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Taking the sub-lexical route: brain dynamics of reading in the semantic variant of Primary Progressive Aphasia

Running title:

Brain dynamics of reading in semantic variant of PPA

V. Borghesani[1], L.B. Hinkley[2], K. G. Ranasinghe[1], M. M. C. Thompson[2,3], W. Shwe[1], D. Mizuiri[2], M. Lauricella[1], E. Europa[1], S. Honma[2], Z. Miller[1], B. Miller[1], K., Vossel[4], J. F. Houde[5], M.L. Gorno-Tempini[1,6*] & S. S. Nagarajan[2,5*]

[1] *Memory and Aging Center, Department of Neurology, University of California San Francisco*
[2] *Department of Radiology and Biomedical Imaging, University of California San Francisco*
[3] *UC Berkeley-UC San Francisco Graduate Program in Bioengineering, University of California, San Francisco*
[4] *Department of Neurology, University of Minnesota, Minneapolis*
[5] *Department of Otolaryngology, University of California San Francisco*
[6] *Department of Neurology, Dyslexia Center, University of California, San Francisco, CA*

[*]Contributed equally to this work

Corresponding Author

Valentina Borghesani, PhD, valentina.borghesani@ucsf.edu
Department of Neurology,
Memory and Aging Center,
University of California San Francisco
675 Nelson Rising Lane, Mission Bay Campus,
San Francisco, CA 94158, USA

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50-word Abbreviated Summary:

Borghesani et al. investigate brain dynamics during irregular word reading using magnetoencephalographic imaging in patients with semantic variant of primary progressive aphasia. Due to anterior temporal lobe neurodegeneration, patients rely more on dorsal, occipito-parietal brain regions – providing novel evidence on the interplay between ventral and dorsal reading routes.

Abstract

Reading aloud requires mapping an orthographic form to a phonological one. The mapping process relies on sub-lexical statistical regularities (e.g., "oo" to |u:|) or on learned lexical associations between a specific visual form and a series of sounds (e.g., *yacht* to /jɑt/). Computational, neuroimaging, and neuropsychological evidence suggest that sub-lexical and lexical processes rely on partially distinct neural substrates: a dorsal (occipito-parietal) and a ventral (occipito-temporal) route, respectively.

Here, we investigated the spatiotemporal features of sub-lexical processes capitalizing the time resolution of magnetoencephalography and the unique clinical model offered by patients with semantic variant of Primary Progressive Aphasia (svPPA). Behaviorally, svPPA patients manifest marked lexico-semantic impairments including difficulties in reading words with exceptional orthographic to phonological correspondance (irregular words). Moreover, they present with focal neurodegeneration in the anterior temporal lobe (ATL), affecting primarily the ventral, occipito-temporal, lexical route. Therefore, this clinical population allows for testing of specific hypotheses on the neural implementation of the dual-route model for reading, such as whether damage to one route can be compensated by over-reliance on the other. To this end, we reconstructed and analyzed time-resolved whole-brain activity in 12 svPPA patients and 12 healthy age-matched controls while reading irregular words (e.g., *yacht*) and pseudowords (e.g., *pook*).

Consistent with previous findings that the dorsal route is involved in sub-lexical processes, in control participants we observed enhanced neural activity over dorsal occipito-parietal cortices for pseudowords, when compared to irregular words. This activation was manifested in the beta-band (13-20 Hz), ramping up slowly over 500 ms after stimulus onset and peaking at ~800 ms, around response selection and production. This temporal pattern of neural activity was not observed in svPPA patients. Furthermore, a direct comparison of neural activity between patients and controls revealed a dorsal spatiotemporal cluster during irregular word reading. These findings suggest that the sub-lexical route is involved in processing both irregular and pseudo- words in svPPA.

Together these results provide further evidence supporting a dual-route model for reading aloud - mediated by the interplay between lexical (ventral) and sub-lexical (dorsal) neuro-cognitive systems. When the lexical route is damaged, as in the case of neurodegeneration affecting the ATL, partial compensation appears to be possible by over-recruitment of the slower, serial attention-dependent, sub-lexical one.

Keywords: surface dyslexia, semantic variant Primary Progressive Aphasia, MEG, dual-model of reading

Introduction

Reading aloud, the process by which a visual input is translated into an auditory output, entails a series of steps involving different neural systems: from vision to motor control. Crucially, this requires mapping an orthographic form to its corresponding phonological form. Language-specific statistical regularities allow readers to spell out words never encountered before (sometimes referred to as pseudowords or nonwords, e.g., *pook*) by selecting the most plausible phonological representations. In non-transparent languages such as English, access to meaning is necessary to correctly pronounce words with exceptional spelling-to-sound correspondence (i.e., irregular words, e.g., *yacht*). Computational models of reading assume that this process involves both storage of the relationship between orthography and phonology (sub-lexical representations), as well as the knowledge of learned words (lexico-semantic representations) (Perry *et al.*, 2007). The most widely accepted model, the dual-route cascaded model, posits an interplay of two computationally distinct routes: a sub-lexical and a lexical one, needed to select the appropriate phonological output for pseudowords and irregular words respectively (Coltheart *et al.*, 1993, 2001).

The idea that these are two different cognitive mechanisms supported by two distinct neural substrates originates in the neuropsychological evidence of a double dissociation, as two kinds of acquired dyslexia have been isolated (Marshall and Newcombe, 1973). Phonological dyslexia is characterized by a deficit in reading pseudowords, with relatively preserved reading of irregular words, suggesting a selective disruption of the grapheme-to-phoneme conversion route (Coltheart, 2006). Typical errors are called lexicalization, where pseudowords are read as real words: e.g., *pook* read as *hook*. Conversely, in surface dyslexia a deficit with irregular words is paired with relatively spared reading of pseudowords, and typical errors are called regularizations: e.g., *yacht* read as /jætʃt/, instead of /jɑt/ (Coltheart, 2006). This profile suggests an impairment of the lexico-semantic system (Woollams *et al.*, 2007).

Neuroimaging studies provide complementary observations indicating that sub-lexical and lexical processes rely on partially different neural substrates. Sub-lexical processes have been

associated with dorsal structures in the inferior parietal lobe (i.e., supramarginal gyrus, angular gyrus, and temporoparietal junction) and the posterior inferior frontal gyrus (IFG) by studies investigating pseudoword reading, i.e., regular orthographic-to-phonological mappings (Jobard *et al.*, 2003; Mechelli *et al.*, 2003; Graves *et al.*, 2010; Taylor *et al.*, 2013; Sliwinska *et al.*, 2015). Lexical processes, which have proven harder to isolate, have been linked to ventral brain structures in the temporal lobe, especially its anterior portion (ATL), which appears to be involved in semantic-mediated reading of low-frequency irregular words (Graves *et al.*, 2010; Wilson *et al.*, 2012; Taylor *et al.*, 2013; Hoffman *et al.*, 2015; Provost *et al.*, 2016).

Computational models and behavioral evidence suggest key computational differences between the two routes: while activated simultaneously for all word-like inputs, only the lexical one can lead to the correct pronunciation of irregular words, while only the sub-lexical one allows reading of pseudowords. To date however, little is known about the neural dynamics characterizing these processes, although different temporal profiles have been suggested. On one hand, serial effects have been associated with the sub-lexical route, arguably indicating a slow grapheme-by-grapheme conversion mechanism (e.g., Weekes, 1997). On the other hand, it has been suggested that the ventral route operates in parallel, within a fast, automatic spreading of activation (Coltheart *et al.*, 2001). Hence, divergence of the two routes should be detected in a relatively late time frame, after ~400 ms, close to response selection and production. Most studies of reading have focused on event-related potential (ERPs), which capture stimulus-locked, phased-locked evoked activity immediately following the presentation of written stimuli (for a review, Salmelin, 2007; Grainger and Holcomb, 2009). These studies may have overlooked slower, later, not necessarily phased-locked effects, which can be better captured by analyses of task-induced neural oscillatory changes.

While neuroimaging studies can provide only correlational evidence, neuromodulation techniques and neuropsychological findings have strengthened the evidence of a neural dissociation between lexical and sub-lexical computations. For instance, recent evidence that repetitive transcranial magnetic stimulation (rTMS) over left ventral ATL leads to regularization errors has corroborated the critical role played by this region in irregular words reading (Ueno *et al.*, 2018). In this context, patients with semantic variant of Primary Progressive Aphasia (svPPA) are an ideal clinical model for testing hypotheses on the interplay between dorsal (parietal) vs. ventral (temporal) routes. SvPPA is associated with (relatively) focal atrophy of the ATL which, in time, spreads towards the orbitofrontal cortex (Galton *et al.*, 2001; Rosen *et al.*, 2002, Brambati *et al.*, 2009*b*). Clinically, svPPA patients present with fluent speech and pervasive semantic memory deficits (Hodges *et al.*, 1992). It is well established that patients with svPPA manifest surface dyslexia (Hodges *et al.*, 1992, 1999; Neary *et al.*, 1998) with a clear effect of word frequency and length on performance accuracy in irregular word reading (Patterson and Hodges, 1992; Jefferies *et al.*, 2004; Patterson *et al.*, 2006). In particular, svPPA patients produce so-called over-regularization errors, such as reading "*sew*" as "*sue*", i.e., the application of legitimate alternative correspondence between grapheme and phonemes (Woollams *et al.*, 2007; Wilson *et al.*, 2009). Crucially, the severity of the reading deficit has been linked to the extent of the semantic

loss (Patterson and Hodges, 1992; Graham *et al.*, 2000; Jefferies *et al.*, 2004). Finally, irregular word reading accuracy has been directly linked to the integrity of left ATL (vs. pseudowords to left temporo-parietal structures, Brambati *et al.*, 2009*a*). To date, only one study has attempt to investigate the correlates of surface dyslexia in svPPA with a neuroimaging experiment: it has been suggested that, given the damage to ATL, svPPA patients recruit the intraparietal sulcus to read irregular words as if they were pseudowords (Wilson *et al.*, 2009).

Here, we capitalize on high temporal resolution neuroimaging (magnetoencephalographic imaging) in svPPA patients with clinical and neuro-anatomical features that enables us to investigate the spatiotemporal dynamics supporting the interplay between ventral and dorsal routes. We hypothesize that svPPA patients, given their ATL atrophy and subsequent lexical-semantic deficit, would rely more on sub-lexical processes to read irregular words, subserved by the relatively structurally intact dorsal, occipito-parietal cortices. Specifically, we predict an over-recruitment of the dorsal route during reading of irregular words in svPPA patients. Given the posited serial and slower nature of the dorsal route computation, we expect this over-recruitment to occur at later latencies.

Materials and methods

Subjects

Twelve svPPA patients (8 female, 67.92 ± 7.33 years old) and 12 healthy age-matched controls (9 female, 72.17 ± 4.04 years old) were recruited through the University of California San Francisco (UCSF) Memory and Aging Center (MAC). All participants were right-handed English native speakers, had no history of developmental dyslexia, and no contraindications to MEG. Patients met currently published diagnostic criteria for svPPA as determined by a team of clinicians and physicians based on a detailed medical history, comprehensive neurological assessment, and standardized neuropsychological and language evaluations (Kramer *et al.*, 2003; Gorno-tempini *et al.*, 2011). All patients included in the study scored at least 15 out of 30 on the Mini-Mental Status Exam (MMSE) and weresufficiently functional to be scanned. In addition, each patient had left-predominant anterior temporal lobe atrophy to maximize our chances of detecting surface dyslexia in a homogenous sample (Binney *et al.*, 2016). Demographic information and neuropsychological data are shown in Table 1 and 2 respectively. Two-sample t-tests (two-tailed distributions, significance threshold set at $p<0.05$) were used to statistically assess group differences between these svPPA patients and healthy controls published data (Gorno-Tempini *et al.*, 2004; Binney *et al.*, 2016; Watson *et al.*, 2018) (Table 2). Approved study protocols by the UCSF Committee on Human Research were followed, and all subjects provided written informed consent.

Stimuli and Experimental Design

Visual stimuli were projected into the magnetically shielded MEG scanner room. Subjects were instructed to read aloud the string of letters immediately following its appearance on the

screen, speaking their responses into a MEG-compatible microphone. The stimuli consisted of 40 regular words, i.e., words with regular grapheme-to-phoneme correspondence (e.g., *fact*), 40 irregular words, i.e., words with inconsistent grapheme-to-phoneme correspondence (e.g., *choir*), and 70 pronounceable strings of letters with no semantic representation (e.g., *pook*). Real words and pseudowords (n=20) were drawn from the Arizona reading list (Beeson and Rising, 2010). An additional 50 pseudowords were generated using an established computerized multi-lingual pseudo-word generator Wuggy (Keuleers and Brysbaert, 2010). Three sets of 50 pseudowords each were generated by submitting a list of 50 real word nouns to the multilingual pseudoword generator using the English language setting for sub-syllabic structures and transition frequencies. The first 50 pseudowords set was checked by a native speaker informant, who suggested no replacement from the backup second or third sets. Examples of stimuli from each category, along with frequency and length measures, are shown in Table 3.

Words and pseudowords were presented in two separate runs. Words were presented twice each in a fixed, sequential order (1 second display, 1.7-2.1 second inter-stimulus interval (ISI)). Pseudowords were presented twice each in randomized order (2 second display, 1.7-2.1 second ISI). Vocal responses were digitized on separate analog-to-digital channels (ADCs), marked through amplitude threshold detection, and verified by hand through visual inspection manually in each dataset. If the patient needed more time respond, duration of the ISI was extended to ensure that responses were captured without interfering with the next trial.

Behavioral data

Responses were recorded with Audacity (www.audacityteam.org) and coded offline by three independent raters as either correct, error, or missed. Reaction times and accuracy were statistically analyzed using an analyss of variance (ANOVA) based on the three word types (regular, irregular, and pseudo- words) and cohorts (controls vs. svPPA patients) using the Python statistical library (statsmodels - www.statsmodels.org).

MRI protocol and analyses

Structural T1-weighted images were acquired on a 3T Siemens system (Siemens, Erlagen, Germany) at the UCSF Neuroscience Imaging Center, equipped with a standard quadrature head coil with sequences, previously described in (Mandelli et al., 2014). MRI scans were acquired within 1 year of the MEG data acquisition. To identify regions of atrophy, svPPA patients were compared to a separate set of 25 healthy controls collected using the same protocol (14 females, mean age 66.2 ± 8.5) using voxel-based morphometry (VBM). Image processing and statistical analyses were performed using the VBM8 Toolbox implemented in Statistical Parametric Mapping (SPM8, Wellcome Trust Center for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm) running under Matlab R2013a (MathWorks). The images were segmented into grey matter, white matter, and CSF, bias corrected, and then registered to the Montreal Neurological Institute (MNI). The grey matter value in each voxel was multiplied by the Jacobian determinant derived from spatial normalization in order to preserve the total amount of

grey matter from the original images. Finally, to ensure the data were normally distributed and to compensate for inexact spatial normalization, the modulated grey matter images were smoothed with a full-width at half-maximum (FWHM) Gaussian kernel filter of 8x8x8 mm. A general linear model (GLM) was then fit at each voxel, with one variable of interest (group), and three confounds of no interest: gender, age, education, and total intracranial volume (calculated by summing across the grey matter, white matter and CSF images). The resulting statistical parametric map (SPM) was thresholded at $p<0.001$ with family wise error (FWE) correction voxel-wise and used to visualize svPPA patients atrophy pattern (see Fig.1C), as well as build an exclusive mask for the MEG source reconstruction analyses (see below).

MEG protocol and analyses

Neuromagnetic recordings were conducted using a whole-head 275 axial gradiometer MEG system (CTF, Coquitlam, BC, Canada) at a sampling rate of 1200 Hz. Head position was recorded before and after each block using three fiducial coils (nasion, left/right preauricular) placed on the participant. After data acquisition, each dataset was visually inspected to identify and remove noisy MEG sensors as well as trials with artifacts or missing responses that exceeded 1 pT fluctuations. Datasets were then epoched with respect to stimuli presentation onset (stimulus-locked trials) or vocal response onset (response-locked trials). In order to further remove excessive noisy artifacts (e.g., dental work, gritting) from some trials, datasets were cleaned using dual signal subspace projection (DSSP) and filtered between 4 and 115 Hz prior to souce reconstruction (Sekihara *et al.*, 2016; Cai *et al.*, 2018).

We then reconstructed whole-brain oscillatory activity using the Neurodynamic Utility Toolbox for MEG (NUTMEG; http://nutmeg.berkeley.edu), which implements a time–frequency optimized adaptive spatial filtering technique to estimate spatiotemporal locations of neural sources. A tomographic volume of source locations was computed through an adaptive spatial filter (8 mm lead field) that weights each location relative to the signal of the MEG sensors (Dalal *et al.*, 2008). Data was reconstructed in the beta (12-30 Hz) range using partially overlapping time windows (200 ms, 50 ms step size) optimized for capturing induced, non-phase locked changes in the MEG signal generated by neural activity. Source power for each location was derived through a noise-corrected pseudo-F statistic expressed in logarithmic units (decibels) comparing signal magnitude during an active experimental time window (i.e., from 0, stimuli onset, to 900 ms) versus a baseline control window (i.e., 250 ms preceding stimuli onset) (Robinson and Vrba, 1999).

We focused our analyses on beta band (12-30 Hz) activations during reading of irregular words and pseudowords for three main reasons. First, we wished to overcome limitations of previous studies by looking not only at evoked but also induced changes in brain activity (i.e., modulations of ongoing oscillatory processes that are not phased-locked). This is especially relevant when the effects might occur later with respect to stimuli onset, as in the current setting, where differences between controls and patients in early, low-level visual processes are not expected, while divergence in later stages is predicted by both behavioral evidence and

neuroanatomical findings. Furthermore, increased latency in response to linguistic stimuli have been observed in svPPA patients, and analyses of oscillatory behavior might be more sensitive than ERPs in detecting abnormalities in slow neural responses with increased trial-by-trial variability and thus decreased phase-locking (Kielar *et al.*, 2018). Second, we aimed at providing functional interpretation of our findings. The beta band has been extensively related to cortical activations. Specifically, desynchronization (i.e., beta band suppression) is a reliable indicator of heightened neural activity (Yuan *et al.*, 2010; Stevenson *et al.*, 2011) and covaries with BOLD signal in fMRI. Also, the beta band has been shown to capture predominantly left lateralized language functions, such as reading, and svPPA is a strongly left lateralized neurodegenerative disease (Wang *et al.*, 2012; Hinkley *et al.*, 2016). Moreover, beta band oscillations have been reliably associated with both memory and motor components of spoken word production (Herman *et al.*, 2013; Piai *et al.*, 2015). Third, in order to highlight the difference between the lexical and sub-lexical route, the key conditions that we compared were irregular words (as they can be read correctly only relying on lexical knowledge) and pseudowords (as they can be read only via sub-lexical processes). However, regular words can read using either route and thus do not offer any clear insight on the neural processes underlying lexical and sub-lexical processes.

Single-subject beamformer reconstructions were spatially normalized by applying each subject's T1-weighted transformation matrix to their statistical map, and group analyses were performed with statistical nonparametric mapping (SnPM). From each voxel, we obtained a permuted distribution, then we estimated the significance of each pseudo-F value from its position in this permuted distribution (Singh *et al.*, 2003). Multiple-comparisons corrections were applied using an adaptive two-step false discovery rate (FDR; (Benjamini and Hochberg, 2000)), wherein both steps' maps were thresholded at $p<0.01$, and the cluster extended spatio-temporal threshold set to 200 voxels and two consecutive time windows. Finally, for visualization purposes, a binarized image generated from patients' group-level atrophy map was used as an exclusive mask applied to the voxelwise statistics (see section *MRI protocol and analyses*). Figures 2-4 focus on the left-hemiphere results, central to our investigation and main component of our results. For completeness, Table 4 reports all statistically significant clusters in both hemispheres.

First, we examined the pattern of activation during irregular word and pseudoword reading separately for controls and svPPA patients (SnPM one-sample t-test against baseline). Then, for both groups, we generated within-subject contrast maps comparing pseudowords and irregular words in order to identify spatiotemporal clusters of heightened activity due sub-lexical processes (SnPM two-sample t-test). Next, we directly compared svPPA patients and controls during irregular word reading in order to highlight spatiotemporal clusters of differential activity between the two groups (SnPM two-sample t-test).

Finally, we conducted two post-hoc analyses. First, we sought to rule out the hypothesis that the differences in neural activation could be explained by differences in reaction times. To this end, the raw datasets were epoched with respect to the onset of vocal response (response-locked trials, from -400 ms before response to +400 ms after vocal response) and the same group comparison (i.e., irregular word reading in controls vs. svPPA patients) was performed. Second,

we directly compared, in the time window of interest, svPPA patients and controls during pseudoword reading (SnPM two-sample t-test) to ascertain whether the observed difference between groups was generalized or specific to irregular word reading.

Data Availability

The clinical and neuroimaging data used in the current paper are available from the corresponding author, upon reasonable request. The sensitive nature of patients' data and our current ethics protocol do not permit open data sharing at this stage.

Results

Behavioral data and cortical atrophy

Two ANOVAs based on three word types (regular, irregular, and pseudo- words) and two cohorts (controls vs. svPPA patients) were used to compare behavioral performance in the task during the MEG scan. For overall accuracy (Fig. 1A), there was a significant main effect of cohort ($F(1)=16.9$, $p <0.001$), but there was no main effect of word type ($F(2)=2.75$, $p =0.07$) nor significant interaction ($F(2)=0.49$, $p =0.6$). For reaction times (Fig.1B), there was a significant main effect of cohort ($F(1)=11.64$, $p =0.001$) and of word type ($F(2)=16.04$, $p <0.001$), but no significant interaction ($F(2)=0.01$, $p =0.9$). Overall, these results are consistent with a clinical diagnosis of svPPA and a pattern of surface dyslexia.

Distribution of cortical atrophy in the svPPA cohort is shown in Figure 1C. Patients present the expected pattern of degeneration of the anterior temporal lobe. Unsurprisingly, given our inclusion criteria, the atrophy appears strongly left-lateralized.

Neural dynamics during reading

Within-group analyses of brain activity (changes in beta power) during irregular word and pseudoword reading are presented for both controls in Figure 2A and svPPA patients in Figure 2B. Following stimuli presentation (0ms), for both groups and conditions we observed significant beta-power suppression (a marker of functional activation) over occipital and parietal areas with a progressive posterior-to-anterior shift in time. This result is coherent with classical findings from both evoked-related fields (Marinkovic *et al.*, 2003) and spectral (Borghesani *et al.*, 2019) analyses.

In order to localize changes in brain activity differential for sub-lexical vs. lexical processes, we then contrasted pseudowords against irregular words separately for each group. In controls, a significant increase in brain activity during pseudoword reading was observed over bilateral occipito-parietal cortices, ramping up ~600 ms post stimulus onset and peaking at ~800 ms (Fig 3a). Table 4 summarizes the temporal windows, peaks of local maxima, and t-values of all main sub-clusters that could be isolated using this comparison when corrected for multiple comparisons. This included a cluster over the left precuneus, right posterior cingulate, and right

temporal and occipital gyri (Fig 3a). These changes in activation over these parieto-occipital regions peaked during pseudoword reading (when compared to irregular word reading) over these later (600-800ms) time windows, the time of response selection and execution. This finding suggests that, in healthy controls, sub-lexical processes rely on the recruitment of the dorsal route. In svPPA, using the same contrast, this effect was absent even at very lenient (uncorrected) threshold (Fig 3b). Thus it appears that, while controls recruit the dorsal route for pseudowords more than for irregular words, svPPA patients process the two types of stimuli in a similar way: relying on the dorsal route.

Next, in order to confirm that this increase in activation during sub-lexical processing was absent in svPPA, we directly contrasted irregular word reading in controls against svPPA patients. This direct comparison is crucial as the failure to detect an effect in one of the two groups (i.e., a difference in significance level) does not necessarily entail a significant difference between the two groups (Gelman and Stern, 2006). As we predicted from the separate within-group analyses, this between-group comparison revealed a large spatiotemporal cluster over bilateral occipito-parietal cortex where svPPA patients significantly manifested more brain activity than controls (Fig 4a). As detailed in Table 4, four sub-clusters could be localized, peaking in the bilateral precuneus and superior parietal lobule. The spatial topography and timing of these clusters are highly similar to those described in the within-group analyses, strengthening the interpretation that during irregular word reading, at the time of response selection, patients with svPPA over-recruit the dorsal route. Critically, our post-hoc analysis contrasting the two cohorts in the time windows of interest during pseudoword reading reveal no differences.

To correct for changes in reaction time between the two groups (which could potentially influence our stimulus-locked analyses presented above) we conducted an additional analysis reconstructing changes in brain activity in datasets aligned to the onset of the response (response-locked) when subjects read the word aloud. We conducted a between-group comparison for irregular word reading between controls and svPPA for response-locked trials (Fig 4). Here, we see increases in brain activity similar to the group comparison presented above. Around response onset, significantly increased beta suppression is identifiable in the svPPA group over bilateral occipito-parietal cortices (Fig 4b), in particular involving left precuneus, left superior parietal lobule, and right precuneus (see Table 4 for details). This additional analysis confirms that, even when differences in reaction time are taken into account, patients with svPPA still over-recruit these regions of parieto-occipital cortex bilaterally.

Discussion

By comparing the spatiotemporal pattern of brain activity associated with reading aloud irregular words and pseudowords in healthy subjects and patients with svPPA, we provide novel evidence supporting a dual-route model. Healthy controls engaged the occipito-parietal cortex to read pseudowords (more than with irregular words), corroborating the involvement of this dorsal route in sub-lexical processes. Interestingly, svPPA patients, who present with surface dyslexia

and left anterior temporal atrophy, appeared to recruit this dorsal cluster equally for irregular words and pseudowords. Direct comparison of controls and patients during irregular word reading highlighted the same spatiotemporal cluster. These results support the interpretation that svPPA patients rely on the spared functions underpinned by the dorsal route (i.e., orthography-to-phonology mapping following language-specific statistical regularities) to read in the context of semantic impairment due to ventral route damage. Crucially, these effects were detected at the time of response preparation and production, consistent with the idea that the dorsal sub-lexical route is supporting serial, slow, attention-dependent processes, in contrast with the parallel, fast, automatic ones underpinned by the ventral lexical route.

Dorsal, occipito-parietal cortices support sub-lexical processes

This is the first study investigating the spatiotemporal dynamics of reading in svPPA, a clinical syndrome whose neuroanatomical (i.e., neurodegeneration of the ATL) and neuropsychological (i.e., surface dyslexia) features allow scrutiny of the interplay (and dissociation) between lexical and sub-lexical processes.

The first main result of our study is that reading pseudowords, as compared with irregular ones, requires heightened recruitment of parietal cortex. This result is in line with previous neuroimaging and neuropsychological evidence associating the dorsal path with sub-lexical processes (Booth *et al.*, 2003; Jobard *et al.*, 2003; Mechelli *et al.*, 2003; Wilson *et al.*, 2009; Graves *et al.*, 2010; Taylor *et al.*, 2013; Sliwinska *et al.*, 2015). Our results also corroborate previous findings that low-level visual processing of symbolic stimuli in primary and secondary visual areas does not differ between words and orthographically regular pseudowords (Vinckier *et al.*, 2007). At these early stages of visual processing, no differences are detected between healthy controls and svPPA patients, as predicted by the pattern of atrophy and the neuropsychological profile of svPPA patients. However, as compared to healthy controls, svPPA patients do not show heightened recruitment of parietal cortex when comparing pseudowords and irregular words. This finding suggests that they are processing the two set of stimuli via the same neuro-cognitive mechanism. This conclusion is supported by the observation that, during irregular word reading, svPPA patients show greater activation (compared to controls) of a very similar parietal cluster. Patients thus appear to rely on dorsal, sub-lexical processes to read both irregular words and pseudowords.

The parietal cortex, in particular the inferior parietal lobule, has been associated with various cognitive functions including pointing, grasping, attention orienting, saccades, calculation, and phoneme detection (Simon *et al.*, 2002). With respect to language, discrete areas preferentially involved in orthography and attention, fluency and phonology, or semantic have been identified (Battistella *et al.*, 2019). Overall, bilateral posterior parietal regions appear to support an array of visuo-spatial attentional processes including visual search and scanning of arrays of objects (Corbetta and Shulman, 2002), endogenous orientation of attention to lateralized visual targets (e.g. Gitelman *et al.*, 1999; Peelen *et al.*, 2004), and switching from global (word) to local (letters) attention (Wilkinson *et al.*, 2001). Readers can harness these specific forms of focused attention

to apply serial reading strategies if they are young and/or unskilled (Church *et al.*, 2008; Dehaene-Lambertz *et al.*, 2018), or to compensate for visual input degradation (Cohen *et al.*, 2008), brain damage causing word blindness (Cohen *et al.*, 2004; Henry *et al.*, 2005), or loss of lexico-semantic information (Wilson *et al.*, 2009). The role of the parietal cortex as the sub-lexical component of the reading network is further supported by the observation of a correlation between its recruitment and reading proficiency, likely mediated by its structural and functional connectivity profile (Bouhali *et al.*, 2019; Broce *et al.*, 2019; Moulton *et al.*, 2019). Our current investigation lacks appropriate spatial resolution, but future studies deploying other techniques might be able to topographically separate executive/attentional contributions from phonological ones (Oberhuber *et al.*, 2016).

Overall, our findings strengthen the topographical dissociation between (ventral) lexical and (dorsal) sub-lexical processes while highlighting the important implications not only for developmental (Pugh *et al.*, 2000; Peyrin *et al.*, 2011) but also acquired reading disorders (Aguilar *et al.*, 2018).

<u>The latency of the dorsal activation indicates slow, serial processing</u>

The dissociation between lexical and sub-lexical processes cannot be resolved in their localization to temporal and parietal cortices respectively. Behavioral evidence suggests that the two routes rely on different computational mechanisms and thus have different timing properties (Paap and Noel, 1991; Coltheart and Rastle, 1994; Weekes, 1997). Both routes are activated by a written stimulus yet the lexical route is characterized by fast, parallel processing while the sub-lexical route by slow, serial processing. The temporal resolution offered by our analyses of MEG recordings corroborates the idea that the first steps of visual information processing do not differ between irregular words and pseudowords, suggesting that both lexical and sub-lexical routes are equally engaged. These early stages do not appear to differ between healthy controls and svPPA patients, consistent with patient's spared occipital areas and preserved basic visual functions (Watson *et al.*, 2018).

Differences between the two groups emerge at the time of response selection and production. In these later, final stages, svPPA patients do not show the regularity effect detected in controls (i.e., pseudowords recruiting the dorsal route more than with irregular words). Hence, svPPA patients appear to rely on the same neuro-cognitive substrate to process both irregular words and pseudowords. This result is strengthened by the detection of a similar spatiotemporal cluster when directly comparing neural activity during irregular word reading across the two groups. These findings were confirmed by both stimulus-locked and response-locked analyses, indicating that the effects are stable in space and time, and cannot be ascribed to differences in reaction time. Thus, in svPPA, surface dyslexia appears to be due to the failure of activating semantic representations stored in the temporal lobe, and the need to rely on sub-lexical grapheme-to-phoneme translation supported by the parietal lobe.

Our findings are in line with converging behavioral and neuroimaging evidence supporting the idea that, while activated at the same time by the presentation of a written stimulus, the lexical

(ventral) route and the sub-lexical (dorsal) one are characterized by different processing dynamics: fast and parallel in the first case, slow and serial in the latter. For instance, the systematic length effect detected for pseudowords is stronger than for real words (Weekes, 1997). Moreover, the strength of the regularity effect declines as a function of the position of the irregular grapheme: reaction times are longer when reading "chef" (i.e., irregular grapheme in first position), than "tomb" (i.e., irregular grapheme in second position), than "glow" (i.e., irregular grapheme in third position) (Coltheart and Rastle, 1994). Electroencephalography (EEG), magnetoencephalography (MEG), and intracranial local field potentials (LFP) have been instrumental in illustrating how basic visual feature analysis occurs within ~100 ms over the occipital midline, followed by a word-selective yet pre-lexical response peaking over the left occipital scalp around 150-200 ms (Bentin *et al.*, 1999; Tarkiainen *et al.*, 1999; Gaillard *et al.*, 2006). These initial sequential stages are followed by parallel processing of nonvisual information in a distributed language network allowing access to lexical, semantic and phonological features of the words (Vinckier *et al.*, 2007; Twomey *et al.*, 2011; Thesen *et al.*, 2012). On one hand, semantic effects are typically detected at around 400-600 ms (e.g. N400) and localized to left ATL (Lau *et al.*, 2008, 2016). On the other hand, consistent with the role played by the parietal lobe in visual attention (Saalmann *et al.*, 2007), late sustained engagement of dorsal regions is observed in cases of effortful reading (Rosazza *et al.*, 2009).

The effects we observe occur close to response production and are strongest after response onset - i.e., when the subjects are spelling out the word. The progressively heightened activity over dorsal cortices suggests that, when relying on the sublexical route, articulation of the word starts as the first grapheme-to-phoneme conversion has been performed and proceed serially grapheme by grapheme. This is in contrast with the parallel processing taking place along the ventral lexical route that allows spelling out once the stimulus has been decoded as a whole. Overall, our findings corroborate the hypothesis that the dorsal sub-lexical, route supports serial and attention-dependent processes, whose effects are most apparent at the time of response selection and production.

<u>Over-recruitment of the dorsal route as the neural signatures of an imperfect compensation</u>

Our results illustrate how a specific cognitive task can be performed via the deployment of distinct cognitive and neural resources. The damage to the ATL in svPPA patients leads to a profound impairment of the lexico-semantic system, whose functionality is needed to retrieve the correct pronunciation of exceptional spelling-to-sound associations. As a compensatory strategy, svPPA patients rely on sub-lexical processes underpinned by the dorsal route to read irregular words. However, patients' over-reliance on serial, slow, grapheme-to-phoneme conversion mechanisms leads to overall slower responses and, in the case of words with atypical spelling, increased number of regularization errors. Results from this study demonstrate that patients can thus only partially, imperfectly compensate for their semantic loss via spared sub-lexical processes.

Our findings align with recent evidence from task-free fMRI studies reporting alterations in intrinsic functional connectivity networks in svPPA patients. Decreased connectivity in the

ventral semantic network (as expected given the atrophy pattern) is accompanied by spared connectivity in the orthography-to-phonology conversion network and increased connectivity in the dorsal articulatory-phonological one (Battistella *et al.*, 2019; Montembeault *et al.*, 2019). Taken together, these results suggest that neurodegeneration leads to a dynamic reorganization of the interplay between ventral and dorsal pathways, where the downregulation of specific neuro-cognitive systems is associated with the upregulation of other ones. Moreover, they exemplify how studying the spatiotemporal dynamics of different language functions in clinical populations has implications for both clinical practice (e.g., understanding patients' symptoms) and basic science (e.g., understanding the neural correlates of language). These studies also stress the need to shift the focus of research in neurodegenerative populations from volume and structural connection loss to also include alterations to regions' functional profiles and temporal dynamics.

MEG has only been deployed recently to investigate PPA (e.g., Kielar *et al.*, 2018), but has already shown its potential as a tool to study the neurophysiological signatures of network-level alterations due to neurodegenerative disorders. It can be instrumental in identifying syndrome-specific changes in the spectral properties of oscillatory responses (Ranasinghe *et al.*, 2017; Sami *et al.*, 2018). As suggested by task-free fMRI evidence, these functional alterations might precede structural ones and may be key for early diagnosis (Bonakdarpour *et al.*, 2017). Given the different features of the signal that can be studied (e.g., delayed latencies, attenuated amplitude) and the wide array of analysis methods available, MEG will provide a broad spectrum of complementary insights into the neural underpinnings of neurodegenerative diseases.

Patients with stroke affecting the left hemisphere might exhibit a different neuropsychological profile from svPPA ones: regularization errors do not appear to correlate with semantic impairments and are associated with damage to the posterior half of the left middle temporal gyrus rather than the ATL (Binder *et al.*, 2016). This finding suggests that the neuro-cognitive profile of svPPA patients (i.e., surface dyslexia, semantic deficits, and ATL damage) is not the only path to over reliance on sub-lexical processes. Additional functional studies comparing stroke and neurodegenerative patients are warranted to clarify whether the spatio-temporal dynamics of the compensatory mechanisms implemented by the two clinical populations are similar.

Limitations and future perspectives

Our sample size is relatively small. However, svPPA is a rare disorder and only a fraction of patients can surmount the difficulties inherent to MEG testing (e.g., percentage of dental work, motion, fatigue). We optimized our analysis pipeline to investigate possible late effects of the key contrast of interest (irregular vs pseudowords) as prior findings suggested a key role of dorsal, sub-lexical mechanisms in svPPA patients with surface dyslexia (Wilson *et al.*, 2009). Follow-up studies of other electrophysiological features (e.g., lower frequencies, evoked fields) might reveal earlier, additional effects.

Conclusions

Together these findings, combining a neuropsychological model and time-resolved MEG imaging, provide further evidence supporting a dual-route model for reading aloud, mediated by the interplay between lexical (ventral and parallel) and sub-lexical (dorsal and serial) neuro-cognitive systems. When the lexical route is damaged, as in the case of neurodegeneration affecting the ATL, partial compensation appears to be possible by over-recruitment of the slower, serial attention-dependent, sub-lexical one. This study also demonstrates how task-based MEG imaging can be leveraged in clinical populations to study the functional interplay of different language networks, with important implication for both models of language and clinical practice.

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Competing interests

The authors declare no competing interests.

Figures and Tables

TABLE 1. Demographics Data		
	svPPA (n= 12)	**NC (n=12)**
	Mean (SD)	*Mean (SD)*
Demographics		
Age (std)	67.80 (7.28)	72.17 (4.04)
Gender (F:M)	7:5	9:3
Education	16.90 (3.87)	17.83 (1.99)

Table 1. Demographic characteristics of participants. All participants were right handed native English speakers demographically matched across the two cohorts.

TABLE 2. Neuropsychological Data	svPPA (n= 12) Mean (SD)	
General Cognition		
CDR - box score	4.42 (2.80)	*
MMSE (30)	21.92 (5.26)	*
Memory		
CVLT-SF 10" Delay (9)	0.58 (1.44)	*
CVLT-SF 30' Delay (9)	1.92 (2.50)	*
CVLT-SF recognition (9)	6.33 (2.99)	*
Benson Figure Delayed Recall (17)	7.25 (5.2)	
Visuospatial/Visuoconstruction		
Benson Figure Copy (17)	15.75 (0.62)	
Spatial Span Forward (9)	5.83 (1.17)	
Executive Functions		
Digit Span Forward	5.36 (1.03)	
Digit Span Backward	4.09 (1.14)	
Modified Trails Completion Time (in seconds)	48.20 (19.14)	
Stroop Inhibition (100)	34.00 (14.44)	*
Language		
Apraxia of Speech (7)	0 (0)	
Dysartria (7)	0 (0)	
Semantic Fluency (animal)	7.33 (5.55)	*
Lexical Fluency (phonemic)	7.00 (4.36)	*
Abbreviated BNT (15)	5.0 (4.02)	*
WAB Repetition (100)	88.00 (6.71)	*
PPVT (16)	7.82 (3.89)	*
Arizona Spelling Real - Regular (10)	7.44 (2.71)	
Arizona Spelling Real - Irregular (10)	2.89 (2.08)	*
Arizona Spelling Pseudo (10)	7.11 (3.45)	
Arizona Reading Real - Regular (18)	15.89 (3.41)	
Arizona Reading Real - Irregular (18)	12.00 (4.67)	*
Arizona Reading Pseudo (18)	13.44 (5.17)	

Table 2. Neuropsychological profile of svPPA patients. The patient group includes 12 cases of semantic variant of Primary Progressive Aphasia (svPPA). Scores shown are mean (standard deviation). *indicate values significantly different from controls ($p<0.05$). CDR = Clinical Dementia Rating, MMSE = Mini-Mental State Exam. CVLT=California Verbal Learning Test, BNT = Boston Naming Test, WAB = Western Aphasia Battery, PPVT = Picture Vocabulary Test.

TABLE 3. Stimuli			
	Regular Words	**Irregular Words**	**Pseudo Words**
	n = 40	n = 40	n = 20 + 50
	Mean (SD)	*Mean (SD)*	*Mean (SD)*
Examples	*fact, bribe, magnet*	*choir, castle, yacht*	*pook, andon, codle*
Frequency (log)	2.43 (0.60)	2.39 (0.70)	n/a
Length (# of letters)	5.1 (0.91)	5.1 (0.91)	4.8 (0.99)

Table 3. Psycholinguistic characteristics of the stimuli. Values shown are mean (standard deviation). All words (n=80) and a portion of the pseudowords (n=20) were taken from the Arizona reading list. An additional set of 50 pseudowords were generated with Wuggy.

TABLE 4. Results of MEG contrasts [Figures 3-4]				
	Time window		**Local Maxima**	
	ms	*MNI [x,y,z]*	*p-value*	*t-value*
HC: irregular - pseudowords [stimulus- locked]				
Left occipito-parietal cluster				
left precuneus	725 to 900 ms	-16, -70, 30	0.01	2.8
Right occipito-temporo-parietal cluster				
right posterior cingulate	575 to 900 ms	25, -60, 13	0.005	3.1
right middle temporal gyrus	675 to 900 ms	55, -65, -1	0.005	3.3
right middle occipital gyrus	575 to 900 ms	33, -89, 4	0.005	3.1
svPPA: irregular - pseudowords [stimulus- locked]				
	no supra-threshold cluster			
Irregular words: svPPA - HC [stimulus- locked]				
Left occipito-parietal cluster				
left superior parietal lobule / precuneus	725 to 900 ms	-18, -78, 44	0.001	3.4
left inferior parietal lobule	825 to 900 ms	-32, -35, 56	0.005	2.9
Right occipito-parietal cluster				
right superior parietal lobule	725 to 900 ms	12, -38, 78	0.001	3.4
right precuneus	725 to 900 ms	18, -72, 44	0.005	2.6
Irregular words: svPPA - HC [response locked]				
Left occipito-parietal cluster				
left superior parietal lobule	25 to 400 ms	-36, -50, 63	0.001	3.5
left precuneus	-25 to 75 ms	-12, -65, 40	0.005	2.4
left superior frontal gyrus	225 to 400 ms	-9, 4, 73	0.001	4
Right occipito-parietal cluster				
right precuneus	-25 to 125 ms	9, -65, 32	0.005	2.9

Table 4. Local maxima in MNI coordinates. Time window, MNI coordinates and t-value of the local maxima of the different MEG whole-brain contrasts performed. The spatiotemporal distribution of these clusters can be appreciated in Fig. 3 and 4.

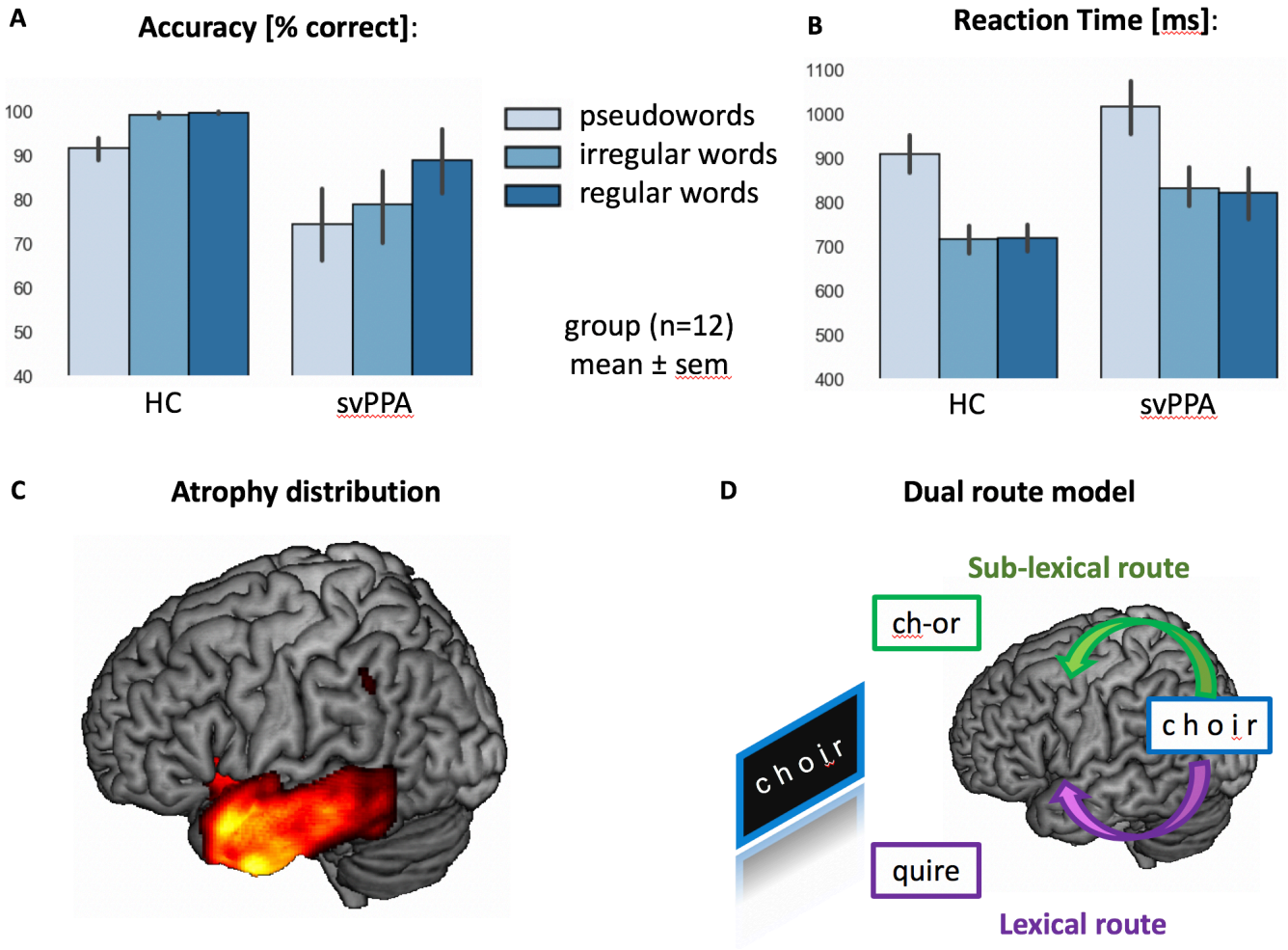

Figure 1. Behavioral data and atrophy distribution in svPPA patients. (A) Percentage accuracy and (B) reaction times in single word reading in each experimental conditions, in controls and svPPA patients. (C) Voxel based morphometry (VBM)-derived atrophy pattern showing significantly reduced grey matter volumes in the anterior temporal lobe for svPPA patients (thresholded at $p<0.001$ with family wise error (FWE) correction). (D) Cartoon representation of the dual route model: the dorsal sub-lexical route supports orthography -to-phonology mapping based on language-specific statistical rules, while the ventral lexical route maps orthographic forms to meaning thus allowing correct reading of irregular words.

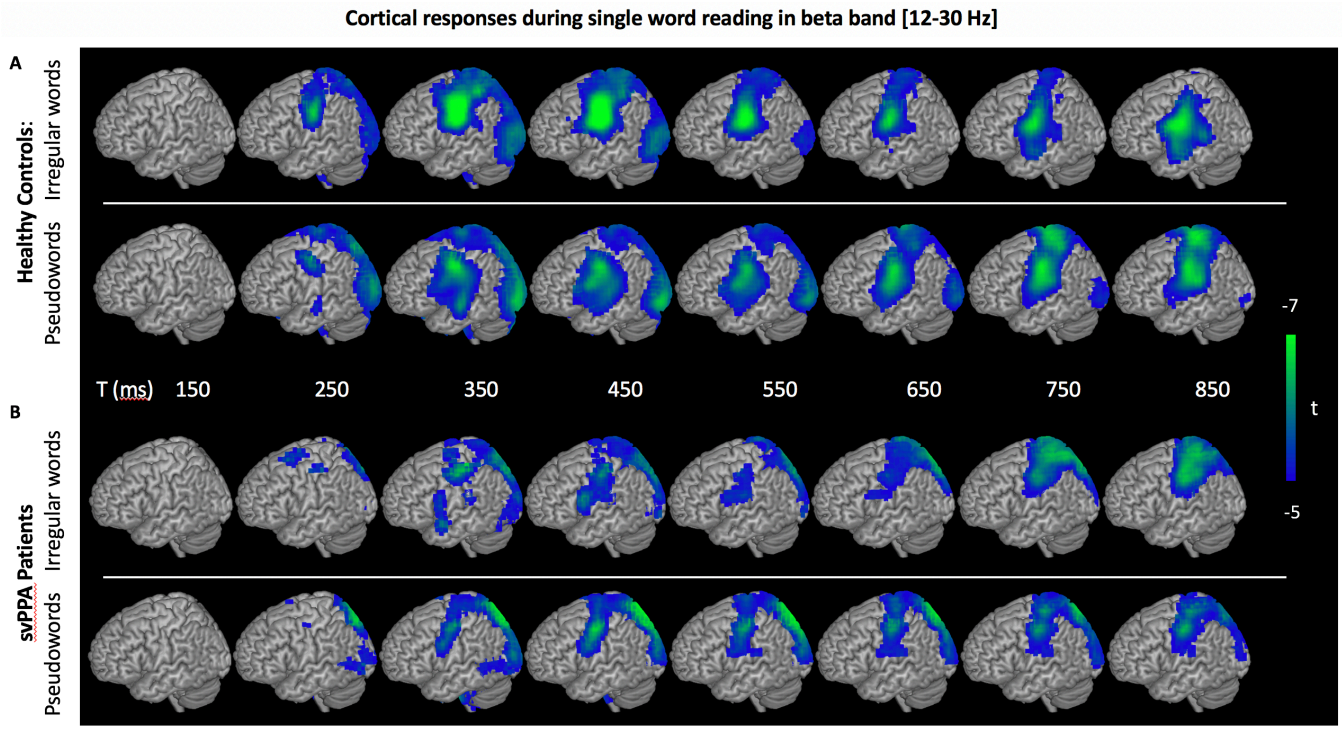

Figure 2. Stimulus-locked (0 ms = written word onset) group analyses of changes in beta (12–30 Hz) oscillatory power during single word reading. A) Pattern of beta suppression in healthy controls for both irregular words (upper row) and pseudowords (lower row). Following stimuli presentation, signifincantly heightened beta suppression tracks the time course of language network activation from occipital towards temporo-parietal areas. B) Same as in A but for the svPPA patients. Results of one-sample t-test.

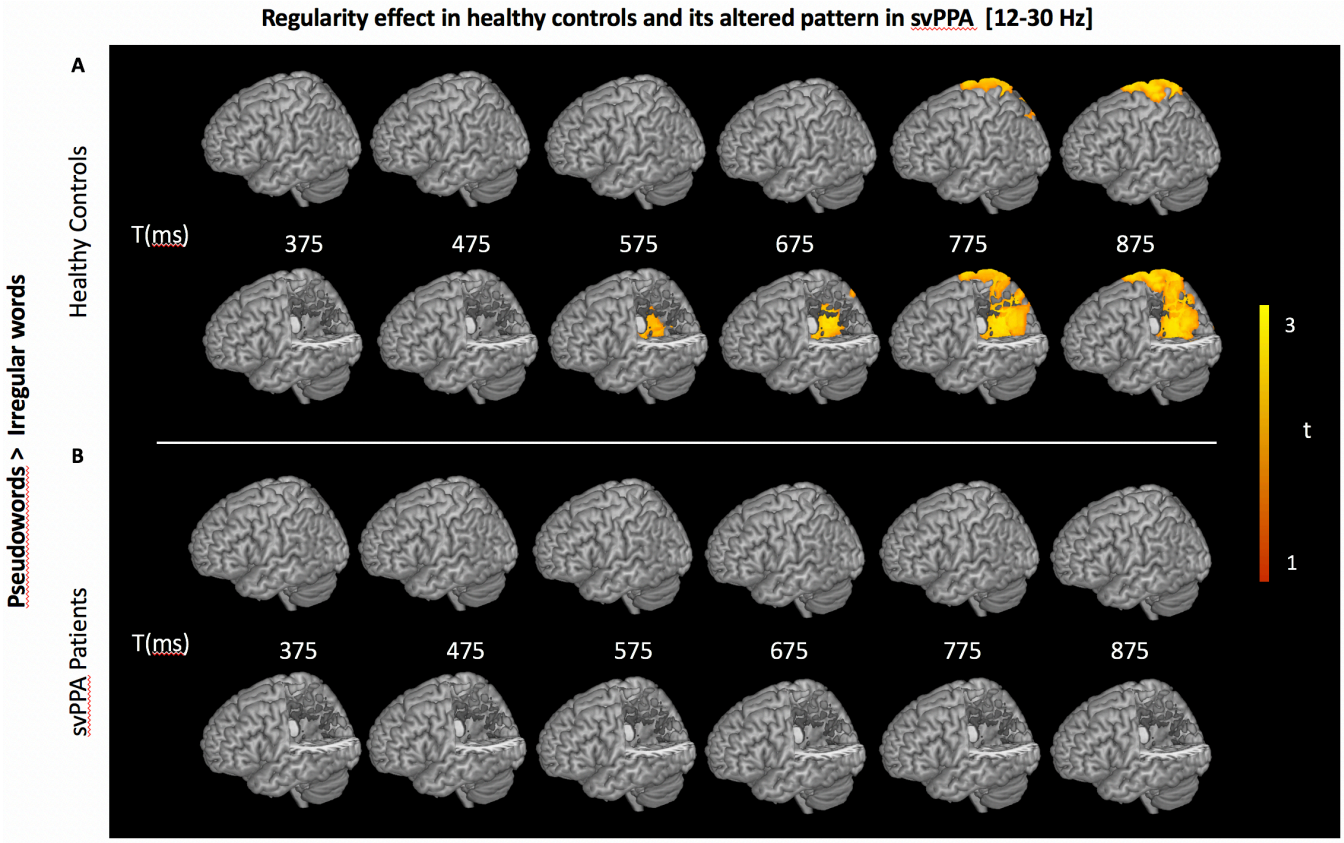

Figure 3. Stimulus-locked (0 ms = written word onset) group analyses of the regularity effect: pseudowords vs. irregular words. A) Results of the contrast between pseudowords and irregular words in healthy controls. A large spatiotemporal cluster of heightened beta suppression for pseudowords (vs. irregular words) is observed over the left parietal cortex from ~ 500ms to ~ 800 ms. B) Same as in A but for the svPPA patients: no supra-threshold cluster can be detected.

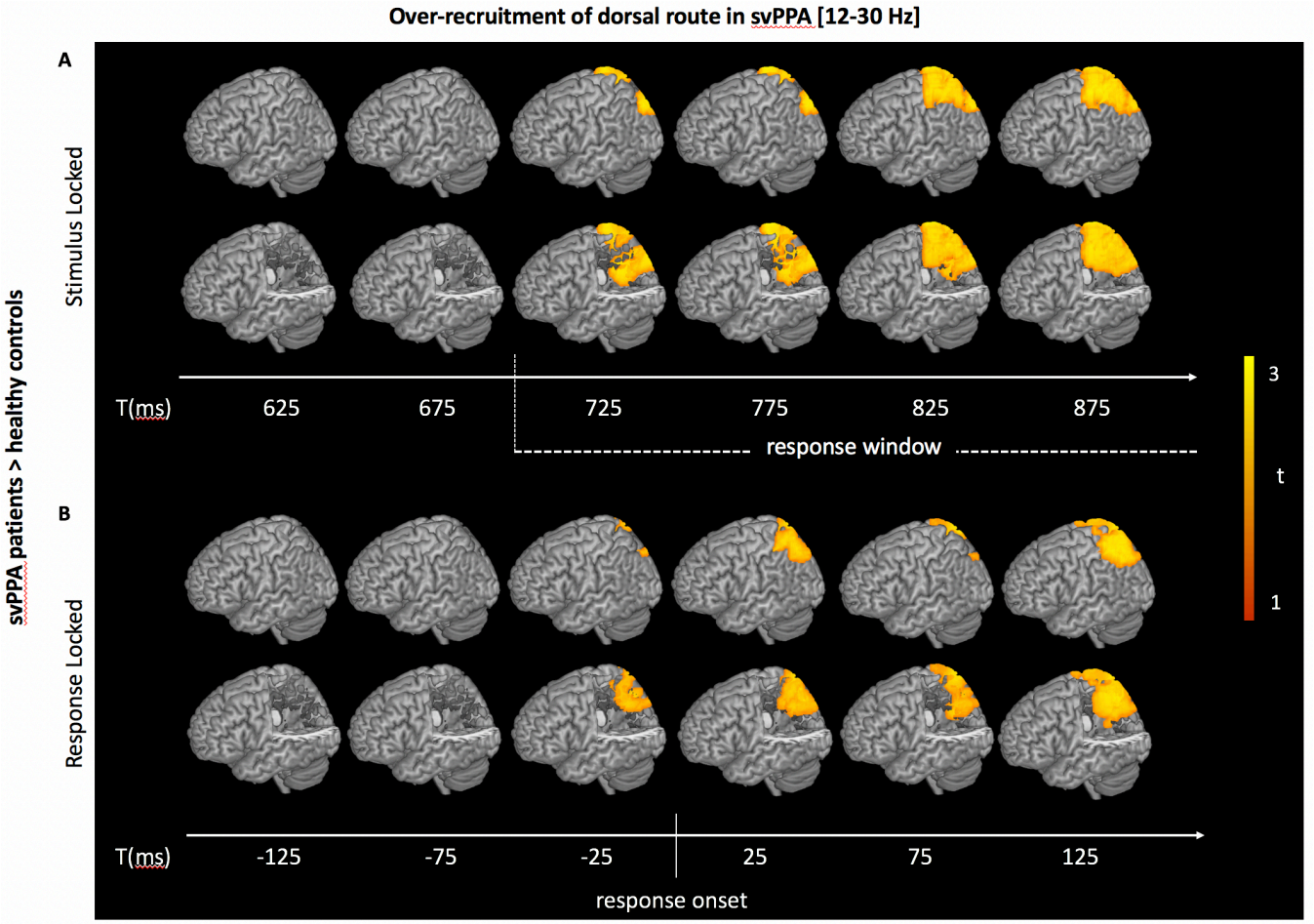

Figure 4. Contrast controls vs. svPPA. A) Results of the contrast between svPPA patients and healthy controls during irregular word reading for stimulus-locked analyses (0 ms = written word onset). A large spatiotemporal cluster of heightened beta suppression for pseudowords (vs. irregular words) is observed over the left parietal cortex from ~ 700ms. B) Same as in A but for response-locked analyses (0 ms = vocal response onset). A similar spatiotemporal cluster is observed starting ~25 ms before stimulus onset.

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