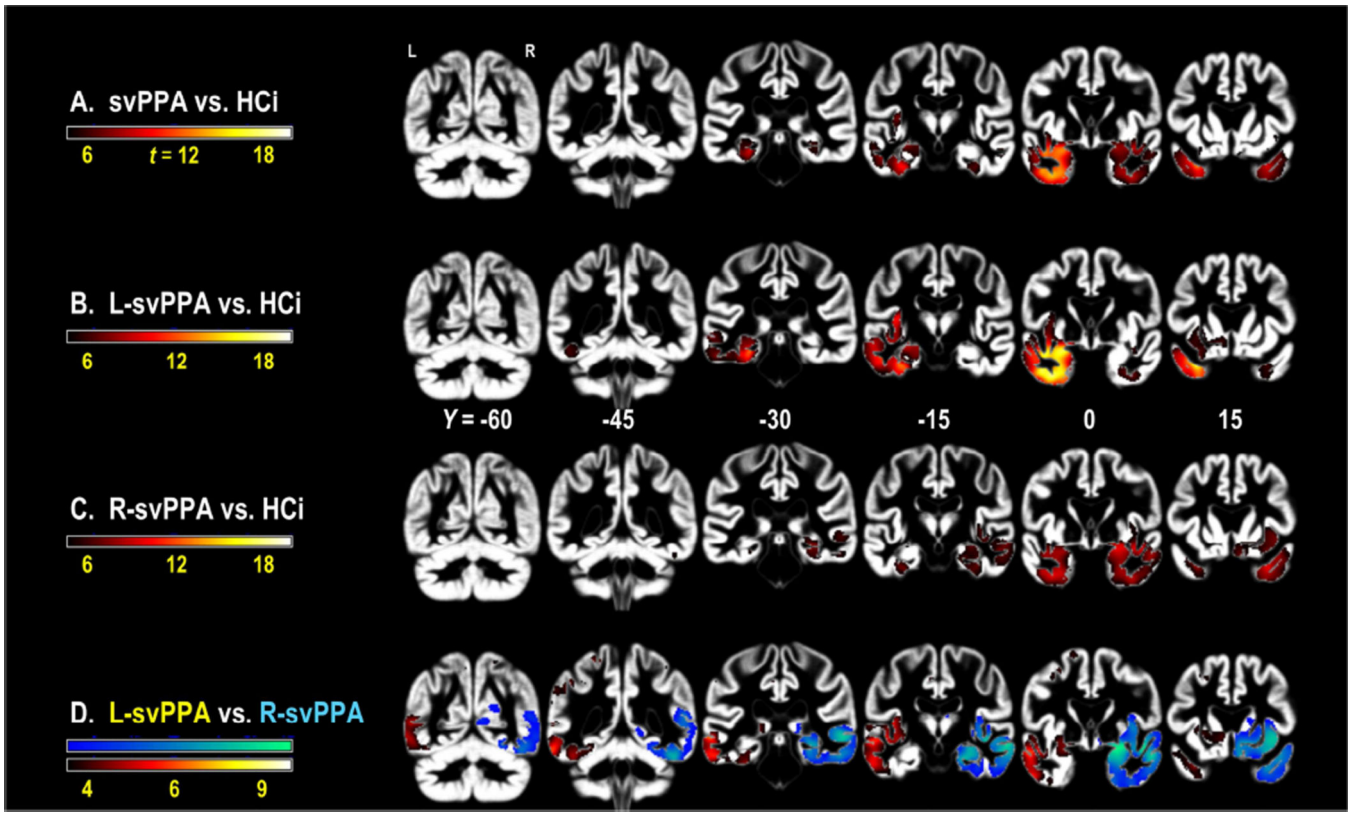

Figure 2.

Patterns of atrophy in semantic variant PPA (svPPA). Voxel-based morphometry was used to identify regions of grey matter volume loss in svPPA relative to age-matched healthy controls (Row A), left predominant svPPA relative to controls (Row B), and right-predominant svPPA relative to controls (Row C; all $p < 0.05$, corrected for multiple comparisons). A direct comparison between the patient sub-groups (Row D) reveals greater volume loss in L-svPPA relative to R-svPPA (red-yellow color scale) and vice versa (blue-green color scale; $p < 0.001$, uncorrected). Coronal slice positions are provided in standard stereotactic coordinates according to the Montreal Neurological Institute (MNI) protocol. L = Left; R = Right. HCi = Healthy (age-matched) controls for imaging analyses.

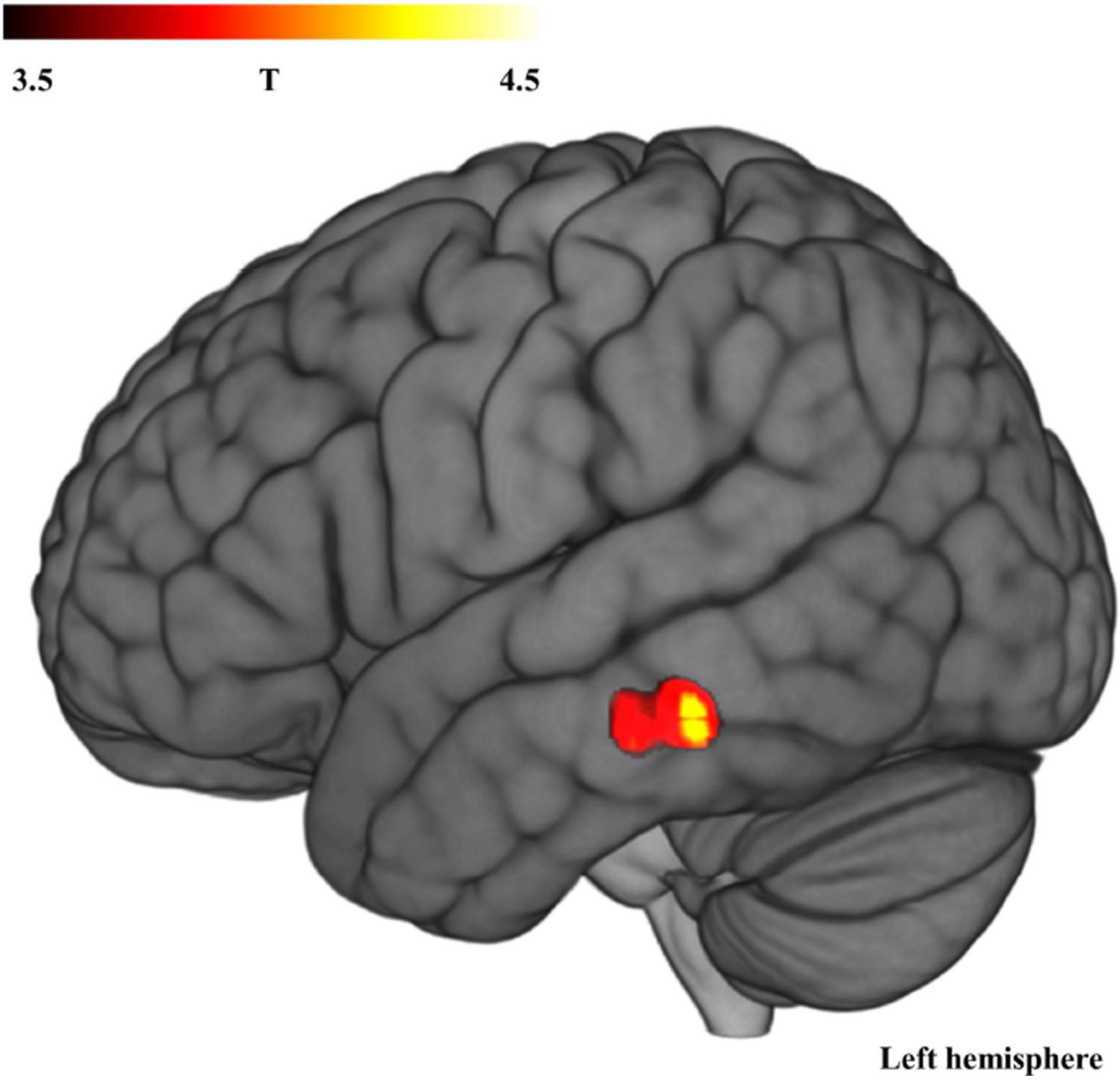

Figure 3.

Brain regions associated with irregular word reading deficits in svPPA. Voxel-based morphometry was used to identify regions of grey matter atrophy that correlated with the regularity effect in reading performance (percentage of correctly read regular words minus percentage of correctly read irregular words) across all svPPA patients ($p < 0.001$, uncorrected; minimum cluster size of 100 contiguous voxels).

Table 1

Demographic, clinical, general neuropsychological characteristics of svPPA patients, the patient sub-groups and controls

	All svPPA	L-svPPA	R-svPPA	Controls
Demographic				
Age	62.0 (6.6, 33)[a]	61.5 (7.2, 21)[a]	62.9 (5.7,12)	66.6 (4.2, 14)
Sex (F/M)	15/18	9/12	6/6	10/4
Years of formal education	16.6 (2.5)[a]	16.8 (2.5)[a]	16.2 (2.5)[a]	18 (0.9)
Handedness (L/R/Ambidextrous)	3/29/1	1/20/0	2/9/1	5/9/0
Status				
Mini Mental Status Examination(30)	25.7 (3.3, 33)[a]	25.3 (3.7, 21)[a]	26.6 (2.3, 12)[a]	29.6 (0.6, 14)
Clinical Dementia Rating - total	0.5 (0.2, 28)[a]	0.5 (0.2, 18)[a]	0.65 (0.2, 10)[a]	0 (0, 14)
Clinical Dementia Rating - sum boxes	2.9 (2.0, 28)[a]	2.6 (1.9, 18)[a]	3.6 (1.9, 10)[a]	0 (0, 14)
Years from First Symptom	4.2 (2.9, 18)[a]	4.6 (3.6, 10)[a]	3.75 (1.5, 8)[a]	N/A
Language Production				
Object Naming (BNT, 15-item)	4.6 (3.4, 32)[a]	3.5 (2.4, 21)[a,b]	6.7 (4.3, 11)[a]	14.7 (0.5, 14)
Phonemic Fluency	7.1 (3.5, 32)[a]	6.9 (3.6, 20)[a]	7.3 (3.4, 12)[a]	18.6 (5.3, 14)
Semantic fluency	7.3 (4.1, 33)[a]	6.6 (3.5, 21)[a]	8.5 (4.9, 12)[a]	24.6 (5.1, 14)
Speech Fluency (WAB, 10)	9.1 (0.6, 30)	8.9 (0.6, 18)[b]	9.4 (0.5, 12)	10[$]
Apraxia of Speech Rating (7)	0 (0, 31)	0 (0, 20)	0 (0, 11)	N/A
Dysarthria Rating (7)	0 (0, 30)	0 (0, 19)	0 (0, 11)	N/A
Repetition % (WAB)	92.1 (5.6, 31)	90.1 (5.9, 19)[b]	95.2 (3.4, 12)	99[$]
Language Comprehension				
PPVT-R Word Comprehension (16)	8.6 (3.5, 23)[a]	7.2 (2.7, 14)[a,b]	10.8 (3.6, 9)[a]	15.6 (0.07, 12)
Sequential Commands (WAB, 80)	75 (7.7, 31)	72.7 (9.1, 19)[b]	78.8 (1.9, 12)	80[$]
Sentence/Syntax Comprehension %	95.2 (5.5, 31)[a]	94.2 (6.7, 19)[a]	96.8 (2.5, 12)[a]	98.6 (1.7, 13)
Semantic Association				
PPT-Words %	76.7 (16.3, 24)	75.8 (15.9, 12)	77.6 (17.4, 12)	98[Δ]
PPT-Pictures %	77.0 (14.7, 31)	77.8 (13.0, 19)	75.8 (17.5, 12)	98[Δ]
Visuo-spatial/Visuo-reconstruction				
Modified Rey-Osterrieth Copy (17)	15.4 (1.3, 33)	15.8 (1.2, 21)	14.7 (1.3, 12)[c]	15.5 (0.5, 10)
Calculation (5)	4.6 (0.5, 32)[a]	4.75 (0.6, 20)	4.4 (0.5, 12)[a]	5.0 (0, 14)
Memory				
Modified Rey-Osterrieth Recall (17)	7.4 (4.3, 33)[a]	8.5 (4.1, 21)[a]	5.7 (4.4, 12)[a,c]	12.1 (2.7, 10)
CVLT-SF trials 1–4 (36)	17.0 (16.9, 32)	14.2 (6.3, 21)[b]	22.1 (3.6, 11)	28.7 (3.1, 24)[*]
CVLT-SF 30s free recall (9)	3.0 (2.4, 32)	2.4 (2.3, 21)[b]	4.2 (2.2, 11)	7.9 (1.6, 24)[*]
CVLT-SF-10min free recall (9)	1.9 (2.2, 32)	1.7 (2.1, 21)	2.4 (2.4, 11)	7.3 (1.6, 24)[*]
Executive				

	All svPPA	L-svPPA	R-svPPA	Controls
Design Fluency	8.0 (3.6, 28)[a]	8.5 (3.6, 17)[a]	7.3 (3.7, 11)[a]	12.3 (3.1, 14)
Modified Trails, lines per minute	21.0 (13.1, 30)[a]	23.1 (12.9, 19)[a]	17.2 (13.3, 11)[a]	41.6 (16.0, 14)
Digit Span backwards	4.8 (0.9, 33)[a]	4.9 (0.9, 21)[a]	4.6 (1.1, 12)[a]	5.8 (1.4, 14)
Person Knowledge and Affect Processing				
UCSF Famous Face Naming %	7.2 (12.0, 23)[a]	3.8 (4.6, 13)[a]	11.5 (17, 10)[a]	75.0 (9.0, 9)[ƒ]
UCSF Famous Face Familiarity %	72.5 (21.8, 16)[a]	84.4 (17.9, 9)	57.1 (16, 7)[a,c]	91.7 (9.0, 9)[ƒ]
CATS Face Matching (12)	11.9 (0.3, 15)	11.9 (0.3, 9)	11.8 (0.4, 6)	11.4 (0.9, 12)
CATS Affect Matching (16)	11.7 (3.1, 15)[a]	13.2 (1.9, 9)	9.0 (3.3, 6)[a,c]	13.5 (1.5, 12)
TASIT Emotion Evaluation (14)	6.4 (2.5, 17)[a]	6.8 (2.6, 10)[a]	5.8 (2.5, 7)[a]	11.6 (0.9, 7)
TASIT SI-M Sincere (20)	17.0 (2.5, 16)	17.1 (1.9, 9)	16.8 (3.2, 7)	17.1 (3.5, 7)
TASIT SI-M Sarcastic (20)	5.1 (3.1, 16)[a]	6.1 (3.4, 9)[a]	3.7 (2.4, 7)[a]	18.7 (1.7, 7)
IRI-EC (24)	21.4 (7.6, 18)	23.0 (6.5, 11)	19.0 (9.0, 7)	24.0 (10.5, 13)
IRI-PT (24)	15.0 (6.8, 18)[a]	16.6 (6.9, 11)	12.6 (6.0, 7)[a]	22.1 (10.0, 13)

Variables were compared between groups using the Student's t test or Welch's t test as appropriate, and a two-tailed probability distribution except for Face and Affect processing tests which were evaluated using a one-tailed distribution. Standard deviation and number of subjects given in parentheses. BNT = Boston Naming Test; WAB = Western Aphasia Battery; PPVT = Peabody Picture Vocabulary Test; PPT = Pyramids and Palm trees Test; CVLT-SF = California Verbal Learning Test - Short Form; CATS = Comprehensive Affect Testing System; TASIT SI-M = The Awareness of Social Inference Test Social Inference - Minimal; IRI-EC/PT = Interpersonal Reactivity Index Empathic Concern/Perspective Taking.

[a] Statistically different to healthy controls ($p<0.05$).

[b] Statistically significant greater impairment in L-svPPA compared to R-svPPA ($p<0.05$).

[c] Statistically significant greater impairment in R-svPPA compared to L-svPPA ($p<0.05$).

[Δ] Statistical comparison between svPPA and controls was not performed as the control group was not tested on these variables. Data reported is the mean score of healthy controls from Howard and Patterson (1992) who propose scores of 90% or lower indicate clinically significant impairment.

[$] Control data from 10 neurologically-normal participants tested in a second WAB standardization reported by Kertesz (2007.

[*] Control data from Wilson et al. (2014).

[ƒ] See main text for details on control group.

Table 2

Single word reading performance of svPPA patients, patient sub-groups and controls

	All svPPA	L-svPPA	R-svPPA	Controls
Regular words %	97.0 (4.7, 33)[a]	96.5 (5.3, 21)[a]	97.8 (3.4, 12)[a]	100 (0, 14)
Exception words %	78.2 (18.2, 33)[a]	74.0 (18.5, 21)[a,b]	85.5 (15.8, 12)[a]	99.8 (0.7, 14)
Pseudo words%	87.6 (12.8, 24)[a]	87.7 (11.9, 15)[a]	87.4 (15.1, 9)[a]	97.8 (3.2, 14)
Regularity Effect	*18.8 (15.9, 33)* [a]	*22.5 (15.6, 21)*[a,b]	*12.2 (14.7, 12)*[a]	*0.2 (0.7, 14)*

Regularity effect = Regular word % - Exception word % (See main text). Variables were compared between groups using the Student's t test or Welch's t test as appropriate, and a one-tailed probability distribution. Standard deviation and number of subjects given in parentheses.

[a]Statistically different to control performance ($p<0.05$).

[b]Statistically significant greater impairment in L-svPPA compared to RsvPPA ($p<0.05$).